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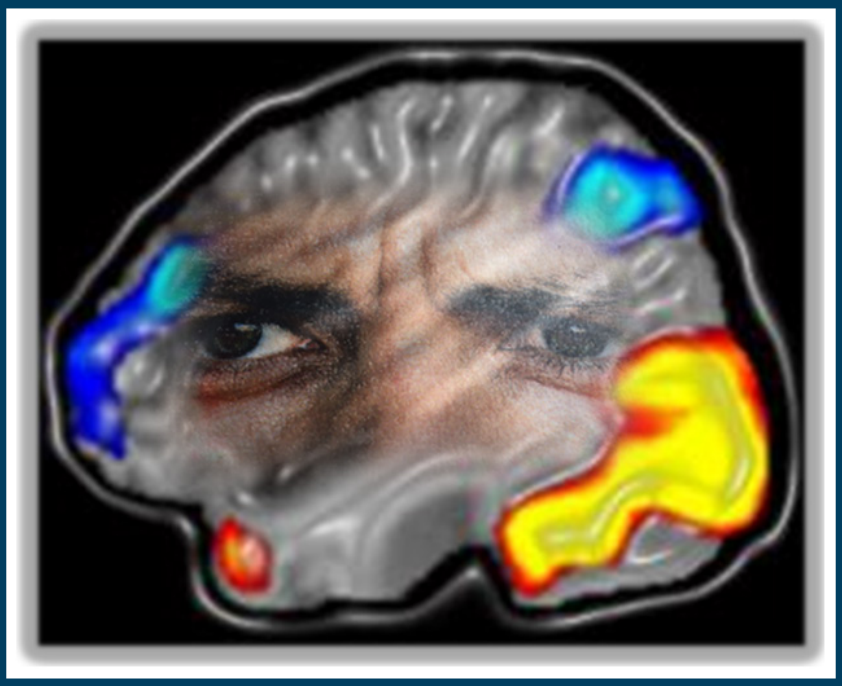

CURRENT RESEARCH AND EMERGING DIRECTIONS IN EMOTION-COGNITION INTERACTIONS

Topic Editors
Florin Dolcos, Lihong Wang and Mara Mather

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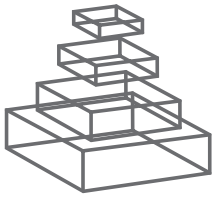

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CURRENT RESEARCH AND EMERGING DIRECTIONS IN EMOTION-COGNITION INTERACTIONS

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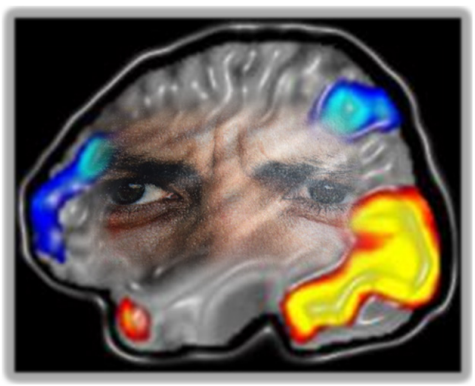

The figure illustrates the intertwined nature of the relationship between the human brain and mind. The color-coded brain activations depict responses in a dorsal neural system involved in "cold" cognitive/executive processing and a ventral system involved in "hot" emotional processing. The human face intersecting with both systems suggests the emergence of the human mind from interactions between emotion and cognition. Design by Florin Dolcos, brain image adapted from Dolcos & McCarthy (2006), face picture provided by Noah Mercer.

Emotion can impact various aspects of our cognition and behavior, by enhancing or impairing them (e.g., enhanced attention to and memory for emotional events, or increased distraction produced by goal-irrelevant emotional information). On the other hand, emotion processing is also susceptible to cognitive influences, typically exerted in the form of cognitive control of motion, or emotion regulation. Despite important recent progress in understanding emotion-cognition interactions, a number of aspects remain unclear. The present book comprises a collection of manuscripts discussing emerging evidence regarding the mechanisms underlying emotion-cognition interactions in healthy functioning and alterations associated with clinical conditions, in which such interactions are dysfunctional. Initiated with a more restricted focus, targeting (1) identification and in depth analysis of the circumstances in which emotion enhances or impairs cognition and (2) identification of the role of individual differences in these effects, our book has emerged into a comprehensive collection of outstanding contributions investigating emotion-cognition interactions, based on approaches spanning from behavioral and lesion to pharmacological and brain imaging, and including empirical, theoretical, and review papers alike.

Co-hosted by the Frontiers in Neuroscience - Integrative Neuroscience and Frontiers in Psychology - Emotion Science, the contributions comprising our book and the associated research topic are grouped around the following seven main themes, distributed across the two hosting journals: I. Emotion and Selectivity in Attention and Memory; II. The Impact of Emotional Distraction; Linking Enhancing and Impairing Effects of Emotion; III. What Really is the Role of the Amygdala?; IV. Age Differences in Emotion Processing; The Role of Emotional Valence; V. Affective Face Processing, Social Cognition, and Personality Neuroscience; VI. Stress, Mood, Emotion, and the Prefrontal Cortex; The Role of Control in the Stress Response; VII. Emotion-Cognition Interactions in Clinical Conditions.

As illustrated by the present collection of contributions, emotion-cognition interactions can be identified at different levels of processing, from perception and attention to long-term memory, decision making processes, and social cognition and behavior. Notably, these effects are subject to individual differences that may affect the way we perceive, experience, and remember emotional experiences, or cope with emotionally challenging situations. Moreover, these opposing effects tend to co-occur in affective disorders, such as depression and PTSD, where uncontrolled recollection of and rumination on distressing memories also lead to impaired cognition due to emotional distraction. Understanding the nature and neural mechanisms of these effects is critical, as their exacerbation and co-occurrence in clinical conditions lead to devastating effects and debilitation. Hence, bringing together such diverse contributions has allowed not only an integrative understanding of the current extant evidence but also identification of emerging directions and concrete venues for future investigations.

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Current research and emerging directions in emotion-cognition interactions

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Emotion is a "double-edged sword" that can either enhance or hinder various aspects of our cognition and behavior. For instance, the emotional charge of an event can increase attention to and memory for that event, whereas task-irrelevant emotional information may lead to increased distraction away from goal-relevant tasks. Sometimes, even the same emotionally arousal event can lead to opposite effects on different aspects of cognitive processing—hearing a gunshot might enhance memory for central aspects of what was happening at the time, while impairing memory for peripheral details. Stress can also lead to quite different effects depending on the context and degree of stress. For example, emotional responses associated with optimal levels of stress (eustress) may increase performance (e.g., positive emotions associated with wedding preparations), whereas emotions associated with exposure to extreme levels of stress impair performance (e.g., overwhelming worry in the anticipation of a difficult exam). Importantly, these effects are also susceptible to cognitive influences, typically exerted in the form of emotion control, which may affect both the immediate and the long-term impact of emotion on cognition. Although during the last decades important progress has been made in understanding emotion-cognition interactions, a number of aspects remain unclear.

The present e-book and research topic comprise a collection of manuscripts discussing emerging evidence regarding the mechanisms underlying emotion-cognition interactions in healthy functioning and alterations associated with clinical conditions, in which such interactions are dysfunctional. Co-hosted by the *Frontiers in Neuroscience—Integrative Neuroscience* and *Frontiers in Psychology—Emotion Science*, our special research topic attracted a large number of outstanding contributions, based on approaches spanning from behavioral and lesion to pharmacological and brain imaging, and including empirical, theoretical, and review papers alike. The contributions are grouped around the following seven main themes distributed across the two hosting journals: *(1) Emotion and Selectivity in Attention and Memory, (2) The Impact of Emotional Distraction; Linking Enhancing and Impairing Effects of Emotion, (3) What Really is the Role of the Amygdala?, (4) Age Differences in Emotion Processing; The Role of Emotional Valence, (5) Affective Face Processing, Social Cognition, and Personality Neuroscience, (6) Stress, Mood, Emotion, and the Prefrontal Cortex; The Role of Control in the Stress Response, (7) Emotion-Cognition Interactions in Clinical Conditions*. This comprehensive approach allowed an integrative understanding of the available evidence and identification of concrete venues for future investigations.

EMOTION AND SELECTIVITY IN ATTENTION AND MEMORY

Perhaps the most studied issue in the history of emotion-cognition interactions is how emotion influences the scope or selectivity of attention and memory. Does arousal or negative emotion lead to the narrowing of the scope of attention? Do arousing stimuli create a trade-off in memory such that they are remembered better than similar neutral stimuli, while they impair memory for surrounding information? How do goals and the type of emotion relate to these selectivity effects? The papers in this section provide an excellent overview of current issues and controversies regarding this topic.

Even in the absence of strong emotion, different stimuli compete for representation in the brain (Desimone and Duncan, 1995; Beck and Kastner, 2009). Attention helps modulate this competition, even at the synaptic level (Briggs et al., 2013). Arousal interacts with these other factors. When a stimulus is inherently emotionally arousing, it has a competitive advantage over stimuli nearby in space or time (Bradley et al., 2012). For instance, people tend to remember foreground objects better when they are emotional than neutral, but at the cost of poorer memory for the background scenes (Steinmetz and Kensinger, 2013). These effects favoring emotionally salient objects over the surrounding less salient context become stronger with a night of sleep (Payne et al., 2012). Such trade-off effects also occur in people with post-traumatic stress disorder (PTSD) but not in those who experienced trauma in the past without developing PTSD (Steinmetz et al., 2012). These intriguing findings suggest that people in whom arousing items do not have as much of a competitive advantage might have a lower propensity toward PTSD.

The competitive advantages for emotional stimuli work across time, as well as space. Wang et al. (2012) review the phenomenon known as emotion-induced blindness, in which emotionally arousing stimuli can disrupt perception of other target stimuli that appear soon afterwards in the same location. They argue that emotion-induced blindness results from competition between the targets and the emotional distractors, with the distractors gaining priority due to their goal relevance. But this raises the question of whether emotional stimuli really do get more attention than would be predicted simply by their visual salience. To test this, Niu et al. (2012) had participants code which regions within pictures were most affectively salient and then had automated software compute which regions were most perceptually salient and measured eye movements to assess attention. They found that affectively salient regions attracted more attention than perceptually salient regions, especially among pictures rated high in arousal. But findings that recalling autobiographical memories in response to emotional cue words impairs subsequent perception more than recalling in response to neutral cue words indicate that emotion can impair perception even if there are no external differences in perceptual salience (Young et al., 2012).

Thus, papers in this section continue a long line of research indicating that emotionally arousing stimuli attract more attention and are remembered better than competing stimuli. However, the question of whether this has to do with arousal, *per se*, and not just with the nature of the stimuli, requires methods in which arousal is manipulated independently of the stimuli characteristics. To do this, Echterhoff and Wolf (2012) manipulated stress after participants watched a video of a burglary, as well as whether participants anticipated something distressing during the video. They found that the recognition advantage for central event items over peripheral event items was largest when distress was anticipated and there was post-event stress. Thus, arousal both during an event and immediately afterwards can enhance the relative memory advantage for salient events that just occurred.

The notion that arousal enhances processing of salient stimuli and impair processing of other stimuli is consistent with Mather and Sutherland's (2011) arousal-biased competition theory, in which arousal increases the stakes of neural competition between stimuli representations, such that there are both "winner-take-more" and "loser-take-less" effects. In their present study, Lee et al. (2012) tested arousal-biased competition mechanisms by manipulating arousal during a 2-session perceptual learning task. One session included interspersed emotionally arousing negative pictures whereas the other session included interspersed neutral pictures. Participants' task was to find the discrepant line from among an array of lines. In one condition, the discrepant line was always tilted 55° among a field of 50° distractors. In another condition, the discrepant line was always tilted 55° among a field of 80° distractors. In both conditions, participants had to identify the exact tilt of the target line from a set of five alternatives every so often. Thus, in one condition, participants were learning about a salient item (a line very different from its competitors) whereas in the other they were learning about a non-salient line. Competition models of salience (e.g., Itti and Koch, 2000) predict that competition will favor the salient line, enhancing its representation, but that mutual suppression will impair the non-salient line, leading its representation to be impaired. Indeed, in the salient-target condition, the interspersed emotional pictures enhanced participants' perceptual tuning curves as indicated by more accurate memory for the tilt of the target line. In contrast, in the non-salient-target condition, emotion impaired learning about the target line, leading to broader estimated tuning curves. Such work follows up on other recent findings that emotional arousal enhances processing of neutral but perceptually salient stimuli while impairing processing of competing less salient stimuli (Sutherland and Mather, 2012; Lee et al., 2014). Also, recent findings indicate that emotional pictures (positive or negative) strengthen high priority memory traces but weaken low priority memory traces, when priority was determined by goal relevance (Sakaki et al., 2014). *Thus, arousal can have opposite effects on low and high priority representations, with both bottom-up salience and top-down goal relevance as key determinants of priority*.

However, two reviews in this book present different views on how emotion influences selectivity. In their review, Harmon-Jones et al. (2012) argue that what really matters is the motivational intensity of emotion. Affective states high in motivational intensity should narrow cognitive scope while those low in motivational intensity should broaden it. Kaplan et al. (2012) also highlight the role of motivation but argue that a critical factor is whether goals have been achieved yet or not. They posit that emotions experienced before goal attainment or loss should lead to memory narrowing while emotions experienced afterwards should broaden the scope of attention and encoding. One key issue in trying to understand whether these motivational accounts contradict or are complementary to arousal-biased competition account is that the measures differ. Most of the studies examining how motivational intensity influences attention have assessed how much people attend to the local or global features of the same information. For instance, in the Navon (1977) letters task participants see large letters composed of smaller letters and attentional biases to the large or small letters is measured. Motivational intensity shifts these local/global biases. But the arousal-biased competition account requires knowledge about the relative baseline priority of the small and large letters. Given that there are individual differences in whether the large or small letters are noticed more quickly, there is no clear high priority item across participants. Arousal-biased competition processes should favor the local features even more for those who already tend to favor the local letters and vice versa for those who tend to favor the global letters. Likewise, it is not clear what motivational intensity would predict in the type of paradigm used by Sutherland and Mather (2012), in which some letters are more perceptually salient because they contrast more with the background, but they are all equally central in the image and all have the same size.

Finally, the opinion paper by Chiu et al. (2013) proposes that other factors should also be considered when investigating the impact of emotion on memory. Namely, while extant theories tend to focus on how attentional biases in the perception of emotional stimuli influence memory, future research would benefit from differentiating between source, contextual, and relational information, as a way to further our understanding of the effects of emotion on various types of memory phenomena (Chiu et al., 2013).

THE IMPACT OF EMOTIONAL DISTRACTION; LINKING ENHANCING AND IMPAIRING EFFECTS OF EMOTION

A related key question in the emotion literature is how emotionally arousing stimuli can also cause distraction and disrupt performance. Novel evidence emerging from human (Hart et al., 2012; Jasinska et al., 2012a,b; Shafer and Dolcos, 2012; Dolcos et al., 2013) and animal (Matthews et al., 2012) research confirm and advance the initial view (Dolcos and McCarthy, 2006) that processing of task-irrelevant emotional information is associated with opposing patterns of response in ventral emotion processing regions, such as the amygdala (showing enhanced activity), and in dorsal executive brain regions, such as the dorsolateral prefrontal cortex (dlPFC, showing reduced activity) (reviewed in Iordan et al., 2013). New evidence shows that the response to emotional distraction can be modulated by actual or expected task difficulty (Hart et al., 2012; Jasinska et al., 2012b; Shafer and Dolcos, 2012), stress hormones (Henckens et al., 2012), and genetic differences (Jasinska et al., 2012a), as well as by personality differences in traits indexing increased sensitivity to processing task-irrelevant information, such as attentional impulsivity (Dolcos et al., 2013). Interestingly, there is also evidence that emotional "distraction" may not always impair performance on the primary task (Jackson et al., 2012; Truebutschek and Egner, 2012). Finally, there is also evidence that increased emotional reactivity in clinical patients with emotional and attentional disorders is associated with increased impact of emotional distraction (Singhal et al., 2012).

Notably, studies in this section also provide initial evidence regarding the neural mechanisms linking enhancing and impairing effects of emotional distraction. Whereas emotional distraction initially *impair*s perception (Shafer and Dolcos, 2012) and working memory (Dolcos et al., 2013), it *enhances* long-term episodic memory for the distractors themselves. The emotional charge of the distracting information and the difficulty of the main cognitive task influence both the initial emotional distraction (Shafer et al., 2012) and long-term memory (Shafer and Dolcos, 2012). Also, Dolcos et al. (2013) showed that the same amygdala area was involved in both enhancing and impairing effects of emotion, but its engagement was associated with opposing influences on activity in brain regions responsible for maintaining performance in the initial main cognitive task (dlPFC, showing reduced response to emotional distraction) vs. those underlying the long-term enhancing effects of emotion (MTL memory system, showing enhanced response) (see also Dolcos and Denkova, 2014).

Interestingly, the study by Dolcos et al. (2013) also shows that the involvement of cognitive control mechanisms to cope with emotional distraction (reflected in increased activity in the ventrolateral prefrontal cortex, vlPFC) not only protects against the emotional distraction but also leads to enhanced memory for the distractors themselves. This finding provides novel evidence regarding the neural mechanisms underlying a behavioral phenomenon that was observed in early studies investigating the initial and long-term effects of emotion regulation. Namely, the engagement of specific emotion regulation strategies to cope with the initial exposure to emotional situations may also lead to increased memory for the emotional aspects of that experience (Dillon et al., 2007). This issue also has relevance for understanding clinical conditions, such as PTSD, where dysfunctional links between immediate and long-term effects of emotion may be associated with erroneous initial encoding of memories for traumatic events due to heightened arousal, as discussed in the opinion article by Dolcos (2013).

WHAT REALLY IS THE ROLE OF THE AMYGDALA?

Current theories give the amygdala a fundamental role in enhancing attention and memory of emotional stimuli (Murty et al., 2010; Dolcos et al., 2011, 2012; Mather and Sutherland, 2011; Pourtois et al., 2013). Yet, there are still multiple debates about the exact nature of its role. For instance, there has been a long-standing debate about the automaticity of emotion processing and about the nature and significance of dissociating between subcortical automatic and non-conscious route to the amygdala from cortical routes for processing emotional stimuli (for recent reviews, see Pessoa and Adolphs, 2010; Tamietto and de Gelder, 2010). Consistent with the traditional view regarding emotion-attention interaction (Ohman et al., 2001), in their present contribution, De Gelder et al. (2012) argue that work using moving bodies expressing emotion or not indicates that there is an early emotion processing route that is independent of attention and involves a subcortical route to the amygdala; for recent evidence reconciling the traditional and competing views, see Shafer et al. (2012).

In their review, Chau and Galvez (2012) argue that while the amygdala is widely acknowledged to play a key role in the initial acquisition and consolidation of fear-related memories, it also is involved in non-fear-related memories, such as eyeblink conditioning. They concur with previous accounts that the amygdala works as a salience detector to enhance learning of biologically significant or behaviorally relevant events (Davis and Whalen, 2001; Sander et al., 2003; Pessoa and Adolphs, 2010; Pourtois et al., 2013), so that other brain regions are more likely to consolidate those important learned responses.

One puzzle in the literature is the finding that patients with Alzheimer's disease, still show emotional enhancement effects in memory (e.g., Kazui et al., 2000; Nashiro and Mather, 2011). In their review, Klein-Koerkamp et al. (2012) argue that Alzheimer's patients may have compensatory or "reinforced" neural projections between brain areas involved in the elicitation of emotional enhancement. This is an intriguing hypothesis, but it would also be useful to consider other aspects of arousal that may contribute to enhanced memory, beyond the amygdala. In their paper, Gold and Korol (2012) review neuroendocrine influences on emotional memory. They argue that increases in blood glucose levels that result from epinephrine release during arousal augment neurotransmitter release and energy metabolism in brain regions involved in learning and memory. However, the impact of glucose on memory is impaired in normal aging and even further in Alzheimer's disease (Gold and Korol, 2012), thus there is no obvious answer as to how memory continues to be enhanced by emotion in those with Alzheimer's disease, albeit to a less robust degree than for healthy older adults.

The amygdala does not always lead to enhanced processing. As discussed in the previous section, the same amygdala

area appears to mediate both impairing and enhancing effects of emotional distraction, but through different effects on activity in the dlPFC (decreased) vs. MTL (increased) (Dolcos et al., 2013). In addition, while it enhances new emotional learning, lesion work with animals indicates that the amygdala impairs the flexibility of learning, such that reversal learning or extinction are facilitated after amygdala lesions (Izquierdo and Murray, 2005; Stalnaker et al., 2007). When intact, the amygdala seems to work against orbitofrontal mechanisms that help update memories. This model is consistent with recent findings that updating the context of emotionally arousing information is more difficult and involves greater activation of frontopolar/orbitofrontal cortex than updating neutral information (Mather and Knight, 2008; Novak and Mather, 2009; Sakaki et al., 2011; Nashiro et al., 2012). As shown in the present contribution by Nashiro et al. (2013b), the behavioral disadvantage in updating emotional compared to neutral associative information is maintained in older adults, as is the increased activity in the orbitofrontal cortex and increased negative amygdala-PFC functional connectivity when doing emotional reversal learning, compared to neutral reversal learning (Nashiro et al., 2013a).

Thus, across the life span, the amygdala works to maintain associations within existing emotional memories, such as what a cue predicts, where a particular picture was, or which item something was paired with, making emotional memories more resistant to flexible updating. Also relevant are the present findings that it is more difficult to learn whether items previously associated with high rewards than those associated with low rewards were in a new list (Madan et al., 2012). Thus, both reward and arousal make it more difficult to learn new contextual information about items. However, more research is needed to understand if the mechanisms of impaired updating are the same for reward and arousal.

AGE DIFFERENCES IN EMOTION PROCESSING; THE ROLE OF EMOTIONAL VALENCE

People's intuition tends to be that emotion should follow the same downward trajectory with age as cognition, such that negative emotion increases as people grow older. However, longitudinal studies reveal that, in fact, rates of negative affect (NA) tend to decrease through much of adulthood (Carstensen et al., 2000; Charles et al., 2001). These shifts in emotional experience are reflected in cognitive processes as well, leading to age-by-valence interactions (known as the "positivity effect") in attention and memory (Mather and Carstensen, 2005). Specifically, older adults tend to favor positive stimuli more and negative stimuli less than younger adults, in their attention and memory. Since initial findings of an age-related positivity effect in attention and memory were published about a decade ago (Charles et al., 2003; Mather and Carstensen, 2003), there has been a great deal of interest in the effect. In their present review paper, Reed and Carstensen (2012), discuss how the pattern of findings indicate that the positivity effect is not a manifestation of cognitive decline, but instead requires controlled processing (Mather and Carstensen, 2005; St. Jacques et al., 2010). Given its reliance on goal-directed processes, the positivity effect is malleable and context sensitive. For instance, manipulating concurrent cognitive load can diminish or reverse it (Mather and Knight, 2005; Knight et al., 2007), something that cannot be accounted for by a cognitive decline account. Reed and Carstensen (2012) also point out that *more work is needed to test whether positivity in cognitive processing helps emotional well-being and influences decisions.*

Several of the empirical papers in this collection addressed other relevant issues. Noh et al. (2012) investigated whether the links between positive and NA and attentional functioning varies as a function of age. They found that higher levels of positive and lower levels of NA were associated with enhanced orienting efficiency in older adults, but neither of them had any influence on executive attention. Overall, the findings by Noh et al. (2012) suggest that positive and NA may influence attentional functioning in distinct ways, but that these patterns may depend on the age group. Pollock et al. (2012) examined adult age differences in processing emotional faces using a psychological refractory period paradigm. Younger adults showed significantly higher P1 responses for angry than for happy faces, whereas older adults showed no difference, revealing another measure on which positivity effect age-by-valence interactions turn up; P1 is a positive event-related potential component occurring ∼100 ms post-stimulus onset, which was linked with amygdala modulation of attention to emotional faces (Rotshtein et al., 2010). Kalpouzos et al. (2012) examined what they call the "negativity effect" or the memory advantage for negative emotional information over neutral information. They assessed recognition memory for neutral and negative scenes after 1 and 3 weeks in younger and older adults using fMRI. As they did not include positive stimuli, they were unable to assess whether age-by-valence interactions changed over multiple testing sessions. However, they found that older participants were better able to discriminate old from new scenes if they were neutral than negative, whereas this was not the case for younger participants. Whereas younger adults showed changes in brain activity during retrieval across the different retention intervals, the older adults did not. While, overall, the effects of delay were similar across age groups, the older adults were close to floor in their performance by the last test, which might have reduced the ability to see effects.

Although the positivity effect occurs in many studies examining attention and memory, it is not clear whether similar factors influence the ability to read facial emotions. Older adults show impaired recognition of emotions such as sadness and anger, but they are equally good or better than younger adults at recognizing disgust (Ruffman et al., 2008). In their present contribution, Ebner et al. (2012) provided new evidence that brain activation patterns are similar across younger and older adults when identifying facial expressions, indicating that, on the whole, similar PFC mechanisms are involved for both age groups. Moreover, Biss et al. (2012) provided new evidence of an emotion-cognition interaction that operates similarly across age groups. Their study revealed that, for older adults, positive mood states led to greater implicit memory for distracting words shown during a task, an effect previously shown in younger adults. Thus, positive affect seems to influence attention regulation similarly across age groups.

AFFECTIVE FACE PROCESSING, SOCIAL COGNITION, AND PERSONALITY NEUROSCIENCE

The emerging fields of social and personality neurosciences also provide important evidence regarding emotion-cognition interactions, while furthering our understanding of the neural mechanisms of adaptive social behaviors and of individual variation in the susceptibility or resilience to emotional disturbances. Human faces are essential in conveying important social information, and facial stimuli have been used to investigate a variety of aspects of social cognition, from simple emotional reactions (Morris et al., 1996) to more complex affective states (Bartels and Zeki, 2004; Nitschke et al., 2004). However, despite a long history of investigation of basic facial emotional expressions (Ekman and Oster, 1979), only relatively recently research has begun to consider other socially relevant dimensions conveyed by faces, such as trustworthiness (Todorov et al., 2009).

Processing of emotional (particularly fearful) faces involves the amygdala and fast, possibly automatic, mechanisms (Whalen et al., 1998; Sergerie et al., 2008; Adolphs, 2010; Iordan et al., 2013); but see Pessoa (2013). However, less is known about the immediate motor and cognitive consequences of such fast processing. New evidence from the present collection (Bocanegra and Zeelenberg, 2012) shows that masked fearful faces enhance the activation and inhibition phases of motor response to a target, even before conscious perception of the target. Evidence from another study suggests that when identification of facial expression occurs, cognitive control mechanisms also come into play (Ebner et al., 2012). Specifically, the authors argue that increased engagement of the dorsomedial PFC (dmPFC) for angry faces reflects cognitive control mechanisms involved to regulate negative emotions. Interestingly, similar findings were observed in both young and older participants, although older participants tended to show more extended activations of dmPFC to angry faces, possibly reflecting increased emotion control (St. Jacques et al., 2010).

Evaluation of emotional faces in social contexts and their encoding into memory are needed in order to navigate in social environments, and to decide whom to thrust and approach or to avoid (Vrticka et al., 2009). Approach and avoidance behaviors are of particular importance in social cognition and have been linked to social inclusion or exclusion, as discussed in the present review by Powers and Heatherton (Powers and Heatherton, 2012). The authors suggest that approach and avoidance behaviors could occur also concomitantly—e.g., people feeling social exclusion may simultaneously employ both affiliating and defending strategies in order to establish new social connections and to avoid negative consequences of social exclusion. Regarding social exclusion, the present review by Cacioppo and Cacioppo (2012) also emphasizes that the impact of subjectively perceived isolation is much greater than that of real isolation, and that perceived (or experimentally induced) social isolation modulates similar brain mechanisms to those involved in the perception of emotional and social stimuli (dmPFC, temporoparietal junction—TPJ, ventral striatum) (Cacioppo and Cacioppo, 2012). Moreover, Masuda et al. (2012) provide evidence regarding the role of cultural differences in processing social cues, and highlights the importance of considering contextual differences in interpreting facial signals as a function of cultural variations. Finally, by considering three affective signals conveyed by faces (emotional expressions, attractiveness, and trustworthiness), Tsukiura (2012) proposes a model suggesting mutual interactions between affective and memory systems, which explain why emotional and socially relevant faces are better remembered than neutral ones.

A long standing view is that approach and avoidant temperamental/motivational tendencies are associated with patterns of lateralization in the frontal regions, with the left side being associated with approach and the right side with avoidance (Harmon-Jones et al., 2010). However, as discussed in the present review by Miller et al. (2013), recent studies provide evidence that different sub-regions within the PFC have different roles in various aspects of emotion processing, and therefore can show different lateralization patterns, which may go beyond the simple left-right frontal conceptualization initially proposed. Other authors adopt a goal-related perspective regarding motivational tendencies, and investigate behavior in terms of *promotion*/accomplishment-oriented tendencies (planning to "make good things happen") vs. *prevention*-oriented tendencies (planning to "avoid bad things from happening") dichotomy (Higgins, 2012). In their present investigation, Strauman et al. (2013) provide evidence regarding the neural mechanisms underlying activation of promotion and prevention goals by priming participants' own *ideal* and *ought* goals, which are mapped onto dissociable neural substrates in healthy functioning (Eddington et al., 2007) and are altered in clinical cohorts (Eddington et al., 2009). *Overall, the evidence emerging from these contributions underscore the importance of considering the interplay between emotion and cognition at various levels, from basic processing of social cues to their integration in larger behavioral and cultural contexts*. Such integration not only influences individuals' own adaptive social behavior but may also have consequences on their moral social decisions, as also discussed here by Cummins and Cummins (2012).

STRESS, MOOD, EMOTION, AND THE PREFRONTAL CORTEX; THE ROLE OF CONTROL IN THE STRESS RESPONSE

Another important question in the emotion literature is how long–term affective states, such as those produced by stressful experiences, mood manipulations, or associated with personality traits, influence cognition and behavior. It is widely accepted that optimal levels of stress benefit cognitive functioning, whereas extreme and/or chronic levels of stress impair it. But how much stress is too much stress, and how do specific stressors and individual differences influence the experienced stress and its impact on cognitive functioning?

Novel evidence from the present collection points to both beneficial and detrimental effects of stress and mood on cognitive functioning and the associated neural mechanisms, which are influenced by manipulations of stress hormones (Henckens et al., 2012), personality traits indexing emotion regulation and NA (Crocker et al., 2012; Wang et al., 2013), and previous history of stress (Wang et al., 2013), as well as by age (Biss et al., 2012) and genetic (Qin et al., 2012) differences. Henckens et al. (2012) provide evidence for (i) rapid effects of cortisol reflected in

impaired selective attention and increased emotional interference, driven by bottom-up processing in the amygdala and its interaction with the PFC, and (ii) slow effects of cortisol promoting sustained attention, by reducing bottom-up driven processing in visual brain areas and potentially leading to restoration of brain functioning after stress. The authors propose a more adaptive view of the impact of cortisol on attention and emotion, with an initial effect optimizing detection of potential threat at the cost of impaired cognitive processing, and a delayed effect normalizing cognitive brain functions following stress (Dolcos, 2014). Crocker et al. (2012) points to joint and dissociable effects of state and trait NA on attention. Specifically, when combined, state and trait NA produced the strongest impact on performance in an attentional task, but they were linked to different aspects of processing—i.e., state NA was linked to excessive stimulus-driven processing of salient irrelevant information, whereas trait NA was linked to difficulty in engaging top-down attentional control to deal with irrelevant information. Wang et al. (2013) show that the impact of early-life stress on activity in the vmPFC (a region involved in emotion control) is linked to variations in personality traits indexing diminished (rumination) or enhanced (mindfulness) emotion control. This, in turn, influences susceptibility or resilience to emotional challenges, in response to exposure to repeated mild stressful situations, linked to reduced vs. enhanced vmPFC activity, respectively. Finally, Qin et al. (2012) further show that the effect of moderate stress on working memory performance and PFC functioning is modulated by genetic variations in the genes encoding the Catechol-O-methyltransferase (COMT; an enzyme that degrades catecholamines such as dopamine, epinephrine, and norepinephrine), with some allele combinations being associated with positive whereas others with negative effects.

Besides individual variations (Kanske, 2012; Qin et al., 2012; Wang et al., 2013), other factors linked to available resources, task-relevance, and top-down modulation can also explain differential impact of affect and stress on cognition, as discussed in the review by Cohen and Henik (2012). Moreover, Froeliger et al. (2012) provides preliminary evidence that the engagement in meditation practice could help avoid the negative impact of emotion on cognition, which is consistent with the idea that the engagement of reactive or proactive strategies of cognitive control can alleviate detrimental effects of emotion (Patterson et al., 2012).

An interesting idea that also emerges from the present studies investigating these issues is that the effect of stress on cognitive functioning and the associated neural mechanisms can be modulated by the feeling of control and/or the subjective experience of stress (Buetti and Lleras, 2012; Henderson et al., 2012; Kerr et al., 2012). Specifically, the presence of controllability can help improve cognitive performance, when stress is perceived as moderate (Henderson et al., 2012), and abolish distortions in time perception of negative compared to positive events (Buetti and Lleras, 2012). Moreover, the presence of controllability also affects the PFC functioning, with the vmPFC showing increased activity during controllable anticipation response (Kerr et al., 2012). This finding can be linked to Wang et al.'s finding revealing decreased vmPFC response in people with early-life stress and high trait rumination (Wang et al., 2013). Interestingly, while there is evidence that extreme subjective experience of stress can have detrimental effects on cognitive functioning, especially in uncontrollable situations (Henderson et al., 2012), the low perceived stress in acute stressful situations can also have detrimental effects on decision making, by favoring risky decisions (Lempert et al., 2012), which has relevance for understanding addictive gambling behavior.

EMOTION-COGNITION INTERACTIONS IN CLINICAL CONDITIONS

Although the terms emotion and cognition describe concepts that involve overlapping functions and recruit overlapping circuits within the brain, thinking about their distinctive features and how they interact can be quite fruitful. This is especially the case in the domain of psychiatric disorders, where dysfunctional emotion-cognition interactions are among the most obvious impairments. For instance, Dolcos (2013) points out that in PTSD both the enhancing and impairing aspects of emotion-cognition interactions are exacerbated and detrimental. This statement is also true for the majority of other psychiatric disorders. A series of original and review articles in the present collection discuss the relationship between emotion and cognition in a variety of psychiatric disorders including, depression, PTSD, schizophrenia, autism, Alzheimer's disease, and substance abuse.

MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) has been posited to result from dis-coordination between cognitive and affective neural systems (Mayberg, 1997), which could be a cause and/or a result of negative affective biases, the core cognitive deficits of MDD. In this book, Foland-Ross and Gotlib (2012) summarize evidence from the literature regarding the negative bias in MDD and note that depression is characterized by difficulty in disengaging from negative material, once it initially captures attention, rather than from rapid orientation to negative stimuli. However, this phenomenon is not specific to depression, as also shown by the Singhal and colleagues' study using event-related potential recordings in adolescents with comorbid psychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, or other psychiatric disorders (Singhal et al., 2012). This study provided evidence that effortful activity is required in these patients to redirect attention from task-irrelevant negative stimuli to processing goal-relevant information (Singhal et al., 2012). The negative affective bias has also been extended to emotionally positive materials (LeMoult et al., 2012). The study by LeMoult et al. (2012) shows that when happy emotional expressions are used as primes, healthy adults show the strongest interference, whereas the MDD group fail to show such positive bias.

PTSD

Like depression, negative affective biases can also be found in PTSD (Aupperle et al., 2012), and reflects difficulty in disengaging from, rather than facilitated detection of, negative stimuli. In PTSD, however, there is also heightened trauma-related reactivity, along with paradoxical changes in memory processing (Cohen et al., 2006; Parsons and Ressler, 2013). On the one

hand, emotionally salient traumatic memories tend to induce uncontrolled recollection and re-experiencing of memories for traumatic events. On the other hand, PTSD patients tend to avoid stimuli associated with the trauma, which may induce amnesia for details of the traumatic event (Brewin et al., 2011). All three review articles on PTSD (Brown and Morey, 2012; Hayes et al., 2012; Dolcos, 2013) in this book point to exacerbated enhancing and hindering effects of emotion on cognition in PTSD. Uncontrolled recollection of distressing memories may lead to impairment in cognitive task performance due to enhanced emotional distraction (Dolcos, 2013). Furthermore, emotional interference in PTSD can be extended beyond trauma-related materials to trauma-unrelated emotional materials, as emphasized in the review by Brown and Morey (2012), who propose two disrupted networks in PTSD, a trauma-activated network and an emotion-activated network. There is also evidence that PTSD patients may be more prone to falsely remembering novel information (Hayes et al., 2012). However, in the study from the present collection mentioned above (Steinmetz et al., 2012), PTSD patients did not show greater emotional trade-offs (greater memory to emotional items than neutral background) than controls or trauma-exposed people without PTSD, unlike the trauma-exposed non-PTSD group which showed such trade-off. More studies are needed to elucidate these issues, and understanding the neural mechanisms underlying emotional and cognitive deficits in PTSD may provide insight for developing novel cognitive-based behavioral therapies.

SCHIZOPHRENIA

According to Anticevic and Corlett (2012), patients with schizophrenia have an intact ability to perceive emotion "in the moment." The core deficit of the illness is a dysfunction in "*cold*" cognitive processes, predominantly in working memory, which is associated with markedly reduced activity in the dlPFC in these patients. Thus, it has been suggested that it is the dysfunction of working memory that gives rise to difficulty in maintaining affective/reward-related information representation in guiding motivational behaviors. Future studies could demonstrate the link between the lack of "maintenance" signals following affective/reward cues to deficits in future goal-directed behavior and negative symptoms (such as anhedonia) in schizophrenia. Unlike depressed patients who are distracted by negative information and unable to disengage from negative events to on-going goal-guided events, schizophrenic patients have difficulty in filtering task-irrelevant distracting information. They tend to abnormally assign neutral stimuli as salient and have deficits in generating appropriate prediction error signals, so that they blur the distinctiveness of responses to events that violate vs. confirm expectations, which could lead to delusions.

AUTISM SPECTRUM DISORDERS (ASD)

These neurodevelopmental disorders affect neural systems largely related to social-emotional and social cognition processes. While the field predominantly views ASD as involving deficits primarily in the "social cognition network," Gaigg's present paper (2012) questions this notion. In his review, Gaigg argues that the social deficits in ASD could be the consequence of abnormal emotional responses to the environment "which modulate a wide range of cognitive processes including those that are relevant to navigating the social world." Gaigg concludes that ASD involves relatively preserved function in basic emotional evaluation (i.e., arousal-related responses to emotionally salient pictures and words), but is associated with difficulties in more complex emotional processes related to social environment, including identification and interpretations of emotions in others. Individuals with ASD have difficulties in the response to ambiguous and unpredictable events in the environment, and in learning about the emotional significance of stimuli that predict biologically relevant events. Gaigg posits an intriguing hypothesis that the basic amygdala functions that are mediated by sub-cortical networks involving sensory afferents from the thalamus and efferents to brain-stem nuclei are preserved in ASD, but the connections with cortical or sub-cortical regions modulating amygdala appear to be compromised. However, this idea needs confirmation from future studies.

ALZHEIMER'S DISEASE (AD)

Turning to alterations in emotion-cognition interactions in clinical conditions affecting later developmental stages, an intriguing aspect concerns the possibility that relatively better preserved emotion processing could buffer memory deficits in AD patients. According to the present review by Klein-Koerkamp et al. (2012), both enhancing and impairing effects of emotion on memory can be found in AD, and that these discrepant findings could be due to differences among studies in a number of factors, as follows. (1) Task difficulty (easy vs. hard): tasks that are too easy for healthy controls or too difficult for AD patients could lead to ceiling vs. floor effect respectively, which may obscure the memory-enhancing effect of emotion. (2) Task type (recollection vs. recognition): typically, the memory-enhancing effect of emotion tends to be stronger in recollection than in recognition tasks, and hence this may also explain discrepant findings observed in AD, depending on the tasks involved. (3) Stimulus properties (exposure time and self-relevance): emotionally intense and self-related stimuli are more likely to induce emotional enhancement effects on declarative memory. Overall, Klein-Koerkamp et al. (2012) emphasize that understanding the underlying mechanisms and the factors influencing the memory-enhancing effect of emotion on memory in AD can potentially guide the development of new therapies, based on using emotionally salient cues to enhance/guide memory in these patients.

SUBSTANCE DEPENDENCE

The emotional disturbances commonly seen across all drug dependencies are: (1) heightened reward sensitivity to drug-related stimuli (incentive sensitization), (2) reduced sensitivity to natural reward stimuli, and (3) weakened cognitive control, reflected in diminished PFC engagement and heightened sensitivity in the brain's stress systems that respond to threats (Murphy et al., 2012; Volkow et al., 2013). In their contribution to the present collection, Murphy et al. (2012) argue that the baseline dopamine levels in these patients are low, and when drug cues (but not natural reward stimuli) are presented, high

levels of dopamine are released, which results in drug craving. This suggests an overall reward deficiency (reduced sensitive to natural reward stimuli) but sensitized reward systems to drug cues in substance dependence. Murphy et al. (2012) also propose that emotional dysregulation could be the causal factors for impulsive behavior and poor decision–making in these patients.

As we have reviewed how disturbances of emotion-cognition interactions result in various types of disorders, we cannot neglect the significant role of puberty in the maturation of emotion-cognition interactions (Ladouceur, 2012). One factor during puberty could be related to changes in the production of sex hormones, which can affect the response to emotionally salient distractors, possibly because of the influence of sex hormones on the functional connectivity of PFC regions. Another important factor that affects the maturity of the affective and cognitive systems is early-life stress. It has been well-documented that early-life stress is associated with psychiatric disorders in adults. Here, Flynn and Rudolph (2012) provide new evidence that maternal depression (but not anxiety) predicts increased negative bias in adolescents with high levels of interpersonal emotional reactivity. However, maternal depression does not predict cognitive biases in those exhibiting low levels of interpersonal emotional reactivity during adolescence. This finding that maternal depression but not maternal anxiety predicts negative bias needs replication to elucidate the mechanisms of possible "depression transmission." Examination of the impact of sex hormones, genetic changes, personality, and of early-life stress on the development and maturity of emotional and cognitive systems are all active research areas, which may shed light on the neural mechanisms and potential treatment for psychiatric disorders, which tend to onset during early developmental stages.

One of the critical issues hampering clinical diagnosis for psychiatric disorders using objective measures (biomarkers) is the heterogeneous manifestations of the mental disorders. There is a need for new models to better accommodate large individual variance. In his review article, Northoff (2012) proposes an interesting theory that our awareness of emotional feelings is determined by the body-environment relation, which may be translated through neural activity. Although there are considerable variations in disruptions of psychological processes among the clinical conditions discussed above, to some degree all these disorders have dysfunctions in the prefrontal-striato-limbic-thalamus networks. Hence, Northoff (2012) proposes that it is necessary to study these disorders together under a new comprehensive model, such as the frame of body-environment relationship. The proposed framework has important empirical and conceptual implications, and ideally future approaches will also involve systematic studies linking abnormal findings at molecular/cellular, system, and psychological levels, to better understand the neuropathology of different psychiatric disorders (Anticevic and Corlett, 2012).

Overall, as illustrated by the present collection of contributions, emotion-cognition interactions can be identified at different levels of processing, from perception and attention to long-term memory, decision making processes, and social cognition and behavior. Notably, these effects are subject to individual differences that may affect the way we perceive, experience, and remember emotional experiences, or cope with emotionally challenging situations. Moreover, these opposing effects tend to co-occur in affective disorders, such as depression and PTSD, where uncontrolled recollection of and rumination on distressing memories also lead to impaired cognition due to emotional distraction. Understanding the nature and neural mechanisms of these effects is critical, as their exacerbation and co-occurrence in clinical conditions lead to devastating effects and debilitation. Hence, bringing together such diverse contributions has allowed not only an integrative understanding of the current extant evidence but also identification of emerging directions and concrete venues for future investigations.

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Orienting and emotional perception: facilitation, attenuation, and interference

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Human emotions are considered here to be founded on motivational circuits in the brain that evolved to protect (defensive) and sustain (appetitive) the life of individuals and species. These circuits are phylogenetically old, shared among mammals, and involve the activation of both subcortical and cortical structures that mediate attention, perception, and action. Circuit activation begins with a feature-match between a cue and an existing representation in memory that has motivational significance. Subsequent processes include rapid cue-directed orienting, information gathering, and action selection – What is it? Where is it? What to do? In our studies of emotional perception, we have found that measures that index orienting to emotional cues generally show enhanced circuit activation and response facilitation, relative to orienting indicators occasioned by affectively neutral cues, whether presented concurrently or independently. Here, we discuss these findings, considering both physiological reflex and brain measures as they are modulated during orienting and emotional perception.

Keywords: emotion, attention, orienting, psychophysiology, interference, competition

INTRODUCTION

Cues that signal danger or reward reflexively activate fundamental motivational circuits prompting heightened orienting and attention, facilitating the selection and implementation of appropriate action (Lang et al., 1997). In studies of emotion, therefore, many of the dependent measures that are regularly monitored, measured, and modulated are those traditionally considered to be components of the orienting response. It was Pavlov who first defined the "investigatory reaction" as a reliable behavioral pattern in which animals oriented receptors (ears, eyes, etc.) toward any novel stimulation (Pavlov, 1927). Later variously called the "novelty reflex," the "exploratory reflex," or the "orienting reflex" (or reaction) – this "*what is it*" response facilitated perceptual identification of a new, unexpected cue. Sokolov (1963) later reformulated the concept as a neuronal model in which orienting was a neurophysiological reaction to changes in the perceptual array. In this broader view, novel stimuli induce physiological changes in autonomic, somatic, and central systems that he collectively called the orienting response.

Subsequent research has confirmed that novel stimuli prompt orienting and that reactivity is heightened if cues are made "significant" through task-relevance and/or instructions. A number of researchers noted, however, that emotional cues seemed to elicit more pronounced orienting even in the absence of specific tasks or instructions (Bernstein, 1979; Maltzman, 1979; O'Gorman, 1979). These cues intrinsically activate motivational circuits, prompting what has been dubbed "*natural selective attention*" (Bradley, 2009). Thus, traditional measures of orienting, such as skin conductance, heart rate deceleration, pupil dilation, and modulation of the brain's electrical activity are reliably enhanced in emotional perception. Pictures are particularly effective cues in activating motivational circuits, as these visual stimuli share many of the sensory and perceptual features with the actual object. This is vividly illustrated in phobic individuals, for whom a picture of a snake can prompt strong physiological reactions (Globisch et al., 1999; Ohman and Mineka, 2001; Sabatinelli et al., 2001) that mirror an actual encounter.

From a methodological viewpoint, the cues in a perceptual array at any moment can be roughly characterized as (1) cues that activate defensive and appetitive motivational circuits (i.e., "emotional" stimuli), and therefore are intrinsic targets of focal processing, and (2) cues that do not have strong, intrinsic motivational associations (i.e., "neutral" stimuli) that are not intrinsically focal and have not been made targets for focal processing on the basis of conditioning, task relatedness, or simple instruction. Functionally, then, the perceptual arrays used in emotion studies can include concurrent presentation of any of these stimulus types, and one or more cues may be the focus of measurement. In this brief review, we report data from our studies of picture perception which illustrate that measures that index orienting to emotional cues are reliably enhanced when presented in the context of neutral cues, whether focal or not; and that neutral cues (task-focal or simply concurrent) tend to show a diminished orienting response when presented in the context of emotional cues.

OCULOMOTOR ORIENTING

As Pavlov noted, orienting is associated with behavioral adjustments that direct relevant sense organs toward focal cues. In visual perception, eye tracking studies have shown that emotional cues systematically modulate the motor control of this receptor organ: focal processing of emotional pictures prompts a significantly greater number of fixations than processing neutral images, and this pattern is found regardless of whether pictures depict simple figure-ground compositions or perceptually more complex scenes (Bradley et al., 2011). Moreover, affectively engaging cues

are scanned more broadly, with larger distance between successive fixations, which again is found regardless of perceptual complexity. When an emotional picture and a neutral picture are presented together in a perceptual array, affective cues draw a greater number of fixations, resulting in overall longer viewing duration; when multiple emotional cues comprise the perceptual array, those that are rated as most arousing (e.g., erotica, violence) draw a great number of fixations that are of longer duration (Bradley et al., unpublished manuscript). Overall, emotionally arousing cues preferentially determine ocular movements, affecting both the duration and breadth of information gathering, simultaneously reducing processing of neutral cues in the perceptual environment.

AUTONOMIC NERVOUS SYSTEM REACTIVITY

Increase in palmar and plantar sweat gland activity is a classic physiological component of the orienting response (Sokolov, 1963; Maltzman, 1979). When measured via changes in the electrical resistance of the skin of the palm, even neutral pictures, when novel, prompt modest conductance increases, as illustrated in **Figure 1A** (Bradley, 2009). However, electrodermal changes are significantly elevated when viewing novel pleasant or unpleasant neutral pictures (**Figure 1A**; Lang et al., 1993). Moreover, pupil dilation shows a similar pattern: following a brief, obligatory pupil constriction associated with the light reflex, pupil diameter during orienting shows significantly greater dilation when viewing pleasant or unpleasant, compared to neutral, pictures (Bradley et al., 2008). For both pupil dilation and skin conductance activity, orienting reactions are largest for the most emotionally arousing cues.

The close relationship between orienting responses in pupil diameter and skin conductance is consistent with the fact that both are mediated by sympathetic nervous system activity (Bradley et al., 2008). In the view presented here, these autonomic reactions begin when a motivational cue is processed in visual cortex and activates the basolateral and then the central nucleus of the amygdala, which subsequently projects to the lateral hypothalamus, prompting broad engagement along the sympathetic chain, including neural connections to the rapidly dilating pupil, as well as to the more slowly responding palmar sweat glands. One function of sympathetic nervous system activity is to prepare the organism for potential action.

A classic measure of orienting is heart rate deceleration (Graham and Clifton, 1966; Lang et al., 1997), mediated by the parasympathetic branch of the autonomic nervous system (ANS). Heart rate orienting is characterized by a rapid, brief deceleration to any novel stimulus. When emotional pictures are presented, however, the deceleration can be deep and prolonged (see **Figure 1A**), particularly when viewing aversive stimuli. Although the sympathetic and parasympathetic branches of the ANS were once thought to be wholly reciprocal, it is now understood that they can be co-active depending on the stimulus context (Berntson et al., 1994). This is clearly seen during orienting, which involves motor inhibition (other than that necessary for directing sense organs) accompanied by heart rate deceleration. Because cardiac deceleration is quickly eliminated when the same picture is re-presented, it may reflect the sensory intake and information gathering function of orienting to novel or significant cues (Bradley, 2009).

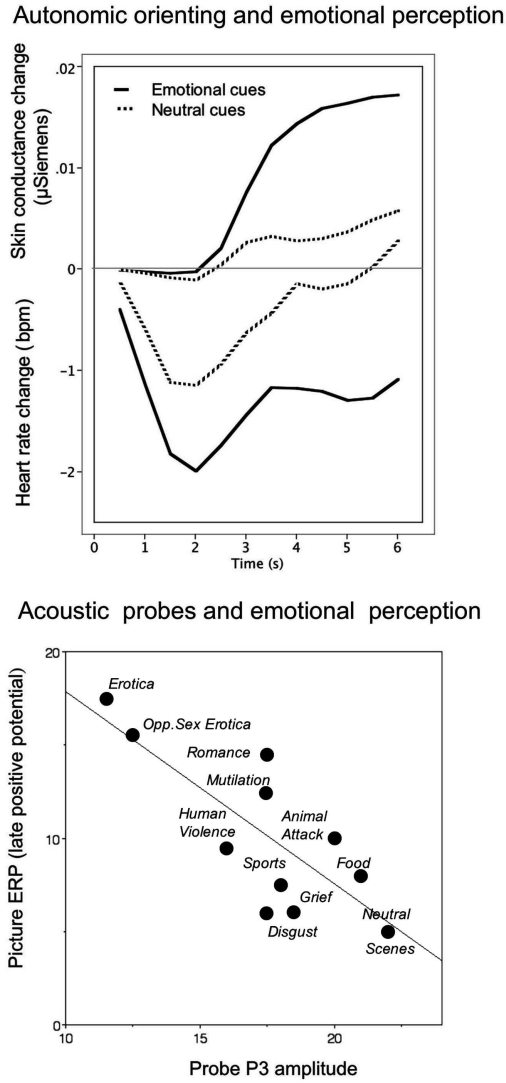

FIGURE 1 | (A) Temporal dynamics of orienting in heart rate and skin conductance during emotional perception, with heightened cardiac deceleration and electrodermal reactivity when viewing emotional, compared to neutral, pictures. **(B)** The amplitude of the P3 component elicited by the presentation of an irrelevant acoustic probe during picture perception is inversely related to the amplitude of the late positive potential elicited by the picture itself. Larger late positive potentials, indicative of greater resource allocation to emotionally arousing cues, is associated with less resource allocation to the probe, resulting in smaller probe P3s.

When a cue indicates the necessity of immediate action, on the other hand, cardiac deceleration reverses and overall sympathetic cardiac control is asserted, prompting acceleration. In a recent experiment (Low et al., 2008), picture cues were presented sequentially, signaling increasingly imminent receipt of reward or loss that was dependent on the participant's response time. In this perceptual context, skin conductance increased progressively in tandem with progressively decreasing heart rate until

the penultimate signal for action. At that point, deceleration was replaced by cardiac tachycardia and a yet steeper increase in conductance until the action was accomplished. Taken together, then, enhanced orienting can be associated with either increased or decreased reactivity, depending upon the specific measure of orienting that is monitored.

THE LATE POSITIVE POTENTIAL

A number of different event-related potentials (ERP) have been linked to orienting and attention, including the P300 (P3), processing negativity, and a late positive complex (Ruchkin and Sutton, 1983; Donchin et al., 1984). An early central index of orienting, called the "orienting" wave (or "O-wave") showed a slow positive change over central-parietal sensors when processing novel or significant stimuli (Connor and Lang, 1969; Loveless and Sanford, 1974; Rohrbaugh and Gaillard, 1983). A similar slow potential that shows enhanced positivity over centro-parietal sensors is the most reliable ERP modulated by hedonic content when emotional pictures are focal cues (e.g., Palomba et al., 1997; Cuthbert et al., 2000). This late positive potential is most enhanced for pictures rated highest in emotional arousal, regardless of whether they depict appetitive (e.g., erotica) or aversive (e.g., violence) hedonic content (Schupp et al., 2004). Directing attention to a focal cue through task-relevance, whether emotional or neutral, prompts a significantly enhanced late positive potential (Ferrari et al., 2008). Unlike the cardiac component of the orienting response, the late positive potential continues to be enhanced when viewing emotional, compared to neutral, pictures, even following multiple contiguous repetitions (Ferrari et al., 2011), suggesting that this component of the orienting response may index motivational activation, which does not change with mere stimulus repetition (Bradley, 2009).

PROBING PERCEPTUAL ORIENTING

In addition to measures which directly reflect enhanced orienting to emotional cues, perceptual processing can be probed by presenting brief, discrete acoustic stimuli (e.g., tones or noise bursts) during picture viewing, and measuring a variety of orienting responses to the secondary probe stimulus. One electrophysiological index of orienting is the amplitude of a centro-parietal P3 component: when an emotional (pleasant or unpleasant), compared to neutral, picture is the focal cue, the amplitude of the P3 elicited by the acoustic probe is attenuated, suggesting reduced orienting to concurrent cues presented during emotional perception (Schupp et al., 1997). Interestingly, the same pattern of reduced P3 amplitude is found when acoustic probes are presented during perception of pleasant and unpleasant environmental sounds (Keil et al., 2007), suggesting that attenuated orienting to secondary cues is not restricted to cross-modal contexts.

Another measure of probe processing – speeded reaction time in a simple detection task – is also consistent with attenuated perceptual processing of the probe during emotional perception. The speed of concurrent probe detection is significantly slower when viewing emotional, compared to neutral, pictures (Bradley et al., 1999), particularly immediately after picture onset, when orienting is maximal. For the reaction time measure, differences in speed of responding disappear about 1 s after picture onset, whereas, interestingly, probe P3 amplitude continues to discriminate between processing of emotional and neutral pictures for up to 4 s following picture onset (Bradley et al., 2008), suggesting that these measures of probe processing reflect different facets of phasic and sustained orienting activity.

When probe P3 amplitude is assessed as it varies with the late positive potential that indexes orienting to the focal picture, an inverse relationship is found as illustrated in **Figure 1B**, with larger LPPs associated with smaller probe P3s, indicative of a trade-off in which heightened attention to the picture results in fewer resources available for processing the probe. Unlike the late positive potential, however, which continues to be modulated following picture repetition, probe P3 amplitude is no longer different when viewing emotional, compared to neutral, pictures after multiple contiguous repetitions (Ferrari et al., 2011), suggesting that this component of the orienting response may index resource allocation, which is expected to diminish with stimulus repetition.

STEADY-STATE VISUAL EVOKED POTENTIALS: PROCESSING FOCAL CUES

Perception of motivationally relevant cues is reliably associated with heightened activity of the visual cortex (Desimone, 1996). Both functional neuroimaging (e.g., Kastner and Ungerleider, 2000) and animal studies of selective attention (e.g., Reynolds et al., 1999) have garnered empirical support for this hypothesis by studying visual responses to significant stimuli in both humans and animals. The visual sensory response to a perceptual cue such as a picture can be easily measured using the ssVEP, a continuous oscillatory brain response elicited by a visual stimulus which, when rapidly brightness-modulated (flickered), prompts electrical activity at the same frequency as the flickered stimulus. The ssVEP can be measured in the EEG by sensors placed over the occipital cortex, and the evoked neural activity subsequently precisely defined in the frequency and time-frequency domains.

Enhanced ssVEP amplitudes to visual stimuli are reliably observed as a function of instructed attention (Muller et al., 2006). However, as with other measures of heightened attention and orienting, the ssVEP elicited by flickering emotional pictures is heightened in amplitude in the absence of instructions or task-relevance. In a first study (Keil et al., 2008), participants simply viewed pictures flickering at a rate of 10 Hz, which included emotional cues that depicted pictures of erotic couples, families, mutilated bodies, and attack scenes, as well as pictures of everyday events and objects. The amplitude of the ssVEP signal was reliably enhanced when processing emotional, compared to neutral, pictures over both occipital, and parietal electrode sites (see **Figure 2A**).

To the extent that the ssVEP is generated in extended visual cortex, these findings may be taken as evidence for sensory facilitation when a stimulus engages motivational systems, in line with a number of fMRI studies showing heightened activation in visual cortex for motivationally relevant cues (Lang et al., 1998; Bradley et al., 2003). Accordingly, the extent of activity in visual cortex during picture viewing is explained to a large extent by intensity of emotional arousal, measured either by ratings of affect or by the skin conductance orienting response (Keil et al., 2008). When examined using advanced time-series statistics (Keil et al., 2009), the spatio-temporal information inherent in the ssVEP points to recurrent,

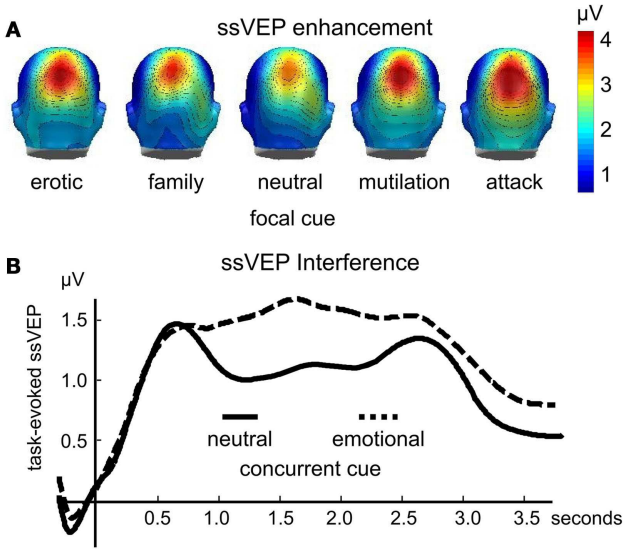

FIGURE 2 | The amplitude of the time varying steady-state visual evoked potential is enhanced when evoked by focal emotional, compared to neutral pictures [(A); redrawn from data in Keil et al., 2008]. Conversely **(B)**, the ssVEP is reduced when evoked by a focal task stimulus that competes with an emotionally engaging distractor (data from Wieser et al., 2012). This interference lasts between several hundreds of milliseconds and several seconds, depending on the complexity and strength of the distractor and the primary task (Müller et al., 2008).

bi-directional information flow from anterior brain areas back into visual cortex, suggesting widespread orienting activity.

Supporting the idea that sensory facilitation for emotionally engaging cues arises as a consequence of recurrent information flow between sensory areas and motivational circuits (Lang, 1979; Sabatinelli et al., 2009), the ssVEP amplitude is also modulated following classical aversive conditioning. Thus, perceptual processing of a neutral CS+ (the conditioned stimulus predicting the aversive unconditioned stimulus) is enhanced, compared to the CS− following contiguous pairing (Moratti and Keil, 2005). Across studies, results show that the enhanced sensory ssVEP for the CS+ parallels the development of broader defense activation, indexed by augmented heart rate orienting and skin conductance increase (Moratti et al., 2006).

STEADY-STATE VISUAL EVOKED POTENTIALS: COMPETITION

One advantage of the steady-state potential technique is that it allows one to tag different cues in the perceptual array by flickering them at different rates. Such frequency tagging yields separable signals even for stimuli that spatially overlap. In addition, time-frequency analyses can describe the time course of perceptual processing to a specific focal or secondary cue in a perceptual array, assessing facilitation, or interference (Wieser and Keil, 2011). Several studies have used this technique to assess effects of concurrent emotional "distractors" on visual processing of neutral cues. For instance, Müller et al. (2008) recorded ssVEPs in response to clouds of randomly moving flickering dots (i.e., random dot kinematograms) in which observers were instructed to detect instances of non-random, coherent movement in a subset of dots. These kinematograms were superimposed on pleasant, unpleasant, neutral, or scrambled pictures, and participants were instructed that the pictures were irrelevant to the focal task. The amplitude of the ssVEP elicited by the dots was reduced for extended periods of several hundreds of milliseconds, when distractors were pleasant and unpleasant pictures, compared to neutral or scrambled pictures (see **Figure 2B**).

In a related study, participants performed a foreground task that required detection of pattern changes in a black-and-white grating that was spatially superimposed on emotional or neutral pictures. The grating and the pictures were tagged at different frequencies (Wieser et al., 2012). Again, the ssVEP evoked by the neutral, task-relevant Gabor grating was reliably diminished specifically for affectively engaging pictures, as illustrated in **Figure 1B**. Both studies converged in terms of the time course of these distractor effects, showing a decrease in both target detection accuracy and ssVEP amplitude diminution that lasted for approximately 800 ms after stimulus onset (see **Figure 1B**). Suppressive or interfering effects of an emotionally engaging distractor also often affect subsequently presented stimuli. Behaviorally, this is evident in RSVP paradigms, in which detection of a neutral target is impaired when it appears between 200 and 800 ms after a task-irrelevant emotional distractor (Most et al., 2005; Ihssen et al., 2007).

ENDNOTE

Taken together, then, a number of the traditional measures used as evidence of affective engagement in studies of emotional perception index the heightened orienting and attention that we suggest reflects activation of defensive or appetitive motivational systems that have evolved to support survival. Adjustment of sensory receptors, enhanced resource allocation, and dedicated perceptual processing are initiated in the service of stimulus identification and preparation for action. Here, we suggest that a critical variable determining whether emotion facilitates or inhibits orienting in emotional perception is the selected dependent measure: measures that index orienting to emotional cues tend to show enhancement and facilitation when these cues are present in the perceptual array – whether as intrinsically focal cues or as concurrent "distractors." On the other hand, orienting indicators occasioned by affectively neutral cues, whether presented concurrently or independently, tend to show attenuation and interference.

Orienting is not a unitary response, and the rate at which specific components change, as well as their timing, often varies with the dependent measure under investigation. Thus, modulation by emotion can be phasic or sustained, immediate or delayed, presumably reflecting the specific function of different components of the orienting response (Bradley, 2009), and adding complexity in understanding effects of emotion during perception. Differential effects of stimulus repetition on specific components of the orienting response provide information which can assist in inferring their function as information intake, vigilance, resource allocation, preparation for action, and other processes mediating perception and action (Bradley, 2009). Importantly, orienting is primarily a hallmark of emotional perception, and emotional modulation of higher-level cognitive domains, such as memory, decision-making, and regulatory processes will likely have different dynamics.

From a cognitive viewpoint, the data presented here are consistent with the conceptualization that perceptual processing draws on a limited pool of shared resources (Deutsch and Deutsch, 1963) in which cues that activate motivational systems naturally utilize more resources, resulting in measurable trade-offs for concurrent cues. From a neurophysiological perspective, the same reciprocal pattern is often conceptualized as reflecting competition in dedicated neural circuits (Shafer et al., 2012), in which cues of high motivational relevance have priority. Although stated at different levels of analysis and using different semantic terms, both accounts are consistent with the hypothesis that emotional cues capture attention, based on their evolutionary significance in the battle for survival, and that perceptual processing of concurrent non-motivationally relevant tends to suffer when competing with emotionally significant stimuli.

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Affective salience can reverse the effects of stimulus-driven salience on eye movements in complex scenes

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In natural vision both stimulus features and cognitive/affective factors influence an observer's attention. However, the relationship between stimulus-driven ("bottom-up") and cognitive/affective ("top-down") factors remains controversial: Can affective salience counteract strong visual stimulus signals and shift attention allocation irrespective of bottom-up features? Is there any difference between negative and positive scenes in terms of their influence on attention deployment? Here we examined the impact of affective factors on eye movement behavior, to understand the competition between visual stimulus-driven salience and affective salience and how they affect gaze allocation in complex scene viewing. Building on our previous research, we compared predictions generated by a visual salience model with measures indexing participant-identified emotionally meaningful regions of each image. To examine how eye movement behavior differs for negative, positive, and neutral scenes, we examined the influence of affective salience in capturing attention according to emotional valence. Taken together, our results show that affective salience can override stimulus-driven salience and overall emotional valence can determine attention allocation in complex scenes. These findings are consistent with the hypothesis that cognitive/affective factors play a dominant role in active gaze control.

Keywords: affective salience, visual salience, eye movements, attention, top-down, bottom-up, stimulus-driven, regions of interest

INTRODUCTION

In natural vision human observers sequentially allocate focal attention to sub-regions of a scene (James, 1890). Such attention shifts are typically associated with eye movement behavior (Rizzolatti et al., 1987). Previous research shows that both visual stimulus-driven ("bottom-up") and cognitive/affective ("top-down") factors influence the competition for a share of our limited attention (Corbetta and Shulman, 2002).

Bottom-up visual salience models explain guidance of eye movements based on the concept of a visual salience map (Koch and Ullman, 1985; Findlay and Walker, 1999). Shifts of attention and eye movements are initiated toward the point with the highest salience, which is then inhibited so that attention can be disengaged and be moved to the next most salient location. In this way, these visual salience models suggest a control mechanism for dynamically targeting eye movements. These models suggest that low-level feature discontinuities represented in the salience map can explain a significant proportion of where people look. Thus they specify filters that quantify visual conspicuity, a measure of what is perceived as significantly distinct from its local background of each part of the scene.

Computational models have been developed with two types of approaches. The first uses known properties of the visual system to generate a salience map. In these models, the visual properties present in an image generate the visual salience map that explicitly marks regions that are different from their surround such as color, intensity, contrast, and edge orientation (Koch and Ullman, 1985; Itti and Koch, 2000; Parkhurst et al., 2002; Torralba, 2003), contour junctions, termination of edges, stereo disparity, and shading (Koch and Ullman, 1985), and dynamic factors such as motion (Koch and Ullman, 1985; Rosenholtz, 1999). The Itti and Koch (2000) model is frequently cited on behalf of this type of computational visual salience model. A second approach uses scene statistics to determine the relative visual salience of regions of a scene. In this approach local scene patches surrounding fixation points are analyzed to determine whether fixated regions differ in some image properties from regions that are not fixated. For example, high spatial frequency content and edge density have been found to be somewhat greater at fixated than non-fixated locations (Mannan et al., 1996, 1997). Furthermore, local contrast is higher and two-point intensity correlation is lower for fixated scene patches than control patches (Reinagel and Zador, 1999; Krieger et al., 2000; Parkhurst and Niebur, 2003). The spectral residual (SR) method (Hou and Zhang, 2007) is an example of this type of computational visual salience model. It is based on the principle that the human visual system tends to suppress responses to frequently occurring features, while at the same time remaining sensitive to features that deviate from the norm. In a previous study (Niu et al., 2012) we compared the capacity of classical Itti bottom-up model and the SR model in predicting eye fixations. Results confirmed that the SR model does a better job at predicting attention allocation than the classical Itti model.

Yet there is evidence that visual salience does not account for all aspects of a scene that bias attention. For example, semantic

meaning and social relevance of elements within a scene also influence allocation of overt attention. A recent study showed that visual salience could not fully account for where observers look within social scenes (Cerf et al., 2008, 2009). Cerf et al. showed that the model that best predicted where observers fixated within scenes was a salience model combined with a face-detection model. This combined-model outperformed the salience model alone. Birmingham et al. (2009a,b) also demonstrated that, when asked to look at a visual scene that includes human faces, participants most frequently fixate on the eyes – a tendency that is not accounted for by computationally modeled bottom-up visual salience. These studies shed light on attentional biases favoring faces and eyes, which cannot be fully explained by the standard bottom-up visual salience models. Thus it is not only visual conspicuity that preferentially commands attention in a complex visual scene.

The affective salience, or motivational importance, of a stimulus may also influence the relatively reflexive allocation of attention. Affective salience engages resources based on the motivational importance of a stimulus in relation to the long-term goals of approaching pleasure or avoiding pain (Todd et al., 2012). Arousal enhanced perceptual learning of salient stimuli but impaired perceptual learning of non-salient stimuli (Lee et al., 2012). Many studies have demonstrated that attention is preferentially allocated to affectively salient relative to neutral stimuli (LaBar et al., 2000; Rosler et al., 2005; Knight et al., 2007). This bias favoring emotional stimuli even occurs under direct instructions to ignore the arousing items (Nummenmaa et al., 2006). Affective salience has also been found to increase viewing duration for both pleasant and unpleasant scenes (Lang et al., 1993) and to capture greater initial attention as well as inhibit subsequent disengagement from a stimulus location (Mogg and Bradley, 1999; Fox et al., 2002). In a recent study, when neutral background scenes were edited to contain a single emotionally salient object and a single visually salient object (Humphrey et al., 2012), more fixations were allocated to affectively salient than visually salient objects. Another recent study found tradeoffs between the influence of visual salience and the reward-punishment value of saccade locations, with value overriding visual salience in attracting saccades at latencies over 184 ms (Schutz et al., 2012). Finally, our own research has revealed that viewers are more likely to fixate emotionally salient than visually salient regions of complex scenes (Niu et al., 2012).

While our previous study demonstrated that observers' attention to affectively salient regions in a scene is influenced by the emotional valence and arousal of such stimuli, it did not quantify the extent to which the fixations allocated to affectively salient regions are associated with arousal measures. Furthermore, we do not know whether there was a specific bias to look at the affectively salient regions of negatively valenced images. Yet a further question related to the specific stage of visual processing at which emotional factors start to influence eye movement behavior in scene viewing. In summary, no study has examined explicitly the role that emotional salience plays in eye movement behavior. The present study set out to address precisely this issue.

In the present study we measured eye movement fixations during free viewing of negative arousing, positive arousing, and neutral scenes in order to capture the allocation of overt attention during naturalistic scene viewing. Building on previous research, we employed item analysis to investigate the influence of emotional valence and arousal on eye movement behavior within scenes. We hypothesized that: (1) Emotional valence of a scene would influence patterns of attention allocation to salient regions within the scene, and (2) participant arousal ratings for each scene would predict the level of attention allocated to affectively salient relative to visually salient regions within the scene.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 50 young adults (24 female, 18–40 years), with normal or corrected to normal vision and no history of neurological problems, recruited from the University of Toronto campus. Twenty five participants (12 Female) participated in the main eye tracking experiment. Three subjects were excluded from the eye tracking experiment due to eye tracker drifting error, and eye movement data from 22 participants were used. Twenty five participants (12 Female) performed a separate affective salience region of interest generation task. All subjects gave written informed consent for participation.

STIMULUS MATERIALS

Twenty five negative and 25 positive photographs were taken from the International Affective Picture System (IAPS). Twenty five neutral photographs were retrieved from the internet as well as the IAPS. Positive and negative images were selected to be similar in overall arousal levels. Positive, negative, and neutral images were equated in log luminance, $F(2, 72) < 1$, and RMS contrast, $F(2, 72) < 1$, which were computed using the Image Processing Toolbox packaged with Matlab 7.0. Positive and negative images were selected to be equivalent in standardized ratings of emotional arousal (emotional salience). Scene complexity and difficulty of figure ground segregation were also rated by a separate set of participants. Participants were asked to rate how difficult it was to discriminate the focal figure of the scene from the background on a scale of 1–7, as well as the composition of each image on from simple to busy or complex on a scale of 1–7. Negative, positive, and neutral images also did not differ in difficulty of figure ground discrimination, $F(2, 72) < 1$, $p > 0.5$, or scene complexity (scale of 1–7), $F(2, 72) < 1$, $p = 0.5$, whether they contained single vs. multiple objects, $F(2, 72) < 1$, or in the number of human figures, $F(2, 72) < 1$, $p > 0.6$.

EYE TRACKING EXPERIMENT

Apparatus

Eye movement recoding experiments were programmed in Experiment Builder and analyzed in DataViewer (SR Research). Eye movements were recorded using an infrared eye tracking desktop monocular system – EyeLink 1000 (SR Research, Mississauga, ON, Canada). Stimuli were shown on a 21W ViewSonic G225f monitor positioned 63 cm away from the participant, with a refresh rate of 140 Hz. Participants sat in front of the computer monitor and a chin rest was used to limit head movements. Throughout the experiment, the observer's right eye position was recorded and sampled at a rate of 1000 Hz. Pictures were presented at a visual

angle of 11.17° × 8.37°. We used the manufacturer's software for calibration, validation, drift-correction, and determining periods of fixation. A nine-point calibration was performed at the start of the experiment followed by a zero-point calibration accuracy test. An additional drift-correction was performed whenever an observer failed to fixate within about 1.4° – (50 pixels) of an initial central fixation cross within 5 s. In all experiments and conditions, each trial started with a central fixation cross which observers had to fixate for 500 ms to trigger stimulus onset.

Experimental procedures

After informed consent and a brief practice session, participants performed the free viewing task while eye movements were recorded. Following calibration and validation, participants were shown each of the 75 images in a randomized sequence. Each image was shown for 2 s, and was preceded and succeeded by 2 s of black screen to minimize the possibility of proactive or retroactive interference, making each trial 6 s in length (2 s blank – 2 s stimulus – 2 s blank). Prior to presenting the stimulus, drift-correction was performed to ensure consistency across all trials. Because pilot data indicated that even simple cognitive or memory tasks could alter the participants' eye movement pattern and fixation compared to a free viewing condition, participants were instructed to view the pictures in a natural manner. To guarantee consistent performance and to maintain concentration throughout the entire testing period (up to 20 min), participants were given two mandatory breaks after the 25th and the 50th trial.

AFFECTIVELY SALIENT REGIONS OF INTEREST GENERATION TASK

Procedure

In order to generate regions of interest (ROIs) reflecting the most affectively salient regions of each image used in the task, participants were shown each of the 75 photo stimuli in a randomized sequence. For each image, they were instructed to click the mouse in the center of each of the five parts of each picture that were the most emotionally charged in order of intensity (from most intense to least intense). Participants were instructed as follows, "You will be shown a series of images. We want to know which parts of each image you find to be the most emotionally important or arousing. Please click the mouse in the center of the five parts of each picture that are the most emotionally charged for you in order of intensity (from most intense to least intense). This region could be a person or object or a part or combination of either."

To justify our choice of emotional salience ROIs generation task, we did a pilot study using a different subject-determined emotional salience ROIs task. In the pilot task participants were asked to click as rapidly as possible on the five parts of each image that caught their interest in order of interest. They were instructed to "go with their guts," and not "over think" their choices. Comparison of the two tasks revealed that the ROIs created by the pilot task were highly correlated with those chosen in the emotional salience task despite different subjects in both studies, suggesting that what is considered interesting is what is most affectively charged and both tasks predicted fixation patterns better than visual saliency maps. In order to precisely predict the *xy* coordinates of fixations without pre-specifying the size or scale of the region that would be chosen, we had participants select a single pixel rather circle whole objects.

The coordinates of the clicked pixel were processed using two-dimensional convolution with a 50-point Gaussian distribution window using Matlab, and an affective salience map representing the average affective salience value across participants was created for each stimulus picture. Then we generated affectively salient regions based on the affective salience map by ensuring that salient regions comprised 10% of the total image as shown in **Figure 1**. An example of 5 pixels identified by clicking each picture at the center of the region that participants find the most emotionally meaningful is shown in **Figure 1A**. **Figure 1B** illustrates the resulting affective salience map. Following the clicking task, participants rated each image for overall affective salience using a numerical scale from 1 (the image was not emotionally arousing) to 7 (the image was extremely emotionally arousing).

Computational visual salience model

The SR computational model was implemented to determine the visually salient regions in each stimulus image. The SR model (see Appendix) was adapted by us to detect salient regions. The model was employed to process each image and generated salience maps that visualized salience values. We then generated visually salient regions controlling the coverage of the salient regions (a region with a salience value higher than threshold was considered a salient region; a region with a salience value lower than threshold was considered a non-salient region). The salient regions covered 10% of the total image. The choice of 10% was based on a precedent for object-detection applications used in engineering (Frintrop et al., 2004). This approach allowed us to compare the performance of

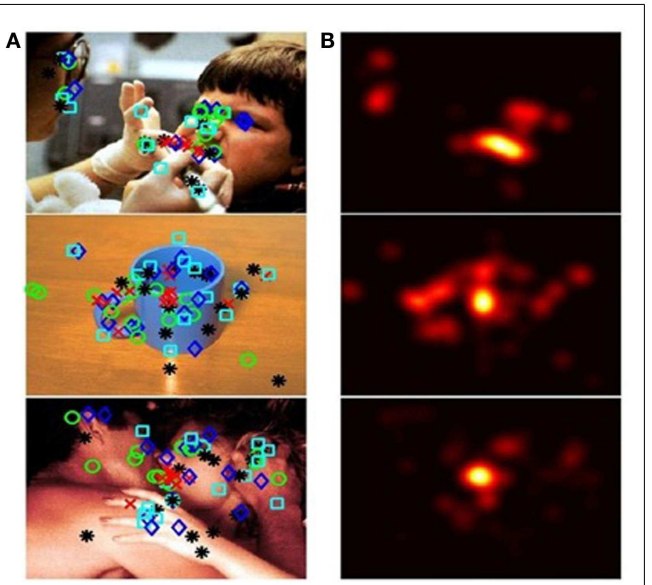

FIGURE 1 | Generation of affectively salient ROIs. Column **(A)** from top to bottom, images categorized as: negative, neutral, or positive. Shapes overlying the images denote spots that participants identified, via mouse clicks, as affectively salient. Different shapes denote participants' order of preference. Column **(B)** affective salience maps, generated from participants' responses to images in column **(A)**.

visual salience and affective salience in predicting eye movement behavior (**Figure 2**). Affective ROIs are shown in red (**Figure 2A**) and visual salience ROIs are shown in yellow (**Figure 2B**).

It is often the case that emotional objects in a scene are also visually salient. We have endeavored to separate these factors by exploring whether emotional regions are still fixated when in competition with other more visually salient regions in the picture. To precisely examine whether emotional salience or visual salience better predicts observed gaze allocation, rather than directly comparing pairs of images or editing the pictures to contain a single emotional stimulus and a single visually salient stimulus, we used methods for emotionally and visually salient region detection within a scene (with emotional salience and visual salience in direct competition). If low-level visual salience is an important factor in attracting attention, then this should still be true when the most visually salient object is not the most emotionally salient one. However, if emotional arousal plays a special role in this attraction, then it could result in the kind of meaning-based override which we have revealed in our previous study (Niu et al., 2012).

Eye tracking data

Fixations were calculated using the built-in software of the Eyelink tracking system. A fixation was defined as anything above 70 ms – micro fixations below 70 ms were discarded. We categorized fixations by their "fixation number" based on a fixation's position in the ordered sequence of fixations (i.e., first, second, third). The "initial fixation" is the fixation occurring before stimulus onset, when the subjects are focusing on the centered fixation cross, and is not counted as part of the ordered sequence of fixations.

Saccades were also determined by the eye tracking system. An eye movement was classified as a saccade when its velocity reached 30°/s or when its acceleration reached 8000°/s^2. The "saccade planning time" is the duration of time between the stimulus onset and the initiation of the first saccade. Saccade planning times smaller than 50 ms or greater than 600 ms were discarded to remove outliers and artifacts.

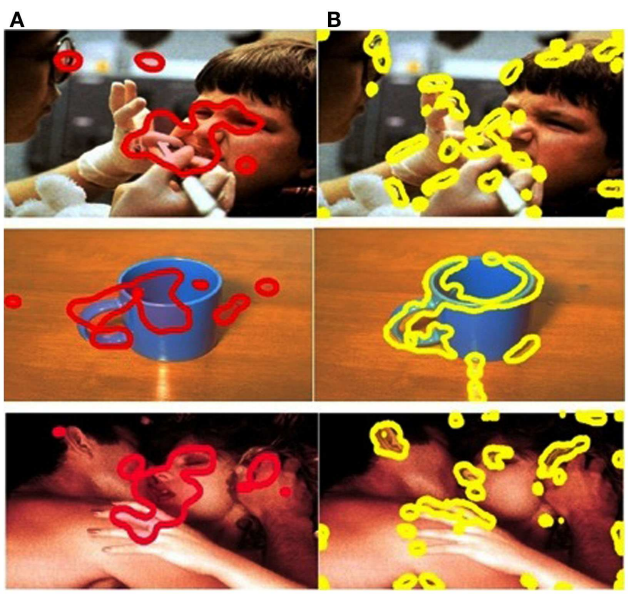

FIGURE 2 | Comparison of ROIs in example positive, negative, and neutral images. Column **(A)** affective ROIs. **(B)** Visually salient ROIs.

The mean number of fixations was calculated for affectively salient and visually salient ROIs to test predictions of eye movement behavior generated by each model. For detailed investigation of eye movement patterns predicted by the emotional category of the image in relation to ROI generated by each model, item analyses were performed examining eye movement behavior image by image for all images used in the task.

RESULTS

ITEM ANALYSIS

Previous findings indicated that affectively salient regions overwhelmingly elicited greater attention allocation than visually salient regions (Niu et al., 2012). In order to further explore the influence of emotional valence and arousal on eye movement behavior in ROIs generated by visual vs. affective salience models, we performed item analyses in which we examined eye movement behavior, averaged across participants, for each of the 75 images used in the task. To control for differences in the overall number of fixations between image categories, we calculated the proportion of fixations within each of the affective vs. visual salient regions relative to the number of all fixations in a given image. These fixation allocation tendency scores thus index an increased tendency to fixate in one type of ROI.

We first compared fixation allocation tendency scores in affective and visual ROIs, image by image, as a function of participant-rated emotional arousal (**Figure 3**), based on self-reported arousal ratings for each image (see Materials and Methods). Correlational analysis revealed that, in affective ROIs, fixation allocation tendency scores were positively correlated with arousal (**Figure 3A**), $R = 0.93$, $p < 0.001$, indicating that participants were more likely to allocate their gaze to affective ROIs when looking at images that were higher in overall arousal. The visual plot of the negative relation between affective salience and allocation tendency scores in **Figure 3A**, $R = -0.90$, $p < 0.001$, reflects the competition between visual and affective salience regions captured by these tendency scores: An increased proportion of fixations allocated to affective ROIs with increased salience is gained at the expense of fixations to visually salient ROIs. These findings further reveal a stronger effect of negatively valenced stimuli on fixation allocation to affective salience ROIs. Although affective salience was correlated with the proportion of fixations allocated to affective ROIs for both positive and negative images, the intercept for each category of images is markedly different, revealing overall higher fixation allocation tendency scores when viewing negative vs. positive images despite equivalent arousal ratings (**Figure 3B**).

SEQUENCE OF FIXATIONS FOR AFFECTIVE VS. VISUAL ROIs BY EMOTION CATEGORY

We next performed a one-way ANOVA with three emotion category on difference scores between the proportion of fixations allocated to each type of ROI (affective salience > visual salience). Results revealed that the difference between the proportion of fixations allocated to affectively vs. visually salient ROIs was greatest

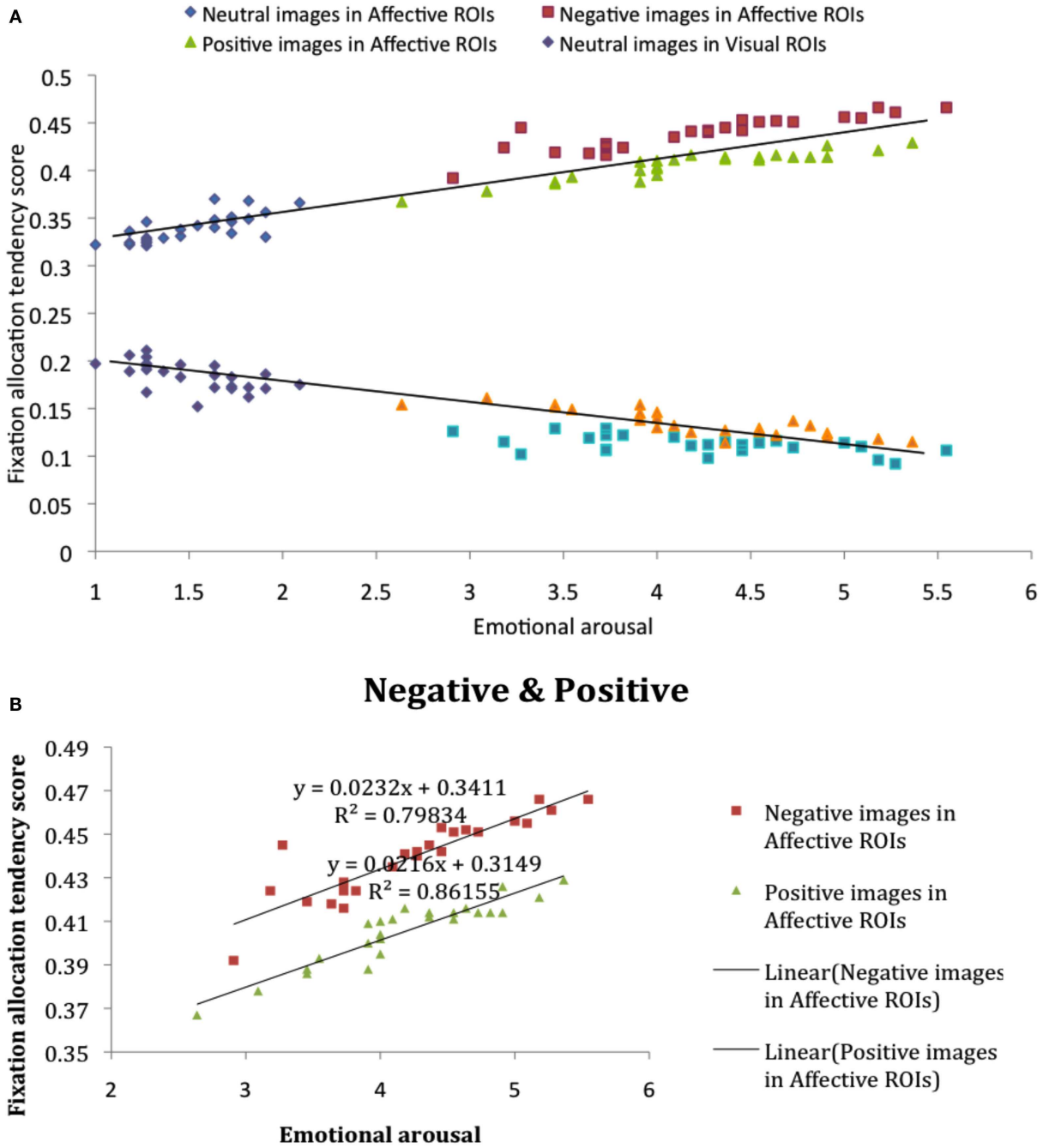

FIGURE 3 | (A) Fixation allocation tendency scores in affective and visual ROIs, image by image, as a function of participant-rated emotional salience. **(B)** Fixation allocation tendency scores in affective ROIs for negative and positive image categories.

for negative and smallest for neutral images, $F(2, 72) = 276.45$, $p < 0.001$, $\eta^2 = 0.88$. Pairwise contrasts showed that for each emotion category ROI difference scores differed from the other two categories (p's < 0.001). In order to further compare the influence of emotion category on sequential looking order in affectively vs. visually salient ROIs, we created difference scores between fixation allocation tendency scores for the first through the fifth fixation in each type of ROI for each emotion category. **Figure 4** illustrates the difference between fixation allocation tendency scores in the two ROIs as a function of ordinal fixation number, showing that the influence of emotion category on the difference in fixations allocated to each type of ROI remains constant across sequential fixations. The results show that the difference in the proportion of fixations allocated to affective vs. visual salience ROIs was greatest

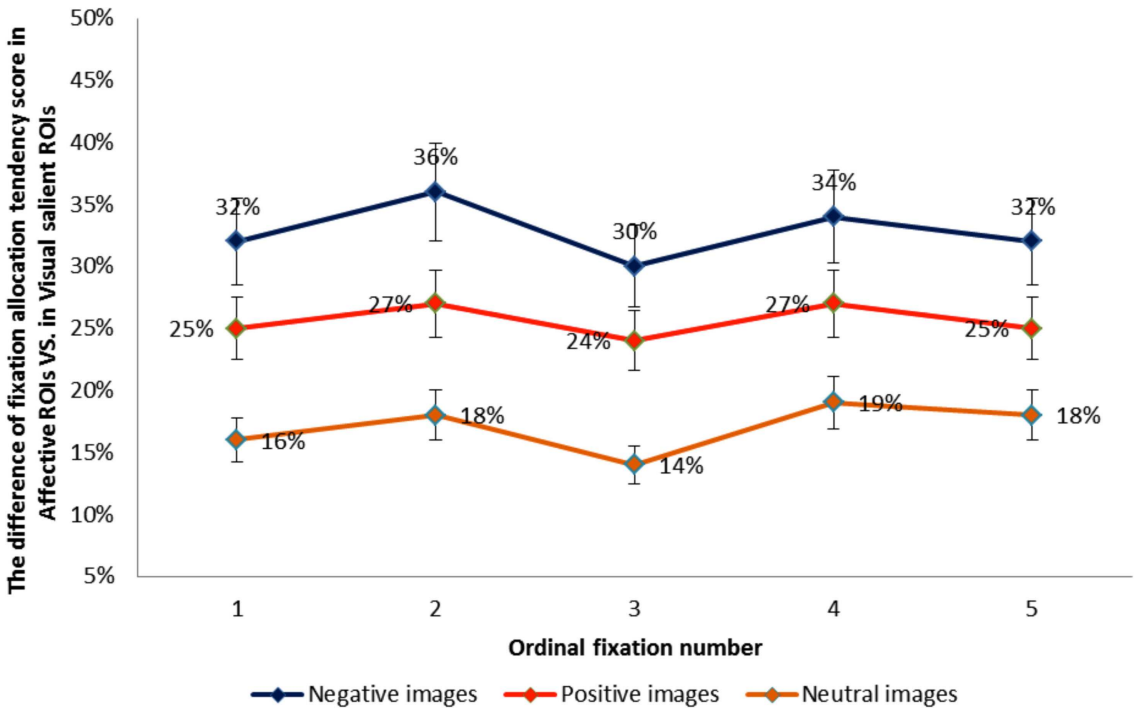

FIGURE 4 | The difference between fixation allocation tendency scores in the visual vs. affective ROIs for each emotion category as a function of ordinal fixation number.

for negative images and smallest for neutral images – and that this pattern of results remained constant from the first to the fifth sequential eye movement, which suggests that the emotional factor influences early on in scene viewing.

EXTENDED ANALYSIS OF EXAMPLE IMAGES

Finally, for a more fine-grained examination of fixation allocation when emotional salience and visual salience are in direct competition, we focused on an example image from each image category, choosing three images where there was the least amount of overlap between the two types of ROIs. First, we investigated eye movement behavior, participant by participant, for each of the three example images. Plots in **Figures 5B,D,F** show the number of participants with 1–7 fixations in affective vs. visual salient ROIs for each of the example images. These plots illustrate the strikingly higher number of fixations allocated to affective over visually salient ROIs when there is minimal overlap between the regions.

For the "needle" image (negative stimulus case), in **Figure 5A** the red curves illustrate the affectively salient regions and the yellow curves illustrate the visually salient regions. Here we show data from one of the participants whose eye movement scan path in is depicted in blue. Note that the size of the circle denotes the fixation duration and the arrow illustrates sequences of fixations. **Figure 5B** illustrates the greater number of participants with 1–6 fixations in affective vs. visual salience ROIs, revealing the advantage for affective ROIs for this image.

For the "couple" image (positive stimulus case), we again see in **Figure 5C** the affectively and visually salient regions, as well as the scan path of one of the participants. In **Figure 5D** we can still observe a greater number of fixations allocated in affective than in visually salient ROIs (although it is less pronounced than in the negative stimuli case **Figure 5B**).

For the "escalator" image (neutral stimulus case) the emotionally and visually salient regions are illustrated in **Figure 5E**. From **Figure 5F** we can observe a marginally greater number of fixations allocated in affective than in visually salient ROIs.

We next generated fixation allocation tendency scores across all participants for the example negative, positive, and neutral images, as shown in **Figure 5G**. These pie charts further illustrate the finding we report from the previous item analysis of all 75 images: When visual and affective salience compete, participants are most likely to allocate fixations to affectively salient ROIs in images with an overall negative valence in the absence of overlap between visual and affective salience.

Summary

Results of the item analysis revealed that, image by image, the proportion of fixations allocated to affective relative to visual salience ROIs was strongly associated with higher ratings of arousal: Viewing more arousing stimuli increased the likelihood of fixating in emotionally salient regions. This was true of both positive and negative images. Moreover, the difference in the proportion of fixations allocated to affective vs. visual salience ROIs was greatest for negative images and smallest for neutral images. This pattern of results remained constant from the first to the fifth sequential eye movement, suggesting patterns of attention allocation are

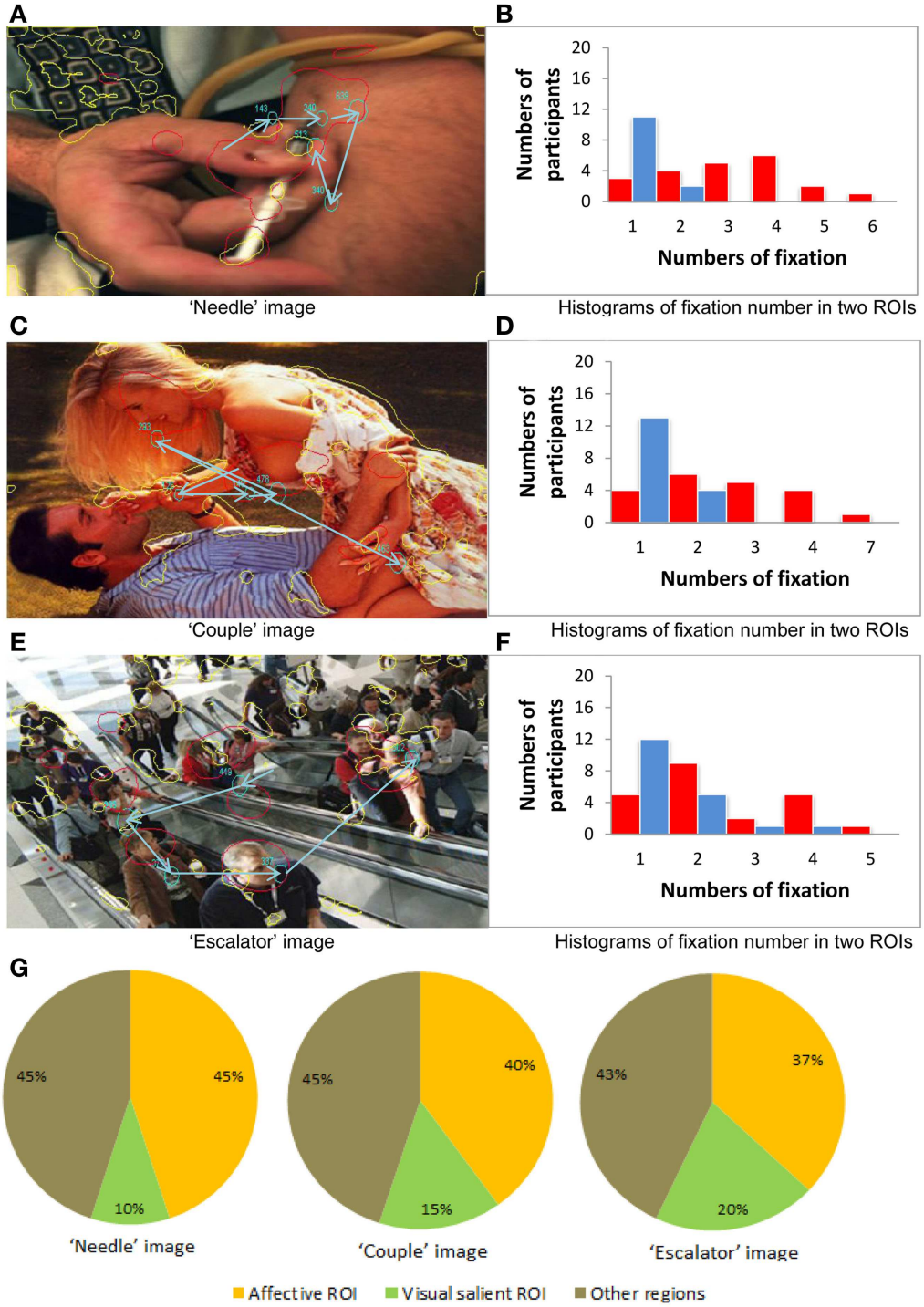

FIGURE 5 | Eye movement behavior analysis of the three example images. (A,C,E) Three example images. **(B,D,F)** The number of participants with 1–7 fixations in affective vs. visual salient ROIs for each of the example images. **(G)** Fixation allocation tendency scores across all participants for the example images.

modulated by the salience of the image early on. Finally, analysis three employed individual participants' data to examine looking patterns for three example images where competition between visual and affective salience was greatest. This analysis illustrated the findings that were typical across the entire image set in conditions of maximum competition between visual and affective

salience: Participants showed more fixations in affective ROIs when looking at each of those images, but the largest proportion of fixations was allocated to affective salience regions in the image with an overall negative valence.

DISCUSSION

Our results showed that, when participants freely viewed complex scenes, the proportion of fixations allocated to affective relative to visual salience ROIs was associated with higher ratings of emotional arousal, such that viewing emotionally arousing stimuli increased the likelihood of fixating in emotionally salient regions. Yet although the relationship between arousal and likelihood of fixating in affectively salient regions was similar for both negative and positive images, there was an overall higher proportion of fixations allocated to affective ROIs in images which had an overall negative valence. Thus, viewing negatively valenced scenes has an even stronger impact on allocation of overt attention to affective ROIs compared to scenes that are equally arousing but positively valenced, suggesting that our attention to emotive regions in a scene is influenced by the valence of such stimuli. These findings build on previous results showing that participants allocated more eye movements to regions of a given scene that were identified as affectively salient than regions identified as visually salient, particularly for negatively valenced scenes (Niu et al., 2012).

Like previous studies examining the role of semantic/affective salience, we examined number of fixations as a measure of foveal sampling of ROIs in each image. Distinct patterns of overt attention have been previously observed for emotional scenes, with higher fixation counts, or greater sampling of the image space, for arousing vs. neutral scenes (Sharot et al., 2008; Riggs et al., 2010), suggesting that scenes that are globally more arousing elicit more sampling of sub-regions of the image. We have extended such findings to show increased sampling for arousing images in sub-regions of an image identified as more affectively salient.

Taken with our previous findings (Niu et al., 2012), our results indicate that visual salience does have an effect on eye movements when one is inspecting an emotionally arousing scene, but the capacity of affective salience to override visual salience can be plausibly observed.

Previous studies have shown that low-level visual salience helps guide eye movements in free viewing (Parkhurst et al., 2002; Parkhurst and Niebur, 2003, 2004). Yet it is not only visual conspicuity that can produce a pop-out effect in the inspection of an image. There is also evidence that higher-level aspects of a stimulus, such as semantic meaning, can bias attention in favor of socially relevant stimuli (Birmingham et al., 2009a,b; Cerf et al., 2009). When semantic meaning is further associated with emotional arousal, commonly feared, or pleasant stimuli (e.g., a murder scene, erotica) can prioritize attention relative to neutral stimuli (LaBar et al., 2000; Nummenmaa et al., 2006, 2009). Only two other studies to date have examined the competition between visual salience and affective salience within a single complex scene: One study found that, when neutral background pictures were edited to contain a single affectively salient and a single visually salient object, fixations were more likely to be on affectively salient objects (Humphrey et al., 2012).

Our results showed a greater likelihood of fixating on affectively salient regions within negative relative to positive scenes. This finding suggests that negatively valenced scenes have an overall stronger impact on attention allocation to affectively salient regions compared to scenes that are equally arousing but positively valenced. Thus, our attention to emotive regions in a scene is influenced by the valence of such stimuli. At the behavioral level, this effect can be interpreted in the light of previous findings from our lab that negative, but not positive, affect enhances selective visual attention (Rowe et al., 2007; Schmitz et al., 2009). Here, it is possible that negative affect generated by the negative arousing images increased selective attention in a form of "weapon focus" on the most affectively salient items in the scene. At the neural level, the influence of a scene's overall valence even on early fixations may be supported by rapid responses to valence that have been demonstrated in the orbitofrontal cortex (OFC; Kawasaki et al., 2001). The OFC is reciprocally connected to temporal regions of the visual cortex (Rempel-Clower and Barbas, 2000), which in turn are connected with the lateral intraparietal cortex (LIP) which is important for allocating overt attention (Blatt et al., 1990; Thompson and Bichot, 2005; Goldberg et al., 2006). Such rapid processing of valence information may contribute to subsequent eye movement planning through LIP integration of either direct or indirect information from the OFC.

It has been suggested that the LIP in functions as a priority map that guides attention based on the moment to moment behavioral priority of aspects of the world (Bisley and Goldberg, 2010). By integrating information from other brain regions, including dorsal and ventral streams of the visual cortex, the anterior cingulate cortex, and regions of the thalamus (Blatt et al., 1990; Baizer et al., 1991, 1993), the LIP has been found to influence attention based on bottom-up visual salience, task-related goals, the expected reward value (including social rewards), and the behavioral relevance of a stimulus (Dorris and Glimcher, 2004; Sugrue et al., 2004; Balan and Gottlieb, 2006). Given considerable overlap between the constructs of behavioral relevance and motivational or affective salience, and given LIP connectivity with regions (e.g., the pulvinar nucleus of thalamus) implicated in affective salience tagging (Pessoa and Adolphs, 2010), the LIP may also play a role in prioritizing attention based on affective salience. The amygdala, which along with the pulvinar has been characterized as a motivational/affective salience detector (Cunningham et al., 2008; Todd and Anderson, 2009; Pessoa and Adolphs, 2010), is densely interconnected with multiple regions of visual cortex as well as well as with thalamic nuclei (Amaral et al., 2003; Shipp, 2003). Thus, the LIP may integrate information from the amygdala either directly or indirectly via other brain regions to integrate information about affective salience into a priority map for determining saccades.

Some limitations to the study qualify our interpretation of the results. First, it should be noted that, whereas the visual salience model was computer-generated the ROI in the affective salience model were based on human ratings. Thus, the findings reported here may be influenced by the difference between human and computer-generated models. Second, there was greater similarity in content between images of erotica within the positive category in comparison to between images in the neutral and negative categories. Although affective salience relates to subjective impressions

elicited by emotion rather than image categories, the fact that there was greater similarity between images in the positive category than in the negative and neutral categories may have influenced the results. Finally, future studies using human-generated affective salience ROIs should measure the reliability and validity of the affective salience ROI generation task, in particularly for the neutral images where rating consistency may be expected to be lower.

Despite significant recent progress, the best available computational visual salience models still lag behind human performance in predicting eye fixations in free viewing of complex scenes. The majority of models are based on low-level visual features and the importance of top-down factors has not yet been fully explored or modeled. Exploration of a cognition-based computational salience model that integrates semantic meaning and affective salience is an important future research direction. There are a number of applications that would benefit from such research. For example, selective rendering in computer graphics could benefit from improvements on eye gaze prediction models.

In conclusion, our results add to the literature about the influence of emotion on cognition by showing that the affective salience of an object – which can be defined by one's previous experience with it in relation to overall motivational goals of maximizing pleasure and avoiding pain (Todd et al., 2012) – can influence allocation of attention. They suggest that the overall emotional salience of an image determines allocation of attention to affectively salient regions of a scene, particularly for negative images. Thus, the affective importance of context can prioritize our attention to specific features of the world that are linked to associations between semantic meaning and emotional arousal. Whether this enhances or impairs cognition may depend on the other goals that are active at the time.

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APPENDIX

SPECTRAL RESIDUAL MODEL

It was discovered that an image's Spectral Residual (SR) of the log amplitude spectrum represented its innovation (Hou and Zhang, 2007). By using the exponential of SR instead of the original amplitude spectrum, the reconstruction of the image results in the salience map. The salience estimation is carried out using this computational model.

$$\mathcal{A}(f) = \Re(\mathfrak{F}[\mathcal{J}(x)]) \tag{A1}$$

$$\mathcal{P}(f) = \Im(\mathfrak{F}[\mathcal{J}(x)]) \tag{A2}$$

$$\mathcal{L}(f) = \log(\mathcal{A}(f)) \tag{A3}$$

$$\mathcal{R}(f) = \mathcal{L}(f) - h_n(f) * \mathcal{L}(f) \tag{A4}$$

$$\mathcal{S}(x) = \mathrm{g}(x) * \mathfrak{F}^{-1}\left[\exp(\mathcal{R}(f) + \mathcal{P}(f))\right]^2 \tag{A5}$$

In this computational model, the SR $\mathcal{R}(f)$ contains the innovation of an image which can be obtained by (4), where $\mathcal{L}(f)$ denotes the logarithm of amplitude spectrum $\mathcal{A}(f)$ of the image $\mathcal{J}(x)$ computed by (3) and $h_n(f)$ is the average filter. Using inverse Fourier transform then squared, the salience map in spatial domain is constructed. For better visual effects, we smoothed the salience map $\mathcal{S}(x)$ with a Gaussian Filter $g(x)$ as (5), where $\mathfrak{F}$ and $\mathfrak{F}^{-1}$ denote the Fourier transform and inverse Fourier transform, and $\mathcal{P}(f)$ denotes the phase spectrum of the image.

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When emotion blinds: a spatiotemporal competition account of emotion-induced blindness

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Emotional visual scenes are such powerful attractors of attention that they can disrupt perception of other stimuli that appear soon afterward, an effect known as *emotion-induced blindness*. What mechanisms underlie this impact of emotion on perception? Evidence suggests that emotion-induced blindness may be distinguishable from closely related phenomena such as the orienting of spatial attention to emotional stimuli or the central resource bottlenecks commonly associated with the attentional blink. Instead, we suggest that emotion-induced blindness reflects relatively early competition between targets and emotional distractors, where spontaneous prioritization of emotional stimuli leads to suppression of competing perceptual representations potentially linked to an overlapping point in time and space.

Keywords: emotion-induced blindness, attention, perception, spatiotemporal competition, biased competition, emotion, visual awareness

Most aspects of the environment resonate with emotional meaning, so an understanding of perception in the real world necessitates understanding how it is impacted by emotion. Evidence suggests that emotional stimuli themselves attract attention more robustly and are more readily detected than are non-emotional stimuli (Anderson and Phelps, 2001; Öhman et al., 2001; Anderson, 2005; Vuilleumier and Huang, 2009), but less well understood is the impact of emotional stimuli on the perception of neighboring non-emotional information. In a sense, this dimension of perception-emotion interactions is especially relevant to everyday life, where – whether one is a soldier on patrol, an emergency room technician, or a highly anxious individual surrounded by perceived threats – it is important to attend to and process non-emotional information despite the emotional context.

Unfortunately, the literature on perception-emotion interactions often seems to contradict itself, with some studies showing that emotional stimuli impair perception of contextually neighboring targets and other studies showing that emotional stimuli enhance perception of such targets. In the former case, for example, studies have shown that when people search for a single target embedded in a rapid, serially presented stream of pictures, the presence of a task-irrelevant emotional picture robustly impairs target perception for about a half-second, a phenomenon labeled *emotion-induced blindness* (e.g., Most et al., 2005; Most and Jungé, 2008; Most and Wang, 2011; Kennedy and Most, 2012). In contrast, other studies have shown that the presentation of a task-irrelevant emotional face can subsequently enhance contrast sensitivity (a function of early vision; Phelps et al., 2006; Bocanergra and Zeelenberg, 2009) and can facilitate visual search for targets (Becker, 2009). Findings that emotional stimuli can benefit subsequent target perception are consistent with a recently proposed "arousal-biased competition" account, which posits that emotional stimuli bias subsequent perceptual competition in favor of high-priority stimuli (which can be classified as "high-priority" by virtue of either their inherent salience or their goal-relevance; Mather and Sutherland, 2011).

But what of the cases where emotional stimuli disrupt perception? Why should emotional stimuli enhance subsequent perception of targets on some occasions but disrupt it on others? In a sense, the competition processes posited within the arousal-biased competition account might suggest insights into emotion-induced blindness, as emotional stimuli themselves could be construed as high-priority stimuli that compete with neighboring targets. Indeed, recent work on emotion-induced blindness in our lab has revealed some clues into the nature of such competition. To anticipate, our evidence suggests that emotion-induced blindness may stem from competition between targets and emotional distractors and that the phenomenon primarily arises when targets and emotional distractors jockey to be the dominant representation linked to a given point in space and time.

EMOTION-INDUCED BLINDNESS

In a series of studies showing emotional disruption of conscious perception, participants viewed rapid serial visual presentations (RSVPs) of upright landscape and architecture photos at a rate of 10 images per second. They were instructed to search within each stream for a landscape or architecture photo that was rotated 90° clockwise or counterclockwise and to report its orientation (see **Figure 1A**). Depending on the trial, a task-irrelevant emotionally negative, neutral, or scrambled negative picture preceded the target picture by either two (lag 2) or eight (lag 8) items (Most et al., 2005). Emotionally negative distractors depicted aversive, highly arousing scenes such as threatening animals, violence, or medical trauma, whereas neutral images depicted people or animals in ways that were not emotionally evocative. Scrambled versions of the negative distractors served to control for the impact of low-level visual properties such as color and luminance. Despite the rapid presentation rate, participants were highly accurate in

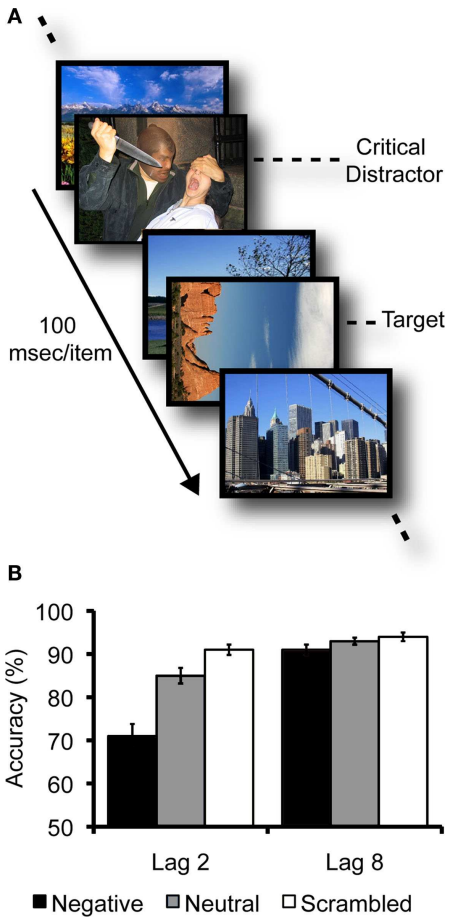

FIGURE 1 | (A) Example of part of a typical emotion-induced blindness trial, where items are presented serially at a rate of 100 ms/item. Here, the target is a landscape picture rotated 90° clockwise. The critical distractor is an emotionally negative picture that appears two items before the target (Lag 2). **(B)** A typical pattern of data (means and standard errors) from an emotion-induced blindness experiment (from Most et al., 2005, Experiment 1). At Lag 2, accuracy in reporting the target's orientation was worse following emotional distractors than following neutral or scrambled distractors. However, by Lag 8, performance in all distractor conditions had recovered to above 90% accuracy.

reporting the target's orientation at lag 8 (when the distractor and the target appeared almost 1 s apart) regardless of distractor condition. However, at the earlier lag, emotionally negative distractors induced greater deficits in target processing than did the scrambled and neutral distractors (see **Figure 1B**). This pattern – emotion-induced blindness – appears to reflect a disruption of conscious perception rather than disrupted maintenance of information in visual working memory, as the size of the effect is comparable regardless of whether participants respond immediately or withhold their response for a brief delay (Kennedy and Most, 2012).

The fact that the scrambled versions of the negative pictures did not induce spontaneous target perception impairments suggests that the impairments elicited by the negative images stemmed from their emotional nature rather than their low-level visual features. This conclusion received further support from a study in which emotionally neutral pictures that participants had learned to associate with an aversive burst of white noise induced similar target perception impairments (Smith et al., 2006). Both emotionally negative and emotionally positive distractors appear capable of driving the effect as long as they elicit a response of relatively high arousal: in one set of experiments, the emotional distractors were erotic scenes – which are generally rated as emotionally positive and highly arousing by both men and women (Bradley et al., 2001; Lang et al., 2001) – and these stimuli consistently elicited emotion-induced blindness effects similar to those caused by negative distractors (Most et al., 2007).

DIFFERENTIATING EMOTION-INDUCED BLINDNESS FROM RELATED PHENOMENA

In some respects, emotion-induced blindness is surprising within the context of the extant literature. As mentioned above, the phenomenon stands in contrast to findings that emotional stimuli can facilitate perceptual processing of subsequent stimuli (Phelps et al., 2006; Becker, 2009; Bocanergra and Zeelenberg, 2009). Because all stimuli appear in the same spatial location in most emotion-induced blindness tasks, the phenomenon also appears to contrast with evidence that emotional stimuli facilitate the processing of subsequent stimuli at their location by attracting or holding spatial attention there (e.g., MacLeod et al., 1986; Mogg and Bradley, 1999; Fox et al., 2001; Jiang et al., 2006; Van Damme et al., 2008). One possibility is that emotion-induced blindness reflects mechanisms other than spatial attention or those involved in enhancing early perception. But if so, what mechanisms might be involved?

On the surface, it seems likely that emotion-induced blindness stems from the same mechanisms as the *attentional blink* (AB; e.g., Raymond et al., 1992; Chun and Potter, 1995), a failure of conscious perception that is widely studied in the visual cognition literature (and which served as the model for the emotion-induced blindness task). In a typical AB task, participants report two targets embedded in a rapid stream of non-targets (e.g., the identities of two letters embedded in a stream of digits). If the two targets appear far enough apart from each other in time, then people can generally report both targets despite the rapid presentation speed. However, if the second target appears within about half a second after the first target, then people can generally report the first but not the second target (cf. Potter et al., 2002). Dominant models of the AB differ somewhat from each other in their details, but most converge on the notion that the AB largely reflects the disruption or distraction of relatively central, late-stage perceptual mechanisms, whether such mechanisms involve a failure of consolidation into visual working memory (e.g., Chun and Potter, 1995), a failure of retrieval from memory (e.g., Shapiro et al., 1994), or disruption of an attentional filter responsible for distinguishing targets from non-targets (e.g., Di Lollo et al., 2005), among other accounts (but also see Giesbrecht et al., 2007, for evidence of the flexibility of the AB locus).

Based on such accounts of the AB, it might be expected that emotion-induced blindness reflects the disruption of some relatively central, high-level mechanism. However, in a recent series of experiments, a surprising pattern of results suggested that – despite its surface-level similarity to the AB – emotion-induced blindness

might stem from mechanisms other than those often presumed to drive the AB. In these experiments, participants searched for a target that could appear in one of two simultaneously presented, vertically aligned rapid streams instead of within a single stream. The target was equally likely to appear in either stream, and the critical distractor (a neutral or emotionally negative picture) was equally likely to appear in the same stream as the target or in the opposite stream. Results revealed that target perception was worse following an emotional distractor only when the critical distractor appeared in the same stream as the target (Most and Wang, 2011). If emotion-induced blindness stemmed from the disruption or distraction of a relatively late-stage, central processing bottleneck, then the perceptual disruption should have been equivalent regardless of the spatial relationship between the targets and critical distractors, as seems to be the case with the AB (e.g., Shih, 2000; Lunau and Olivers, 2010; but see Kristjánsson and Nakayama, 2002). The fact that the emotion-induced impairment of target perception was greater at, compared to away from, the location of the emotional distractor suggests that the mechanisms underlying emotion-induced blindness may be dissociable both from central bottlenecks involved in the AB and from the spatial attention mechanisms that have been the focus of most emotion-perception research over the past several decades.

Notably, further evidence for a dissociation between spatial attention mechanisms and those underlying emotion-induced blindness emerged from an emotion-induced blindness experiment in which conditions that were more or less conducive to spatiotemporal competition between targets and emotional distractors were manipulated. In most emotion-induced blindness tasks, the targets and critical distractors are both embedded in the middle of a rapid stream, rendering their temporal order hard to judge and increasing the likelihood of the perceptual system linking them to a common point in time and space. However, in this follow-up experiment, the targets were sometimes the last item in their stream (Most and Wang, 2011, Experiment 2). With no subsequently appearing items masking the targets, the targets could persist in iconic memory and their temporal relationship with the critical distractors was rendered unambiguous. Under these conditions, the spatial pattern of emotion-induced impairment reversed, with target accuracy now worse away from – rather than at – the location of the emotional distractor. This reversed pattern is consistent with the large corpus of studies suggesting that emotional distractors capture spatial attention and delay or otherwise impair processing of targets at other locations. In other words, when the hypothesized impact of spatiotemporal competition was minimized, a dissociable impact of spatial attention appeared to emerge.

A SPATIOTEMPORAL COMPETITION ACCOUNT OF EMOTION-INDUCED BLINDNESS

Although the localization of emotion-induced blindness to the location of an emotional distractor appears to run counter to what might have been predicted on the basis of the spatial attention literature, it accords well with research on *localized attentional interference* (Mounts, 2000, 2005; Mounts and Gavett, 2004; Mounts and Tomaselli, 2005; McCarley and Mounts, 2007; McCarley et al., 2007; Mounts et al., 2007). This refers to the finding that processing of one stimulus can impair processing of a second stimulus that appears in close spatial proximity and that this impairment grows stronger with decreasing distance between the two targets (also see Cave and Zimmerman, 1997; Caputo and Guerra, 1998; Bahcall and Kowler, 1999; Kristjánsson and Nakayama, 2002; Theeuwes et al., 2004; Doran and Hoffman, 2010). Given the degree to which such localized interference seems similar to the spatial pattern of emotion-induced blindness, the mechanisms underlying it may suggest insights into the nature of emotion-induced blindness.

Patterns of localized attentional interference are consistent with an overarching "biased competition" model of attentional selection (e.g., Desimone and Duncan, 1995; Desimone, 1998), one of the foundations of which is the recognition that visual stimuli in a cluttered visual environment compete with each other to drive the responses of neurons in the visual system. According to this account, two or more simultaneously appearing stimuli will evoke neural patterns of activation in parallel. When the stimuli lie far apart enough in the visual field, they may evoke activity in minimally overlapping neuron populations. However, the smaller the distance between the stimuli, the greater the overlap in the neuron populations activated, leading to increased competition between the neural representations. In this situation, selective attention is conceptualized as a biasing of the competition in favor of one stimulus over the others. This competition can be biased in bottom up fashion – in favor of items that are visually salient – or by top-down strategy – in favor of items that are goal-relevant (Desimone and Duncan, 1995; Desimone, 1998). Recordings of neural activity have provided evidence consistent with the biased competition account. For example, visual cortical neurons that are highly responsive to one stimulus are less responsive when a second, competing stimulus simultaneously occupies their receptive fields, but attention to either of the stimuli leads to a neural response similar to that observed when the attended item appears alone (e.g., Chelazzi et al., 2001). Notably, receptive fields are small in early regions of the visual cortex, where neural activity appears to be driven largely by low-level visual properties; however, they grow larger in later, more anterior visual regions, which have been found to be more globally responsive to complex stimuli such as objects and faces (Desimone and Gross, 1979; Gattass et al., 1981, 1988; Kastner and Ungerleider, 2000; Kastner et al., 2001). Competition between neural representations has been observed in a number of regions, including V1, V2, V4, and inferotemporal cortex, the hierarchical organization of which suggests that competitive spatiotemporal interactions could occur not only at the level of discrete features, but also at the level of meaningful representations. Since the time that the biased competition model of attention was first proposed, empirical and theoretical advances have extended and refined it, as reflected in (for example) more recent "normalization" and "feature-similarity gain" models (e.g., Treue and Martinez-Trujillo, 1999; Martinez-Trujillo and Treue, 2004; Lee and Maunsell, 2009; Reynolds and Heeger, 2009). Nevertheless, the biased competition account provides a useful framework for understanding the relatively limited number of emotion-induced blindness findings to date, with a fuller consideration of the distinctions between related models and their implications for emotion-induced blindness likely to provide ever more insight as research on this topic progresses.

In an insightful review, Keysers and Perrett (2002) noted that – when presented rapidly enough – temporally neighboring stimuli within RSVP streams are likely to give rise to spatiotemporal competition despite their sequentially presented nature. This is because, even though the stimuli do not appear simultaneously with each other, they elicit neural responses that themselves overlap in time. Framed within this context, spatial localization of emotion-induced blindness makes sense. When a target appears soon after an emotional distractor (or soon before; Most and Jungé, 2008), the stimuli compete to be the dominant representation linked to an overlapping point in time and space. Because of the human tendency to spontaneously prioritize emotional stimuli, the distractor frequently dominates and suppresses visual processing of the target.

Notably, if emotion-induced blindness arises due to competition between targets and emotional distractors, then it may be possible to apply manipulations to either strengthen the bias for emotional distractors or boost the competitive edge of targets, thereby modulating – possibly via reentrant mechanisms (e.g., Lamme and Roelfsema, 2000) – the degree of emotion-induced blindness observed. In fact, this appears to be the case. For example, in one experiment participants were informed in some blocks that their target could be a rotated picture of either (a) a building or (b) a landscape with no building, and in the remaining blocks they were informed that their rotated target would always be a picture of a building (Most et al., 2005, Experiment 2). The latter case – labeled the "specific attentional set" condition – enabled participants to establish a more concrete attentional template of what their target would look like, and the results revealed that emotion-induced blindness decreased in this condition, at least among participants who had scored low in a measure associated with trait anxiety. This is consistent with the notion that attentional competition can be biased via goal-relevant information held in working memory (e.g., Desimone and Duncan, 1995; Desimone, 1998). This instruction did not reduce emotion-induced blindness among participants who had scored high in the anxiety-related measure, however, perhaps because for them the bias to prioritize emotional stimuli was more difficult to overcome.

Indeed, in another set of experiments, participants' level of anxiety was directly manipulated, with participants who reported high levels of unease exhibiting greater emotion-induced blindness than those who did not. In this set of experiments, male and female romantic partners were seated at computers a few feet away from each other. The female partner engaged in an emotion-induced blindness task, first while her male partner rated the attractiveness of landscape pictures and then while he rated the attractiveness of women who ostensibly were single and on campus (although, in truth, the pictures had been gathered from the internet and had no known relationship with the university). At the end of the experiment, the female participants were asked to rate their level of unease about the fact that their partner had been rating other women; in two separate experiments, there was a robust correlation between self-rated unease and emotion-induced blindness (Most et al., 2010). Intriguingly, this correlation emerged only when the distractors were emotionally negative, not when they were emotionally positive. Moreover, self-rated unease predicted emotion-induced blindness only during the time that the male partner was rating the attractiveness of other women and not when he was rating the attractiveness of landscapes, helping to rule out individual differences unrelated to the manipulation (e.g., the possibility that participants who experienced unease also happened to be more sensitive to emotionally negative images in general). In short, such evidence is consistent with the notion that emotion-induced blindness is driven by competition between target and emotional distractor representations: whereas the competition can be skewed in favor of targets by providing more descriptive information about their visual appearance (Most et al., 2005, Experiment 2), it appears that anxiety can enhance the bias in favor of emotional distractors (Most et al., 2010).

ATTENTIONAL CAPTURE VS. EMOTIONAL CAPTURE

An important question regarding the nature of emotion-induced blindness is whether the mechanisms underlying it are simply identical to those that would be triggered by any attention-capturing stimulus, or whether emotion-induced blindness instead stems from processes triggered uniquely by the heightened meaningfulness of the emotional distractor. While attention can be captured by emotional stimuli, it can also be captured by stimuli that either share a defining feature with the target (i.e., that match participants' "attentional set;" Folk et al., 1992; Folk and Remington, 1998) or by stimuli that are featurally salient or unique in the environment (e.g., Yantis and Jonides, 1990; Theeuwes, 1991, 1992, 1994; Yantis, 1993). Within RSVP tasks, such non-emotional, attention-grabbing stimuli have been found to induce spontaneous attentional blinks for subsequent targets (Spalek et al., 2006; Folk et al., 2007). Given the ability of non-emotional, attention-capturing stimuli to induce spontaneous perceptual disruptions resembling those caused by emotional stimuli, it may be that emotion-induced blindness simply reflects attentional capture rather than a more elaborate process through which emotion impacts perception.

In a recent series of studies, we capitalized on the spatially localized nature of emotion-induced blindness to examine whether target perception impairments caused by emotional and non-emotional, but attention-grabbing, distractors share common underlying mechanisms (Wang and Most, 2011; Wang and Most, in preparation). If emotion-induced blindness stems simply from the tendency of attention to spontaneously orient to emotional stimuli, then target perception deficits caused by the non-emotional, attention-grabbing distractors should also be spatially localized. To this end, we varied the nature of critical distractors in the dual-stream RSVP paradigm. In a set of two experiments, participants searched for a red letter embedded within one of two simultaneously presented rapid streams of white letters, and the critical distractor (which could appear in either stream) was either a red digit or a green letter. In a third experiment, participants searched for a rotated color landscape photo embedded in one of two simultaneous streams of grayscale landscape photos, and the critical distractor was an upright color landscape photo (thereby matching participants' attentional set for color). In all three cases, the non-emotional, but attention-grabbing, distractors impaired subsequent target perception, but this impairment was not spatially localized.

In a fourth experiment designed to ensure identical task demands across conditions, the target was a rotated color landscape photograph embedded among rapidly presented, upright grayscale landscape photos, and the distractor was either an upright color landscape photo, an emotional color picture, or a neutral non-landscape color photo. Target perception impairments caused by the landscape and neutral color photos were not spatially localized, but the impairments caused by the emotional pictures were specific to the distractors' location (Wang and Most, 2011; Wang and Most, in preparation).

In sum, although non-emotional, attention-grabbing distractors disrupted target perception, the spatially localized nature of the impairment seemed to emerge specifically in the temporal wake of emotional distractors. Our lab is currently in the process of further verifying these results and testing whether they can be accounted for by mechanisms other than spatiotemporal competition. Thus far, the data are consistent with the suggestion that emotion-induced blindness does not stem simply from the tendency of attention to orient to emotional distractors. Neuroimaging studies along these lines would likely be fruitful, as the behavioral findings to date yield intriguing predictions. Framed in terms of neural architecture, competition between targets and emotional distractors may involve relatively anterior visual brain regions that are responsive to complex, meaningful representations, and such regions may function as the neural locus where emotional stimuli gain a competitive edge.

CONCLUSION

Although emotional stimuli can sometimes facilitate perception of subsequent items, they can also disrupt perception, yielding results that seem contradictory at first glance. Research on emotion-induced blindness and its underlying mechanisms can help reconcile such discrepancies. For example, evidence suggests that, consistent with a biased competition account of attention, emotional disruption of perception may occur primarily when emotional distractors and targets appear in such way as to be linked by the visual system to overlapping points in time and space. In the absence of such spatiotemporal competition, emotional stimuli have sometimes been found to enhance perception (e.g., see Bocanergra and Zeelenberg, 2009; Ciesielski et al., 2010). Follow-up neurophysiological studies will greatly improve our understanding of the neural locus of this competition; behavioral evidence so far suggests that it may functionally lie earlier than consolidation into working memory (evidenced, for example, by patterns of spatial localization) but late enough in perceptual processing to involve competition between meaningful representations.

Of course, the impact of emotion on perception is multifaceted. Depending on the intensity of the emotional stimuli, the conditions under which they appear, or the personality of the perceiver, there may be circumstances where emotional stimuli impair (or facilitate) perception of neighboring targets through relatively central, late-stage mechanisms as well (e.g., consolidation into visual working memory). The evidence reviewed in the present discussion highlights potential spatiotemporal competition mechanisms; further characterization of the loci at which emotion can impact visual processing holds promise for more fully understanding the myriad ways that it can shape our conscious perception of the world.

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Differential effects of emotionally versus neutrally cued autobiographical memories on performance of a subsequent cognitive task: effects of task difficulty

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Attention is a limited resource, and in order to improve processing of the attended information, competing processes must be suppressed. Although it is well established that an experimentally induced change in mood state comprises one type of competing process that can impair performance on a subsequent task, no study has investigated whether an emotionally valenced autobiographical memory (AM) also can alter performance on a subsequent task. We therefore examined the effects of AM recall on cognitive performance. Healthy participants ($n = 20$ per experiment) recalled AMs in response to positive, negative, and neutral cue words. Following each AM participants completed a simple perceptual task (Experiment 1) or solved moderately difficult subtraction problems (Experiment 2). In Experiment 1 participants performed less accurately following exposure to positive or negative versus neutral cue words ($ps < 0.001$), and also were less accurate following negative versus positive cue words ($p < 0.001$). In Experiment 2, in contrast, no difference in accuracy or response times reached statistical significance. Performance accuracy even trended toward being *higher* following exposure to negative versus neutral cue words ($p = 0.08$). The results of Experiment 1 suggested that recalling emotionally salient AMs reduces the attention directed toward a simple continuous performance task administered immediately following the AM task, conceivably due to persistent contemplation of the AM. The negative results of Experiment 2 suggested that the effect of AMs on attention was attenuated, however, by increasing the difficulty of the subsequent task. Our results have implications for patients with major depressive disorder (MDD), as performing cognitively demanding tasks may allow them to attenuate the impairing effects of negative rumination on cognition.

Keywords: autobiographical memory, cognition, task difficulty, episodic memory, emotion, rumination

INTRODUCTION

Attention is a limited resource, and in order to improve processing of the attended information, competing processes must be suppressed (Posner and Peterson, 1990; Posner, 1995). When such a competing process is not successfully suppressed, performance is impaired on subsequent attention-demanding tasks. An experimentally induced change in mood state is one such competing process that can affect attention and impair performance on a subsequent cognitive task (Martin and Kerns, 2011; Melcher et al., 2011). Research using mood induction techniques such as those that require participants to read statements intended to be elating or depressing (Velton, 1968) has shown that both positive and negative mood induction can impair performance on a variety of cognitive tasks (reviewed in Mitchell and Phillips, 2007). Impaired cognitive performance following positive mood induction has been demonstrated in tasks involving working memory as assessed using digit span, spatial planning as measured using the Tower of Hanoi task, and attention as evaluated using the Stroop task. Impaired performance following negative mood induction also has been reported on tasks of working memory and spatial planning.

Although it is well established in the literature that the induction of a change in emotional experience can impair performance on a subsequent cognitive task, no study has investigated whether eliciting an emotionally valenced autobiographical memory (AM) can alter performance on a subsequent task. The cognitive response that follows an emotionally evocative AM, whereby an individual contemplates the experience and its associated feelings, meanings, and consequences, forms one type of competing process that can interfere with the disengagement of attention to such an extent that the reallocation of attention toward new tasks is impaired (Nolen-Hoeksema, 1991; Levens et al., 2009). Although AMs can induce mood states such that positive AM retrieval increases post-retrieval positive mood and negative AM retrieval increases post-retrieval negative mood (Denkova et al., 2012), AMs have the additional representations of the physical, cognitive, and social environment as well as the emotional representation of the memory, and can exist independently

of mood states (Tulving, 2002). Possibly related to this process, the episodic memory for such experiences is *enhanced* by the emotional salience or arousal associated with the event (Conway, 2003). Additionally, in young adults, both positively and negatively valenced memories are recalled more often (Schlagman et al., 2006) and more vividly than neutral AMs (Comblain et al., 2005).

One aim of the current study was to investigate whether the recall of emotional and neutral AMs differentially affects performance on a subsequent cognitive task. If simply recalling a memory is enough to impair performance on a subsequent cognitive task, then performance on that task should not differ following neutral and emotional autographical memory recall. If however, the emotional component is necessary for subsequent cognitive performance to be affected then performance accuracy should differ following neutral and emotionally valenced memories.

A second aim was to determine whether altering the difficulty level of a cognitive task performed immediately following AM recall would influence the memory's effect on performance of the subsequent task. The corollary to such an effect was demonstrated by Erber and Tesser (1992) in a study of the relationship between mood alteration, cognitive performance, and task difficulty, which showed that increasing the cognitive demand of a task decreased ratings of both positive and negative emotions experienced during a preceding mood induction. In this study participants underwent either negative or positive mood induction by watching a video clip and then completed either simple or difficult math problems. Solving the difficult problems—but not the simple problems—resulted in a decrease in the self-reported ratings of both positive and negative mood. These results suggest that increasing the cognitive demand of a task can reduce the intensity of an emotional experience.

We aimed to determine whether increasing the cognitive demand of an experimental task might reduce the capacity for emotional AM recall to degrade task performance, presumably by maintaining attention toward the cognitive task. By setting the task difficulty sufficiently high so that a dominant portion of an individual's attentional resources must be committed to maintain task performance, it is conceivable that an insufficient amount of attentional reserve can be allocated to support the contemplation of emotionally valenced AMs (Morrow and Nolen-Hoeskema, 1990). Therefore while we expected AM recall to degrade performance on a simple cognitive task performed in Experiment 1, we predicted that the increased difficulty of a task performed in Experiment 2 would reduce this effect. Our goal in this research was to contribute to the literature on emotion and cognition by determining whether emotionally valenced *AM recall* impairs performance on a subsequent cognitive task, and to assess whether increasing the task difficulty attenuates this effect. These results conceivably hold implications for patients with major depressive disorder who often are unable to interrupt ruminative ideation regarding past experiences to an extent that allows them to focus attention on other tasks (Levens et al., 2009).

The effects of recalling AMs on a simple continuous performance task that involved counting the number of t's in a letter string (Experiment 1), and a more difficult task that involved subtraction problems (Experiment 2) were examined. Participants were shown either a positively, negatively, or neutrally valenced cue word, and then were instructed to retrieve an AM related to the cue word and to focus on the memory. Following each memory retrieval the count-the-t's task or the subtraction task was performed. Our hypothesis was that recalling AMs would affect performance on a subsequent task and that the effect on performance could be altered or abolished by increasing the cognitive demand of the subsequent task.

EXPERIMENT 1

MATERIALS AND METHODS

Participants

Twenty medically and psychiatrically healthy (10 females) individuals participated in the study. Right-handed volunteers (as established using the Edinburgh Handedness Inventory; Oldfield, 1971) between 18 and 55 years of age were recruited through media advertisements in the Washington, D.C. and Tulsa, OK metropolitan areas. Half of the participants were tested at each site, and the same experimenter conducted testing at both locations. Participants underwent a screening evaluation prior to enrollment that included medical and psychiatric history. Psychiatric health was established using the Structured Clinical Interview for DSM-IV Disorders (SCID; First et al., 2002) administered by trained research nurses with at least 0.80 interrater reliability, and confirmed via unstructured interview with a psychiatrist. The Family Interview for Genetic Studies (FIGS; Maxwell, 1992) was used to assess the family history of psychiatric disorders. Participants were also administered the two-subtest version (vocabulary and matrix reasoning) of the Wechsler Abbreviated Scale of Intelligence to determine IQ (Wechsler, 1999).

Participants were excluded if they had: (a) exposure to psychotropic or other medications likely to influence cognitive function within three weeks of testing (excepting nicotine and caffeine), (b) major medical (including endocrine) or neurological disorders, (c) a history of drug or alcohol abuse within one year or a lifetime history of alcohol or drug dependence (excepting nicotine), (d) current pregnancy (as documented by urine testing), (e) a current or past history of a major psychiatric disorder, or (f) a first-degree relative with a psychiatric disorder. After receiving a complete explanation of the study procedures, participants provided written informed consent as approved by the NIH Combined Neuroscience IRB and the Western IRB. The research was conducted in accord with APA standards for ethical treatment of participants. Participants received financial compensation for their participation.

Material, design, and procedure

A computerized version of the AM Test (Williams and Broadbent, 1986) was employed in the current study that had been developed previously for use during functional magnetic resonance imaging (fMRI), such that participant responses were recorded via keypad entry, in order to avoid movement associated with verbal responses (Young et al., 2012). One goal of the current study was to characterize the behavioral performance on tasks that would be used to control for nonspecific cognitive processing components encountered during fMRI studies of AM recall.

Participants were presented with a total of 60 words (20 positive, 20 neutral, 20 negative) selected from Bradley and Lang's (1999) "Affective norms for English words." All words were matched for frequency of use in spoken English. Positive and negative words were matched on arousal ratings, which ranged from 2.8 to 7.6. Neutral words ranged from 2.5 to 5.24 in arousal ratings. Valence ratings of the positive and negative words were equally different from the neutral words. Negative words selected ranged in valence ranged from 1 to 2.75, while positive words ranged from 7 to 8.75, and neutral words from 4.90 to 6.10.

Table 1 presents the average ratings of the selected cue words with respect to valence and arousal, compiled from the word lists assessed and normed by Bradley and Lang (1999). A repeated measures ANOVA with the dependent variable's deviation from the neutral rating of five, arousal rating, and frequency rating for the factor experimenter-assigned valence (Positive, Negative, Neutral). There was no main effect of Frequency [$F_{(2,\ 55)} = 1.39$, $p = 0.26$] but there was a main effect of both arousal [$F_{(2,\ 55)} = 12.4$, $p < 0.001$] and deviation from neutral [$F_{(2,\ 55)} = 144$, $p < 0.001$]. Follow up paired t-tests revealed that the neutral words were less arousing than the positive or negative words [$t_{(38)} = 5.38$, $p < 0.001$], and had a smaller deviation from the mean neutral value of five than the positive or negative words [$ts_{(38)} > 4.31$, $ps < 0.001$]. Positive and negative words did not differ from each other on arousal [$t_{(38)} = 0.47$, $p = 0.64$] or in their deviation from neutral [$t_{(38)} = 1.31$, $p = 0.20$]. Stimuli were presented on a computer using e-prime (Psychology Software Tools, Inc., Sharpsburg, PA).

Participants were presented with a cue word and instructed to press a key on the computer once they recalled a specific memory (defined as a memory for an event that occurred during a period of no longer than one day). They had 60 s to perform this task, and if after 60 s no key had been pressed, the question, "Do you have a memory?" appeared on the computer monitor with the response options Yes/No. There was no time limit to answer this question. After participants indicated whether they had retrieved a memory, a fixation-cross appeared for 5 s during which participants were instructed to attend to the memory, focusing on the details and emotions associated with the remembered event if they had retrieved a memory, or to simply relax and clear their minds during the fixation cross presentation if no memory had been retrieved.

Following the post cue-word fixation cross a distractor task was presented. Participants were presented with a letter string and instructed to count the number of times the letter "t" appeared in the letter string. Letter strings consisted of consonants presented in all capital letters and were matched in length to the cue words. Strings were visible while participants selected their response. The number of "t"s ranged from 0 to 5 and response options to the question "How many t's are there?" were "0–1," "2–3," "4 or more." Participants had unlimited time to select an answer. Following this task, a fixation-cross appeared for 8 s before the next cue word was presented. Participants were instructed to "clear their minds" during this time in preparation for the next cue word. The order of cue word presentation was pseudo-random; we placed restrictions on the order of presentation to prevent sequential presentations of a particular valence category.

Following completion of the task, participants underwent an interview with the experimenter in which they were asked a set of pre-determined questions regarding their experiences during the task. These included whether the participant was actively engaged in the task, if there were any cue words that stood out as particularly difficult to recall a memory for, how difficult they found the distractor task, and whether the distractor task was effective at distracting them from the previously recalled memory.

A subset of the participants ($n = 10$) also completed mood ratings immediately prior to and following completion of the task. This was later added after an interim analysis of the data from the first 10 participants from each experiment suggested performance differences may be influenced by the emotional valence of the cue word. These scales were added to assess whether the mood sate was altered consistently by AM recall and to evaluate potential relationships between such a mood change and behavioral performance. To rate the mood state the Profile of Mood States (POMS; McNair et al., 1971) and a 10-point Visual Analogue Scale (VAS) measuring current levels of happiness, sadness, anxiety, anger, and alertness were administered.

Table 1 | Characteristics of selected words.

Ratings according to Bradley and Lang (1999)	Experimenter assigned valence		
	Negative	Neutral	Positive
Valence	2.25 (0.62)	5.05 (0.36)	7.73 (0.39)
Arousal	5.78 (1.22)*	4.10 (0.67)	5.58 (1.38)*
Frequency	92.3 (97.2)	102 (93.1)	92.7 (123)
Deviation from Neutral (5)	2.75 (0.62)*	0.05 (0.26)	2.73 (0.59)*

Numbers in parentheses indicates one standard deviation of the mean.

**Indicates a significant difference from the neutral cue word condition at $p \leq 0.001$.*

Statistical analysis

Data were analyzed using SPSS 14.0. One sample t-tests were used to determine if mood ratings changed between pre- and post- task assessments. Independent samples t-tests were used to determine if the participants in Experiments 1 and 2 differed on demographic characteristics or mood ratings. A repeated measures analysis of variance (ANOVA) was performed on the factor Valence (positive, negative, neutral) and the between subjects factor Sex (male, female) for accuracy and response times. Paired samples t-tests were conducted to determine whether there were differences in accuracy or response time following the differently valenced cue words (positive, negative, neutral). A p-value of ≤ 0.05, two-tailed, was selected as the statistical criterion for significance. The Bonferonni correction was applied to adjust p-values for the effect of multiple testing. Only trials on which a memory was retrieved were included in the analysis.

RESULTS

Table 2 provides the demographic characteristics and mood ratings of the participants for each study. Mood ratings on the POMS and VAS did not significantly change from pre- to post-task in Experiment 1 (one sample t-test comparing change scores to 0,

Table 2 | Demographic characteristics and mood ratings for participants in each Experiment.

	Experiment 1	Experiment 2
n [% female]	20 [50]	20 [50]
Age	32.2 (12.7)	32.2 (10.1)
WASI	104 (13.1)	105 (8.72)
POMS TOTAL*		
Pre Task	−36.6 (13.7)	−40.1 (11.9)
Post Task	−35.6 (19.4)	−37.3 (12.4)
Change	1.00 (17.1)	2.80 (4.10)
VAS – HAPPY*		
Pre Task	6.55 (1.78)	6.40 (1.76)
Post Task	6.45 (2.59)	6.15 (2.11)
Change	−0.10 (1.66)	−0.25 (0.54)
VAS – SAD*		
Pre Task	0.40 (0.70)	0.45 (1.12)
Post Task	0.30 (0.67)	0.35 (1.11)
Change	−0.10 (0.32)	−0.10 (0.32)
VAS – ANGRY*		
Pre Task	0.60 (0.84)	0.10 (0.21)
Post Task	0.20 (0.42)	0.05 (0.16)
Change	−0.40 (0.97)	−0.05 (0.16)
VAS – ALERT*		
Pre Task	7.25 (1.65)	6.85 (2.29)
Post Task	6.80 (2.30)	5.65 (2.71)
Change	−0.45 (1.61)	−1.20 (2.62)
VAS – ANXIOUS*		
Pre Task	0.90 (0.99)	0.60 (1.15)
Post Task	0.70 (1.49)	0.39 (1.17)
Change	−0.20 (1.14)	−0.25 (0.54)

Number in parentheses indicate one standard deviation of the mean.

**Only one half of the sample contributed to this data (5 Males and 5 Females per experiment). POMS = Profile of Mood States; VAS = Visual Analogue Scale; WASI = Wechsler Abbreviated Scale of Intelligence.*

which indicates no change; $ts_{(9)} < 1.31$ $ps > 0.22$). There was no significant differences between males and females on these measures [$ts_{(8)} < 1.82$ $ps > 0.11$].

Participants recalled a memory for an average of 91.5% (55 out of 60) of the cues presented. This number didn't differ across the differently valenced cues (91% for positive, 93% for negative, 90% for neutral words). Participants selected the correct response during the count the t's distractor task 75.2 ± 12.2% of the time, and took an average of 2.38 ± 0.85 s to respond. **Table 3** shows the task performance following each type of memory cue. We first examined accuracy during the count the t's task. There was no main effect of, or interaction with, sex [$Fs_{(1,\ 18)} < 0.228$, $ps > 0.64$] The main effect of Valence was significant [$F_{(2,\ 38)} = 417$, $p < 0.001$]. Follow up paired *t*-tests revealed participants were more accurate following exposure to neutral cue words than to positive cue words [$t_{(19)} = 34.6$, $p_{\text{corrected}} < 0.001$]. Participants demonstrated the worst performance following exposure to negative cue words; performance was significantly lower than that following exposure to neutral [$t_{(19)} = 22.0$, $p_{\text{corrected}} < 0.001$] and positive [$t_{(19)} = 4.79$, $p_{\text{corrected}} < 0.001$] cue words.

Table 3 | Mean accuracy and response times for the Count the t's task in Experiment 1.

	Accuracy (%)	RTs in seconds
Neutral	91.3 (3.93)#	2.27 (0.84)
Positive	69.8 (3.80)*#	2.39 (0.77)
Negative	64.5 (2.76)*	2.47 (0.96)

Numbers in parentheses indicate one standard deviation of the mean.

** Indicates a significant difference from the neutral cue word condition at $p \leq 0.05$.*

 # Indicates a significant difference from the negative cue word condition at $p \leq 0.05$.

We next examined latency to select a response during the count the t's task. The ANOVA for response times was not significant [$F_{(2,\ 38)} = 1, 22$, $p = 0.31$]. While participants responded most rapidly following exposure to neutral cue words and most slowly following negative cue words, no difference in latency approached significance (negative versus neutral cue words: $t_{(19)} = 1.36$, $p_{\text{corrected}} = 0.57$; negative versus positive cue words: $t_{(19)} = 0.60$, $p_{\text{corrected}} = 0.91$; positive versus neutral cue words: $t_{(19)} = 1.28$, $p_{\text{corrected}} = 0.65$). Power for the Experiment 1 ANOVA = 0.99.

DISCUSSION

Participants performed less accurately on a simple continuous performance task requiring them to count the number of t's in a letter string when this task followed AM retrieval in response to emotionally valenced cues versus neutral cues. Performance accuracy was lowest following attempts to recall a memory related to a negative cue word than following attempts to retrieve a memory prompted by either positive or neutral cue words. Performance accuracy also was reduced to a greater extent following AMs cued by positive words than following those cued by neutral words. This performance degradation demonstrates that both emotionally positive and negative memory recall can impair performance on a simple cognitive task. Mood ratings did not change significantly from pre- to post-task, suggesting that the performance differences identified were unlikely to have been attributed simply to a difference in mood state.

The specificity of our results for AM retrieval is informed by the contrasting results of the study of Siegle et al. (2002), which used a task that involved similar cue words but required participants only to rate the valence of the word. In this task the affective valence of the cue words did not differentially alter behavioral performance on a subsequent task. In their task, cue words, taken from the same word pool as that used herein, were presented and participants were instructed to read the word and indicate its valence; immediately following each trial the participants performed a Sternberg search task in which they indicated whether a target number appeared within a series of number strings. There was no difference in performance on this latter task based on the affective valence of the cue word presented. The researchers suggested that the lack of behavioral effects might have been due to the simple nature of the number detection task. However, the emotionally-valenced cognitive task we used herein significantly influenced performance on a subsequent simple task. The crucial

difference between our task series and that of Siegle et al. (2002) may have been that they required participants only to identify the valence of the words, so that mnemonic processing and emotional state were not explicitly influenced, whereas participants in the present study were instructed to retrieve memories related to the cue word. This indicates that simply reading emotionally valenced words does not induce emotional arousal to an extent that is sufficient to impair performance on a subsequent task, and that generating a memory for the cue words may be a crucial factor for the observed impairments.

Another potential difference between studies may have been that the AM task we used was more likely to alter mood than the affective evaluation task employed by Siegle et al. (2002). This explanation is inconsistent with our results in the subset of participants that completed the mood ratings, suggesting mood did not change over the course of the study. However, we cannot completely rule out an effect of mood alterations as it is possible that transient emotional changes were induced in our participants that only lasted while they were contemplating their AMs and did not persist long enough to affect mood ratings collected post-task.

Furthermore, other evidence exists which suggests that alterations in the mood state alone may not account for the impairment we found on the Count the t's task. The results from Erber and Tesser (1992), who found that solving difficult but not simple math problems resulted in a decrease in self-report ratings of both positive and negative mood (in response to a preceding mood induction) suggests that a more difficult cognitive task can either terminate or distract from an experimentally induced mood state so that the task performance is not degraded. In their study the number of simple or difficult math problems solved did not differ significantly between the positive and negative induction groups. In contrast, we observed that generating AMs to emotional cues impaired performance on a relatively simple attention task, and that this effect was greatest for memories elicited using negatively-valenced cue words. This apparent difference in the results across studies suggests that with respect to performance of a simple cognitive task, the impairment induced by the recall of an emotionally evocative event may exceed that of a mood change induced by other means (as in Erber and Tesser, 1992). Nevertheless, other design differences existed across studies that also may have influenced the results [e.g., the absence of a neutral comparator condition and the time limit imposed on response in the task used by Erber and Tesser (1992)].

The relationship between subjective emotion and task difficulty identified by Erber and Tesser (1992) raises the question of whether the impact of positive and/or negative AM recall on cognitive performance may be reduced by tasks involving a relatively higher level of difficulty. To explore this hypothesis, the distractor task used in Experiment 1 was replaced by a more difficult task involving math problems in the design of Experiment 2.

EXPERIMENT 2

METHODS

Twenty participants (10 females) who did not participate in Experiment 1, but met the same eligibility requirements were recruited for Experiment 2. Participant characteristics can be found in **Table 2**. The experimental task was identical to that in Experiment 1 with the following exception: instead of the Count the t's distractor task, participants were presented with subtraction problems. In all cases a two-digit number was subtracted from a three-digit number and participants were instructed to select the correct answer from three response options. Subtraction problems were of moderate difficulty, and response options were designed so that the correct answer was not readily identifiable. Participants had unlimited time to select their response to the subtraction problem. Similar to Experiment 1, 10 of the participants completed the POMS and VAS immediately prior to and after the task.

RESULTS

The participants in Experiment 2 did not differ significantly from those in Experiment 1 with respect to age, IQ [$ts_{(38)} < 0.24$, $ps > 0.81$], or any mood rating (either pre- or post-task or change $ts_{(18)} < 1.02$, $ps > 0.32$]. We again did not find significant changes in mood ratings on the POMS or the VAS from pre- to post-task (**Table 2**; $ts_{(9)} < 1.46$, $ps > 0.18$], and there was no significant difference between males and females on these measures [$ts_{(8)} < 1.28$, $ps > 0.24$]. An additional analysis of the combined participants groups from Experiments 1 and 2 also did not identify a significant change in mood between the pre- and post-task conditions [$ts_{(19)} < 1.72$, $ps > 0.11$].

Participants were able to recall a memory for an average of 87.3% (53 out of 60) of the cue words presented. This number did not differ significantly across the distinctly valenced cue words (88% for positive, 89% for negative, and 87% for neutral words). **Table 4** shows the results of Experiment 2. Overall, participants selected the correct answer to the subtraction problem 90.4 ± 7.72% of the time and took an average of 9.03 ± 3.48 s to respond. As in Experiment 1, there was no main effect of, or interaction with, sex [$Fs_{(1,\ 18)} < 1.06$, $ps > 0.32$]. The main effect of Valence approached significance for the accuracy ratings [$F_{(2,\ 38)} = 2, 76$, $p = 0.076$]. In contrast to Experiment 1, participants nominally were *most* accurate following exposure to negative cue words. However, the difference in accuracy between the trials that followed a negative cue and those that followed a neutral cue only reached a non-significant trend [$t_{(19)} = 2.08$, $p_{\text{corrected}} = 0.08$]. No significant difference was found for accuracy following the negative versus positive cues [$t_{(19)} = 1.82$, $p_{\text{corrected}} = 0.25$], or following positive versus neutral cues [$t_{(19)} = 1.06$, $p_{\text{corrected}} = 0.91$]. There was no difference in the response time to select an answer to the subtraction problem across distinct cue valences (ANOVA for response times [$F_{(2,\ 38)} = 1.87$, $p = 0.17$]; $ts_{(9)} < 1.84$, $ps_{\text{corrected}} > 0.25$). Power for the ANOVA in Experiment 2 = 0.77.

Finally, we compared performance accuracy between Experiments 1 and 2. While accuracy differed between experiments following positive and negative AM cue words [$ts_{(38)} > 9.31$, $ps < 0.001$], the performance accuracy following neutral cue words did not differ significantly between the continuous performance and subtraction tasks [$t_{(38)} = 1.26$, $p = 0.31$].

DISCUSSION

These results indicate that a subtraction task, which differs from the continuous performance task used in Experiment 1

Table 4 | Mean accuracy and response times for the subtraction problems in Experiment 2.

	Accuracy (%)	RTs in seconds
Neutral	88.0 (5.48)	9.98 (4.04)
Positive	90.0 (9.46)	8.89 (2.95)
Negative	93.3 (7.12)	8.22 (3.31)

Numbers in parentheses indicate one standard deviation of the mean.

with respect to being more difficult and attentionally demanding, is effective at reducing or terminating impaired cognitive performance following AM recall. In contrast to the results of Experiment 1, the highest accuracy on the subtraction task was seen after participants recalled an AM to a negative cue word, although this difference only trended toward significance. Taken together these results suggest that the more difficult task reversed the detrimental effects on performance following memory retrieval for these cue words that had been observed during performance of the simpler continuous performance task. We also did not find any significant change in mood ratings on the POMS or VAS pre- to post-task.

GENERAL DISCUSSION

The results of Experiment 2 support the hypothesis that more difficult tasks reduce the performance deficit induced by AM recall, as demonstrated by no difference in performance following AM recall in response to the differently valenced cue words on a moderately difficult subtraction task. These results contrast with those obtained in Experiment 1 where performance on a very simple task was impaired following AM retrieval cued by the same emotionally valenced versus neutral cue words.

These observations are consistent with evidence that as the attentional demand required to perform a cognitive task increases, neurophysiological activity in the limbic and medial prefrontal cortical regions that support emotional processing and AM is suppressed (Drevets and Raichle, 1998; Simpson et al., 2000; Svoboda et al., 2006). This neural mechanism of suppressing task-irrelevant background processes that compete for the attentional resources needed to optimally perform a new, more attentionally demanding task may facilitate the disengagement from AM processing (Posner, 1995). The trend toward performance accuracy being higher following negative AM cue words in Experiment 2 suggests the hypothesis that the greater the attentional demand posed by the subtraction distractor task enables healthy individuals to attenuate the negative emotions they experienced as a consequence of recalling negative AMs.

Our results conceivably may reflect an effect of rumination, a cognitive response, often following an emotionally evocative experience, where an individual repeatedly thinks about a past experience, focusing on the feelings, meanings, and consequences of that experience (Nolen-Hoeksema, 1991). Rumination has been assessed using the Ruminative Responses Scale (Nolen-Hoeksema and Morrow, 1991), which asks participants to indicate how often they engage in ruminative thoughts or behaviors when they feel sad. As the standard assessment of rumination is a self-report scale that focuses on negative moods, previous research has emphasized the effects of negatively valenced thoughts or memories without investigating the potential effects of positive ruminations on cognitive tasks. Our results suggest the hypothesis that both negative and positive rumination can affect performance in simple cognitive tasks, but that presenting a more difficult task can attenuate the competitive effects of both types of rumination (Morrow and Nolen-Hoeskema, 1990). Our experimental design did not afford a test of these hypotheses, however, as no state measure of both positive and negative rumination exists which would have allowed us to more definitively characterize this process. Instead we inferred the presence of rumination based on the self-reported statements of participants during debriefing interviews. All but three participants reported that they often continued to think about their memories during the "Count the t's" distractor task, supporting the conclusion that rumination on the previous memory occurred and that disengaging from the memory in order to complete the Count the t's task was sometimes difficult. In contrast when participants in Experiment 2 were asked whether they were able to stop thinking about the previously recalled memory in order to complete the subtraction problems, all but one participant indicated that they were able to do so. We did not, however, inquire about how or if rumination differed between AM recall following neutral versus emotional cue words. Understanding how these ruminations are similar or different could further help to elucidate how ruminative processes are able to disrupt cognitive performance.

Although the mood ratings did not change significantly during task performance, we cannot refute the possibility that performance of the AM task induced a transient emotional state that contributed to the observed results. It is inevitable that recalling emotional memories elicits the originally experienced emotions to some degree (Talarico et al., 2004), and this can, in turn, interfere with subsequent task performance.

Another potential explanation for impaired performance on simple but not difficult tasks following emotional AM recall is that after emotional memory recall participants engage in regulatory strategies to modulate the change in emotional experience elicited by the memories, and that this engagement requires the allocation of substantial cognitive resources. In support of this hypothesis, previous studies have shown that as participants more effectively regulate their emotions, working memory performance decreases (Scheibe and Blanchard-Fields, 2009), and that as participants suppress "forbidden thoughts" they are quicker to give up solving anagrams (Muraven et al., 1998). This explanation of increased emotional regulation is potentially compatible with our hypothesized role of rumination, as increased rumination on emotional memories would likely activate emotion regulation strategies in healthy participants.

Our findings have implications for understanding the nature of the altered cognitive processing associated with MDD, as the tendency toward rumination on negative thoughts and feelings has been found to predict both the onset of MDD and the development of more severe and sustained depressive symptoms (Nolen-Hoeksema, 1991; Just and Alloy, 1997). Future studies should examine whether engaging these patients in challenging cognitive tasks can provide relief from negative ruminations.

Siegle et al. (2007) proposed such an approach via Cognitive Control Training (CCT), and found that compared to standard treatment with medication and psychotherapy, six 35-min sessions performing selective and serial attentional tasks over the course of two weeks significantly improved depressive symptoms and reduced self-reported ruminations (Siegle et al., 2007).

One limitation of the current study was that we did not have a baseline measure of performance on the count the t's or subtraction task to give us an absolute effect; our results were obtained by comparing performance following presentation of emotional AM cue words compared to performance obtained following neutral cues. Additionally, although our cue words were matched in terms of frequency, other potentially relevant characteristics such as imageability (the ease with which a word arouses a mental image), were not controlled for, and could have potentially influenced the results. The phenomenological properties of the retrieved memories (arousal, valence, etc.) also were not examined and therefore whether the properties of the recalled memories (beyond cue valence) affected performance could not be determined. Because these properties were not measured we cannot refute the possibility that the subtraction task used in Experiment 2 itself impaired AM recall. Because AM retrieval depends on executive resources, and insufficient cognitive resources may lead to overgeneral AM retrieval (Dalgleish et al., 2007) the use of subtraction problems may have led to less emotional personal recollections in which the participants were not engaged enough in their memory recall enough to disrupt the performance on the subtraction task.

Furthermore, although our claims that the two tasks differed in perceived difficulty and cognitive demand have face validity and were supported by debriefing interviews in which nearly all participants perceived the subtraction task difficult and the Count the t's task as easy to perform, we did not systematically measure participants' perceived difficulty of the task. The two tasks clearly differed in other domains as well (most noticeably linguistic versus mathematical). Future studies should match cue words and subsequent tasks on as many dimensions as possible in order to minimize differences in task sets. Finally, although a sample size of 20 per experiment is lower than that typically involved in behavioral studies, the power for the ANOVAs was 0.99 and 0.77, for Experiments 1 and 2 respectively. Our observed power either exceeds or approaches the 0.80 power level that conventionally has been considered by statistical experts to provide sufficient power during experimental design. Therefore, it is unlikely that adding participants would further influence the direction or significance of results. Our relatively low sample size did, however, preclude us from investigating whether different participant characteristics might have mediated some of the observed results. Previous studies have found extroversion and neuroticism to mediate the valence of AMs recalled and subsequent effects on mood (Denkova et al., 2012), and emotional reactivity and family history of depression to mediate cognitive biases in recall of emotionally valenced items (Flynn and Rudolph, 2012). Future investigation into the interaction between personality factors and the effect of emotional AM recall on cognition may help to further elucidate the results found in the current study.

In summary, our results suggest that both positive and negative AM recall can affect performance on simple tasks (potentially due to rumination or employment of emotion regulation strategies on these memories), but that as the task difficulty increases, healthy humans can interrupt these processes and preserve performance accuracy. Our results may hold implications for cognitive behavioral therapeutic strategies involving patients with MDD, as increasing task difficulty may allow them to attenuate the potentially impairing effects of negative rumination on neuropsychological performance of tasks within a variety of cognitive domains.

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The stressed eyewitness: the interaction of thematic arousal and post-event stress in memory for central and peripheral event information

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Both arousal during the encoding of stimuli and subsequent stress can affect memory, often by increasing memory for important or central information. We explored whether event-based (thematic) arousal and post-event stress interact to selectively enhance eyewitnesses' memory for the central aspects of an observed incident. Specifically, we argue that memory for stimuli should be enhanced when (1) the stimuli are encoded under arousal (vs. non-arousal), and (2) stress is experienced soon after the encoding episode. We designed an experiment that extended previous research by manipulating arousal without changing the stimulus material, distinguishing between central and peripheral event information, and using a dynamic, life-like event instead of static pictures. After watching a video depicting a burglary under high or low thematic arousal, psychosocial stress was induced or not induced by the Trier Social Stress Test (TSST). Salivary cortisol was measured at standard intervals. Consistent with our prediction, we found a significant post-event stress × thematic arousal × centrality interaction, indicating that the recognition advantage for central event items over peripheral event items was most pronounced under both high thematic arousal and post-event stress. Because stress was induced after encoding this interaction cannot be explained by possible differences at encoding, such as narrowed attention. The centrality effect of post-event stress under high thematic arousal was statistically mediated by the cortisol increase, which suggests a key role of the stress hormone. We discuss implications of our findings for psychological and neuroscientific theories of emotional memory formation.

Keywords: eyewitness memory, stress, arousal, salivary cortisol, social influence

INTRODUCTION

Imagine the following scene: from your window you see someone moving around in the neighbor's house in a suspicious manner. Soon, you feel confident that you are witnessing a burglary in the middle of the day. You know that your neighbors have just returned early from their vacation and are taking an afternoon nap upstairs. Envisioning a possibly harmful encounter between the burglar and your neighbors you start feeling agitated. After watching in petrified anticipation for a little while, you call the police. The burglar has disappeared when the police arrive. A police officer immediately starts a brief interrogation, asking you who you are and what you were doing. You cannot help feeling being treated like a suspect. You feel stressed and your heart is beating. While you wait for more questions, you meet another witness who retells the incident in some detail. Finally, after you have calmed down, you try to remember the incident, including central aspects (e.g., items carried by the burglar) but also peripheral details (e.g., items that remained untouched).

This episode illustrates the questions we address in our research: How is one's memory for an event, specifically memory for central and peripheral information, affected by arousal during the encoding of the event (in our example, the witnessing of the burglary), post-event stress (the first, stressful interrogation), and additional post-event information (the other witness's retelling)? Laboratory research over the last decades has started to characterize the effects of emotional arousal and stress on memory. Arousing material is typically better remembered than neutral material, an effect mediated by the sympathetic nervous system (SNS) and its release of the catecholamines adrenalin and noradrenalin (see Cahill and McGaugh, 1998). The emotional memory enhancement appears to be especially pronounced for central aspects of the arousing item, whereas emotional arousal often impairs memory for peripheral details. This has been interpreted as a result of attentional narrowing (Easterbrook, 1959; Christianson, 1992). Post-encoding effects mediated via a modulation of to be consolidated information might also contribute to this effect.

Arousal is associated with an activation of the SNS, a more serious threat to the physical or social self in contrast leads to stress, accompanied by activation of the hypothalamus pituitary

adrenal (HPA) axis (Mason, 1968; Dickerson and Kemeny, 2004). The hormones of the HPA axis, namely Corticotrophin Releasing Hormone (CRH), Adrenocorticotrophin (ACTH), and cortisol are known to influence learning and memory. In real life, as illustrated by our example, arousal and stress may occur in short succession. Thus, an important research question is how stress interacts with arousal to influence memory.

The influence of post-learning stress on memory has been investigated by Cahill et al. (2003). The authors employed pictures that evoked different levels of arousal. It was found that post-learning stress selectively enhanced memory for the arousing slides. Hence, in this study memory depended on the interaction between post-learning stress and the level of arousal during encoding. Similar findings have been reported by others (e.g., Smeets et al., 2008). This observation is also consistent with findings from animal studies indicating that noradrenergic arousal is a prerequisite for the modulatory effects of cortisol or other glucocorticoids on memory (for a review, see Roozendaal et al., 2006).

Although some studies did not find an interaction between arousal and the effects of stress or glucocorticoid manipulations on memory (e.g., Preuss and Wolf, 2009), the above findings suggest a possible interaction between arousal and post-encoding stress: memory for stimuli is enhanced when (1) the stimuli are encoded under arousal (vs. non-arousal), and (2) stress is experienced soon after the encoding episode.

However, extant research faces three main limitations. First, existing manipulations of emotion or arousal have been particularly afflicted by the problem of potential confounds to the extent that they have relied on different stimulus material (negative or arousing vs. neutral). Stimulus-based variations in arousal lead to unavoidable confounds between arousing vs. neutral pictures. Effects for emotionally arousing visual stimuli, such as the sight of a wound or a weapon, may be due to attentional capturing, visual salience, or novelty rather than arousal *per se* (see Mather and Sutherland, 2011). An alternative approach is the use of thematic arousal, for instance, arousal induced by an accompanying story or by the instructions given to the subjects (Laney et al., 2004; Payne et al., 2007; also see Heuer and Reisberg, 1990; Cahill and McGaugh, 1995). A manipulation of thematic arousal induces different experiences of the same stimulus material, thus circumventing the problems of stimulus-based manipulations. Studies that have manipulated thematic arousal, however, have not examined the interplay between thematic arousal and post-learning stress.

Second, most research on emotional memory has used static pictures with different emotional contents as stimulus material, for instance, from the International Affective Picture System (IAPS) data base. While this approach has several advantages, real-life events are dynamic rather than static. Hence, the focus on static pictures constrains generality and external validity of the research. Beckner and coworkers (2006) have used a movie in order to assess the impact of post-learning stress on memory. They found, in line with Cahill et al. (2003), enhancing effects of post-event stress on memory. However, those authors did not vary the level of arousal induced by the movie and reported that the movie about a dinner party was not intended to be arousing (Beckner et al., 2006). In the domain of military survival training, Morgan and colleagues (2004) tested the accuracy of eyewitness identification of military personnel who had interrogated the participants under either extremely high or low stress. Overall, identification accuracy was better under low stress. However, the study differed in several respects from the present approach, mainly because the source of stress and the to-be-remembered stimulus were confounded, there was no separate induction of arousal, and stress occurred already during the encoding phase.

Third, previous studies of post-event stress effects on memory have not distinguished between central and peripheral details (Cahill et al., 2003; Rimmele et al., 2003). However, classical research has found that memory for peripheral and central information can be differentially affected by arousal (Christianson, 1992). Studies on patients with amygdala damage suggest that the effect of emotional arousal on memory for central (vs. peripheral) material is subserved by the amygdala (Adolphs et al., 2005). It has been found that glucocorticoids released during stress influence memory consolidation via a modulatory effect on the amygdala (Cahill and McGaugh, 1998). Hence, effects of post-event stress might differ for central versus peripheral details of an arousing event.

The goal of the present study was to investigate how post-encoding stress will affect memory depending on the thematic arousal of the initial learning episode. In so doing, we wanted to redress the shortcomings described above. Specifically, we examined whether this effect differs for peripheral and central details of the witnessed event. Drawing on the research discussed above we predicted that under high thematic arousal post-learning stress would enhance memory for the central elements of an event (e.g., a cashbox grabbed by the burglar) at the expense of peripheral items (e.g., a video tape remaining untouched on a shelf). We also examined whether the increase in cortisol would statistically mediate such a potential stress effect. To our knowledge, such an analysis has not been reported.

Furthermore, we explored possible effects on memory for false post-event information. Published research on the role of stress in experimentally induced false memories is scarce. The few extant studies (Payne et al., 2002; Smeets et al., 2006, 2008) have focused on false memories for word stimuli resulting from semantic associations in the Deese-Roediger-McDermott paradigm (Roediger and McDermott, 1995), yielding mixed evidence. In the present study, we examined whether thematic arousal during observation and post-event stress would moderate the extent to which participants would falsely remember post-event misinformation. Participants read a post-event narrative about the witnessed event that contained several false details. These false details were minor additions to the actual scenes (e.g., a tennis racket on a basement shelf in the background) and thus were more similar to peripheral (vs. central) information. Impaired memory for peripheral information resulting from stress or arousal (e.g., Christianson, 1992) could thus facilitate the implantation of false details, leading to a greater effect of post-event misinformation on eyewitness memory. On the other hand, it has been found that negative mood reduces the effect of post-event misinformation, presumably due to enhanced,

and more "suspicious," bottom-up scrutiny of the environment (Forgas et al., 2005).

Because the event description predominantly reported correct information, it also allowed participants to rehearse, or re-encode, the described parts of the witnessed event. Hence, we also examined the effect of this rehearsal on memory for correct event details.

MATERIALS AND METHODS

OVERVIEW

The experiment consisted of four main stages (see **Figure 1**), (1) encoding of a target event (with or without thematic emotional arousal), (2) manipulation of psychosocial stress, (3) rehearsal of the event information based on an event description, which contained many correct event details and some additional false, non-event details, and (4) a recognition test for the target event.

In the first stage, participants witnessed a video-filmed event depicting a burglary. Arousal during the viewing of the event (low vs. high arousal) and subsequent stress (post-event stress vs. no-post-event stress control) were varied independently. In the high thematic arousal condition, participants received instructions that were designed to produce heightened emotional arousal during the encoding of the target event. Specifically, participants were induced to anticipate seeing a version of the video showing a distressing, possibly violent incident. In the low thematic arousal condition, participants learned that the event they would see was unlikely to be experienced as distressing. This manipulation induces different emotional arousal concerning the *same* content material. Thus, it avoids potential confounds of manipulations inducing different levels of arousal by presenting participants with to-be-remembered material that is either emotionally arousing (for instance, shocking pictures) or neutral (see Cahill and McGaugh, 1995; Laney et al., 2004).

In the second stage, after event encoding, a stress manipulation was employed. For approximately half of the participants from both thematic arousal groups we administered the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) to induce psychosocial stress (*post-event stress* condition). The remaining participants experienced a non-stressful situation (*no-stress control* condition). In the third stage, after the stress manipulation, participants were asked to read a narrative description of the witnessed incident. No further reason was given for including this description. For the most part, the description correctly described the original event but also contained some non-event items (i.e., items not shown in the original event).

After a short interval, we administered a yes/no recognition test. The test contained event items (i.e., items that did appear in the video-filmed event) and non-event items (i.e., items that did not appear in the video-filmed event). Based on previous research employing the same material (Echterhoff et al., 2007), we distinguished between peripheral and central event items. Among the non-event items, half were items that were falsely mentioned in the event description (false additional items), the other half were items that appeared in neither the video-filmed event nor the narrative (new items). Cortisol measures were taken at the beginning of the test session (baseline), and then approximately 1, 10, and 20 min after the TSST.

PARTICIPANTS

Participants were 88 male students at Bielefeld University (mean age 24.3 years, ranging from 19 to 37). They were informed

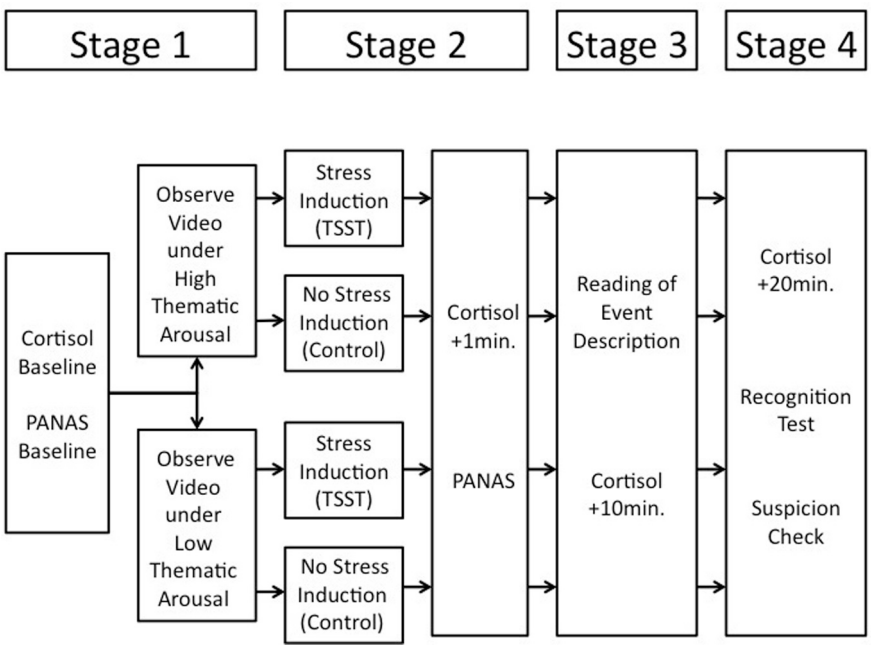

FIGURE 1 | Overview of the procedure; the duration of the video was ~12 min, the duration of the TSST was ~15 min.

that the study was about the perception and communication of events. None of the participants reported suffering from acute or chronic diseases or taking medication. The data were collected in two main waves, with the first wave ($n = 43$) taking place one semester before the second wave ($n = 45$). Each participant received either a compensation of 10 € or curricular credit. The experiment, including the treatment of human subjects, was approved by the ethics committee of the German Psychological Association (Deutsche Gesellschaft für Psychologie). The guidelines of the Declaration of Helsinki and standards of the American Psychological Association (APA) were followed. Informed consent was obtained from all participants.

DESIGN

The basic design of the experiment was 2 (low vs. high thematic arousal) × 2 (post-event stress vs. no post-event stress), varied between participants. For analyses of event items, we also included centrality (central vs. peripheral) and rehearsal (rehearsed vs. non-rehearsed) as two within-participants factors, yielding a 2 × 2 × 2 × 2 mixed design. For analyses of non-event items, addition in the event description (false additional vs. new) was employed as a within-participants factor, yielding a 2 × 2 × 2 mixed design. The primary dependent variable was the proportion of "yes" responses in the recognition test, analyzed separately for the different levels of the within-participants factors (i.e., the different item types).

MATERIALS

As the target event we used a video (lasting ∼12 min) that had been employed successfully in previous studies of eyewitness memory (Echterhoff et al., 2005, Experiment 4; Echterhoff et al., 2007). The video depicted a burglar searching a house for valuables after a resident (a young woman) has left. Following Echterhoff et al. (2007), we distinguished between central or peripheral event items. *Central event items* were clearly visible for an extended period of time, often at the center of the video image, and were manipulated by a protagonist (e.g., a cashbox grabbed by the burglar). In contrast, *peripheral event items* were presented for a shorter time, mostly at the periphery of the video image, and were not visibly manipulated by a protagonist (e.g., a video tape on a shelf in the living room). In the present study we employed 16 central and 16 peripheral event items. In previous pretests of the stimulus material, which did not include post-event information (Echterhoff et al., 2007), correct recognition for the central event items was high, without reaching a ceiling (hit rates between 0.80 and 0.90), whereas correct recognition for the peripheral event items was significantly lower, without reaching a floor (hit rates between 0.25 and 0.50). Thus, central event items were better remembered than were peripheral event items.

In the *high thematic arousal* condition participants received the following instruction just before watching the target video: "You will be watching one of two different versions of the video. In one of the two versions there is a surprising turn, involving a physical confrontation between the protagonists. In the other version there will be no such a confrontation. Although the version is selected by chance, it is more likely that you will see the version depicting the confrontation than the other version." The expression "the protagonists" obviously referred to the young woman and the burglar. In the *low thematic arousal* condition, participants were just told that they would be watching one of two different versions of the video, and that these versions would differ in some visual features. A possible confrontation was not mentioned. In truth, there was no violent version of the video—the same (non-violent) version of the video was presented to all participants. We designed this type of manipulation to ensure that differences in participants' emotional states were not due to differences in the observed stimulus material but to differences in their expectation of possibly seeing arousing material. Thus, we could avoid confounds which are faced by arousal manipulations based on different content of the stimulus material, for instance shocking, unfamiliar, or perceptually salient vs. non-shocking, familiar, or non-salient (see Laney et al., 2004).

The effectiveness of this arousal manipulation was established in a pretest with 50 male participants (students at Bielefeld University, mean age 26.7 years) who received a compensation of 3 €. The pretest participants were randomly assigned to the high-arousal instruction condition ($n = 25$) or the low-arousal instruction condition ($n = 25$). Participants' arousal was assessed at two times: (1) midway through the video (after approximately half of the running time), and (2) immediately after the end of the video. At each time, participants completed four rating items on eight-point scales, each anchored with 1 (*not at all*) and 8 (*very much*): *How nervous do you feel? How tense do you feel? How calm are you right now? How relaxed are you?* (The latter two items were reverse coded.) To permit participants to provide their ratings at time 1 (i.e., in the middle of the video), the video was briefly interrupted. We did not probe for arousal by this procedure in the main experiment because the interruption could interfere with relevant memory processes such as the encoding of the target event. The reliability of the eight ratings (i.e., the four items administered during and after the video) was high (Cronbach's $\alpha = 0.92$). The eight single scores were averaged, yielding one mean score of arousal for each participant. Arousal was significantly higher for participants in the high-arousal instruction ($M = 3.24$, SD = 1.42) than for participants in the low-arousal instruction condition ($M = 2.65$, SD = 1.24), $t_{(48)} = 2.03$, $p = 0.048$, $\eta^2 = 0.08$ (two-tailed test).

As in previous studies (Echterhoff et al., 2005, Experiment 4; Echterhoff et al., 2007) we employed two different versions of the event description (each approximately 1000 words). Version A contained one half of the 32 event items, while version B contained the other half of the event items. Event items that were included in an event description were rehearsed (*rehearsed event items*), whereas event items that were not included in the event description were not rehearsed (*non-rehearsed event items*). The sets of 16 rehearsed and 16 non-rehearsed event items each consisted of eight central and eight peripheral items. Thus, the event description contained an equal number of central event items (e.g., the cashbox grabbed by the burglar) and peripheral event items (e.g., the video tape on a living-room shelf).

The event description also contained *non-event items*, i.e., items that were not shown in the target event (e.g., a tennis racket on a basement shelf). We used the same pool of 32

non-event items used in previous studies (Echterhoff et al., 2005, Experiment 4; Echterhoff et al., 2007). Version A of the event description contained one half (i.e., 16) of the non-event items, while version B contained the other half (i.e., 16) of the non-event items. Non-event items included in a description are called *false additional items*, whereas non-event items not included in a description are called *new items*. (New items were thus not presented in either the target event or the event description.) In previous pretests of the stimulus material, which did no employ post-event information (Echterhoff et al., 2007), false alarm rates for non-event items were significantly above 0 (between 0.15 and 0.25).

In the yes/no recognition test, participants decided whether items had appeared in the original event. The test consisted of 32 event items (eight non-rehearsed peripheral event items, eight rehearsed peripheral event items, eight non-rehearsed central event items, eight rehearsed central event items) and 32 non-event items (16 false additional items and 16 new items).

SALIVARY COLLECTION AND ANALYSIS

Saliva was collected using Salivette collection devices (Sarstedt, Nuembrecht, Germany). Samples were kept in a freezer until completion of the study. Salivary cortisol was measured out of these samples using a commercially available Immuno-Assay (IBL, Hamburg). Inter- and intra-variations of this assay are below 10%. The analyses were conducted in a biochemical laboratory under direction of Professor Clemens Kirschbaum at the Technical University of Dresden, Germany.

PROCEDURE

Stage 1

Upon entering the lab, participants read and signed an informed consent form that described the procedure of the study. To obtain a baseline measure of cortisol (referred to as cortisol baseline) a first saliva sample was taken from participants. Participants also completed the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). The PANAS consists of 20 adjectives describing negative (e.g., *angry*, *irritated*) and positive affective states (e.g., *attentive*, *excited*). The participants were asked to indicate how much the words matched their current mood (on rating scales from 0 to 5, with higher numbers indicating stronger agreement). Positive and negative affect measures can be independent, and related studies have typically found effects of stress on negative affect (see Schoofs et al., 2008); hence we focus on the analysis of negative affect. The mean score of the negative affect items from the PANAS scale from this initial administration served as a baseline measure.

Participants then watched the video depicting the target event on a TV monitor with a screen diagonal of 60 cm (24″) at a distance of approximately 1.50 m (5 ft.) either under low or high arousal. The low thematic arousal condition was employed in the first wave of the study, while the high thematic arousal condition was employed in the second wave of the study.

Stage 2

Next, post-event stress was manipulated. In the *post-event stress* condition ($n = 44$), we induced psychosocial stress with the TSST (Kirschbaum et al., 1993). The TSST consists of a short preparation period (2 min) followed by a 5-min self-produced speech (i.e., a speech in a fictitious job interview focusing on personal strengths and weaknesses) in front of a committee (consisting of a female and male confederate wearing white coats) and a 5-min mental arithmetic exercise (counting backwards from 2043 in steps of 17). During these procedures, participants are videotaped and can see themselves on a monitor in the back of the room. The TSST has been shown to reliably induce a significant activation of the HPA axis and the SNS (Kirschbaum et al., 1993). In the *no-post-event-stress* condition ($n = 44$), participants were asked to give a 5-min speech about a movie or a book of their choice and to perform mental arithmetic in an empty room for another 5 min (see Het et al., 2009). This control condition is relatively similar in physical and mental workload but lacks the stress-inducing components of the TSST, which are social evaluative threat and uncontrollability (Mason, 1968). In a recent meta-analysis, the TSST was found to provoke the most robust physiological stress responses (i.e., cortisol stress responses) relative to various other laboratory stress tasks (Dickerson and Kemeny, 2004).

Approximately 1 min after the TSST, a second saliva sample (cortisol +1 min) was taken. Participants completed again the PANAS (post-stress induction measure). As for the baseline measure, the mean negative affect score served as a subjective measure of the impact of post-event stress on participants' mood.

Stage 3

All following materials were presented on a Laptop with a 15-inch monitor using the experimental software MediaLab (Jarvis, 2005). Participants read the *event description*, which contained one of the two sets of 16 event items (eight central, eight peripheral) and one of the two sets of 16 non-event items, depending on the version of the description (A or B). We counterbalanced rehearsed and non-rehearsed event items as well as false additional versus new items by providing one half of the participants with version A of the event description and the other half of the participants with version B. An equal distribution of the two versions was ensured within the between-participants conditions.

After the presentation of the event description, ∼10 min after the post-event stress manipulation, a third saliva sample (cortisol +10 min) was taken. We then administered two rating scales, which served as a filler task (lasting ∼10 min).

Stage 4

Approximately 20 min after the post-event stress manipulation a fourth saliva sample (cortisol +20 min) was collected. Immediately afterwards, the yes/no recognition test was administered (for the items, see "*Materials*"). The items were presented in a random order and remained on the computer screen until participants responded by pressing a *yes* or *no* button. In a funneled post-experimental suspicion check, participants were first asked to guess the purpose of the study and then probed more specifically about their beliefs concerning the role of the TSST and the post-event description. The data of four participants were excluded from the analyses because the participants exhibited high insight into the rationale of the study, resulting in the

sample described above (see "*Participants*"). In the debriefing session great care was taken to reduce the likelihood of negative consequences for participants in the post-event stress condition (see, e.g., Het et al., 2009).

All statistical tests were two-tailed, except when noted otherwise. Regarding effect size, we report η^2 (eta squared) and η_p^2 (partial eta squared).

RESULTS

INDUCTION OF POST-EVENT STRESS

As can be seen in **Figure 2**, the TSST successfully induced post-event stress at all three measurement times (+1, +10, and +20 min). We conducted a mixed 2 (post-event stress vs. no post-event stress) × 2 (low vs. high thematic arousal) × 4 (baseline vs. +1 vs. +10 vs. +20) ANOVA, with the first two variables varying between subjects and time of measurement varying within subjects. Cortisol concentrations were overall higher in the post-event-stress group (vs. the no-post-event-stress group), as indicated by a main effect of post-event stress, $F_{(1,\ 84)} = 30.67$, $p < 0.001$, $\eta_p^2 = 0.27$. Importantly, a significant main effect of measurement time [$F_{(3,\ 252)} = 42.76$, $p < 0.001$, $\eta_p^2 = 0.34$] was qualified by a significant two-way interaction between post-event stress and measurement time [$F_{(3,\ 258)} = 40.83$, $p < 0.001$, $\eta_p^2 = 0.33$], reflecting the larger increase in cortisol in the post-event-stress (vs. no-post-event-stress) condition. No other significant effects emerged, all Fs < 1, *ns*. We also tested effects of post-event stress at each measurement time with pairwise comparisons. Whereas no effect of post-event stress was found for cortisol baseline ($F < 1$, *ns*), cortisol was significantly higher for the post-event-stress group than the no-post-event-stress group for other measurement times, $F_{(1,\ 84)} = 14.28$, 54.78, and 53.94; all ps < 0.001, $\eta_p^2 = 0.15$, 0.40, and 0.39; for cortisol +1, +10, and +20, respectively.

Within the post-event stress condition alone, all three cortisol measures after the TSST were significantly higher than the baseline measure, all ts$_{(43)} > 7.85$, all ps < 0.001 (calculated by pairwise comparisons). In this condition, the peak cortisol level was reached at +10 min; this level was the only one differing significantly from all three other levels, all ts$_{(43)} > 4.25$, all ps < 0.001. We calculated cortisol increase for use in subsequent analyses by subtracting the baseline scores from the mean of the three post-treatment cortisol measures. Existing research suggests that the thematic arousal manipulation would not induce changes in cortisol concentrations (Dickerson and Kemeny, 2004). Indeed, we found no evidence for arousal-induced cortisol changes, Fs < 1.

In the stress condition participants' reported affect became more negative (see **Figure 3**), as indicated by a significant interaction between post-event stress and measurement time [$F_{(1,\ 84)} = 53.52$, $p < 0.001$, $\eta_p^2 = 0.39$] from a mixed 2 (post-event stress vs. no post-event stress) × 2 (low vs. high thematic arousal) × 2 (baseline vs. post-stress measure) ANOVA. This interaction qualified significant main effects of post-event stress [$F_{(1,\ 84)} = 27.58$, $p < 0.001$, $\eta_p^2 = 0.25$] and measurement time stress

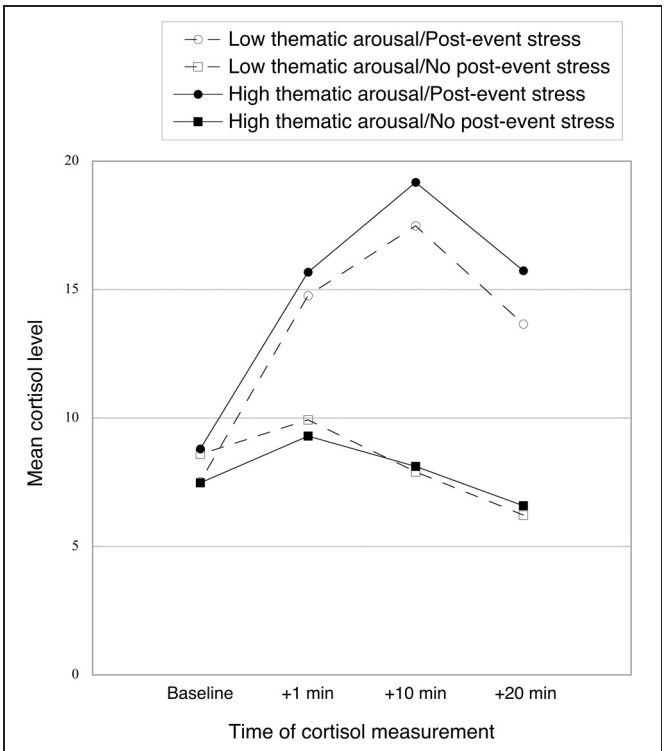

FIGURE 2 | Mean cortisol level (baseline and at 1, 10, and 20 min after the post-event stress manipulation) as a function of thematic arousal and post-event stress.

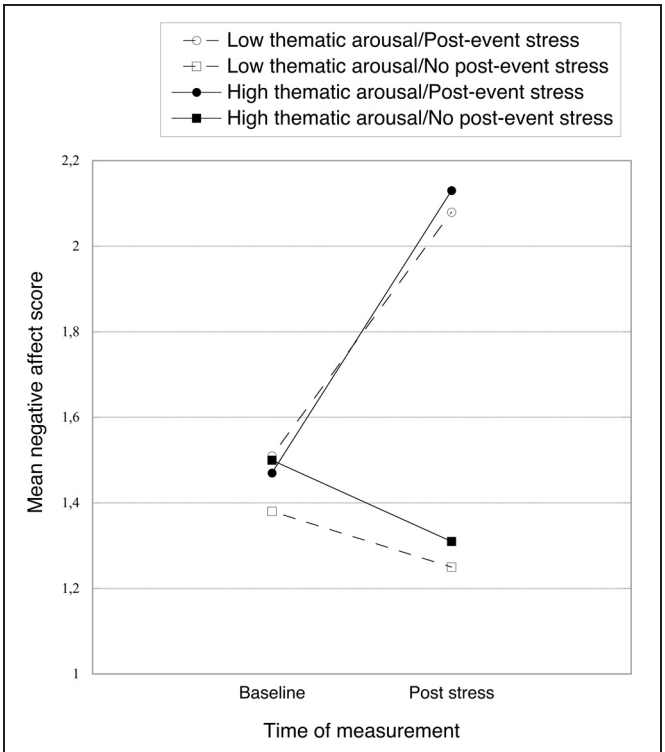

FIGURE 3 | Mean negative affect scores from PANAS (baseline and post-stress) as a function of thematic arousal and post-event stress. Higher values indicate more negative affect.

[$F_{(1, 84)} = 19.05$, $p < 0.001$, $\eta_p^2 = 0.19$]. Whereas negative affect did not differ between the stress group ($M = 1.49$, SD = 0.42) and the no-stress control group at baseline ($M = 1.44$, SD = 0.36) [$F < 1$, *ns*], it was significantly more negative after the stress induction ($M = 2.10$, SD = 0.67, vs. $M = 1.28$, SD = 0.27; for the stress and control group, respectively), $F_{(1, 84)} = 55.10$, $p < 0.001$, $\eta_p^2 = 0.40$. No other significant effects emerged, all Fs < 1, *ns*.

MEMORY FOR EVENT ITEMS

Table 1 (left panel) contains the mean recognition rates for event items (proportions of hits, i.e., correct *yes*-responses). The data were entered into a mixed 2 (post-event stress vs. no post-event stress) × 2 (low vs. high thematic arousal) × 2 (central vs. peripheral items) × 2 (rehearsed vs. non-rehearsed item) ANOVA, with the first two variables varied between subjects and the latter two varied within subjects. Consistent with previous findings for the present eyewitness material (Echterhoff et al., 2007), the hit rate for central event items ($M = 0.82$, SE = 0.01) was higher than the hit rate for peripheral event items ($M = 0.42$, SE = 0.02), as indicated by a significant main effect of item centrality, $F_{(1, 84)} = 317.51$, $p < 0.001$, $\eta_p^2 = 0.79$. Also, the additional presentation of information in the post-event description enhanced recognition memory: the hit rate for rehearsed event items ($M = 0.67$, SE = 0.02) was higher than for non-rehearsed event items, i.e., event items not included in the post-event description ($M = 0.57$, SE = 0.02), as revealed by a significant main effect of rehearsal, $F_{(1, 84)} = 26.84$, $p < 0.001$, $\eta_p^2 = 0.24$. We found no significant interactions between rehearsal, on the one hand, and arousal and/or post-event stress, on the other hand, all Fs < 1. Hence, it was not necessary to include rehearsal in the subsequent analyses of arousal and stress effects.

Importantly, the ANOVA also yielded the predicted significant post-event stress × thematic arousal × centrality interaction, $F_{(1, 84)} = 7.26$, $p = 0.009$, $\eta_p^2 = 0.08$. (The ANOVA yielded no other significant effects, all Fs < 1.84, all ps > 0.18.) This three-way interaction supports the notion that the level of memory enhancement for central (vs. peripheral) event items depends on the interaction of thematic arousal and post-event stress. We note that this interaction remained significant in separate analyses for both rehearsed and non-rehearsed event items, $F_{(1, 84)} = 5.12$, $p = 0.026$, $\eta_p^2 = 0.06$, and $F_{(1, 84)} = 4.31$, $p = 0.041$, $\eta_p^2 = 0.05$, respectively.

A closer examination of the interaction showed that, consistent with our prediction, the recognition advantage of central event items over peripheral event items was most pronounced under high thematic arousal and post-event stress (see the recognition rates for periperhal/all and central/all event items in **Table 1**). We used a complex, weighted contrast to test whether this difference was significant, coding the high thematic arousal/post-event-stress condition with +1, and each of the other three conditions with −1/3. For ease of interpretation, we calculated a *centrality bias* by subtracting the hit rate for peripheral event items from the hit rate for central event items, with greater values indicating a stronger centrality bias. The means and standard errors for the four experimental groups are depicted in **Figure 4**. Importantly, the mean centrality bias in the high thematic arousal/post-event-stress group ($MD = 0.49$, SD = 0.21) was significantly greater than the mean centrality bias in the three other conditions ($MD = 0.38$, SD = 0.22), $F_{(1, 84)} = 4.41$, $p = 0.039$, $\eta_p^2 = 0.05$. According to Cohen (1988), both the critical interaction and the latter contrast yielded medium-size effects.

There was no significant difference between the low thematic arousal/no-post-event-stress group and the low thematic arousal/post-event-stress group, $F = 1.19$, *ns*. When no post-event stress was induced, the centrality bias was even greater in the low thematic arousal condition than in the high thematic arousal condition, $F_{(1, 84)} = 4.32$, $p = 0.041$, $\eta_p^2 = 0.05$.

We also explored possible differences between the four arousal/post-event stress groups *separately* for central and peripheral details. The hit rate for central event items was significantly higher under thematic arousal plus post-event stress ($M = 0.86$) than under thematic arousal without post-event stress ($M = 0.78$), $F_{(1, 84)} = 5.17$, $p = 0.026$, $\eta_p^2 = 0.06$. This effect is consistent with the idea that additional post-event stress after arousal enhances memory for central information.

No other difference reached conventional significance levels; for central event items, Fs < 2.13, ps > 0.15. For peripheral event items we found the following trends: there was a trend toward a lower hit rate in the high thematic arousal plus post-event

Table 1 | Mean recognition rates (standard deviations) as a function of thematic arousal, post-event stress, and item type.

Group	Event items						Non-event items	
	Peripheral/ non-rehearsed	Peripheral/ rehearsed	Peripheral/ all	Central/ non-rehearsed	Central/ rehearsed	Central/ all	False additional	New
	M (SD)	*M* (SD)	*M* (SD)	*M* (SD)	*M* (SD)	*M* (SD)	*M* (SD)	*M* (SD)
LOW THEMATIC AROUSAL								
Post-event stress	0.39 (0.21)	0.53 (0.23)	0.46 (0.18)	0.79 (0.14)	0.88 (0.13)	0.83 (0.09)	0.52 (0.20)	0.32 (0.19)
No post-event stress	0.29 (0.24)	0.43 (0.30)	0.36 (0.24)	0.78 (0.15)	0.84 (0.16)	0.81 (0.13)	0.37 (0.26)	0.26 (0.15)
HIGH THEMATIC AROUSAL								
Post-event stress	0.33 (0.22)	0.42 (0.26)	0.37 (0.20)	0.83 (0.14)	0.89 (0.13)	0.86 (0.10)	0.42 (0.25)	0.28 (0.17)
No post-event stress	0.40 (0.24)	0.54 (0.24)	0.47 (0.18)	0.76 (0.18)	0.80 (0.14)	0.78 (0.13)	0.50 (0.21)	0.39 (0.20)

Note: The scores for peripheral/all and central/all are collapsed across the non-rehearsed and rehearsed data. See text for further explanations of item types.

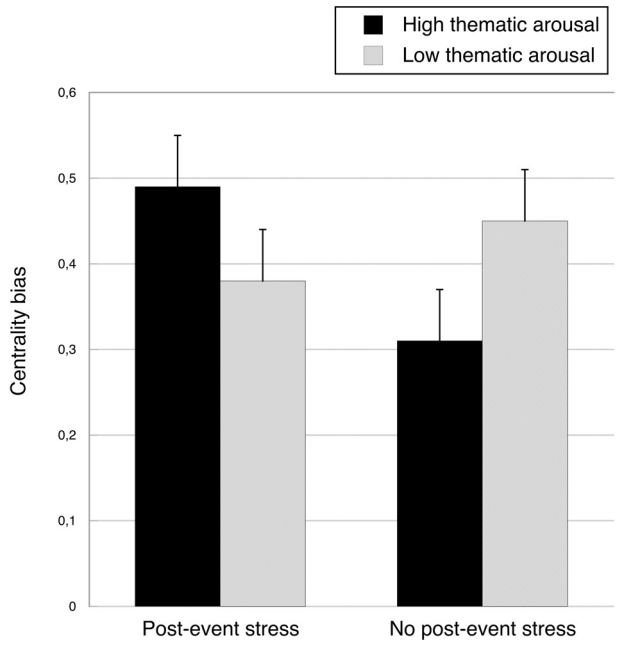

FIGURE 4 | Mean centrality bias (hit rate for central event items—hit rate for peripheral event items) as a function of post-event stress and thematic arousal, collapsed across rehearsal conditions. Bars represent standard errors.

stress group ($M = 0.37$) than in the high thematic arousal/no post-event stress group ($M = 0.47$), $F_{(1, 84)} = 2.60$, $p = 0.111$, $\eta_p^2 = 0.03$, and toward a higher hit rate in the latter group compared to the low thematic arousal/no-post-event stress group ($M = 0.36$), $F_{(1, 84)} = 3.19$, $p = 0.078$, $\eta_p^2 = 0.04$. Hence, in the absence of stress, thematic arousal did not reduce but, if anything, even enhanced the hit rate for peripheral event items. There was also a trend toward a lower hit rate for peripheral items in the no-post-event stress/low thematic arousal group ($M = 0.36$) compared to the post-event stress/low thematic arousal group ($M = 0.46$), $F_{(1, 84)} = 2.54$, $p = 0.115$, $\eta_p^2 = 0.03$.

MEMORY FOR NON-EVENT ITEMS

Table 1 (right panel) contains the mean recognition rates for non-event items, separately for items falsely added in the post-event description and completely new items. Overall, the rate of erroneous *yes*-responses for false additional items was significantly higher than the rate of erroneous *yes*-responses for completely new items [$F_{(1, 84)} = 36.69$, $p < 0.001$, $\eta_p^2 = 0.30$], as calculated with a mixed 2 (post-event stress vs. no post-event stress) × 2 (low vs. high thematic arousal) × 2 (false additional vs. new) ANOVA. This effect captures the well-known effect of post-event misinformation (Loftus, 2005). The effect did not differ across the experimental groups, all Fs < 1.24, *ns*. Thus, there was no evidence that stress and/or thematic arousal moderated the influence of falsely suggested misinformation.

RESPONSE BIAS

We also examined if the key finding (i.e., the interaction between thematic arousal and post-event stress for the acceptance of central vs. peripheral event items) could possibly be due to differences participants' response bias. We calculated a standard response bias estimate (B_r) following the formula proposed by Snodgrass and Corwin (1988), FA/[1 − (H − FA)], with FA representing the false alarm rate (accepted new items) and H the hit rate for all event items (central and peripheral). The 2 (post-event stress vs. no post-event stress) × 2 (low vs. high thematic arousal) ANOVA yielded no significant interaction effect, $F_{(1, 84)} = 2.10$, $p = 0.16$. When we included the hit rate only for central items and only for peripheral items in the calculation of the response bias, the interaction effects remained non-significant, both Fs < 1, ps > 0.44. Hence, there was no evidence that response bias differences contributed to our main finding.

MEDIATION OF THE CENTRALITY EFFECT OF POST-EVENT STRESS UNDER HIGH THEMATIC AROUSAL

The previous analyses revealed that participants experiencing post-event stress under high thematic arousal exhibited a greater memory centrality bias (a positive difference between the recognition rate for central event items and the recognition rate for peripheral event items) than participants experiencing only high thematic or post-event-stress. Finally, we examined whether this centrality effect of post-event stress under high thematic arousal condition was statistically mediated by the cortisol response, our main biological stress marker.

As recommended by Baron and Kenny (1986) we conducted bivariate regressions from post-event stress on cortisol increase and from cortisol increase on centrality bias and a stepwise linear regression for the memory centrality bias as dependent variable, with post-event stress as the single independent variable entered in Step 1, and the proposed mediator, cortisol increase, as an additional independent variable entered in Step 2. The main findings from these regressions are summarized in **Figure 5**. We found that all four standard conditions of mediation proposed by Baron and Kenny (1986) were met. Consistent with the above ANOVAs, both the centrality bias and cortisol increase were significantly higher in the post-event-stress condition than the no-stress condition, $\beta = 0.39$, $t_{(43)} = 2.75$, $p = 0.009$, and $\beta = 0.59$, $t_{(43)} = 4.77$, $p < 0.001$ (Conditions 1 and 2, respectively). Also, larger cortisol increase was associated with a higher centrality bias, $\beta = 0.46$, $t_{(43)} = 3.34$, $p = 0.002$ (Condition 3). When post-event stress (contrast-coded: without stress = −1, with stress = +1) and cortisol increase were both included as predictors of centrality bias, only cortisol increase remained significant, $\beta = 0.35$, $t_{(42)} = 2.07$, $p = 0.045$, whereas the effect of post-event stress was reduced to non-significance, $\beta = 0.18$, $t_{(42)} = 1.09$, $p = 0.283$ (Condition 4). The indirect effect of post-event stress on the centrality bias via cortisol increase was significant in a Sobel test of mediation (Sobel, 1982), $Z = 1.86$, $p = 0.031$ (one-tailed). These findings show that the effect of post-event stress on the centrality bias under high thematic arousal was mediated by the cortisol response.

DISCUSSION

In our study, eyewitnesses' memory for a witnessed event was influenced by the combined effect of thematic arousal during

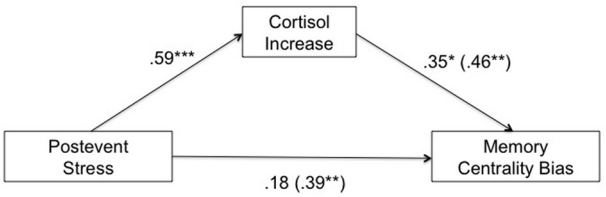

FIGURE 5 | Mediation analysis for the high thematic arousal condition, with post-event stress (control = −1, stress = +1) as independent variable, cortisol increase as mediator, and memory centrality bias (proportion of accepted central event items minus proportion of accepted peripheral event items) as dependent variable. Path coefficients are standardized β-coefficients from (multiple) regression analyses. The numbers in parentheses represent the direct effect (bivariate β-coefficients) of each of the two predictors (post-event stress and cortisol increase) prior to the inclusion of the other predictor. See text for the calculation of cortisol increase. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (two-tailed).

encoding and subsequent social stress, which was unrelated to the event itself. The affected dimension was the centrality bias in recognition memory, that is, the recognition advantage for central event items over peripheral event items. This centrality bias was more pronounced under high thematic arousal and post-event stress than under high thematic arousal without post-event stress or under post-event stress without thematic arousal. In other words, the centrality bias in memory was greater when thematic arousal during the witnessing of the incident was followed by stress compared to the conditions in which participants experienced either arousal or post-event stress. The effect on the centrality bias was apparently due to both an increased hit rate for central event items and a decreased hit rate for peripheral event items. Thus, although we did not find effects on the overall quantity of remembered information, we could demonstrate differences in the type or quality of remembered information (central vs. peripheral).

This finding is consistent with previous research that found an interaction between arousal during encoding and post-encoding stress (Cahill et al., 2003). However, our study remedies a weakness of this extant work, that is, the potential confounds of the arousal manipulation. Inevitably, arousing stimulus material differs from non-arousing material in ways that are unrelated to arousal or emotional valence, for instance, unexpectedness, visual salience, or relatedness to other knowledge. In contrast, by manipulating the perception of the material with identical stimulus material, we avoided such potential confounds (also see, e.g., Laney et al., 2004; Payne et al., 2007). Furthermore, we distinguished between peripheral and central stimulus information. The design of our study allowed us to detect opposite effects of arousal followed by post-event stress for peripheral and central event items. We could thus demonstrate previously unknown conditions for the narrowing of memory, which has been a key concept of research on the interplay of emotion and cognition (see Christianson, 1992).

Our results have implications for legal and criminological practice, particularly the treatment of eyewitnesses. Legally relevant events like accidents and crimes are likely to induce arousal in common eyewitnesses. Hence, eyewitnesses are likely to have experienced arousal during observation of an incident. They may also be exposed to social stress shortly after the incident, for instance, during an interrogation. Our study suggests that legal practitioners should be aware that such a combination of arousal during observation and post-observation stress could lead to a focus on central aspects at the expense of peripheral details in eyewitnesses' subsequent memory. This would be particularly undesirable when information about peripheral elements of an incident, for example, details indicating the use of a tool or weapon, is relevant to the investigation (see Osterburg, 2010).

To our knowledge, our study is the first to examine the role of neuroendocrine processes in stress effects on eyewitness memory, which is a key domain of applied cognitive psychology. We obtained evidence for the neuroendocrine mechanism underlying the observed centrality bias in eyewitness memory by means of a mediation analysis. Since post-event stress led to a centrality bias only under high thematic arousal, we restricted the analysis for the stress effect to the high-arousal condition. We found that—under high thematic arousal—the stress effect was statistically mediated by cortisol increase. This finding is consistent with the notion that cortisol increase is a key biopsychological process driving the effect of social stress on memory (Wolf, 2009).

Taken together, the findings in the stress condition are in line with the idea that an interaction of the SNS and the HPA axis boosts emotional memory via their joint effects on the amygdala (Cahill and McGaugh, 1998; Roozendaal et al., 2009). The enhanced memory for the central, or gist, information, which resulted from the interaction of thematic arousal and stress, is consistent with neuropsychological evidence of a special role of the amygdala in memory for the gist of emotional events (Adolphs et al., 2005).

In the current study we did not obtain a physiological measure of arousal during the presentation of the video. Future studies could assess heart rate, electrodermal activity, the startle reflex, or the enzyme salivary alpha amylase. All these measures have been shown to be responsive to the presentation of emotional arousing material (Lang et al., 1990, 1993; Segal and Cahill, 2009). Moreover, previous work suggests that when these measures are obtained during stress, they can predict, in combination with cortisol measures, emotional long-term memory (Smeets et al., 2008; Zoladz et al., 2011).

We found no evidence that thematic arousal and/or post-event stress affected participants' memory for false post-event information. Given the extant evidence, this result should not be taken as a surprise. For other types of false memory the findings are inconsistent: Some researchers have found effects (Payne et al., 2002), whereas others have not (Smeets et al., 2006, 2008). Also, the scant evidence in the domain of memory suggestibility has not revealed any stress effects (Eisen et al., 2002).

Apart from a few false details, the post-event narrative correctly described the events in the eyewitness video, which provided participants with an opportunity to rehearse the original stimulus material. As expected, rehearsal (that is, inclusion

vs. omission in the post-event narrative) enhanced the correct recognition rate. We note that the presentation of the post-event narrative fell into the phase of pronounced cortisol response to the previous stress induction. However, rehearsal of event items was not found to interact with post-event stress (and neither with thematic arousal). Hence, there was no evidence that post-event stress moderated the rehearsal effects.

Interestingly, when post-event stress was absent, the centrality bias was lower under high (vs. low) thematic arousal. Also, when arousal was low, the centrality bias was relatively small under post-event stress. Thus, there was no evidence for memory narrowing when arousal or post-event stress occurred alone. As the data presented in **Figure 4** suggest, the centrality bias found in the baseline condition (low arousal, no stress) apparently decreased when either arousal or post-event stress were added, but then increased again when arousal and stress were combined. The exploratory data analyses suggest that these differences in the centrality bias were predominantly due to differences in the memory for peripheral event items: In the absence of post-event stress, thematic arousal did not lead to a reduction but, if anything, an increase in the hit rate for peripheral event items. In the low-thematic arousal group, post-event stress did not lead to a decrease but, if anything, a rise in the hit rate for peripheral event items.

While we have no data that directly speak to this issue, we think it is stimulating to consider possible factors that could account for this interesting pattern. According to the arousal-biased competition model (Mather and Sutherland, 2011), arousal enhances the priority of goal-relevant information over goal-irrelevant information (for an application to eyewitness memory, see Hope et al., 2012). This approach could explain the findings in the stress/low-arousal and no-stress/high-arousal groups if one can make a convincing case why peripheral details were perceived as more relevant than central details. For instance, given the nature of our stimulus materials our student participants might have believed that details of the incident were particularly important. However, we have no evidence that bears directly on this claim. Also, a challenge for this approach is to explain the enhanced centrality bias in the arousal-plus-post-event-stress condition.

According to other research, thematic arousal can enhance memory for all aspects, including peripheral elements, of an observed event (Laney et al., 2004; also see Libkuman et al., 1999). This account could explain the enhanced memory for peripheral details in the high arousal/no-stress group. Indeed, thematic arousal, specifically apprehension about an upsetting turn of events, could induce participants to explore the witnessed material in more detail. However, it remains unclear how this account could cover the effects of post-event stress and the increased centrality bias in the arousal-plus-post-event-stress condition.

Another perspective is offered by research on mood effects on information processing. According to the mood-as-information approach (see Schwarz and Clore, 1996; Bless and Fiedler, 2006), positive and pleasant mood states inform the perceiver that the current situation poses no problems or risks, whereas negative and unpleasant mood states signal potential problems or threats in the current situation. While positive mood allows global, gist-oriented processing, negative mood induces the perceiver to engage in detail-oriented processing, which is typically adaptive in problem handling. By this view, the hit rate for peripheral details under arousal or post-event stress might be due to an increase in detail-oriented information processing that is triggered by the corresponding unpleasant mood state. A difficulty faced by this view is the lack of increased negative affect in the no stress/high arousal condition in our study (see **Figure 3**). However, the affect measure was administered approximately 15 min after the arousal manipulation, which may have been too late to detect existing mood differences.

A mood-as-information account would have to be supplemented by an explanation for the reduced memory for peripheral details under both arousal and post-event stress: such an explanation would have to assume the existence of a critical threshold of activation or arousal, at which gist- or priority-oriented information processing (Mather and Sutherland, 2011) takes over and subdues or prevents detailed-oriented processing. In our study, this threshold might be reached when high arousal is immediately followed by the stress induction. By this view, the effect of arousal on information processing, specifically memory for central vs. peripheral details, approximates an inverted U-shape function (for similar concepts, see Abercrombie et al., 2003; Rimmele et al., 2003; Diamond et al., 2007). A moderate increase in arousal induces detail-oriented processing, whereas a stronger increase reduces detail-oriented processing in favor of a focus on central or globally relevant stimuli. At the neuroendocrine level, a strong increase would be reflected by a joint activation of the SNS and the HPA.

In sum, our experiment demonstrates that thematically induced arousal and post learning stress interact in a complex fashion to enhance the centrality bias in recognition memory. Because we used thematic arousal, the results cannot reflect differences in stimulus quality. Moreover, since stress was administered after learning we can exclude effects on attention or initial encoding. The mediation analysis revealed that the increased centrality bias was mediated by the stress induced cortisol increase. These findings extend previous observations (e.g., Cahill et al., 2003) and suggest that the interaction of noradrenergic arousal with the stress hormone cortisol, most likely via joint effects on the amygdala, enhances emotional memories for central details.

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Evidence for arousal-biased competition in perceptual learning

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Arousal-biased competition theory predicts that arousal biases competition in favor of perceptually salient stimuli and against non-salient stimuli (Mather and Sutherland, 2011). The current study tested this hypothesis by having observers complete many trials in a visual search task in which the target either always was salient (a 55˚ tilted line among 80˚ distractors) or non-salient (a 55˚ tilted line among 50˚ distractors). Each participant completed one session in an emotional condition, in which visual search trials were preceded by negative arousing images, and one session in a non-emotional condition, in which the arousing images were replaced with neutral images (with session order counterbalanced). Test trials in which the target line had to be selected from among a set of lines with different tilts revealed that the emotional condition enhanced identification of the salient target line tilt but impaired identification of the non-salient target line tilt. Thus, arousal enhanced perceptual learning of salient stimuli but impaired perceptual learning of non-salient stimuli.

Keywords: bottom-up salience, emotional arousal, optimal gain bias, pop-out search, threat, visual search

EVIDENCE FOR AROUSAL-BIASED COMPETITION IN PERCEPTUAL LEARNING

Years of research have documented that emotion affects higher order cognitive processes such as decision making and memory in many ways (Bechara, 2004; Mather, 2007; Kensinger, 2009; Levine and Edelstein, 2009; Pessoa, 2009). More recent evidence indicates that emotion's influence extends to perceptual processes as well, in part due to interactions between the amygdala and sensory cortices (for more details, see Phelps, 2006). For instance, Phelps et al. (2006) showed that presenting a fearful face rather than a neutral face could make a subsequent neutral stimulus (a Gabor patch) more easily perceived even at low contrast levels. Furthermore, Padmala and Pessoa (2008) showed that arousal-induced perceptual enhancements are associated with increased brain activation in area V1–V4 of the visual cortex. Also, seeing fearful faces can speed up people's subsequent visual search (Becker, 2009; Olatunji et al., 2011; but see Quinlan and Johnson, 2011). However, emotion does not always enhance perceptual processing. For example, inserting an arousing distractor in a rapid serial visual presentation paradigm (RSVP) impairs identification of a subsequent neutral target stimulus (Most et al., 2005, 2006; Ciesielski et al., 2010).

Arousal-biased competition theory attempts to explain how arousal can both enhance and impair perception and memory (Mather and Sutherland, 2011; Sutherland and Mather, 2012). The theory builds on models of biased competition (Bundesen, 1990; Desimone and Duncan, 1995; Miller and Cohen, 2001; Deco and Rolls, 2005; Beck and Kastner, 2009) by positing that arousal amplifies biased competition processes, leading to "winner-take-more" and "loser-take-less" effects. More specifically, arousal-biased competition theory builds on a computational model of visual attention (Itti and Koch, 2000), which proposes that incoming information is first analyzed by early visual neurons to represent the perceptual contrast at each location for a variety of elementary visual features (e.g., luminance, color, orientation, motion, etc.). Within each of these feature maps, locations compete for activation via a center-surround competitive process in which excitation at a particular location leads to further excitation at that location while suppressing its surrounding locations. As depicted in **Figure 1A**, if one location starts with higher activity than the other locations, after several iterations, that location will dominate the map even more. In contrast (**Figure 1B**), if several locations in the map have similar initial activation levels due to similar perceptual contrast, these regions will be mutually suppressed. The contrast values across individual feature maps (e.g., individual maps for luminance, color, etc.) are integrated to obtain the overall saliency at each location.

According to arousal-biased competition theory, arousal increases the impact of these competitive processes, such that when there is one salient location (e.g., **Figure 1A**), that location will gain even more activation than under non-arousing conditions. This should lead to enhanced processing of the stimulus in that location, increasing learning about it and increasing the specificity of neural representations of that stimulus. In contrast, in situations with multiple similar competitors (e.g., **Figure 1B**), arousal will lead to even greater suppression of all initially active locations, impairing processing of any stimulus in one of those locations and decreasing the specificity of neural representations of that stimulus compared with non-arousing situations.

In the current study, we tested these hypotheses in the domain of visual search, examining how arousal affects perceptual learning of salient targets versus non-salient targets. We adapted the

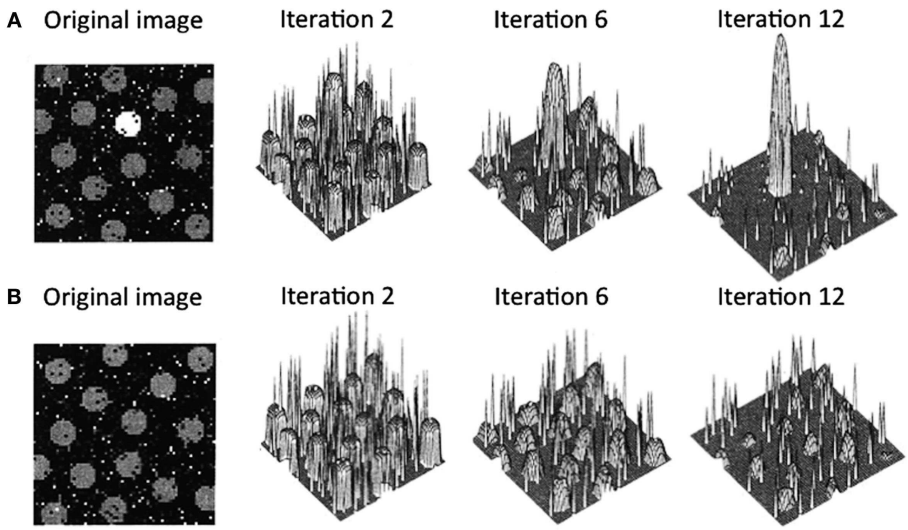

FIGURE 1 | Output from Itti and Koch's (2000) computational saliency map model. In case **(A)**, the original image has one location that is strongly activated by its bottom-up perceptual contrast surrounded by several locations with weaker initial activations. In this case, after an initial few iterations, the initial maximally activated location gains strength while suppressing the weaker activation locations. In case **(B)**, the original image has multiple locations that initially have similar activation levels. Here, all the peaks mutually suppress each other, leading to overall suppression of activation in the saliency map. Figure adapted from Itti and Koch (2000).

general outline of a procedure in a previous study (Navalpakkam and Itti, 2007). In our version of the search task, we included both low and high-salience target conditions, and both arousing and non-arousing sessions (**Figure 2**). During the learning trials of the task, participants were trained to detect a target line oriented at 55˚ among 24 distractors oriented either at 50˚ (in the low-salience condition) or at 80˚ (in the high-salience condition). To test learning of the tilt of the target line, probe trials were interspersed in a random manner between learning trials. The probe trials had five different lines in a circular array, and, as in Navalpakkam and Itti (2007), participants' task was to find the target line. To investigate the effects of arousal on learning performance, negative arousing, or neutral non-arousing pictures were presented before stimuli arrays in the learning phase.

In early visual cortex, neurons represent specific sensory features (Hubel and Wiesel, 1959). For instance, one neuron might fire most in response to a line tilted at 55˚ whereas another neuron might fire most in response to an 80˚ line (Somers et al., 1995). Neural selectivity is imperfect, in part due to noise, such that a neuron stimulated most by 55˚ tilted lines still fires – at a less intense rate – to similarly tilted lines. The plot of a neuron's average firing rate as a function of stimulus parameters such as tilt orientation is known as its "tuning curve" (Solla, 2006). Neuronal tuning curves shift as a result of experience and learning (e.g., Yang and Maunsell, 2004). While behavioral responses cannot indicate the specific responses at the neuronal level, they can provide analogous psychophysical tuning curves that reveal the accuracy and specificity of the neural representation of a particular feature or stimulus (e.g., Lee et al., 1999). In the current study, we used the data from the probe trials to assess the target line memory representations and to model the tuning curves associated with these representations.

We predicted that we would observe arousal effects on perceptual representations as a function of target prominence and the competitive processes enhancing high-salience stimuli and suppressing low-salience stimuli. Specifically, in the high-salience condition, we predicted that experiencing arousal would enhance perceptual learning of the highly salient target features. As competitive processes between stimuli representations influence the variability or noise in the perceptual representations as well as their signal strength (Ling and Blake, 2009), we predicted that the enhanced perceptual learning would be evident in decreased noise in the tuning curves (evident in decreased bandwidth of the curves) as well as in increased amplitude of the tuning curves at the correct 55˚ point. In contrast, in the low-salience condition, we predicted that arousal would impair learning target features, decreasing amplitude, and increasing noise.

In addition, in the low-salience condition, Navalpakkam and Itti (2007) documented an interesting phenomenon they called "optimal feature gain," in which the neural tuning curve that represents the target is shifted away from the distractor features, when the target and distractors are similar. Thus, for instance, when the participants completed visual search trials in which the target was a 55˚ line seen among 50˚ distractors, Navalpakkam and Itti found that the peak amplitude of participants' tuning curves for the target was not 55˚, as might be expected, but instead was shifted to 60˚. This shift in representation away from the distractor optimizes discrimination because the 55˚ target and 50˚ distractor now fell on a region of the tuning curve that has a higher slope than the peak of the curve, and similar stimuli are most easily discriminated in high-slope regions of a tuning curve. However, this discrimination advantage for high-slope regions of tuning curves disappears with increasing noise level in the representation (Butts and Goldman, 2006). Thus, given that we predicted that arousal

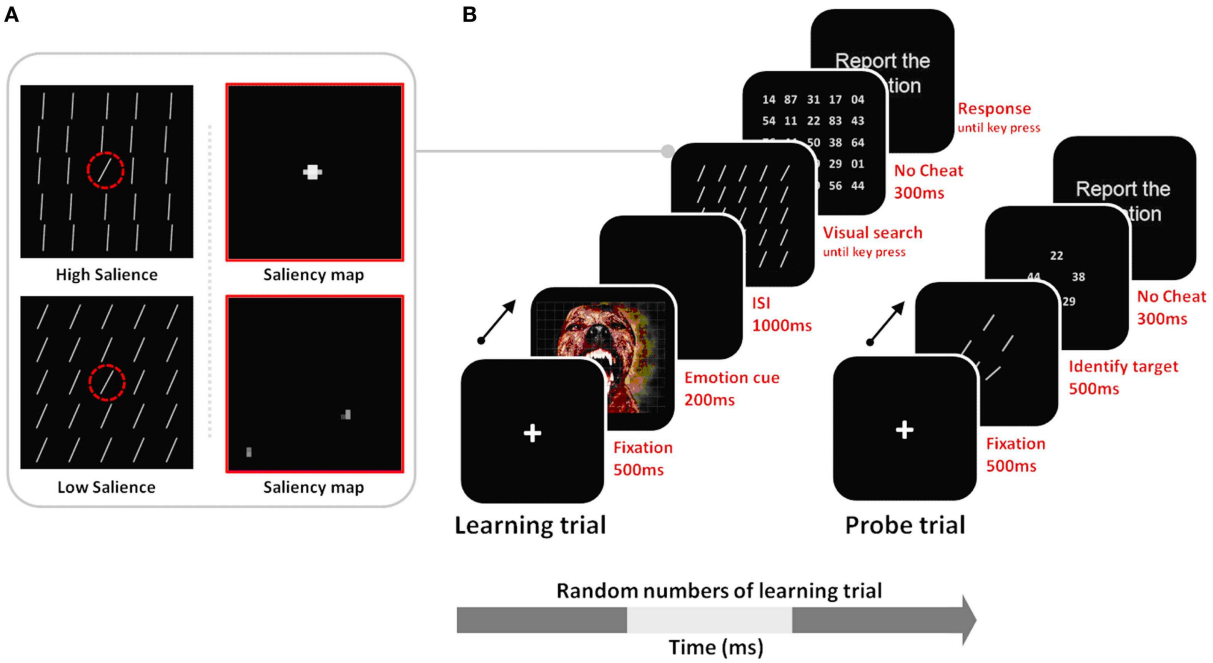

FIGURE 2 | (A) Stimulus examples of low vs. high salience targets with their corresponding saliency maps derived from Itti and Koch's (2000) computational model. For the high-salience condition, the distractor lines were tilted at 80˚, creating a 25˚ difference between them and the 55˚ target; therefore iterative spatial competition leads the target's location to gain further strength while suppressing surrounding regions. In the low-salience condition, the target and the distractor differ in tilt only by 5˚, and therefore the similarly activated locations in the saliency map inhibit each other, leading to mutual suppression of all locations in the saliency map. The dashed red circle indicates the target location, but it was not seen by participants. **(B)** Learning trials involved visual search for the 55˚ target, allowing perceptual learning about that target; probe trials were interspersed with the learning trials and tested recognition of the target tilt as observers had to select the 55˚ target from among a set of five differently tilted lines. Note that stimuli are not drawn to scale here.

would make it harder to distinguish the non-salient target from its distractors because of increased noise in the tuning curve for the target, arousal should also reduce the likelihood that participants will show "optimal feature gain" in the low-salience condition.

MATERIALS AND METHODS

OBSERVERS AND PSYCHOPHYSICAL SESSIONS

Twenty observers (10 males, 10 females; ages 25–36) with corrected-to-normal vision volunteered for this study and gave informed consent. Observers were naïve to the purpose of the experiment (except one, TL).

Ten (six males and four females) were assigned to the high-salience and the other ten (four males and six females) to the low-salience condition. For each salience type, observers completed two emotion sessions (arousing and non-arousing) in a counterbalanced order.

STIMULI AND APPARATUS

Line stimuli consisted of five types of line orientation (30˚, 50˚, 55˚, 60˚, and 80˚). The images used in the learning trials (32 negative images for the arousing session and 32 neutral images for the non-arousing session) and the additional images used in the subsequent memory task (32 negative and 32 neutral) were selected from the International Affective Pictures System (IAPS: Lang et al., 1999) and the Mather and Nesmith stimulus set (Mather and Nesmith, 2008). Nine additional participants rated the images for arousal (on a scale of 1 = calm to 9 = arousing) and valence (on a scale of 1 = unpleasant to 9 = pleasant). The 32 negative images had more negative valence ($M = 1.97$, SE = 0.38) and higher arousal ratings ($M = 7.77$, SE = 0.41) than the 32 non-arousing images (M valence = 5.45, SE = 0.33; M arousal = 1.88, SE = 0.38). The size of each line stimulus and emotional images corresponded to 1.5˚ × 0.6˚ and 30.5˚ × 22.5˚ visual angles, respectively. The stimuli were displayed on a 19″ CRT monitor with a refresh rate of 100 Hz. All observers were tested individually in a soundproof room, seated approximately 65 cm away from a screen, using a chin-rest.

PROCEDURE

As shown in **Figure 2A**, observers performed both learning trials and probe trials. Every so often, after a random number of learning trials, knowledge about the target was measured in a probe trial. Learning trials proceeded as follows: (A) A 500-ms fixation cross display; (B) a 200 ms-emotional picture; (C) a 1000 ms blank screen; (D) a search array containing one target (55˚) among 24 distractors. Based on the salience type assigned to observers, the target line was presented among distractors tilted either 80˚ or 50˚ (see **Figure 2A**). To manipulate observers' arousal levels during the session, we presented pictures in an approximately 60% partial schedule in both the arousing and non-arousing sessions. In trials without a picture, the search display was presented right after the first 500-ms fixation event.

Observers were instructed to find the target (55°) and press any key. To verify that observers indeed found the target on every trial, following the key press, a grid of fine-print numbers appeared briefly (300 ms) and observers were asked to report the number at the target's location (**Figure 2B**). Feedback ("correct" or "incorrect") on performance was given after each trial. After a random number of learning trials, a probe trial was presented. The probe trial consisted of a 500-ms fixation display, followed by a 500-ms display of five items representing five lines (30°, 50°, 55°, 60°, and 80°) within a 6.0° × 6.0° rectangular box, and then by a 300-ms display of five fine-print random numbers. The task was the same as in the learning trials. Observers were asked to report the number at the target location. Observers first completed 14 trials in a practice session, followed by the main task phase. Both sessions started with these practice trials and in both cases, no emotional pictures were shown during the practice session.

The line-search task consisted of ten 50-trial blocks (each with 34 learning trials and 16 probe trials). Each observer performed the task with 160 probe trials randomly presented in between 340 learning trials for each session (arousing and non-arousing). Thus, 1000 trials (2 emotion sessions × 50 trials × 10 blocks) were administered for each observer. Each observer either saw all low-salience or all high-salience targets. Observers were allowed to take a break in between blocks. The order of emotion sessions was randomly assigned across the observers. To avoid learning effects across sessions for the target line, we adopted two different orientations (original and reversed). For example, when the observer performed and completed the first session with the original orientation (e.g., 55°), the second session was administered with the reversed orientation (e.g., 125°). Immediately after each session, observers performed a recognition memory task as a manipulation check that they processed the pictures. For the recognition task, a randomly selected half of the main task images served as old items intermixed with 16 new images. The old and new items were presented in a random order and the observer was asked to indicate "old" or "new" for each image.

RESULTS

PROBE TRIAL PERFORMANCE

We first examine our measure of interest, the ability to correctly recognize the exact tilt of the target line in each of the conditions. For each observer, the percentage of "target" responses on probe trials was calculated for each orientation (30°, 50°, 55°, 60°, and 80°) separately for each emotion session (**Figure 3**). These were analyzed with salience type (2: high- and low-salience) as between-subject variables, and session (2: arousing and non-arousing) and orientation (5: 30°, 50°, 55°, 60°, and 80°) as within-subject variables. There was a significant main effect of orientation, $F(4,72) = 145.20$, $p < 0.001$, $\eta^2 = 0.89$, and a salience × emotion × orientation interaction, $F(4,72) = 3.90$, $p < 0.01$, $\eta^2 = 0.18$. Subsequent simple-effects analyses comparing performance in the two session types revealed that, in the high-salience condition, participants selected the correct target (i.e., 55° responses) more frequently in the arousing condition than in the non-arousing condition ($p < 0.05$). In contrast, in the low-salience condition, emotion condition did not significantly affect the percent of responses identifying the correct target. However, the arousing condition led to a significant decrease in selecting the 60° target (or its corresponding opposite line in the flipped condition; $p < 0.001$) in the low-salience condition.

To understand the nature of these results better, we estimated each observer's tuning curve to fit responses from each emotion session via a Gaussian function known to be well represented in tuning curves:

$$f(x) = ae^{\frac{-(x-\mu)^2}{2\sigma^2}} \quad (1)$$

where a represents response amplitude (i.e., the height of the curve's peak), μ specifies the position of the center of the peak, and σ is the bandwidth (i.e., standard deviation of the curve). The goodness of fit was evaluated by the r^2 for each arousing condition and non-arousing condition:

$$r^2 = 1.0 - \frac{\sum \left(y_i^{\text{Predicted}} - y_i^{\text{Observed}}\right)^2}{\sum \left[y_i^{\text{Observed}} - \text{mean}\left(y_i^{\text{Observed}}\right)\right]^2} \quad (2)$$

To evaluate the curve fit model using the parametric values (i.e., a, μ, and σ) for each condition, a nested model testing (separate fits for each emotion condition vs. one fit for both conditions collapsed together) was applied. Specifically, an F-test for nested models was used to statistically compare the models based on

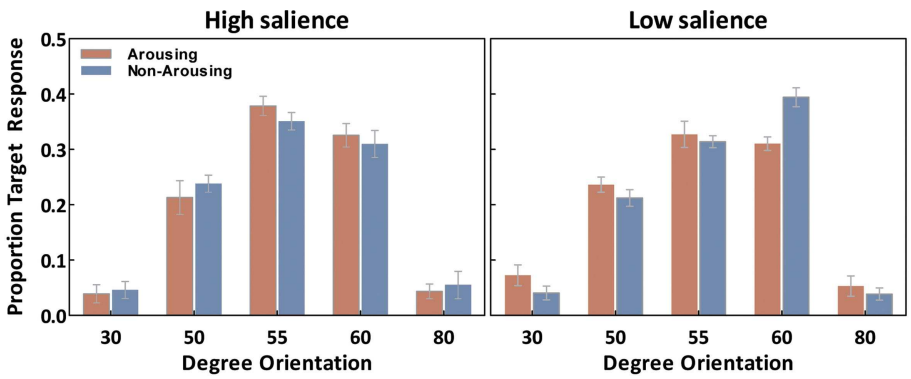

FIGURE 3 | Averaged "target" responses for each orientation in the probe trials as a function of emotion and salience. Error bars represent SEM.

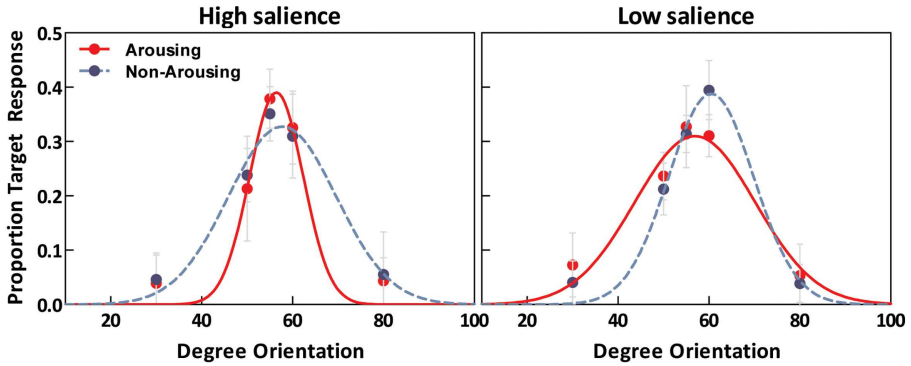

FIGURE 4 | Estimated tuning curves for averaged "target" responses as a function of emotion in the high-salience condition (left) and low-salience condition (right).

the averaged r^2s for the arousing and non-arousing conditions. For two nested models with k_{full} and k_{reduced} parameters, the F statistic is defined as:

$$F\left(df_1, df_2\right) = \frac{\left(r^2_{\text{full}} - r^2_{\text{reduced}}\right)/df_1}{\left(1 - r^2_{\text{full}}\right)/df_2} \quad (3)$$

where $df_1 = k_{\text{full}} - k_{\text{reduced}}$, and $df_2 = N - k_{\text{full}}$; N is the number of data points. All these procedures were performed using the GraphPad Prism version 5.04 for Windows (GraphPad Prism Software, La Jolla, CA, USA; see also Motulsky and Christopoulos, 2004).

As illustrated in **Figure 4**, estimated tuning curves for the averaged "target" responses across all observers revealed that emotional arousal modulated response patterns differently depending on salience. When the target was conspicuous among distractors (i.e., high-salience condition), arousal enhanced the accuracy and strength of the target's representation; this was evident in the decreased bandwidth, $F(1,94) = 4.91$, $p < 0.05$, and increased amplitude, $F(1,94) = 4.71$, $p < 0.05$. On the contrary, when target salience was low, arousal widened the tuning curve leading to specificity loss. This was evidenced by increased bandwidth, $F(1,94) = 8.86$, $p < 0.005$, and decreased amplitude, $F(1,94) = 13.85$, $p < 0.0005$. The position of the peak amplitude also shifted, $F(1,94) = 7.03$, $p < 0.01$. This shift in the position of the peak amplitude indicated that when target salience was low, arousal also disrupted the "optimal feature gain" exaggeration of target-distractor differences seen in the non-arousing condition and in a previous study not involving emotion (Navalpakkam and Itti, 2007). The parameters of the best fitting functions are listed in **Table 1**[1]. In the following sections, we describe performance on the other aspects of the task.

[1]The estimated parameters were compared via a repeated-measures ANOVA which revealed the same pattern of results as nested model testing (**Figure 6**). For the curve position parameter (i.e., μ), there was a main effect of emotion, $F(1,18) = 9.05$, $p < 0.01$, and an interaction between emotion and salience $F(1,18) = 7.87$, $p < 0.05$. For the curve amplitude parameter (i.e., a), there was a significant emotion by salience interaction, $F(1,18) = 12.283$, $p < 0.005$. The curve bandwidth parameter (i.e., σ) also showed a significant emotion by salience interaction, $F(1,18) = 8.99$, $p < 0.01$.

Table 1 | Parameters of the best fit for the averaged "target" response in probe trials for the arousing versus the non-arousing sessions and *p* values from the comparisons of each parameter using nested model testing.

Saliency	Parameters	Emotion	
		Arousing	None
High	μ	56.46	57.77
	a	0.39	0.33*
	σ	5.89	11.87*
Low	μ	56.94	60.51***
	a	0.31	0.39****
	σ	13.27	9.35***

*****p* < 0.0005, ****p* < 0.005, ***p* < 0.01, **p* < 0.05.*

MEMORY FOR THE PICTURES

An analysis of variance (ANOVA) with salience type (2: high- vs. low-salience) as a between-observers variable and session type (2: arousing vs. non-arousing) as a within-observers variable revealed that observers' d-prime (d') values from the picture recognition memory task were significantly higher in the arousing picture sessions ($d' = 3.37$, SE = 0.09) than in the non-arousing picture sessions ($d' = 2.80$, SE = 0.14), $F(1,18) = 8.58$, $p < 0.001$, $\eta^2 = 0.52$. There was no significant main effect of salience type nor interaction with salience type (both $p > 0.3$). Thus, as seen across many previous studies, memory was better for the emotional pictures than the neutral pictures (for a review see Reisberg and Hertel, 2004). For the purposes of the current study, however, the relevant finding was that participants had similar memory for the pictures across the two salience conditions.

LEARNING TRIAL PERFORMANCE

Averaged median response times (RTs) for the learning trials were calculated for each session for both high- and low-salience conditions. A repeated ANOVA on target search latencies was conducted with salience type (2: high- vs. low-salience) as a between-observers variable, and session type (2: arousing vs. non-arousing)

as a within-observers variable. Not surprisingly, there was a main effect of salience type, $F(1,18) = 134.17$, $p < 0.001$, $\eta^2 = 0.88$, with slower RTs in the low-salience condition ($M = 1443.45$, SE = 132.16) than in the high-salience condition ($M = 581.53$, SE = 36.37). However, there was no significant main effect of session type and no significant interaction between the two variables (**Figure 5**).

Overall, observers had near-ceiling accuracy ($M = 0.977$, SE = 0.005) on the learning trials. More specifically, in the high-salience condition, the averaged correct ratio was 0.991 in arousing condition and 0.988 in non-arousing condition. In the low-salience condition, the mean was 0.975 in the arousing condition, and 0.956 in the non-arousing condition. A repeated-measures ANOVA with salience type (2: high- vs. low-salience) as a between-observers variable and session type (2: arousing vs. non-arousing) as a within-observers variable revealed that there was a main effect of session type, $F(1,18) = 11.12$, $p < 0.005$, $\eta^2 = 0.38$, and a main effect of salience type, $F(1,18) = 10.27$, $p < 0.005$, $\eta^2 = 0.36$. There was an interaction with salience type, $F(1,18) = 5.63$, $p < 0.05$, $\eta^2 = 0.24$. Subsequent simple-effects analyses for each salience type across the two session types revealed that, in the low-salience condition, the correct ratio was significantly greater in the arousing condition than in the non-arousing condition ($p < 0.05$). In contrast, in the high-salience condition, emotion condition did not significantly affect the percent of responses identifying the correct target ($p > 0.1$). However, it is not clear if this interaction is simply an artifact of the near-ceiling accuracy in the high-salience condition, as the near-perfect accuracy in this condition may have diminished the effects of arousal on accuracy (which appear to be in the direction of enhancing performance, as in the low-salience condition). In summary, arousal generally increased accuracy in the search task, even in the low-salience condition in which arousal impaired perceptual learning about the target.

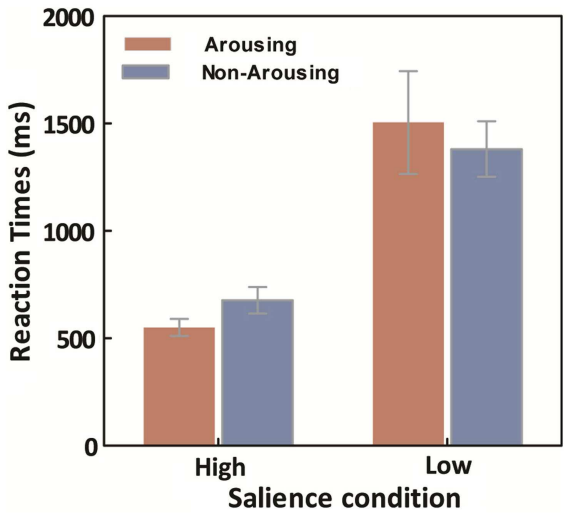

FIGURE 5 | Average across participants of within-participant median learning-trial response times, as a function of emotion and salience. Error bars represent SEM.

COMPARING LEARNING TRIALS PRECEDED BY PICTURES TO THOSE NOT PRECEDED BY PICTURES

In our study, although emotion type was manipulated across sessions, within each session we did not show a picture on every trial. To provide more information about whether the presence or absence of an image on a particular learning trial mattered for the speed of the response, we conducted a follow-up ANOVA with salience type (2: high- vs. low-salience) as between-observer variables, and image presence (2: image present before visual search, vs. image absent) and session (2: arousing vs. non-arousing) as within-observer variables, and the learning phase median RT as the dependent variable. There was a significant interaction of image presence (2: presence vs. absent) and salience condition (2: high vs. low-salience), $F(1, 18) = 8.00$, $p < 0.05$, $\eta^2 = 0.31$. However, there was no session main effect, $F(1, 18) = 0.84$, n.s., nor any interactions with session ($Ps > 0.4$). To clarify the nature of the image presence and salience condition interaction, we carried out a separate repeated ANOVA for each salience condition with image presence as a factor. There were no statistically significant effects in the high-salience condition ($Ps > 0.1$). In contrast, in the low-salience condition, there was a main effect of image presence, $F(1,9) = 11.06$, $p < 0.01$, $\eta^2 = 0.55$. In this condition, the RT was generally slower with an image absent ($M = 1592.90$ ms, SE = 199.05) than present ($M = 1345$ ms, SE = 147.49) regardless of emotion condition. However, there was no interaction or main effect of session. Thus, in addition to not detecting session differences in reaction times during the learning phase, we did not detect trial-by-trial differences in reaction time based on whether the picture was emotional or not – indicating emotion did not significantly influence response speed in the learning trials.

DISCUSSION

In this study, we tested the hypothesis that arousing stimuli increase the effects of competition among stimuli in perceptual learning. We compared the effects of arousal in two types of visual search situations. In the high-salience condition, the target line was tilted 55° and the distractor lines were tilted 80°. In this type of visual display, the target had high perceptual contrast with the surrounding stimuli and so center-surround competition should increase the perceptual salience of the target compared with its surrounding stimuli (Itti and Koch, 2000). Arousal-biased competition theory (Mather and Sutherland, 2011) predicts that arousal should further increase the activation of this perceptual "winner," making it more precisely represented and encoded.

In the high-salience condition, when asked to identify which of five alternative lines was the target discrepant line in the visual search trials, in both the arousing and non-arousing sessions participants were most likely to select the correct 55° tilted line. However, in the arousing session, participants were significantly more likely to select the correct 55° option than the other options, leading to a higher amplitude and a lower bandwidth for their psychophysical tuning curve representing the target line tilt.

In the low-salience condition, the target line (tilted 55°) and the distractor lines (tilted 50°) were similar. In this situation of competition between stimuli with similar perceptual contrast, center-surround competition mechanisms should mutually inhibit both target and distractor locations (Itti and Koch, 2000). If, as predicted

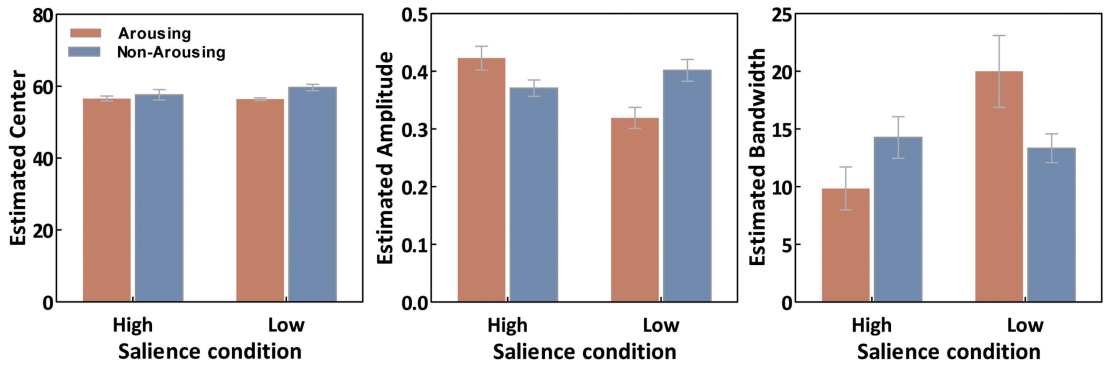

FIGURE 6 | Averaged curve position (μ), amplitude (*a*), and bandwidth (σ) of tuning curves as a function of conditions. Error bars represent SEM.

by arousal-biased competition, arousal amplifies the effects of these competition processes, then learning of low-salience targets should be worse under arousing than non-arousing situations. Consistent with these predictions, in the arousing sessions, observers learned the target line tilt less precisely than in the non-arousing sessions. Thus, emotional arousal had opposite effects on perceptual learning of salient and non-salient stimuli. Previous research indicates that competitive processes in binocular rivalry lead not only to relative differences in signal strength between the dominant and suppressed stimuli, but also to less noise in the representation of the dominant stimulus than in the representation of the suppressed stimulus (Ling and Blake, 2009). Consistent with this, in our study, arousal decreased the noise in the tuning curves of salient stimuli but increased it for non-salient stimuli.

Previous studies have shown that if people see emotionally arousing pictures while they are trying to remember several neutral stimuli, they are less able to recognize the neutral stimuli at the end of the trial (Dolcos and McCarthy, 2006; Dolcos et al., 2006). However, impaired working memory between learning and probe trials cannot account for our findings, as in the high-salience condition, arousal enhanced memory for the target line. Instead, arousal-biased competition provides a framework to account for when arousal will impair working memory and when it will enhance it. The prediction is that arousal will impair working memory when multiple equally salient stimuli are competing for representation, such as on working memory trials with several neutral faces as the memoranda and distracting arousing or neutral pictures (Dolcos and McCarthy, 2006; Dolcos et al., 2006). Arousal can even impair memory for associated features of arousing stimuli when the features of multiple arousing stimuli are competing for representation (Mather et al., 2006; Mitchell et al., 2006). However, when arousing stimuli compete with neutral stimuli in an N-back working memory task, the arousing stimuli, which presumably have higher priority due to both salience and goal-relevance, are remembered better than the neutral stimuli (Lindstrom and Bohlin, 2011).

Research on perception reveals similar issues regarding how arousing stimuli can both modulate competition among independent neutral stimuli and also compete directly against those stimuli. For instance, previous research indicates that arousing stimuli such as fearful faces can enhance perception of subsequent neutral stimuli (e.g., Phelps et al., 2006; Padmala and Pessoa, 2008). However, these studies did not evaluate how arousal affected the competition among more and less salient stimuli. The prediction from our study is that arousal would enhance perception only of the most salient stimuli while impairing perception of less salient stimuli. But a critical issue here, as in the working memory studies, is that arousing stimuli also compete for representation. Thus, when pictures are rapidly displayed in a sequence, arousing pictures impair perception of subsequent targets (Most et al., 2005, 2006, 2007; Smith et al., 2006; Most and Junge, 2008; Ciesielski et al., 2010; Wang et al., in press). The timing between a cue inducing arousal and a subsequent neutral target is critical in determining whether the arousing cue itself dominates everything else, or whether it can enhance perception of a salient target. For instance, in one study (Bocanegra and Zeelenberg, 2009), when the interval between the cue and the target was 50 or 500 ms, participants were less likely to correctly identify the target when the cue was arousing. However, increasing the interval to 1000 ms led to enhanced identification of targets following arousing cues. In our study, the inter-trial interval was 1000 ms, at which point the arousing stimulus was no longer in direct competition with subsequent stimuli.

It is interesting that we did not see any effects of arousing stimuli on RTs to detect the visual search target, whereas two previous studies (Becker, 2009; Olatunji et al., 2011) found that showing fearful faces 600 ms or immediately before a search array enhanced target detection. Olatunji et al. found that this advantage was specific to fear face cues and did not appear for anger or disgust face cues. Thus, it may be that the enhanced search detection is specific to fear and so was not elicited by the mixed negative emotionally arousing pictures we showed. Furthermore, it is worth noting that enhanced visual search after fearful face cues was not replicated in another study (Quinlan and Johnson, 2011). In any case, the fact that we did not see significant effects of arousal on visual search speed rules out the possibility that the perceptual learning effects we found were mediated by target detection speed differences across emotion conditions. Also, search accuracy did not show arousal-biased competition effects; instead arousal seemed to have a general enhancing effect on initial search accuracy, which may have been due to enhancing effects of arousal on sustained attention. The lack of arousal-biased competition effects in initial search speed or accuracy suggests that the differences in perceptual learning induced by emotional arousal were due to competitive processes acting on representations after target detection.

In the current study, there was an additional interesting finding in the low-salience condition. Here, the visual search parameters were the same as in Navalpakkam and Itti's (2007) study, in which they found evidence that, in difficult search without any emotion induction, people shift their perceptual representation of the target item such that it is less accurate, but more optimal for discriminating the target from its distractors. Standard models of attention assume that attention increases the activity of neurons tuned to respond to the target's features (Carrasco, 2011). Navalpakkam and Itti modeled situations in which the target and the distractors are highly similar, such as search for a 55˚ target among 50˚ distractors. Their model suggests that boosting activity of neurons tuned for the exact target feature can be suboptimal when the target and distractors are very similar. In this case, the optimal strategy is to increase the signal strength of neurons representing features like the target, but that differ more from the distractors than the target does. In the case of a 55˚ target among 50˚ distractors, this would mean it would be optimal to boost the responsiveness of neurons tuned to respond to 60˚ lines, as these neurons should have the steepest part of their tuning curve coincide with the small differences in the feature value between the target and distractor (see Purushothaman and Bradley, 2005).

Navalpakkam and Itti confirmed their model in behavioral studies in which people showed this "optimal feature gain" strategy when learning the features of targets that were very similar to distractors. This strategy requires relatively sharp tuning curves, as with broader tuning curves there would be little difference in the tuning curve slope height at 50˚ (the distractor) between neurons tuned for 55˚ and 60˚ lines. Indeed, other modeling work indicates that similar stimuli are most easily discriminated in high-slope regions of the tuning curve only when there are low noise levels in tuning curves (Butts and Goldman, 2006). In our study, we replicated Navalpakkam and Itti's "optimal feature gain" effects in the non-arousing low-salience condition, such that observers were more likely to incorrectly identify the target as having a 60˚ tilt rather than its actual 55˚ tilt. However, in the arousing condition, representations of the target line were significantly less shifted away from the distractor tilt, and revealed a significantly broader tuning curve with lower amplitude. This finding suggests that, in difficult discrimination tasks involving similar targets and distractors, emotional arousal disrupts people's ability to make subtle shifts in perceptual representations that optimize discrimination of targets from distractors.

We used negative stimuli in our study as they generally induce stronger arousal responses than positive stimuli (Lang et al., 1998; Baumeister et al., 2001). However, this means that we cannot be sure whether our results are due to the effects of negative valence or emotional arousal. Previous research reveals that highly arousing positive and negative stimuli affect subsequent perceptual processing in similar ways; for instance, like negative arousing pictures, erotic pictures impair perception of visual targets (Most et al., 2007). However, additional research is needed to test whether, like negative arousing stimuli, positive arousing stimuli amplify biased competition processes.

One of the most critical aspects of our perceptual processes is that they allow us to be selective about what we attend to. Being able to focus on some aspects of incoming perceptual stimuli while ignoring others is critical for being able to process and respond to high priority stimuli in the environment. Perceptual contrast is one cue that helps determine priority. Stimuli that move suddenly or are brighter than their surroundings are salient and win out over other stimuli to draw attention. Our study suggests that when people experience negative emotional arousal, these competitive processes are amplified such that salient stimuli are represented even more and non-salient stimuli even less accurately than they would be otherwise. Such processes should enable the type of focused processing necessary under threatening or critical circumstances, but they come at the cost of reduced learning about non-salient information.

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Sleep promotes lasting changes in selective memory for emotional scenes

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Although we know that emotional events enjoy a privileged status in our memories, we still have much to learn about how emotional memories are processed, stored, and how they change over time. Here we show a positive association between REM sleep and the selective consolidation of central, negative aspects of complex scenes. Moreover, we show that the placement of sleep is critical for this selective emotional memory benefit. When testing occurred 24 h post-encoding, subjects who slept soon after learning (24 h Sleep First group) had superior memory for emotional objects compared to subjects whose sleep was delayed for 16 h post-encoding following a full day of wakefulness (24 h Wake First group). However, this increase in memory for emotional objects corresponded with a decrease in memory for the neutral backgrounds on which these objects were placed. Furthermore, memory for emotional objects in the 24 h Sleep First group was comparable to performance after just a 12 h delay containing a night of sleep, suggesting that sleep soon after learning selectively stabilizes emotional memory. These results suggest that the sleeping brain preserves in long-term memory only what is emotionally salient and perhaps most adaptive to remember.

Keywords: emotional memory formation, emotional memory enhancement, sleep, sleep and memory, memory consolidation, memory, emotion

Emotional memories form the core of our personal histories. They shape our personalities by representing our greatest achievements and our worst defeats, mark the milestones in our changing lives, and figure prominently in anxiety and mood disorders (see Payne et al., 2004; Kensinger, 2009; Brewin et al., 2010 for review). Although we know that emotional experiences enjoy a privileged status in our memories, being better remembered than most neutral events, researchers are still learning how memories for emotional events are processed and stored (McGaugh, 2004; LaBar and Cabeza, 2006), and how they change over time (Payne and Kensinger, 2010).

The notion that memories are not static, but rather form gradually, dates back to Muller and Pilzecker (1900), who coined the term "memory consolidation" (reviewed in McGaugh, 2000; Dudai, 2004). Memory consolidation is (at least) a two-stage process, including molecular and cellular events that support the strengthening of synapses over minutes and hours ("cellular consolidation"), and system-wide changes that occur in the hours and days following learning ("systems consolidation"). Growing evidence suggests that the offline brain state of sleep provides ideal conditions for memory consolidation, particularly on a systems level (reviewed by Stickgold, 2005; Ellenbogen et al., 2006; Walker and Stickgold, 2006; Diekelmann and Born, 2010; Payne, 2011). For example, neural activation patterns seen during daytime task training are reactivated during subsequent sleep in both rats and humans (Diekelmann and Born, 2010; Girardeau and Zugaro, 2011), and such reactivations can lead to performance enhancements the following day (Peigneux et al., 2004; Rasch et al., 2007).

Several studies demonstrate that sleep preferentially enhances emotional episodic memories over neutral ones. When presented with both negative arousing and neutral information as part of the same learning experience, subjects who sleep between training and test preferentially consolidate negative over neutral narratives (Wagner et al., 2001, 2006), pictures (Hu et al., 2006), and components of scenes (Payne and Kensinger, 2010 for review). For example, Payne et al. (2008) showed that when presented with scenes consisting of either neutral (e.g., a chipmunk) or negative arousing (e.g., a snake) objects placed on neutral backgrounds (e.g., a forest), participants who slept selectively consolidated memory for the emotional objects, while memory for the accompanying backgrounds deteriorated. Thus, as compared to a 30-min control group, those who slept showed selective memory benefits for the emotional objects, but showed no corresponding benefit for their backgrounds or for either the objects or the backgrounds composing neutral scenes. Those who stayed awake, on the other hand, showed poorer memory for all elements as compared to those tested after a 30-min delay. These results are interesting for two reasons. First, they contribute to a growing literature suggesting that the effects of emotion on memory are intensified during sleep (see Walker, 2009; Payne, 2011; Payne and Kensinger, 2011 for review). Second, the sleeping brain, rather than simply influencing the consolidation of all recently encountered information, appears to select for consolidation only what is most emotionally

salient about experience and perhaps most relevant to future goals (see also Payne et al., 2009; Payne and Kensinger, 2010). The idea of goal relevance is particularly apropos in this task given that the way emotion affects memory (i.e., narrowing vs. broadening) depends on a person's current goal (Levine and Edelstein, 2009); a negative or threatening stimulus, such as the snake in the forest described above, might trigger a survival goal, which might in turn trigger a narrowing of one's focus onto the threatening object (the snake) at the expense of the background (the forest) in a way the neutral object (the chipmunk) might not.

Although there is currently much debate about which features of sleep are most important for memory consolidation, converging lines of evidence suggest that rapid eye movement sleep (REM) critically modulates memory for highly arousing emotional information. Hennevin et al. (1998) demonstrate that aversive conditioning in rodents is followed by increases in REM sleep that often continue until the task is mastered (Hennevin et al., 1995). Further, depriving rats of REM sleep can lead to performance deficits in avoidance tasks, particularly if the deprivation occurs within so-called "REM-windows" (Smith and Butler, 1982; Smith, 1995; Smith and Rose, 1996).

Preliminary human research suggests a similarly beneficial effect of REM sleep on emotional memory consolidation. Wagner et al. (2001) found that 3 h of late night, REM-rich sleep (but not 3 h of early night slow-wave-rich sleep) facilitated memory for negative arousing narratives, an effect that could still be observed years later when the subjects were re-contacted for a second memory test (Wagner et al., 2006), and REM sleep theta activity has been positively correlated with memory for emotional pictures (Nishida et al., 2009; see Walker, 2009, for review). Sleep's importance to emotional processing is also suggested by the emotionally charged and vivid dreams of REM sleep, which may utilize elements of past experiences to simulate and practice for threatening future situations (Levin and Nielsen, 2009; Payne and Kensinger, 2011). Moreover, affective disorders such as depression are characterized not only by changes in emotional memory (e.g., Hamilton and Gotlib, 2008), but also by marked changes in REM sleep architecture (Berger and Riemann, 1993; Pillai et al., 2011).

Each of these lines of evidence is interesting given that the amygdala and hippocampus are among the most active brain regions during REM sleep (Maquet et al., 1996), perhaps signaling interactions between these regions as they selectively process emotional memories offline. While neutral episodic memories rely on the hippocampus and adjacent structures for their processing, emotional episodic memories receive a special boost from the amygdala, which modulates activity in the hippocampus to preferentially influence emotional memory formation. Interestingly, a recent study showed greater activity in these regions and greater connectivity among them following sleep compared to wakefulness (Payne and Kensinger, 2011; see also Sterpenich et al., 2009).

Although the tendency to remember emotional over neutral events can be observed after short delays, at times emotional arousal has a more potent influence on memory across long delays (24 h) than short ones (e.g., Kleinsmith and Kaplan, 1963; Walker and Tarte, 1963; Sharot et al., 2007; Sharot and Yonelinas, 2008), and damage to the amygdala disproportionately affects retention of emotional information over long delays while having less influence on short-term retention (Phelps et al., 1997, 1998; LaBar and Phelps, 1998). These results may be in part explained by neurohormonal modulation of amygdala-hippocampus interactions that occur "offline," post-encoding (Payne, 2011 for review). For example, the memory modulation hypothesis (McGaugh, 2004) argues that greater long-term memory for emotional over neutral information reflects the neuromodulatory influence of the amygdala on hippocampus-based consolidation processes, via stress hormone engagement. In this issue, for example, Echterhoff and Wolf (2012) show that the combination of viewing a highly arousing event coupled with a subsequent increase in stress produces an increase in bias to remember central aspects of the event in an eyewitness memory task. Notably, the release of the stress hormone cortisol parallels REM episodes throughout the night, and reaches its diurnal zenith during late night REM–rich sleep (reviewed in Payne and Kensinger, 2011).

Clearly, there is good reason for emotional memories to be preferentially consolidated during sleep, perhaps especially during REM. However, in spite of converging evidence from the lines of work described above, this idea is not without its problems. Most problematic are interference arguments that provide compelling alternative explanations for sleep-based consolidation effects (Wixted, 2004; Mednick et al., 2011). To date, most of the studies to directly examine the relationship between sleep (vs. wakefulness) and emotional memory formation are confounded by the amount of interference encountered during the waking delay interval. For example, both the Hu et al. (2006) and Payne et al. (2008) studies demonstrated that a 12 h period containing nocturnal sleep selectively benefits memory for negative arousing stimuli relative to an equivalent period of daytime wakefulness. An interference account would argue that sleep, rather than conferring an active neurobiological benefit on these memories, merely provided a passive and temporary shield against interfering stimulation because it is a time of reduced sensory input (Wixted, 2004).

Because this "nocturnal sleep vs. daytime wake" design (e.g., see the 12 h Wake and 12 h Sleep conditions in **Figure 1**, labeled "a") is open to interference criticisms, Wagner et al. (2001) used a split-night procedure to demonstrate that emotional memories benefit from 3 h of late night REM-rich sleep, relative to 3 h of early slow-wave-rich sleep, or equivalent periods of wakefulness during the night. Although this finding is not easy to reconcile with an interference account, it is subject to circadian and sleep deprivation confounds. Encoding and retrieval processes may vary as a function of circadian phase in ways that are not easily revealed through task performance, and there is also a possibility that consolidation processes are modulated by circadian time, rather than by REM-sleep *per se*. Moreover, the wake control groups may have performed poorly because they were sleep deprived during the first or second half of the night.

Given these confounds, we investigated the influence of sleep on emotional memory formation via a third method: Following the incidental encoding of negative and neutral scenes in the morning or evening, memory was tested following a 24 h delay interval. Time spent sleeping and awake were thus

FIGURE 1 | Experimental timeline. The 30 min ($n = 40$), 12 h wake ($n = 24$) and 12 h sleep ($n = 24$) groups (labeled "a") are from Payne et al. (2008). Note: Because there were no differences in performance in the 30 min groups (30 min am, $n = 20$ and 30 min pm, $n = 20$), they were combined into a single 30 min variable for analyses reported in the current paper. The overnight polysomnography study reported here (Experiment 1, $n = 27$) follows the 12 h Sleep protocol (labeled "a"), with the addition of overnight sleep monitoring in the laboratory. The 24 h delay study (Experiment 2, labeled "b") follows the 24 h Wake 1st ($n = 22$) and 24 h Sleep 1st ($n = 22$) protocols.

equated (see the 24 h Wake First and 24 h Sleep First conditions in **Figure 1**, labeled "b"). By an interference account, sleep directly following learning should merely post-pone the deleterious effects of interference that would ensue upon subsequent waking. Memory performance should therefore be equivalent regardless of whether sleep comes soon after learning, or after a day of wakefulness. Alternatively, if memory processing continues on a normal, or perhaps facilitated, level during sleep, performance should be better when sleep comes shortly after learning than when it comes later in the retention interval, despite equal time spent awake during which interference would be expected to occur. A consolidation account would argue for this latter possibility because key events of the consolidation process occur in the minutes and hours following learning (McGaugh, 2000); thus, sleeping soon after encoding should help stabilize the memories and protect them from subsequent interference.

To examine how the positioning of sleep would affect emotional memory formation across a 24 h delay, we presented subjects with neutral or negatively arousing objects (e.g., an intact car or a wrecked car) on a neutral background (e.g., a street), and later tested recognition memory separately for the objects and backgrounds (see **Figure 2**). This task consistently reveals an "emotional memory trade-off" following brief (e.g., 30 min) time delays (Kensinger et al., 2007). Such trade-offs are said to occur when negatively arousing objects are better remembered than neutral objects, yet the neutral backgrounds associated with negative objects are remembered more poorly than similar backgrounds presented with neutral objects (**Figure 2**). A real world example of this trade-off is the weapon-focus effect, where victims vividly remember an assailant's weapon but have poor memory for peripheral aspects of the scene (Stanny and Johnson, 2000).

Such trade-offs are thought to be produced at encoding, because attention during memory acquisition is focused on the emotionally salient central aspects of the scene at the expense of the neutral features of the background, an effect supported by an eye-tracking study presented in this issue (Niu et al., 2012). However, the emotional memory trade-off is also clearly influenced by post-encoding consolidation processes, as the magnitude of the effect is larger after a delay that includes sleep (Payne et al., 2008). Thus, preliminary evidence suggests that

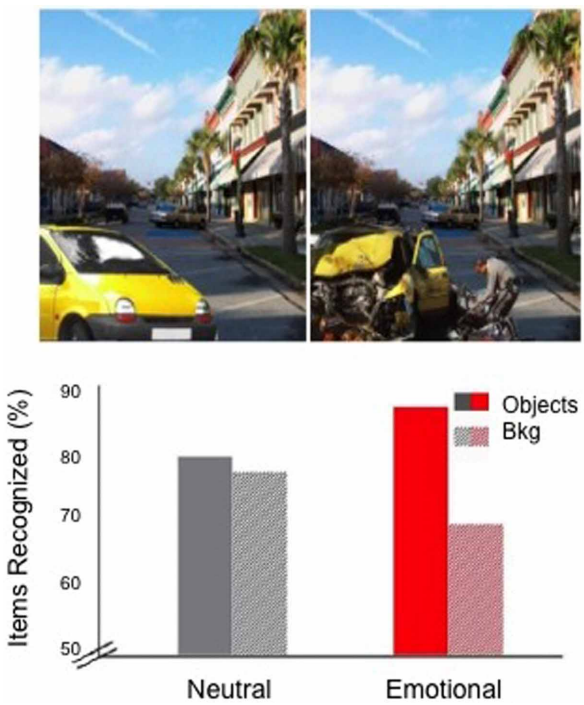

FIGURE 2 | The emotional memory trade-off effect. Top—Sample stimuli with the identical neutral backgrounds and either a neutral (left) or negative emotional (right) object in the foreground; **Bottom**—Emotional trade-off (following a 30 min delay, from Payne et al., 2008) is seen on right as increased recognition of emotional objects with impaired recognition of neutral backgrounds. Figure adapted from Payne and Kensinger (2010).

the discrete components of emotional scenes (objects, backgrounds) continue to undergo qualitatively different processing post-encoding. Little is known, however, about how the different components of emotional memories continue to be processed and transformed over longer periods of time following sleep. For example, it is unclear how long such trade-offs last in memory, whether memory for objects and backgrounds remain stable over time, or continue to diverge, and whether the initial positioning of sleep is important for these effects.

The current study had several goals. In the first experiment, we asked whether preferential memory for emotional objects following a night of sleep would be positively correlated with time spent in REM sleep. In the second experiment, we examined whether such preferential emotional remembering would persist across a longer delay of 24 h. Here we also examined the impact of sleep's placement on memory for the components of scenes in two conditions, comparing a condition where sleep occurred shortly after learning to a condition where sleep did not occur until after a day of wakefulness. Importantly, time spent awake and thus subject to interference was equated in these two 24 h delay conditions. While an interference account would predict no differences between the two conditions, a consolidation account would predict a lasting change in the trade-off effect, and perhaps a magnification of it if sleep triggers changes that continue throughout the following day.

METHODS

PARTICIPANTS

In the first experiment, which was designed to polysomnographically (PSG) examine the overnight sleep stage correlates of selective emotional memory consolidation, students from the University of Notre Dame and Boston College ($n = 27$) participated for payment (age 18–25). In the second study, designed to examine patterns of memory performance across the longer delay (24 h), 44 college students (age 18–22) from Boston College participated for course credit or payment. All subjects slept for >7 h between training and test ($M = 8.2$ for the overnight PSG group, $M = 8.0$ h for the sleep first group, and $M = 7.5$ h for the wake first group; $t > 0.30$, *ns*), and for 7.1 h on average the night prior to the experiment ($M = 7.3$ h for the overnight PSG group, $M = 7.1$ h for the sleep first group, and $M = 7.0$ h for the wake first group; $t > 0.90$, *ns*). All participants were native English speakers with normal or corrected-to-normal vision. Participants reported no history of psychiatric or sleep disorders, nor were they taking medications that affect the central nervous system or sleep architecture.

MATERIALS

Stimuli in both experiments consisted of negative arousing or neutral objects placed on neutral backgrounds to create realistic scenes (Kensinger et al., 2007; Payne et al., 2008). The scenes were crafted by placing one of a pair of negative arousing objects (e.g., one of two crashed cars) or neutral objects (e.g., one of two intact cars) against one of a pair of neutral backgrounds (e.g., one of two streets). The pairs of objects and backgrounds were selected such that the items of a pair shared the same verbal label (e.g., both were intact cars) but differed in perceptual feature (e.g., color, shape, size, and orientation). Each scene thus consisted of an object (either neutral or negative in valence) placed on a background (which was always neutral). For example, a neutral scene might consist of an avocado (a neutral object) placed on a countertop (a neutral background), while a negative scene might consist of a spider (a negative object) on a countertop (a neutral background). By varying the object type (neutral or negative), the object version (one of two paired objects), and the background version (one of two paired backgrounds), eight versions of the 64 scenes were created.

Objects and backgrounds were selected from a group of stimuli that had been previously rated for arousal and valence using 7-point scales (Kensinger et al., 2006). Negative objects were all given arousal ratings of 5–7 (with high scores indicating an exciting or agitating image and low scores indicating a calming or soothing image) and valence ratings lower than 3 (with lower scores indicating a negative image and high scores indicating a positive image). Neutral objects and backgrounds were rated as non-arousing (with arousal scores lower than 4) and neutral (with valence scores between 3 and 5; see Kensinger et al., 2007 for more details about the rating procedures).

PROCEDURE

Participants in the first, overnight PSG, study arrived at the sleep laboratory between the hours of 9 and 10 pm. Electrodes were applied while they watched a non-arousing video. Sleep was recorded with Grass/Telefactor/Comet polysomnography systems. The montage included electrooculography (EOG), electromyography (EMG), and EEG leads (F3, F4, C3, Cz, C4), with each electrode referenced to the contralateral mastoid. Sleep data were scored according to the standards of Rechtschaffen and Kales (1968). Following PSG hookup, participants viewed the stimuli (between 10:15 and 11:30 pm) prior to going to bed. After a full night of sleep, and at least 30 min after awakening (to allow for recovery from sleep inertia), recognition memory was tested (between 7 and 9 am). A summary of sleep measures is provided in **Table 1**.

Table 1 | Sleep parameters for subjects in overnight sleep study.

Sleep parameter	Mean time (min) ± SEM	% Total sleep time ± SEM
Total sleep time	435 ± 12	–
Wake after sleep onset	28 ± 4	–
Sleep latency	12 ± 2	–
Stage 1	23 ± 2	5.3 ± 0.5
Stage 2	228 ± 8	52.3 ± 1.4
Stage 3	30 ± 2	6.9 ± 0.5
Stage 4	60 ± 4	14.0 ± 0.9
SWS (Stages 3 + 4)	90 ± 4	20.7 ± 0.9
REM	94 ± 5	21.6 ± 1.1

An overview of the amount of time spent in various stages of sleep (Sleep Parameters) for the participants in the overnight PSG study. Time is given in both mean time in bed and percentage of the total time asleep. Note: All measures are in minutes. Sleep Latency = latency to sleep onset (first epoch of sleep). S1–S4, Stages 1–4; SWS, Slow Wave Sleep; REM, Rapid Eye Movement sleep.

In the second study, participants were randomly assigned to the "Sleep First" condition ($n = 22$), or the "Wake First" condition ($n = 22$). Subjects in the Sleep First condition viewed the stimuli between the hours of 7 and 9 pm and were tested ∼24 h later, again between the hours of 7 and 9 pm. Subjects in the Wake First condition viewed the stimuli between the hours of 9 and 11 am and were tested ∼24 h later, again between the hours of 9 and 11 am.

All participants studied a set of 64 scenes (32 with a negative arousing object on a neutral background and 32 with a neutral object on a neutral background) for 5 s each. The version of the scene shown during the study phase was counterbalanced across participants. Once a given scene was removed from the screen, participants were asked to indicate whether they would want to approach or move away from the scene if they were to encounter it in real life, a procedure used to ensure deep encoding in this otherwise incidental learning task. Responses were made by button press, using the numbers 1–7, with "1" indicating that they would move closer, "7" indicating that they would move away, and "4" indicating that they would stay at the same distance.

After the relevant delay period, subjects performed an unexpected, self-paced recognition test. They viewed objects and backgrounds separately and one at a time (i.e., subjects never saw the scenes in their entirety at test). Some of the objects and backgrounds presented were identical to those that had been previously studied (*same)*, others were the alternate version of the object or background pair and thus differed from the studied version in perceptual features but not verbal label (*similar*), and some were new objects or backgrounds that had not been studied (*new*). Participants saw either the *same* or the *similar* version of an object or background on the recognition test, never both versions. Each object and background presented on the screen was accompanied by a question (e.g., "Did you see a spider?"). Participants responded "same" if the answer to the question was "yes" and if the object or background presented was the exact match to what had been viewed during the study phase. Participants responded "similar" if the object or background shared the same verbal label, but was not an exact match to a studied component. If the answer to the question was "no," participants responded "new," indicating that the object or background had not been seen during the study phase. All responses were made on the keyboard, with "i" indicating "same/identical," "s" indicating "similar," and "n" indicating "new."

The recognition task included 32 *same* objects (16 negative, 16 neutral), 32 *similar* objects (16 negative, 16 neutral), 32 *new* objects (16 negative, 16 neutral), 32 *same* backgrounds (16 previously shown with a negative object, 16 previously shown with a neutral object), 32 *similar* backgrounds (16 previously shown with a negative object, 16 previously shown with a neutral object), and 32 *new* backgrounds.

DATA ANALYSIS

As in other studies requiring subjects to make same/similar distinctions at retrieval (Garoff et al., 2005; Kensinger et al., 2006), we considered "same" responses to *same* items to reflect memory for the visual details of the studied object or background ("specific recognition"). However, this is a highly stringent measure of memory accuracy, particularly in light of the long delay used here. Thus, we also examined memory by a less stringent "overall recognition" measure ("same" + "similar" response to *same* items, see Kensinger et al., 2007). Consistent with previous studies using this measure (e.g., Kensinger et al., 2007; Payne et al., 2008), *same* items given either a "same" or a "similar" (and not a "new") response were considered to reflect memory for at least some aspects of the studied item, because subjects have to remember at least that a given type of object or background had been studied (i.e., that they had seen some kind of avocado or some kind of countertop)—otherwise, they would have indicated that the item was "new." Both overall and specific recognition scores were computed separately for the central object (negative or neutral) and for the background on which objects were presented (always neutral). Although false alarms ("same" responses to *new* items) were relatively low (less than 14% in all cases), and did not differ between groups on any measure, all recognition scores were corrected for false alarms. By examining memory performance across 24 h in the "Sleep First" and "Wake First" conditions, we were able to examine how the passage of time influenced memory depending on the placement of sleep.

RESULTS

IS MEMORY FOR EMOTIONAL OBJECTS ASSOCIATED WITH REM SLEEP?

Our first goal was to determine whether selective emotional memory was specifically associated with REM sleep. As in Payne et al. (2008), we found clear evidence for the emotional memory trade-off following the 12 h overnight delay. The 2 (Object valence: Negative, Neutral) × 2 (Scene component: Object, Background) repeated measures ANOVA revealed a significant interaction between Object valence and Scene component, both for specific recognition, [$F_{(1,\ 26)} = 26.7$, $p < 0.001$], and overall recognition [$F_{(1,\ 26)} = 23.6$, $p < 0.001$]. While specific recognition of negative objects was significantly better than for neutral objects, [$t_{(26)} = 5.9$, $p < 0.001$], memory for backgrounds that had contained these negative objects was impaired relative to backgrounds that had contained neutral objects [$t_{(26)} = 2.9$, $p = 0.007$]. The same was true for overall recognition memory [$t_{(26)} = 3.3$, $p = 0.003$ and $t_{(26)} = 4.1$, $p < 0.001$, respectively].

As predicted, Pearson's r correlations revealed that overnight memory for emotional objects was positively correlated with both the total amount of time spent in REM and percent of total sleep time spent in REM (REM%) (**Figure 3**). This was the case for specific recognition ("same" responses), [REM, $r_{(27)} = 0.57$, $p = 0.002$; REM%, $r_{(27)} = 0.58$, $p = 0.002$] as well as overall recognition ("same" + "similar" responses), [REM $r_{(27)} = 0.54$, $p = 0.003$; REM%, $r_{(27)} = 0.52$, $p = 0.006$]. The specificity of this effect is highlighted by the fact that no other sleep stage (stage 1, 2, SWS), or total sleep time, correlated with emotional object memory, nor did any sleep stage correlate with any of the other memory measures (neutral objects or backgrounds that were associated with either negative or neutral objects).

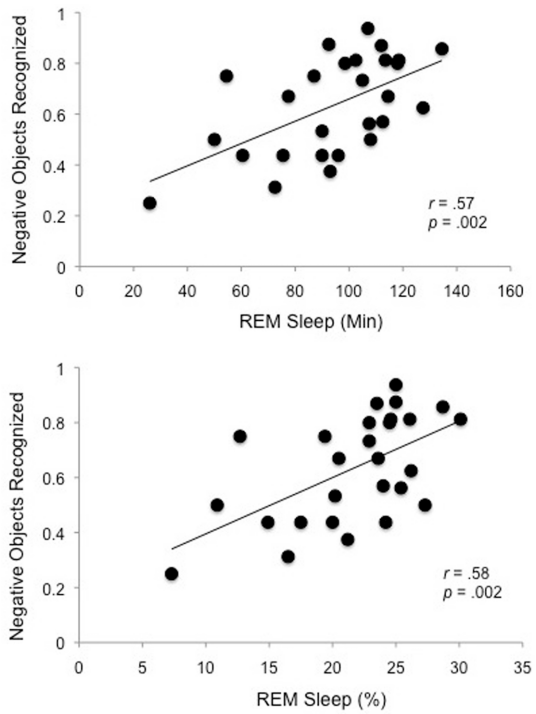

FIGURE 3 | REM sleep correlations. Specific recognition of negative objects is selectively positively correlated with time spent in REM sleep (REM Sleep Min) and with percent of the night spent in REM sleep (REM Sleep %).

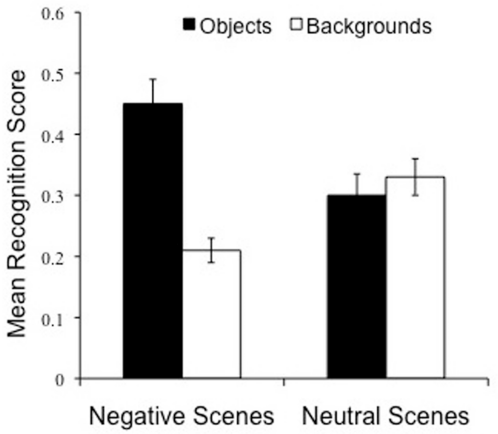

FIGURE 4 | Twenty-four hours delay memory performance overall. The emotional memory trade-off effect is preserved following a 24 h delay. Note that object memory is superior for negative, compared to neutral, scenes ($p < 0.001$), while scene backgrounds are more poorly remembered if they are paired with negative, compared to neutral, objects ($p < 0.001$).

DOES THE EMOTIONAL MEMORY TRADE-OFF PERSIST ACROSS A 24 H DELAY?

Our next goal was to examine whether there would be evidence for the emotional memory trade-off 24 h post-encoding, or rather this long delay would weaken or eliminate it completely. We thus conducted a 2 (Object valence: Negative, Neutral) × 2 (Scene component: Object, Background) repeated measures ANOVA on specific recognition. As predicted, there was a highly significant interaction between Object valence and Scene component, [$F_{(1,\ 42)} = 60.1\ p < 0.001$], which confirms the existence of the trade-off 24 h post-encoding (**Figure 4**). While negative object memory was significantly better than neutral object memory, [$t_{(43)} = 5.6$, $p < 0.001$], memory for backgrounds that had contained these negative objects was impaired relative to backgrounds that had contained neutral objects [$t_{(43)} = 3.8$, $p < 0.001$]. In addition, although objects and backgrounds were recognized at similar rates within neutral scenes, [$t_{(43)} = 0.7$, $p = 0.48$, *ns*] (**Figure 4**, right), objects were significantly better recognized than backgrounds within negative scenes, [$t_{(43)} = 4.4$, $p < 0.001$] (**Figure 4**, left). The Valence by Scene component interaction also emerged in overall recognition, [$F_{(1,\ 42)} = 56.9$, $p < 0.001$]. Again, while negative object memory was significantly better than neutral object memory, [$t_{(43)} = 5.7$, $p < 0.001$], memory for backgrounds that had contained negative objects was impaired relative to backgrounds containing neutral objects [$t_{(43)} = 3.3$, $p = 0.002$]. Moreover, although objects and backgrounds were recognized at similar rates within neutral scenes, [$t_{(43)} = 0.5$, $p > 0.60$, *ns*], objects were significantly better recognized than backgrounds within negative scenes, [$t_{(43)} = 6.8$, $p < 0.001$]. These findings confirm and extend the well-documented trade-off for the central and peripheral components of emotional scenes seen after brief time delays (Kensinger et al., 2007; Payne et al., submitted), and after a 12 h delay (Payne et al., 2008; Payne and Kensinger, 2011), revealing that the effect is still present 24 h after study.

THE TRADE-OFF EFFECT IN THE SLEEP FIRST VS. WAKE FIRST CONDITIONS

Nevertheless, the strength of the trade-off effect is strongly modulated by the nature of the delay between training and test. In the Payne et al. (2008) study, we found evidence for a magnified trade-off following a night of sleep relative to both a 30 min baseline condition and a period of daytime wakefulness. An interference account would deem this effect merely passive and temporary, and would thus predict no differences between the Sleep First and Wake First groups in a memory test given 24 h post-encoding. A consolidation account, on the other hand, would predict a lasting change in the trade-off, and perhaps a magnification of it if sleep triggers changes that continue throughout the following day. To differentiate between these possibilities, we examined whether Object valence (Negative, Neutral) and Scene component (Object, Background) further interacted with the Delay variable (24 h Sleep First vs. 24 h Wake First). There was a highly significant 3-way interaction among the variables, both for Specific recognition, [$F_{(1,\ 42)} = 21.3$, $p < 0.001$], and Overall recognition [$F_{(1,\ 42)} = 18.3$, $p < 0.001$], which reveals distinct patterns of emotional remembering in the Sleep First and Wake First conditions (**Figure 5**). Negative, but not neutral, objects were better remembered in the Sleep First condition than in the Wake First condition. This effect was significant for Specific recognition, [$t_{(42)} = 2.0$, $p < 0.05$], and emerged as a strong trend for Overall recognition, [$t_{(42)} = 1.8$, $p = 0.08$]. Moreover,

the backgrounds associated with negative, but not neutral, objects were more poorly remembered in the Sleep First condition than in the Wake First condition, an effect that was significant for both Overall recognition, [$t_{(42)} = 2.2$, $p = 0.03$] and Specific recognition, [$t_{(42)} = 2.7$, $p = 0.01$]. Thus, while negative object memory was enhanced in the Sleep First relative to the Wake First condition, memory for the backgrounds on which they were presented was impaired in the Sleep First relative to the Wake First condition (see **Figure 5A**).

In addition, the emotional memory trade-off effect emerged in the Sleep First, but not the Wake First, condition. Although the 2-way interaction between Object Valence and Scene Component was significant in both the Sleep First group, [$F_{(1, 21)} = 73.3$, $p < 0.0001$] and the Wake First group, [$F_{(1, 21)} = 5.1$, $p = 0.03$], only the Sleep First group showed evidence *both* of superior memory for negative over neutral objects, [$t_{(21)} = 6.3$, $p < 0.0001$], and impaired memory for backgrounds associated with negative over neutral objects, [$t_{(21)} = 5.0$, $p < 0.0001$]. The Wake First group, on the other hand, showed evidence only for the former, [$t_{(21)} = 2.5$, $p = 0.02$], but not the latter comparison, [$t_{(21)} = 0.12$, $p = 0.90$, *ns*]. These patterns can be seen in **Figure 6**. This finding demonstrates that the trade-off effect following a 24 h delay is driven largely by the Sleep First, and not the Wake First, condition.

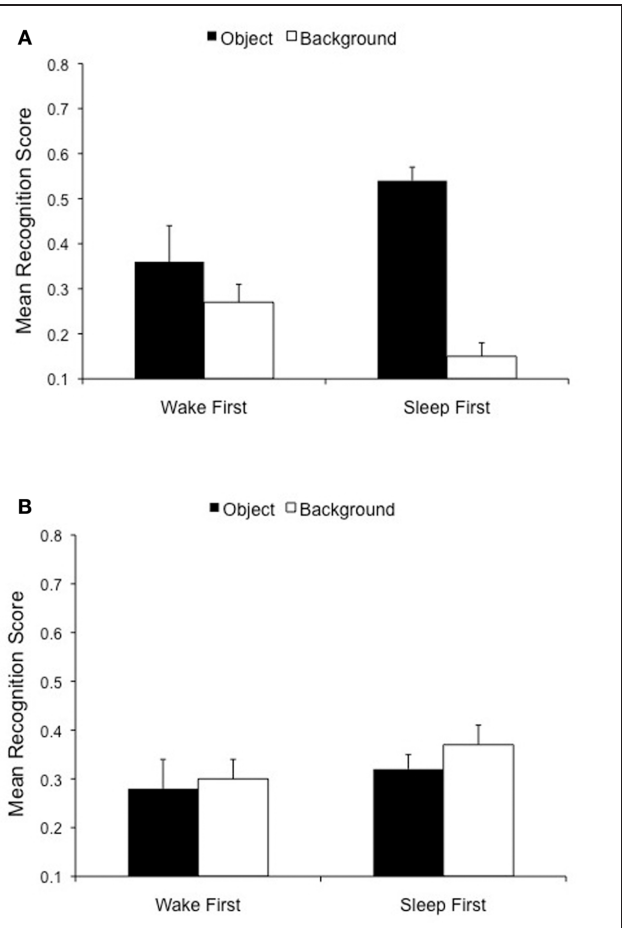

FIGURE 5 | Twenty-four hours delay memory performance is modulated by the placement of sleep. (A) Negative objects are better remembered in the Sleep First ($p < 0.05$), compared to the Wake First, condition, but the opposite is true for associated backgrounds ($p < 0.05$). **(B)** The Sleep First and Wake First groups do not differ on memory for any component of the neutral scenes.

CHANGES IN SCENE MEMORY OVER TIME

In a previous study using identical methods (Payne et al., 2008), we examined memory for these scenes across three additional time intervals: 30 min, 12 h spanning a night of sleep, and 12 h spanning a day of wakefulness (**Figure 1**, labeled "a"). We present this information in relation to the 24-h (i.e., Sleep First and Wake First) delay intervals because it helps us understand how the components of these emotional scenes continue to change over time, and whether sleep has a longer lasting influence on their

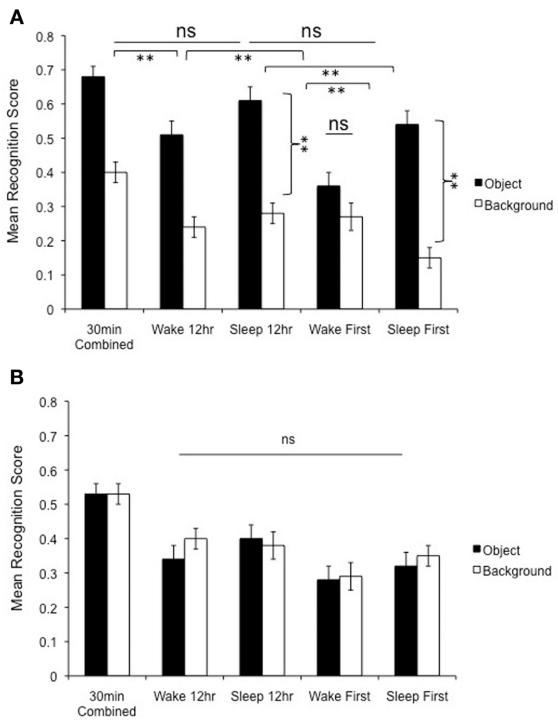

FIGURE 6 | (A) Change in memory across time. Relative to the 30 min condition, negative object memory was preserved 12 h later provided that subjects slept in the delay interval (Sleep 12 h group). Moreover, there was no further deterioration in negative object memory over the next 12 h (comparison between the Sleep 12 and 24 h Sleep First group). However, the backgrounds associated with these negative objects continued to deteriorate across these delay intervals, suggesting that sleeping soon after learning is key for protecting memory for emotional components of scenes. In the wake groups, on the other hand, memory for negative objects continued to deteriorate from the 30 min to Wake 12 h and from Wake 12 to 24 h Wake First delays, which depicts a pattern of increasing memory deterioration for negative objects in the wake groups. Note also the absence of the trade-off effect in the 24 h Wake First group (no difference in memory for objects vs. backgrounds), as well as the increased magnitude of the trade-off effect in the two sleep conditions (sleep 12 and 24 h Sleep First—see brackets). $^{**}p < 0.01$. **(B)** Memory for neutral scenes shows a net decline over time, but note that the groups groups do not differ in memory for objects vs. backgrounds at any of the delay intervals.

consolidation. As a caveat, it should be noted that these are cross-experiment comparisons; we are not tracking changes in memory in the same individuals. Still, given the similarity of the samples in the two studies (subjects were university students of the same age), we think these comparisons provide important preliminary evidence for how the components of these emotional scenes are retained over different delays, and can help us understand whether sleep has a longer lasting influence on their consolidation. Although the pattern of findings reported below was similar for all types of memory measured, we report corrected specific memory scores here[1] because those data (i.e., for the 12 h sleep and wake groups) were not reported in the Payne et al. (2008) study.

A 2 (Object valence: Negative, Neutral) × 2 (Scene component: Object, Background) × 5 (Delay: 30 min, 12 h Sleep, 12 h Wake, Sleep First, Wake First) repeated measures ANOVA conducted on corrected specific recognition memory revealed a highly significant interaction among the three factors, [$F_{(4,\ 126)} = 5.4$, $p = 0.001$] (**Figures 6A,B**). Several interesting patterns emerge when comparing the 30 min, 12 h Sleep, and 24 h Sleep First conditions (see **Figure 6A**). First, there was no impairment in memory for negative objects tested after a 30 min delay vs. a 12 h delay, provided that delay contained sleep ($p = 0.25$); if, however, this delay occurred across a 12 h delay of wakefulness, memory for negative objects suffered significant deterioration ($p = 0.002$). Backgrounds, on the other hand, continued to deteriorate regardless of delay condition (12 h wake, $p = 0.001$, 12 h sleep, $p = 0.006$), suggesting that sleep selectively preserves only the emotional components of these scenes (see Payne et al., 2008). Strikingly, this selective benefit of sleep may last across even longer delays: there was no significant difference in memory for negative objects tested after 12 h vs. 24 h when sleep occurred soon after study (i.e., when comparing the 12 h Sleep and 24 h Sleep First conditions; $p = 0.20$), but there was an additional, precipitous decline in memory for their associated backgrounds that occurred over this additional twelve hour delay ($p = 0.009$).

An interesting consequence of this continued deterioration of negative scene backgrounds is a further magnification of the trade-off in the 12 h Sleep and 24 h Sleep First condition, which can be seen by examining the difference between objects and backgrounds (see curved connectors in **Figure 6A**). Clearly, sleeping soon after encoding the scenes leads to the largest trade-off effects 12 and 24 h later. In fact, while the trade-off effect is present in the 12 h Wake condition, it dissipates in the 24 h Wake First condition (**Figure 6A**).

Looking next at the neutral scenes (**Figure 6B**), one can see that there is little to report, other than a continual decline in recognition rates for both objects and backgrounds across increasing delays. There were no significant differences between objects and backgrounds in any condition, nor were there differences, in either objects or backgrounds, between the 12 h Sleep and 12 h Wake conditions, or the Sleep First and the Wake First conditions. Thus, while the placement of sleep appears very important for selectively remembering the components of emotionally negative scenes, it has no influence on memory for the backgrounds associated with negative objects, or for neutral scenes in their entirety.

DISCUSSION

The field of emotional memory research is growing rapidly, but there is still much to learn about how memories for emotional events are processed, stored, and how they change over time (Payne and Kensinger, 2010). Although substantial evidence now suggests that the offline brain state of sleep provides ideal conditions for memory consolidation (reviewed by Stickgold, 2005; Ellenbogen et al., 2006; Diekelmann and Born, 2010) and transformation (reviewed in Payne and Kensinger, 2010, 2011), considerably less work has examined sleep's role in emotional memory formation. While several studies have shown that sleep enhances emotional episodic memories over neutral ones, the time course of these effects remains to be fully understood (although see Wagner et al., 2006 for an excellent preliminary study), as do the sleep stages involved.

Here, we show a clear relationship between REM sleep and preferential emotional memory consolidation. Memory for emotional objects (but not neutral objects or the backgrounds associated with either emotional or neutral objects) was positively correlated with REM sleep, but not with any other sleep stage. Indeed, the only correlations to emerge between any of the measures of memory and sleep were those between the two REM measures (time spent in REM sleep and % of the night spent in REM sleep) and correct recognition of emotional objects (for both specific and overall recognition). This finding builds on previous studies using naps (Nishida et al., 2009) and split-night designs (Wagner et al., 2001) to implicate REM sleep in emotional memory consolidation. To our knowledge, however, it is the first to reveal a positive correlation between REM sleep and *selective* consolidation of emotional aspects of scenes in an overnight design. The fact that emotional memory retention correlates with a specific sleep stage reduces concerns that exposure to waking interference in the wake group (rather than active consolidation processes in the sleep group) drives the emotional memory benefit observed in the sleep group. If sleep served to merely passively protect memories from waking interference, one might expect total sleep time to correlate with memory performance, yet that was not the case here. Instead, a particular sleep stage—REM sleep—correlated specifically and exclusively with retention of emotional objects. The specificity of this correlation also reduces concerns that our results are due to time of day influences alone.

Further evidence against an interference interpretation is provided by the 24 h data. By an interference account, sleep passively, and transiently protects memories from retroactive interference, but only until they are exposed to interference the subsequent day (Wixted, 2004). Recently, an "opportunistic theory" of memory consolidation has been posited (Mednick et al., 2011), which

[1] False alarms, i.e., "new" responses to "same/identical" items, were subtracted from the specific memory hit rate. We refer the interested reader to the Payne et al. (2008) study for information on overall recognition memory following the sleep and wake delays. Because those data were previously published, we do not report them here. We note, however, that the ANOVA referred to above (i.e., with the 5-level Delay variable), when conducted on corrected overall recognition, returned a similarly significant interaction among the 3 factors, [$F_{(4,126)} = 5.7$, $p < 0.0001$].

argues that *any* condition resulting in reduced exposure to interference will benefit declarative memory consolidation. Thus, sleep *per se* is not uniquely beneficial to memory. However, even in our prior study (Payne et al., 2008), sleep's benefit to memory was strongly modulated by emotionality and scene component; that is, sleep and wake exerted a similar effect on memory for neutral objects and all backgrounds, but gave a specific boost to memory for emotional objects. Thus, while the broad pattern of results reported in that study appear to fit a more opportunistic account of memory consolidation, the dissociable and differential effects of wake and sleep on consolidation of emotional and neutral objects, and backgrounds is not parsimoniously explained by such an account. The current study further rules out an interference interpretation by assessing memory after two 24 h delay intervals, which, critically, contained equal amounts of sleep and wakefulness. In spite of the fact that waking interference was equated in the two groups, participants who slept shortly after learning (24 h Sleep First condition) had superior memory for emotional objects compared to those whose sleep was delayed for 16 h post-encoding following a full day of wakefulness (24 h Wake First condition). Together with the selective REM sleep correlation reported above, it becomes difficult to explain the current data via an interference account alone. Similarly, while we recognize that the 24 h data are subject to circadian confounds, and concede that a time of day explanation cannot be fully ruled out in that design (see Schmidt et al., 2007 for an excellent review of circadian influences on cognition), the selective correlation with REM sleep minimizes concerns about a strict circadian interpretation of our results (although we acknowledge that circadian influences could be operating in concert with REM sleep physiology, especially as chronotype was not controlled for). Given that emotional memory performance has also been associated with REM sleep in a daytime nap study (Nishida et al., 2009), where all subjects were trained and tested in the afternoon, we believe that active (neurobiological) processes occurring during (REM) sleep are likely to play a key role (Ellenbogen et al., 2006; Diekelmann and Born, 2010) in the selective emotional memory consolidation effects observed here.

The 24 h data not only suggest an active sleep-dependent consolidation process, but also emphasize that the *selectivity* of the process is maximized when sleep follows soon after learning. As can be seen in **Figure 5**, the difference in memory between negative objects and their backgrounds was larger in the Sleep First condition than in the Wake First condition, and only in the Sleep First condition did memory for backgrounds accompanying negative objects fall below the levels of memory for backgrounds accompanying neutral objects. Thus, although sleep conveys a benefit to memory regardless of how soon after learning the placement of sleep occurs, it is the *selectivity* of that benefit that is enhanced when sleep follows soon after learning.

The selective effects of sleep on memory are further emphasized in the comparisons of the 24 h conditions to the 12 h data from Payne et al. (2008). Memory for emotional objects did not deteriorate between the first 12 h (12 h sleep group) and the second 12 h (24 h Sleep-First group), suggesting that sleeping shortly after learning selectively stabilizes the emotional components of scene memories, such that subsequent wakefulness has a diminished negative effect. Notably, this "sleep first" effect has also been seen with tasks examining memory for paired associates (Payne et al., 2012), vocabulary learning (Gais et al., 2006), face-location pairs (Talamini et al., 2008), and an observational learning task (Van Der Werf et al., 2009), and has clear implications for learning (maximizing sleep's benefit by sleeping at the appropriate time after learning, e.g., studying one final time for an exam prior to bedtime). However, the backgrounds associated with the emotional objects suffered profound deterioration, above and beyond that seen after the first 12 h. This suggests that while the sleeping brain apparently "selects" emotional components of scenes for preferential consolidation, a benefit that lasts across a longer (24 h) delay interval, it does not give similar weight to memory for backgrounds, instead letting them continue to deteriorate (or perhaps actively suppressing them).

These findings suggest that the sleeping brain selects for consolidation only what is most emotionally salient about an experience and perhaps most relevant to future goals (Payne and Kensinger, 2010). Previous accounts have conceptualized such preferential emotional remembering as an encoding phenomenon (Loftus et al., 1987; Reisberg and Heuer, 2004; Talmi et al., 2008; Niu et al., 2012). More attention is paid to emotionally salient information at encoding; thus it is better remembered later on. But here we show that post-encoding, sleep-based consolidation processes also play a role in cementing and magnifying the emotional memory trade-off effect. If encoding factors alone were responsible for the trade-off effect, we would expect memory for scene components to be identical in the two delay conditions. If, on the other hand, sleep-based consolidation processes influence the development of the trade-off effect, then we might expect a divergence in the scene components in the two conditions, perhaps with a greater magnification of the trade-off in the Sleep First group than in the Wake First group, which is exactly what we find here. Between the 12 and 24 h delay groups, the trade-off was magnified across time when sleep occurred soon after learning. However, if wake occurred first in this 24 h interval, the trade-off that was observed even in the 12 h wake group becomes non-existent. This finding provides strong evidence that sleep-dependent consolidation processes are critical for the development and maintenance of the trade-off effect, not exclusively processes that occur during encoding.

A number of other studies support this notion of sleep continuing to protect and promote emotional memory processing over the long-term (Wagner et al., 2006; Sterpenich et al., 2009). Wagner et al. (2006) found that memory for emotional, but not neutral, narrative descriptions persisted 4 years later in subjects who had slept shortly after learning as compared to those who first remained awake. A potential mechanism for such effects is the refinement and redistribution of these memories to different regions of the brain, which sleep appears to support more effectively than wakefulness (Payne and Kensinger, 2011), and which results in changing activation patterns as delays grow longer (Sterpenich et al., 2007, 2009). For instance, Sterpenich et al. (2007, 2009) found that remembering emotional pictures studied before a period of sleep transferred activation from the medial temporal lobe to the cortex during testing occurring 3 days to 6 months after learning, a pattern

of activation that was much weaker in those who had remained awake after learning. Thus, there is compelling evidence that sleep, but not wake, soon after learning acts at the neural level to efficiently consolidate emotional memories, and these effects remain visible months and even years later.

An alternative interpretation of these and other sleep data is provided by the synaptic homeostasis hypothesis (Tononi and Cirelli, 2003). According to this hypothesis, learning increases the strength of synapses in the brain, which in turn requires synaptic downscaling during sleep, and specifically slow wave sleep, to return synaptic strength to baseline levels (Tononi and Cirelli, 2003). By this account, stronger memories are preserved because even after downscaling, these memories persevere the reduction in synaptic strength. Our results could be broadly consistent with this theory insofar as we find a degradation of memory over time for all scene elements, but with the least degradation for the most salient aspects of the scenes, the emotional objects. However, rather than observing a positive correlation between memory enhancement and SWS, as would be predicted by the synaptic homeostasis hypothesis, we find that emotional memory enhancement is correlated with REM sleep. While our results are not easily explained by synaptic homeostasis, and instead appear to be the result of active consolidation processes occurring during specific sleep stages, the two accounts are not mutually exclusive. It may well be that some refinement of memory traces occurs during slow wave sleep, which is in turn followed by REM sleep-based processes that are key for emotional experiences.

Collectively, these results have important implications for adaptive remembering. It has long been known that forgetting is adaptive, but optimal memory functioning demands that we maintain a record of the events that hold future relevance (Levine and Edelstein, 2009). It thus seems reasonable that sleep-specific processes would selectively preserve the most salient, negative aspects of the scenes used here, even if this comes at the cost of the peripheral information, because knowledge of the emotional component will provide a greater benefit to the individual in the future. However, preferential retention of emotional information may also come at a cost; rumination and flashbacks may reflect vivid memories of negative events that are removed from the context in which they occurred, and as such, the present research may have implications for the etiology and prognosis of diseases like depression and post-traumatic stress disorder (PTSD). Both disorders are associated with sleep disturbances and abnormal sleep architecture, with several studies pointing to specific disruptions in REM sleep (Berger and Riemann, 1993). In fact, recent studies suggest that those with a history of trauma but not current PTSD do not exhibit the typical emotional memory trade-off, instead showing an overall memory bias for both the emotional and neutral objects at the expense of the backgrounds associated with both stimulus types (Mickley Steinmetz et al., 2012). Investigating what makes these individuals different from traumatized individuals who do develop PTSD, and what role sleep may play in this relationship, will be important topics for future study.

Understanding the cognitive and neural mechanisms underlying the development, maintenance, and long-term consequences of emotional memory trade-offs, and how sleep is involved, is critical for knowledge of healthy emotional processing as well as its dysfunction. The present data contribute to that larger goal by showing that sleep soon after learning triggers lasting memory for negative emotional components of an experience, at the expense of neutral components. The findings reported here cannot be easily accounted for by an interference account, and instead reveal that selective emotional remembering is associated with active processing during REM sleep.

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The influence of affective states varying in motivational intensity on cognitive scope

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We review a program of research that has suggested that affective states high in motivationally intensity (e.g., enthusiasm, disgust) narrow cognitive scope, whereas affective states low in motivationally intensity (e.g., joy, sadness) broaden cognitive scope. Further supporting this interpretation, indices of brain activations, derived from human electroencephalography, suggest that the motivational intensity of the affective state predicts the narrowing of cognitive scope. Finally, research suggests that the relationship between emotive intensity and cognitive scope is bi-directional, such that manipulated changes in cognitive scope influence early brain activations associated with emotive intensity. In the end, the review highlights how emotion can impair and improve certain cognitive processes.

Keywords: approach motivation, broadening, cognitive scope, EEG, emotion, ERP, narrowing, positive affect

We review research that has examined the effects of emotional states varying in motivational intensity on cognitive scope (narrowing/broadening). This research may yield insight into the issues with which this special issue is concerned. In particular, the research sheds light on the circumstances in which emotion may enhance vs. impair cognition and identifies individual differences that influence these effects.

Emotions (affective states) are complex psychophysiological constructs composed of many underlying dimensions. We define valence as the positive to negative evaluation of the subjectively experienced state (Harmon-Jones et al., 2011a,c). We define motivational intensity as the urge to move toward/away from a stimulus; it can range from low to high (Harmon-Jones et al., in press). Arousal, as measured subjectively and by activation of the sympathetic nervous system, is often posited to be a proxy for motivational intensity (Bradley and Lang, 2007). We concur with this definition but also posit that motivational intensity and arousal may be separable, as when one is aroused but not driven to engage in action (e.g., caffeine).

Our program of research has examined how affective states differing in motivational intensity influence the broadening or narrowing of cognition, which is defined as similar to cognitive expansiveness. It can occur at attentional or conceptual levels, it may involve the amount of information available in central executive resources (for comparing, maintaining, and manipulating) as well as perceptual resources (e.g., encoding), and it has been used in past discussions of the effects of emotions on cognition (e.g., Fredrickson, 2001). It has been measured in a number of ways, such as local/global attentional scope (Fredrickson and Branigan, 2005), visual selective attention (Rowe et al., 2007; Moriya and Nittono, 2011), perceptual encoding in the visual cortices (Schmitz et al., 2009), cognitive categorization (Isen and Daubman, 1984), and unusualness of associations (Isen et al., 1985).

As will be reviewed, affective states low in motivational intensity cause broadening, whereas affective states high in motivational intensity cause narrowing of cognitive scope. Thus, with regard to whether affective states impair or enhance cognition, we suggest on the basis of our research that certain affective states can enhance certain aspects of cognition while simultaneously impairing other aspects of cognition. Below, we explain our position in more detail.

POSITIVE AFFECTS VARY IN MOTIVATIONAL INTENSITY

Most previous research on the relationship between affective states and cognitive scope (broad vs. narrow) has examined positive affective states low in motivational intensity (amusement) and negative affective states high in motivational intensity (fear; Harmon-Jones and Gable, 2008). This confounding of affective valence with motivational intensity makes it difficult to claim that positive affect broadens (Fredrickson, 2001) and negative affect narrows cognitive scope (Easterbrook, 1959).

The prior research manipulated positive affect via gifts (Isen and Daubman, 1984), recall of past positive events (Gasper and Clore, 2002), or clips of humorous or satisfying events (Fredrickson and Branigan, 2005). We suggest that the positive affective state created by these manipulations is low in approach motivation because these manipulations create relatively passive states not associated with goal pursuit. Other positive affective states are higher in approach motivation, but they were not examined in past research on positive affect and cognitive scope.

This distinction between low and high approach motivated positive affect (which is on a continuum) is similar to other conceptualizations, such as ones that posit that appetitive or pre-goal positive states are different from consummatory or post-goal positive states (Knutson and Wimmer, 2007). Pre-goal and post-goal positive affect states are associated with different neural structures

and neurochemicals (Panksepp, 1998; Knutson and Wimmer, 2007; Harmon-Jones et al., 2008).

We posit that pre-goal, high approach-motivated positive affective states, such as desire and enthusiasm, narrow cognitive scope, so that organisms are not distracted by peripheral details that may impede goal pursuit. In contrast, post-goal, low approach-motivated positive affective states, such as satisfaction, promote openness to new opportunities. After the goal is accomplished, a broad cognitive scope allows new goal opportunities to be identified and later pursued. Low approach-motivated negative affect, such as sadness, also broadens cognitive scope. When goals are terminally blocked and motivation lowers, broadened attention may assist in finding new solutions to the goal or finding a new goal.

ATTENTIONAL SCOPE FOLLOWING LOW vs. HIGH APPROACH POSITIVE AFFECT

In our program of research, we measured attentional scope using two commonly used measures of local/global processing. The first, the Kimchi and Palmer (1982) task, presents several trials. In each trial, three figures, each comprising three to nine local elements (triangles or squares), are presented. One figure, the standard, is positioned on top, and the two other figures, the comparisons, are positioned below. One of the comparison figures has local elements that matched the local elements of the standard, whereas the other comparison figure has a global element that matches the global element of the standard. Thus, judgments of which comparison figure are more similar to the standard figure are based on either the global element of one comparison figure or the local elements of the other comparison figure. Participants indicate their "first and most immediate impression" as to which of the two comparison figures in each triad best matches the standard figure, and their choice indicates whether they were more locally (narrowly) or globally (broadly) focused at the moment.

The second, the Navon (1977) letters task, also presents several trials. The stimuli in the letters task are large letters composed of smaller letters. Each vertical and horizontal line of a large letter is made up of five closely spaced local letters (e.g., an *H* made up of *F*s). Participants are asked to indicate "as quickly as possible" whether the picture contains the letter *T* or the letter *H*, by pressing one button for *T* and another button for *H*. Global targets are those in which a *T* or an *H* is composed of smaller *L*s or *F*s. Local targets are those in which a large *L* or *F* is composed of smaller *T*s or *H*s. Faster responses to the large than to the small letters indicate a global (broad) focus, whereas faster responses to the small than to the large letters indicates a local (narrow) focus.

To test the effects of low vs. high approach-motivated positive affect on attentional scope (using the Kimchi and Palmer, 1982, task), low approach positive affect was created with a film clip of funny cats, and high approach positive affect was created with a film clip of desserts (Gable and Harmon-Jones, 2008, Experiment 1). Self-report manipulation checks indicated that the appropriate positive affective states were evoked without any negative affect. In support of the hypothesis, the dessert film (which caused high approach positive affect) caused less broadening of attention than the funny cats film (which caused low approach positive affect).

Other experiments found that dessert pictures caused more narrowing of attention than neutral pictures (Gable and Harmon-Jones, 2008, Experiment 2). Also, individuals who scored higher in trait approach motivation showed even more narrowing of attention following appetitive pictures (Gable and Harmon-Jones, 2008, Experiment 3). Increased approach motivation caused by leading individuals to believe they would get to eat desserts following picture viewing evoked even more narrowing of attention (Gable and Harmon-Jones, 2008, Experiment 4). In addition, alcohol-related pictures cause narrowed attention for individuals who are motivated to consume alcohol (Hicks et al., 2012). The above experiments measured attentional scope with the Navon (1977) task. These positive affect manipulations increase self-reported positive affect (e.g., excited, enthusiastic) but not negative affect.

EVOKING LOW vs. HIGH APPROACH-MOTIVATED POSITIVE AFFECT WITH MONEY

Other experiments have tested the primary hypothesis by evoking positive affect using stimuli other than emotional pictures. Low vs. high approach positive affect was manipulated in one experiment using the monetary incentive delay paradigm (Knutson et al., 2000; Knutson and Wimmer, 2007). In this task, cues indicating the possibility of gaining money for task performance are used to evoke pre-goal (high approach) positive affect, and different cues indicating the outcome of the task performance (whether a reward was obtained) are used to evoke post-goal (low approach) positive affect.

In one experiment (Gable and Harmon-Jones, 2010a), cognitive scope was measured by assessing recognition memory for neutral words that were presented either in the center of the computer monitor or in the periphery of the computer monitor. We found that superior memory for centrally presented words after pre-goal positive affect cues than after post-goal positive affect cues. In contrast, memory for peripherally presented words was superior after post-goal positive affect cues than pre-goal positive affect cues. Two experiments have conceptually replicated these results with Navon's (1977) local/global attentional scope task (Gable and Harmon-Jones, 2011a).

PERCEPTUAL vs. CONCEPTUAL PROCESSING FOLLOWING LOW vs. HIGH APPROACH POSITIVE AFFECT

To test whether low vs. high approach positive affect would influence other, more conceptual cognitive processes, we conducted two experiments in which narrowing/broadening of cognition was measured using Isen and Daubman's (1984) cognitive categorization task (Price and Harmon-Jones, 2010). In addition, we manipulated low and high approach positive states with an embodiment manipulation (Harmon-Jones et al., 2011b). In the high approach positive affect condition, participants smiled and leaned forward in a chair, similar to how one might lean toward an object of desire. In the low approach positive affect condition, participants smiled and reclined backward in a reclining chair, similar to how one might recline after goal accomplishment. In a moderate approach positive affect condition, participants sat upright and smiled. In the categorization task, which was completed while participants were in one of these postures,

participants rated the extent to which weakly associated exemplars (e.g., camel) of a particular category (e.g., vehicle) fit within that category. The high approach positive condition produced the most narrow categorizations (i.e., participants were more likely to indicate that the exemplars did not belong to the category), followed by the moderate approach positive condition, and then the low approach positive condition.

NEUROSCIENTIFIC EVIDENCE

To examine neural processes underlying the effects of approach positive affect on cognitive narrowing, we have conducted experiments using measures of electrical brain activity. In one experiment (Harmon-Jones and Gable, 2009), we measured electroencephalographic (EEG) alpha power to neutral and dessert picture primes and measured attentional scope following each prime using the Navon (1977) letters task. We focused on asymmetric frontal cortical activity, because greater relative left frontal cortical activity has been found to relate to approach motivation (Coan and Allen, 2004; Harmon-Jones et al., 2010). Results indicated that greater relative left frontal activity to the dessert pictures (but not neutral pictures) predicted attentional narrowing immediately following the dessert picture primes (Harmon-Jones and Gable, 2009).

In another experiment, we used the same methods (affective pictures and Navon letters task) but examined event-related brain potentials (ERP), specifically the late positive potential (LPP) of the ERP (Gable and Harmon-Jones, 2010b), which is sensitive to the motivational significance of stimuli (for review, see Hajcak et al., 2012). We found that the LPP was larger to dessert than neutral pictures. This LPP effect occurred over several brain regions, including medial central and parietal cortices. It also showed an asymmetric effect over the frontal cortex, with the dessert pictures evoking larger LPPs over the left than right frontal cortex. Importantly, LPPs to dessert pictures predicted attentional narrowing following the dessert pictures (no significant correlations were observed for neutral stimuli).

COMPARING NEGATIVE AFFECTIVE STATES DIFFERING IN MOTIVATIONAL INTENSITY

Based on the reviewed research, we suggest that the motivational intensity of the positive affect determines whether positive affect causes broadening or narrowing of cognitive scope. Does the motivational intensity of the negative affective state influence cognitive scope? Some past research on depression suggested that low intensity negative affect causes broadening (von Hecker and Meiser, 2005). We examined whether negative affects varying in motivational intensity influence cognitive scope (Gable and Harmon-Jones, 2010c). Low motivationally intense negative affect was created with pictures of sad events, whereas high motivationally intense negative affect was created with pictures of disgusting events. Both types of pictures evoked greater self-reported negative affect than neutral pictures did. However, sad pictures evoked lower self-reported arousal than disgust pictures. This suggests that the disgust pictures evoked greater motivational intensity than the sadness pictures. Conceptually consistent with the positive affect results, sad pictures broadened attention, whereas disgust pictures narrowed attention relative to neutral pictures (measured with the Navon, 1977, task).

In contrast to the above results, past studies suggest different outcomes for sadness. Gasper and Clore (2002) had participants write about "a personal life event that had made them feel either 'happy and positive' or 'sad and negative'." In Study 1, the manipulation check was similarly worded. In Study 2, the same manipulation was used and negative affect was measured with a wide array of negative emotion words. Gasper and Clore averaged all of these words together, suggesting that the affective state manipulated was a mix of negative states and not sadness alone. Rowe et al. (2007) found no differences between a neutral state and a sad state on attentional narrowing. We suggest that the effect of sadness on attentional scope may depend on whether the sadness evoked is lower or higher in motivational intensity; the latter may occur when sadness is mixed with other negative affects. Research is needed to test this idea.

These results suggest the need for a concept that explains how certain positive (e.g., desire) *and* negative (e.g., disgust) affects cause narrowing, whereas other positive (e.g., amusement) *and* negative (e.g., sadness) affects cause broadening. We suggest that the concept of motivational intensity explains these effects: low motivationally intense affects broaden cognitive scope whereas high motivationally intense affects narrow cognitive scope.

AFFECTIVE STATES, AROUSAL, AND MOTIVATIONAL INTENSITY

Does arousal rather than motivational intensity better explain how these different affective states influence cognitive scope? If arousal is the same as motivational intensity, as some have posited (Bradley and Lang, 2007), then the arousal explanation is the same as the motivational intensity explanation.

On the other hand, arousal and motivational intensity may occasionally be separate constructs. Humor evokes an arousing state that is low in approach motivational intensity: humor does not urge action toward something. Humorous films cause more attentional broadening than neutral films (Fredrickson and Branigan, 2005; Gable and Harmon-Jones, 2008), thus suggesting that arousal per se cannot account for the effect of high approach positive affective states on attentional narrowing.

We recently tested another instance where arousal and motivational intensity are separable. That is, arousal can be prompted by physical exercise but this state is not necessarily associated with motivational intensity (Gable and Harmon-Jones, under review). In this experiment, participants were randomly assigned to pedal a stationary bike or not while performing the appetitive vs. neutral picture/attentional scope task (Navon, 1977). Individuals who pedaled had faster heart rates than individuals who did not. More importantly, manipulated arousal had no effect on attentional scope. These results suggest that motivational intensity, rather than arousal *per se*, causes attentional narrowing.

THE EFFECT OF COGNITIVE SCOPE ON MOTIVATIONAL INTENSITY

Several experiments have revealed that affective states differing in motivational intensity influence attentional scope. Does attentional scope influence motivational intensity? Focusing narrowly on a motivationally significant object may increase motivation for the object, whereas considering the same object

from a broader perspective may decrease motivation for the object.

We have tested this hypothesis in two experiments with appetitive and aversive stimuli. In these tests, we examined motivational processing by measuring ERPs to appetitive and neutral pictures. We focused on the N1 component, an early ERP component related to selective attention that is larger to motivationally significant stimuli (Keil et al., 2001; Foti et al., 2009).

Immediately prior to the presentation of each affective or neutral picture, attentional scope was manipulated by having participants simply indicate what letter was displayed at the local or global level in a between-subjects design. That is, participants viewed Navon (1977) letters and indicated the letter that was displayed as a local element or they indicated the letter that was displayed in the global configuration.

As compared to a global attentional scope, a local attentional scope caused larger N1 amplitudes to appetitive (Gable and Harmon-Jones, 2011b) and aversive pictures (Gable and Harmon-Jones, under review) but not to neutral pictures. These results suggest that the relationship between narrowed attentional scope and motivational intensity is bi-directional. Other work suggests that priming a local vs. global attentional scope can influence how positive and negative moods (with unknown levels of motivational intensity) influence attentional scope (Huntsinger et al., 2010).

CONCLUSION

The evidence we reviewed suggests a revision to the well-accepted idea that positive affect broadens and negative affect narrows the scope of cognition. The reviewed evidence is consistent with previous evidence but suggests that previous results likely occurred because affective valence was confounded with motivational intensity: low motivationally intense positive affects were compared with high motivationally intense negative affects. The reviewed research manipulated affective valence independently of motivational intensity, and found that affective states low in motivational intensity broaden and affective states high in motivational intensity narrow the scope of cognition. Further research is needed to investigate the role of specific neural regions (e.g., amygdala, nucleus accumbens) and neurochemical processes (e.g., dopamine, opioids) within these regions in the effect of emotive states on attentional scope.

We suspect that motivationally intense affective states cause narrowing of cognitive scope because this often facilitates adaptive behavior that results in goal accomplishment (approach or avoidance of the stimulus). However, the narrowed cognitive scope that occurs with high motivationally intense affective states may hinder perception and processing of peripheral (or global) information that would prove useful. On the other hand, low motivationally intense affective states broaden cognitive scope, which may allow new goal opportunities to be identified and later pursued. However, the broadened scope that occurs with low motivationally intense affective states may hinder perception and processing of central (or local) information that would prove useful. Together, this body of research suggests that emotion may impair and improve cognitive processes depending on the situation in which the emotion occurs.

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Motivation matters: differing effects of pre-goal and post-goal emotions on attention and memory

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People often show enhanced memory for information that is central to emotional events and impaired memory for peripheral details. The intensity of arousal elicited by an emotional event is commonly held to be the mechanism underlying memory narrowing, with the implication that all sources of emotional arousal should have comparable effects. Discrete emotions differ in their effects on memory, however, with some emotions broadening rather than narrowing the range of information attended to and remembered. Thus, features of emotion other than arousal appear to play a critical role in memory narrowing. We review theory and research on emotional memory narrowing and argue that motivation matters. Recent evidence suggests that emotions experienced prior to goal attainment or loss lead to memory narrowing whereas emotions experienced after goal attainment or loss broaden the range of information encoded in memory. The motivational component of emotion is an important but understudied feature that can help to clarify the conditions under which emotions enhance and impair attention and memory.

Keywords: emotion, arousal, memory narrowing, motivation, goal relevance

Our most vivid and lasting memories are typically emotional ones. These memories are selective, however. People show excellent memory for information that is central to an emotional event, but poorer memory for peripheral details. Memory narrowing as a result of emotion has been demonstrated in numerous studies but sources of controversy remain. Researchers disagree about what constitutes central information versus peripheral detail, about whether emotion always leads to memory narrowing, and about underlying mechanisms. This review scrutinizes theory and research on memory narrowing and questions the common view that arousal is the primary mechanism underlying this effect. Inconsistencies in the literature are discussed, and alternative mechanisms are evaluated. We argue that several controversies can be clarified by the view that the goals or motivations associated with discrete emotions determine the breadth of cognitive processing. Taking into account the motivational function of emotions leads to a better understanding of when and why emotions enhance and impair cognition.

EMOTIONAL MEMORY NARROWING

The terms "emotional memory narrowing" (Reisberg and Heuer, 2007), "tunnel memory" (Safer et al., 1998), and "central/peripheral trade-off" (Kensinger et al., 2007) all refer to the finding that people tend to remember information central to, or at the core of, an emotional event, and have poorer memory for peripheral or background features of the event (e.g., Christianson and Loftus, 1991). Emotional memory narrowing has been demonstrated most famously via the "weapon focus" effect. In laboratory studies in which a crime is staged, witnesses tend to focus on and remember the weapon used to commit the crime at the expense of memory for details such as the perpetrator's face and clothing (e.g., Loftus et al., 1987; Kramer et al., 1990; Steblay, 1992). The weapon, or immediate source of danger, is the central and emotionally arousing stimulus whereas other information, such as the perpetrator's face or clothing, is peripheral to the concern of remaining safe. Thus, emotion is associated with the narrowing of attentional resources to a central threat at the expense of peripheral or background details.

Considerable evidence for emotional memory narrowing has been obtained in other laboratory-based studies as well (for reviews, see Christianson, 1992; Mather, 2007; Kensinger, 2009; Levine and Edelstein, 2009). For example, Christianson and Loftus (1987) showed participants slides that depicted a traumatic event (a boy getting hit by a car) or a neutral event (a boy crossing a street) and tested memory for the slides later. Participants who saw the traumatic event displayed better memory for central features of the slides, but were worse at remembering which specific slides they had seen, relative to those who saw the neutral event. This suggests that people remember different aspects of events depending on whether or not the events evoked emotion (also, see Christianson, 1984; Christianson and Loftus, 1991). Similarly, Kensinger et al. (2007) had participants view emotion-eliciting objects (e.g., a snake) and neutral objects (e.g., a chipmunk) in front of neutral backgrounds (e.g., a river). Participants showed more detailed memory for emotional than neutral objects but remembered backgrounds paired with neutral objects better than backgrounds paired with emotional objects. Thus, emotion was associated with enhanced memory for central information at the expense of peripheral details.

Outside the laboratory, people have shown enhanced memory for central features of emotional events as varied as natural disasters (Bahrick et al., 1998), physical injuries

(Peterson and Bell, 1996), crime scenes (Reisberg and Heuer, 2007), and personal events that evoked shock, anger, and fear (Berntsen, 2002). For instance, when asked to recount autobiographical events that were highly emotional, people showed enhanced memory for features that were integral to the events and essential to their meaning but poorer memory for peripheral details that made no difference to the meaning of the events (Talarico et al., 2009). In summary, a large body of research, both inside and outside the laboratory, indicates that emotion induces memory narrowing. Several unresolved issues remain, however. These include the aspects of emotion responsible for memory narrowing, whether all emotions lead to memory narrowing, and what constitutes central information versus peripheral detail. We turn to these issues next, reviewing approaches to emotional memory narrowing that emphasize arousal, valence, and goal relevance.

EMOTIONAL AROUSAL AND MEMORY NARROWING

Emotional arousal, a physiological state that ranges from calm relaxation to excitement and tension, is one of the major features of emotion (Russell, 2003), and is commonly considered to be the primary mechanism underlying memory narrowing. A high level of arousal results from activation of the autonomic nervous system and the release of stress hormones such as epinephrine and cortisol, and can be measured by indices such as heart rate and skin conductance. The view that emotional arousal induces narrowing of attention and memory dates back to the 1950s. Callaway and Dembo (1958) showed that people given stress hormones responded less to stimuli outside of their central line of vision. Similarly, Easterbrook's (1959) cue-utilization hypothesis states that emotional arousal reduces the number of cues that an organism can process at a time, decreasing attention allocated to peripheral information. The greater the intensity of arousal, the narrower the attentional focus. Because of this narrow focus, encoding of central information is enhanced, whereas encoding of peripheral details is impaired (for reviews, see Reisberg and Heuer, 2007; Mather and Sutherland, 2011). This assists organisms in reaching current goals by blocking out information irrelevant to those goals (e.g., LaBar and Cabeza, 2006).

In addition to influencing attention and encoding, arousal has been shown to promote consolidation of emotional information in long term memory through activation of the amygdala (e.g., Cahill et al., 1994; van Stegeren et al., 1998; Nielson et al., 2005; Dolcos et al., 2011). Infusing norepinephrine directly into the basolateral amygdala after the experience of emotional events enhances long term memory for those events. Inactivating this region, using lesions or drugs, attenuates memory enhancement (McGaugh, 2004, 2006). Stressful circumstances leading to cortisol release prior to retrieval of an emotional event can also lead to more pronounced memory narrowing relative to less stressful conditions (Echterhoff and Wolf, 2012). Thus, arousal affects attention, encoding, consolidation, and retrieval, and is thought to underlie enhanced memory for central information and poorer memory for information that is peripheral to the emotional event.

FINDINGS NOT EXPLAINED BY THE AROUSAL MODEL

Despite general agreement that arousal leads to memory narrowing, inconsistent results have been obtained. Emotion has been shown to enhance memory for both central and peripheral information (e.g., Heuer and Reisberg, 1990; Cahill and McGaugh, 1995; Libkuman et al., 1999; Dutton and Carroll, 2001; Laney et al., 2004), to impair memory for both central and peripheral information (e.g., Morgan et al., 2004), and to enhance memory for peripheral details (e.g., Fredrickson and Branigan, 2005; Talarico et al., 2009). Moreover, the effect of emotion on memory narrowing appears to be influenced by the valence of the event or stimulus (e.g., Berntsen, 2002; Waring and Kensinger, 2009; Mickley Steinmetz et al., 2010; van Steenbergen et al., 2011; Van Damme and Smets, submitted).

The most frequently reported violation of the arousal model of emotional memory narrowing is an enhancement of memory for both central and peripheral information. Laney et al. (2004) asked participants to view a series of slides that was rendered emotionally evocative or emotionally neutral via voice narration. Relative to participants in the neutral group, participants for whom the slides were placed in an emotionally arousing context reported greater subjective emotional intensity and showed greater physiological arousal. They also displayed enhanced memory for both central and peripheral features of the slides. Emotional arousal thus improved overall memory accuracy. These investigators argued that emotional memory narrowing may not occur without the presence of an "attention magnet" – a shocking and salient sensory stimulus such as a picture of a gruesome injury. They concluded that memory narrowing may not be an inevitable effect of emotional arousal but rather a byproduct of the type of shocking sensory stimuli most typically used to study the phenomenon.

A second set of findings conflicts with the view that emotional arousal enhances memory for central information by finding general memory impairment. For example, soldiers undergoing extremely stressful circumstances during military survival training (e.g., lack of food, sleep deprivation, and physical threats) were worse at identifying the faces of their interrogators than soldiers who underwent a less stressful interrogation (Morgan et al., 2004). A meta-analysis on the effects of stress on eyewitness memory also revealed that stress can impair memory for both the face of a perpetrator and details of the crime (Deffenbacher et al., 2004). In a spatial learning task, seeking monetary reward resulted in better memory than avoiding electrical stimulation, except when seeking reward led to high arousal (Murty et al., 2011). Thus, emotional arousal can lead to deficits in memory accuracy, including information of central importance to the emotion-eliciting event.

A third set of findings shows that emotional arousal can enhance, rather than impair, memory for peripheral details. For instance, Talarico et al. (2009) demonstrated that certain emotions (e.g., surprise, happiness, and sadness) were associated with greater recall of peripheral features of the emotion-eliciting events because they promoted broader reflection on the event as a whole. In addition, happiness and amusement have been found to enhance memory for global features of stimuli rather than leading to narrowing of attention or memory (e.g., Gasper and Clore, 2002; Fredrickson and Branigan, 2005).

Finally, the extent to which emotion leads to memory narrowing has been shown to vary depending on the valence of the emotion. Waring and Kensinger (2009) showed participants pictures of emotionally arousing objects placed within neutral

backgrounds and pictures of neutral objects placed within neutral backgrounds. The valence (positive, negative) and the level of arousal (low, high) of the emotional objects were manipulated. Background memory was generally worse for emotionally arousing objects than for neutral objects, but the effect was weakest for positive low arousal objects. After a 24 h study-test delay, a central-peripheral memory trade-off remained only for negative high arousal pictures, not for positive high arousal pictures or for low arousal pictures of either valence (also, see Mickley Steinmetz et al., 2010; Yegiyan and Yonelinas, 2011). This suggests that valence and arousal interact in determining the extent of emotional memory narrowing. Berntsen (2002) obtained similar findings with respect to autobiographical memories, with accounts of shocking events, but not happy events, containing more central than peripheral information.

REASONS FOR INCONSISTENT FINDINGS

We have reviewed research showing that emotional arousal narrows the range of information attended to and encoded in memory as well as findings that contradict this view. To make sense of emotional memory narrowing, and of results that violate this pattern of findings, it is necessary to be more explicit about what constitutes high versus low levels of emotional arousal, and what constitutes information that is central as opposed to peripheral to an emotional event. It is also necessary to consider mechanisms other than arousal that may underlie accurate and lasting memory for central information and poor memory for peripheral detail.

VARYING INTENSITIES OF EMOTION ACROSS STUDIES

One reason for inconsistencies in the findings is consistent with the arousal model. The effect of emotion on memory may differ depending on the degree of arousal, but "high arousal" is defined very differently across studies. Many studies contrast memory for stimuli or events that are deemed emotionally arousing versus emotionally neutral. The stimuli and events defined as arousing, however, range from relatively mild laboratory stimuli (e.g., Laney et al., 2004) to real world events that evoke extreme levels of stress (e.g., Morgan et al., 2004). Thus, emotion may enhance memory generally when the level of arousal is relatively low, lead to memory narrowing when the level of arousal is moderate, and impair memory generally when the level of arousal is extremely high (Baldi and Bucherelli, 2005). To the extent that investigators neglect to contrast increasing levels of arousal, and define high arousal differently across studies, non-linear relationships between arousal and memory would be difficult to identify.

VARYING DEFINITIONS OF CENTRAL AND PERIPHERAL INFORMATION

Another reason for inconsistencies in the findings concerning emotional memory narrowing may be that definitions of central and peripheral details vary widely across studies and theoretical frameworks (Kensinger, 2009; Levine and Edelstein, 2009). Central information has been variously defined as information that is spatially (e.g., Christianson and Loftus, 1991), temporally (e.g., Strange et al., 2003), or conceptually (e.g., Peterson and Whalen, 2001) integral to the emotion-eliciting event or stimulus, or as information that is relevant to the individual's current goals (e.g., Levine and Edelstein, 2009). Information considered to be central in one study may be viewed as peripheral in another. For instance, in research on the weapon focus effect, the clothing of the perpetrator holding the weapon may be considered spatially integral, and hence central, due to its proximity to the weapon (e.g., Christianson and Loftus, 1991). Alternatively, clothing can be considered a peripheral detail because it is distinct from the weapon or central attention magnet (Laney et al., 2004) and has no significance for the goal of avoiding threat (e.g., Levine and Edelstein, 2009).

In an effort to more clearly define "central" versus "peripheral" information, Mather and Sutherland (2011, 2012) proposed the "arousal-biased competition" (ABC) model. According to this model, emotional arousal enhances encoding of high priority information at the expense of low priority information. Information can attain high priority as a result of bottom-up perceptual processes or as a result of top-down conceptual processes. For instance, recent work on the ABC model has demonstrated that when participants were exposed to a loud, arousing noise or to negatively arousing images, they were more likely to recall perceptually salient stimuli (high contrast symbols and letters) versus less salient stimuli (low contrast symbols and letters), compared to when they were exposed to a neutral noise or image (Lee et al., 2012; Mather and Sutherland, 2012). The perceptual contrast of the symbols and letters is an example of salience resulting from bottom-up perceptual processes. In addition, the ABC model posits that memory for information that is relevant to a person's goals will be enhanced whereas memory for information that is not relevant will be impaired. This is an example of salience resulting from top-down processes. Thus, this model holds that emotional arousal enhances attention to, and memory for, information that has high priority at the expense of information that has low priority, regardless of whether the priority derives from bottom-up processes (perceptual salience) or top-down processes (goal relevance).

ALTERNATIVE MECHANISMS

As previously discussed, arousal is commonly viewed as the feature of emotion that leads to memory narrowing. However, a third reason for inconsistencies in the findings concerning emotional memory narrowing may be that features of emotion other than arousal play an important role in determining the range of information attended to and remembered. Investigations of alternative mechanisms are scarce, however, and potential mechanisms are often confounded in research on emotional memory narrowing. Turning again to studies of weapon focus, the sight of the weapon elicits physiological arousal, negative affect, the discrete emotion of fear, and the goal to protect the self from harm. Memory narrowing may be due to any one of these factors or to a combination of factors. Yet few studies experimentally manipulate one factor while holding other factors constant or controlling for them statistically (e.g., Ritchie et al., 2006). Thus, to account for findings that discrete emotions vary with respect to the range of information encoded in memory (e.g., Berntsen, 2002; Waring and Kensinger, 2009), it is necessary to consider other potentially important features of emotion. Two alternative approaches are discussed which suggest that features of emotion other than arousal influence the breadth of information attended to and remembered.

EMOTIONAL VALENCE AND MEMORY NARROWING

An alternative to the arousal model is the view that the valence of an emotion determines the type of information processing in which people engage and, as a result, the extent of memory narrowing. Kensinger (2009) reviewed evidence that negative emotion increases the processing and retrieval of sensory information, leading people to remember specific (central) details; in contrast, positive emotion increases the processing and retrieval of conceptual information, leading people to remember the gist of an event. In other words, negative emotion induces a focus on local details and therefore elicits a central-peripheral trade-off, whereas positive emotion leads to broadening of attention and reliance on gist or heuristics.

The affect-as-information model explains functions that may be served by these differing information processing strategies (e.g., Bless and Schwarz, 1999; Bless and Fiedler, 2006; Clore and Huntsinger, 2007; Clore and Palmer, 2009). According to this model, people use their affective state as a short-cut to infer their evaluative reactions to a situation, and this influences attention and memory. Negative emotion typically signifies that there is a problem to solve, and therefore signals the need to carefully monitor the environment for relevant information. Positive emotion signifies a safe situation in which no problems require immediate attention, so there is little need to focus on specific details. Hence, negative emotion triggers narrow item-specific or stimulus-driven processing, whereas positive emotion triggers broader relational or knowledge-driven processing. Extending this approach, Fredrickson's (1998, 2001) broaden-and-build theory holds that positive emotions broaden people's thought-action repertoires, promoting activities such as play, exploration, and integration of different types of information in the environment. This allows people to establish and build enduring cognitive, behavioral, and social resources. In contrast, negative emotions promote specific action tendencies (e.g., withdrawal when feeling fear) and narrow attention.

Empirical research on the attention broadening effects of positive emotion dates back to the 1980s. Isen et al. (1985, 1987) showed that positive emotion (induced through watching amusing film clips or receiving small gifts) enhances creativity and cognitive flexibility. More recently, positive emotion has been shown to enhance the accessibility of global information (Gasper, 2004), to promote attention to peripheral features of visual stimuli (e.g., Wadlinger and Isaacowitz, 2006; Rowe et al., 2007), and to broaden the scope of information encoded in memory (Gasper and Clore, 2002; Johnson and Fredrickson, 2005). For instance, Fredrickson and Branigan (2005) elicited positive, negative, or neutral affect in participants and then had them perform a global-local visual processing task (e.g., Navon, 1977; Kimchi and Palmer, 1982). Participants experiencing positive emotions (amusement or contentment) displayed a global attention bias relative to those experiencing neutral affect or negative emotions (anger or anxiety). This effect is thought to occur early on in visual processing (Kuhbandner et al., 2011).

Valence has also been shown to influence people's susceptibility to memory distortion and false memories. By promoting heuristic processing, positive emotion can increase suggestibility and susceptibility to incorporating misinformation into memory; by promoting systematic processing, negative emotion can render people more resistant to misinformation (e.g., Bless et al., 1996; Levine and Bluck, 2004; Forgas et al., 2005; Storbeck and Clore, 2005; Kensinger and Schacter, 2006). In summary, although both positive and negative emotion can be accompanied by physiological arousal, some research indicates that negative emotion leads to narrowing of the range of information attended to and remembered, whereas positive emotion leads to broadening.

MOTIVATION OR GOAL RELEVANCE AND MEMORY NARROWING

Despite incorporating one of the most crucial differences among emotions, a focus on valence alone cannot account for some recent findings. Even emotions of the same valence and the same level of arousal have been shown to vary with respect to the range of information attended to and the degree of memory narrowing. Thus, a more complete understanding of the effects of emotion on memory may require moving beyond arousal and valence to consider the motivational state underlying discrete emotions (e.g., Sander et al., 2003; Larson and Steuer, 2009; Levine and Edelstein, 2009; Gable and Harmon-Jones, 2010b,c,d; Lench et al., 2011; Harmon-Jones et al., 2012a,b). The goal relevance model contains elements of both the arousal and valence approaches but makes more specific predictions about the types of emotions that should lead to memory narrowing. According to this model, the motivational intensity (Gable and Harmon-Jones, 2010d) or goal status (Levine and Pizarro, 2004; Levine and Edelstein, 2009) of an emotion determines the degree of memory narrowing.

MOTIVATION AFFECTS ATTENTION AND MEMORY

A wealth of research supports the view that people's goals affect what they remember. Information relevant to a goal that has not yet been achieved remains more accessible in memory than the same information after the goal has been achieved (Förster et al., 2005). People remember information exceptionally well if it is framed in terms of enduring, universal goals such as survival (e.g., Nairne et al., 2008). In part, this occurs because people deliberately prioritize information relevant to active goals, putting more effort into encoding and retrieving it (e.g., Adcock et al., 2006). But memory enhancement for goal-relevant information also occurs automatically even when people are not instructed to remember the information or rewarded for doing so. In one study, participants showed enhanced performance on both an explicit memory task and an implicit memory task (facilitated access in lexical decision) for words that had been assigned a high point value. They also showed memory narrowing – poorer memory for the context in which high reward words had been learned. This occurred even though memory for words with high point values was not rewarded and no instructions to remember those words were given (Madan et al., 2012). Thus, consistent with prior research on the effects of emotional arousal on memory (e.g., Mather and Sutherland, 2011), these findings suggest that memory for goal-relevant stimuli is enhanced and that this benefit can occur at the expense of contextual details.

People's goals differ depending on their developmental stage, personality traits, and coping styles. In each case, memory serves an adaptive function by retaining information that helps people reach

their goals (Nairne et al., 2007). For example, older adults, who are motivated to regulate emotion to promote well-being, attend to and remember positive information more readily than younger adults (Mather and Carstensen, 2005). People high in extraversion and approach motivation (traits characterized by the goal to approach positive outcomes) remember reward-relevant stimuli better, and recall more positively valenced autobiographical memories, relative to people high in anxiety and introversion, who remember more threat-relevant information (e.g., Derryberry and Reed, 1994; Gable and Harmon-Jones, 2008; Denkova et al., 2012; Study 3; Hicks et al., 2012). With respect to coping, people recall self-enhancing information more readily than self-threatening information (Taylor and Brown, 1988; Sedikides and Green, 2009) and may selectively remember the past as worse than it actually was in order to bolster the belief that they have improved over time (e.g., Wilson and Ross, 2001; Ross and Wilson, 2003; Walker and Skowronski, 2009). People with an avoidant attachment style, characterized by the goal of avoiding intimate relationships with others, display impaired memory for relationship-relevant words on a working memory task (Edelstein, 2006).

This research shows that people's goals, whether universal or individual, systematically shape what they attend to and remember. Motivation is a critically important component of emotion and may account to the effects of emotion on cognitive processing. Goals associated with discrete emotions (e.g., the goal of avoiding threat when feeling fear) may promote processing of goal-relevant information and impair processing of information that is peripheral to the goal. Thus, motivation or goal relevance represents an alternative mechanism that may account for emotional memory narrowing.

THE CONTRIBUTION OF MOTIVATION TO EMOTIONAL MEMORY NARROWING

According to appraisal theories, goals are at the heart of what it means for an event to be emotional. People continuously monitor the environment for information relevant to their current goals or well-being (e.g., Scherer, 1998). They experience emotions when they perceive a change in the status of a goal that makes it necessary for them to modify their beliefs or plans. This motivational component of emotion may contribute to memory narrowing. Levine and Edelstein (2009) distinguish between pre-goal and post-goal emotions. Pre-goal emotions such as desire, excitement, fear, and anger, reflect appraisals that goal attainment or failure may occur in the future but have not yet occurred or that goal-directed efforts are ongoing. Post-goal emotions, such as happiness, contentment, sadness, and grief, reflect appraisals that goal attainment or failure has already occurred. Gable and Harmon-Jones (2010d) make a similar distinction when they refer to "motivational intensity." High motivational intensity is experienced when a person is driven to approach or avoid specific stimuli in the environment because goal attainment or failure is anticipated but has not yet occurred.

Because information processing capacity is limited, the information most relevant to a person's goals in a given context is likely to be noticed and remembered, whereas less relevant information is likely to be ignored or quickly forgotten. When motivational intensity is high, it is functional to attend to and remember information that is relevant to the active goal at the expense of less relevant information. However, when goal attainment or failure has already occurred, it is functional to attend to and remember a broader range of information. This allows the person to take into account the consequences of success or failure, change their beliefs and expectations, and orient toward possible new goals. In other words, emotions reflect the status of goals, and influence the scope of attention and the range of information encoded in memory accordingly. If goal attainment or failure is anticipated, the range of stimuli attended to and encoded in memory narrows to central, goal-relevant information. After goal attainment or failure, the range of stimuli attended to and encoded in memory broadens to incorporate more peripheral information. Importantly, according to this model, even if pre-goal and post-goal emotions elicit similar levels of arousal, they should differ in their effects on attention and memory. Moreover, valence only exerts an influence through goal relevance or motivational intensity: People typically feel negative emotion when goals are threatened and positive emotion when goals have been achieved. Nevertheless, both pre-goal and post-goal emotions can be either positive or negative.

Although studies investigating the effects of emotional valence on subsequent cognition typically assess positive emotion following goal attainment (e.g., receiving a gift, watching amusing film clips, recalling past successes), people also feel a range of positive emotions when they *anticipate* attaining goals (e.g., desire, enthusiasm, excitement). A number of researchers, using different terminologies, have described distinctions between pre-goal and post-goal positive affective states, and have demonstrated that they have different effects on subsequent cognition (Panksepp, 1998; Knutson et al., 2000; Berridge, 2006; Knutson and Wimmer, 2007; Levine and Edelstein, 2009). Berridge and colleagues distinguish between "wanting" and "liking." Wanting is associated with left frontal and nucleus accumbens activation, along with the release of dopamine, which enhances the desire to seek reward (e.g., Adcock et al., 2006; Knutson and Wimmer, 2007; Harmon-Jones et al., 2008). Liking is associated with opioid stimulation, which is related to feelings of pleasure following goal attainment (Berridge and Robinson, 2003; Berridge and Kringelbach, 2008). Similarly, Panksepp (1998) distinguishes between the seeking versus playing emotive systems. Seeking aids goal-pursuit by narrowing attention to goal-relevant information (e.g., locating food or a mate). Playing promotes exploration of new territory and affiliation with others. Thus, pre-goal and post-goal positive emotions differ with respect to neural activity, the functions they serve, and breadth of processing.

Empirical studies support the view that pre-goal positive emotions promote memory narrowing. Gable and Harmon-Jones (2008) induced participants to feel either pre-goal desire or post-goal happiness. This was done by having participants view a film clip of delicious desserts or a humorous film clip. They found that desire narrowed attentional focus relative to happiness in global-local visual processing tasks. Other researchers found similar results when the desire to approach objects was elicited by displaying erotic stimuli (Moyer, 2004, unpublished study cited in Reisberg and Heuer, 2004), or by displaying stimuli that evoke feelings of nurturance, such as faces of human infants (Brosch et al., 2008), and animal infants (Gable and Harmon-Jones, 2008). Gable and Harmon-Jones (2011) also manipulated pre- and post-goal

positive emotion within the same participants, and concerning the same goal, by giving participants the opportunity to win money in a game. Positive emotion experienced in anticipation of winning led to narrowing of attention, whereas positive emotion experienced after winning led to broadening of attention. Importantly, this effect extends to memory. Relative to people experiencing post-goal positive emotion, people experiencing pre-goal positive emotion remembered words presented in the center of a screen better than those presented peripherally (Gable and Harmon-Jones, 2010b; for a review, see Harmon-Jones et al., 2012a).

Just as not all positive emotions are associated with broadening of attention and memory, not all negative emotions are associated with narrowing of attention and memory. For instance, von Hecker and Meiser (2005) found that people in a depressed mood paid attention to, and later remembered, more irrelevant as opposed to central information on a source monitoring task in comparison to people who were not feeling depressed. Similarly, Gable and Harmon-Jones (2010a) showed that sadness, an emotion evoked by appraising goal failure as irrevocable, broadened attention in global-local figures tasks. Sad participants responded faster to global features of the figures than to details relative to those in a neutral mood. Thus, evidence suggests that post-goal emotion, whether positive or negative, broadens the range of stimuli attended to and encoded in memory.

In contrast, pre-goal negative emotions, such as disgust, fear, and anger, narrow attention, allowing people to concentrate on current goals such as avoiding or eliminating potential threat (Moons and Mackie, 2007; Levine and Edelstein, 2009; Gable and Harmon-Jones, 2010a; Finucane, 2011). This closely mirrors the effects of pre-goal positive emotions, activating the same brain regions and narrowing the range of stimuli attended to and encoded in memory (Berridge, 2006). Amygdala activation, previously assumed to be associated primarily with detection of threatening stimuli, has also been linked with the elicitation of pre-goal positive emotions such as desire and with the detection of rewarding stimuli. This suggests that the function of the amygdala can be viewed more broadly as preparing people to approach or avoid specific goals or outcomes (Cunningham and Brosch, 2012).

SUMMARY

Approaches to understanding the effects of emotion on attention and memory differ substantially in their predictions. The predominant view in the literature is that when experiencing emotional arousal, the range of stimuli attended to and encoded in memory narrows toward central information. Hence, any source of emotional arousal should result in attention and memory narrowing. Not all findings in the literature support this view, however. Conflicting findings have led researchers to investigate mechanisms other than arousal that may explain when and why emotion enhances versus impairs cognitive processes. The view that emotional valence determines the breadth of cognitive processing explains some but not all recent findings. Even emotions of the same valence and the same level of arousal have been shown to vary with respect to the range of information attended to and remembered (e.g., Gable and Harmon-Jones, 2010b). Taking into account the motivational component of emotion helps to explain inconsistent findings in the literature.

Recent evidence suggests that the effect of emotion on memory differs depending on the goal status associated with the emotion (e.g., Levine and Edelstein, 2009; Gable and Harmon-Jones, 2010d). When emotional arousal is elicited by the goal of pursuing or avoiding a particular outcome, the range of details attended to and encoded in memory narrows, with a focus on central or goal-relevant information. In contrast, when emotional arousal is experienced as a result of goal attainment or loss, the range of details attended to and encoded in memory broadens, resulting in enhanced memory for more peripheral features of events or stimuli. This broader perspective facilitates building on goal attainment or adjusting to goal failure. In sum, pre-goal emotions promote a narrow focus on information that will facilitate goal attainment or prevent loss, shutting out irrelevant details. Post-goal emotions help people adjust to goal attainment or loss, and orient toward possible new goals, by broadening the range of information attended to and remembered.

FUTURE DIRECTIONS

Previous research has focused largely on how arousal and valence influence attention and memory. We have argued that investigating features of emotion beyond arousal and valence yields a more thorough understanding of how emotions influence attention and memory (Levine and Pizarro, 2004; Larson and Steuer, 2009; Levine and Edelstein, 2009; Gable and Harmon-Jones, 2010a; Lench et al., 2011; Harmon-Jones et al., 2012b). In the future, researchers should systematically vary the goal status of emotion as well as examining the effects of arousal and valence on attention and memory narrowing (see Ritchie et al., 2006; Larson and Steuer, 2009). In addition, varying the relevance of the information to be remembered will help to determine whether information relevant to current goals is enhanced at the expense of irrelevant information.

Research is also needed on the extent to which the types of information considered to be of central importance differ across discrete emotions. Central information to a person feeling desire might consist of rewarding and appetitive stimuli (e.g., Gable and Harmon-Jones, 2008). Central information to someone experiencing anger may be the perpetrator who is obstructing the person's goals (Levine and Pizarro, 2004). Threat-related information may be central to someone experiencing fear (e.g., Lench and Levine, 2005). Drawing on a motivational approach, one would also expect pre- and post-goal emotional states to differentially influence people's susceptibility to false memories. Pre-goal emotions should promote more careful and focused information processing than post-goal emotions, decreasing the likelihood of memory distortion for central or goal-relevant information. This has yet to be examined and provides an interesting avenue for further study. Finally, research examining neural correlates of emotional memory has begun to shed light on the underlying mechanisms involved in encoding and retrieving emotional information (e.g., Adcock et al., 2006; Dolcos et al., 2011, 2012; Shafer et al., 2011), and constitutes an important avenue for further research distinguishing the effects of pre- versus post-goal emotions on attention and memory. These are promising approaches that will

help pinpoint how the motivational component of emotion shapes memory, and more broadly, the conditions under which emotion enhances versus impairs cognition.

CONCLUSION

The motivational component of emotion is an important but understudied issue in the emotional memory narrowing literature. Future research on how motivation and goal relevance influence attention and memory will help clarify why, and under what conditions, people attend to and recall different types of information. Understanding the interaction between emotion and memory is a fundamental issue in the field of psychology. People are faced daily with the need to remember information while experiencing a range of emotional states. An attorney angered by the acts of opposing counsel, a patient saddened by a diagnosis, a rescue worker frightened by a disaster, must encode and retrieve detailed information accurately if they are to make good decisions. The link between people's emotions and their goals provides an important key to understanding the selective nature of memory for emotional events. Arousal is an essential component of emotion which certainly affects attention and memory. But people frequently experience specific emotions such as happiness, desire, grief, and fear at high levels of arousal, yet they differ with respect to the types of information they are likely to attend to and the scope of their memories. Thus, taking into account the goal status and information processing strategies associated with discrete emotions can provide a more complete understanding of how emotion enhances and impairs cognitive processes.

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On opposing effects of emotion on contextual or relational memory

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INTRODUCTION

An extensive literature has firmly established the role of emotion on memory. For example, behavioral experiments have shown robustly that emotional stimuli are better remembered than neutral stimuli (see Mather and Sutherland, 2011). Mechanisms identified for such enhancements in memory include prioritized initial perceptual processing of emotional stimuli (Nummenmaa et al., 2006; Phelps et al., 2006), and amygdala (AMY)-dependent neurohormonal changes that modulate memory processes supported by the hippocampus (HC) and surrounding medial temporal lobe (MTL) structures (McGaugh, 2000), leading to memory enhancements for emotional material (Dolcos et al., 2012) as well as making such information more resistant to forgetting over time (Dolcos et al., 2005; Ritchey et al., 2008).

A caveat to the above-mentioned phenomena is that they tend to be concerned with the remembering of individual *items* in isolation, such as a word or an image. But interest in the effects of emotion on memory for real-world events, involving more than solitary items, has led to research on emotion's effects on memory for items *in the context of* or *in relation to* other items (*contextual* or *relational* information). Puzzlingly, while this recent research has confirmed the enhancing effects of emotion on memory for individual items, outcomes for the effects of emotion on memory for accompanying contextual or relational information have been contradictory, with some studies showing enhanced remembering, while others reporting impaired performances, and some reporting no effect of emotion.

In this article, we highlight two issues that that may help toward resolving the seeming contradictions in the pattern of results in this literature. The first is the need for a more nuanced conceptualization and nomenclature of the types of memory representations being tested. The second is the necessity of considering the differential engagement of HC-dependent, *relational* memory representations (Cohen and Eichenbaum, 1993; Cohen et al., 1999; Eichenbaum and Cohen, 2001), as opposed to item memory representations, that might be taxed by various experiments.

INCONSISTENT FINDINGS ON MEMORY FOR CONTEXTUAL/RELATIONAL INFORMATION

Research on the effects of emotion on memory for contextual or relational information shows decidedly mixed results (**Table 1**). Some studies find *enhanced* memory for such information—e.g., better remembering of color information associated with emotional words or scenes (Doerksen and Shimamura, 2001; D'Argembeau and Van der Linden, 2005; MacKay and Ahmetzanov, 2005), screen location memory of negative arousing scenes (Mather and Nesmith, 2008), and temporal order of emotional items within a list (Schmidt et al., 2011). By contrast, other investigations find *impaired* memory for contextual or relational information—e.g., less detailed memory for scene contexts that form the background for centrally presented emotional items (Kensinger et al., 2007, experiments 1–3), and worse memory for cognitive tasks performed on items (Kensinger and Schacter, 2006b; Cook et al., 2007; but see Kensinger and Schacter, 2006a), for relations of objects superimposed on emotional scenes (Touryan et al., 2007; Rimmele et al., 2011), and for relational bindings between item pairs (Mather and Knight, 2008; Nashiro and Mather, 2011; Pierce and Kensinger, 2011; but see Guillet and Arndt, 2009). Finally, other studies do not find any differences in memory for contextual/relational information for emotional vs. neutral trials (Sharot and Phelps, 2004; Mather et al., 2009).

RESOLUTION OF CONTRADICTIONS

Studies of the effects of emotion on memory for contextual or relational information vary widely in the modality and informational structure of the contents tested. We suggest that this variation among studies critically involves different types of relational content and, consequently, differences in the memory representations they test; understanding these differences may help resolve some of the seemingly contradicting findings in the literature.

DIFFERENTIATION OF INFORMATION CONTENT TESTED

In a subset of designs commonly referred to as "source" memory studies in the literature, contextual/relational information has been operationalized across a wide range of modalities, including visual-perceptual stimulus features (color, location of item), temporal information (item order within a list), or cognitive operations performed (size, animacy judgments). What gives rise to the collective term "source" used to describe the contextual/relational information in these instances, is commonalities in the way such information is structured. That is, "source" information is always far fewer in number compared to the number of trials and can be conceptualized as grouping labels for items. For example, responses in source studies consist of a limited number of alternative choices for each modality (one of two colors or lists, or a specific quadrant on the screen) which can often be specified with a single descriptor (such as "red," "list 2," or "animacy"). In

Table 1 | Sample of relevant studies on emotion's effect on contextual and relational information, organized by outcome and study design.

Enhanced	Impaired

Source memory
• Word-color, word-color frame (Doerksen and Shimamura, 2001)
• Word-location (MacKay and Ahmetzanov, 2005)
• Word-color, word-location (D'Argembeau and Van der Linden, 2004)
• Picture-location
  ○ (Mather and Nesmith, 2008)
  ○ (Nashiro and Mather, 2011)
• Scenes-location, within list order (Schmidt et al., 2011)
• Temporal context: predictive preceding neutral item (Knight and Mather, 2009)
• Word-task (seen vs. imagined) (Kensinger and Schacter, 2006b)
Paired Design
• Taboo word-neutral word in sentence, or taboo word-word pairs (Guillet and Arndt, 2009)
	Source memory
	• Word, picture-task (animacy vs. commonness) (Kensinger and Schacter, 2006a)
	• Word-task (seen vs. heard) (Cook et al., 2007)
	• Scene-color frame (Rimmele et al., 2011)
	• Scene-locations (set of 4 scenes in 1/8 locations (Mather et al., 2006)
	• Face-location (Mather and Knight, 2008)
	Scene context
	• Emotional item embedded in scene, impaired detailed memory for scene
	  ○ (Kensinger et al., 2007)
	  ○ (Christianson et al., 1991)
	• Neutral peripheral object embedded in emotional scene; binding of scene-object
	  ○ (Touryan et al., 2007)
	  ○ (Rimmele et al., 2011)
	• Temporal context: non-predictive preceding neutral item (Knight and Mather, 2009)
	Paired designs
	• Word-word pairs (Pierce and Kensinger, 2011)
	• Sound-digit, face-hat pairs (Mather and Knight, 2008)
	• Picture-shape pairs (Nashiro and Mather, 2011)

No effect of emotion	
Source Memory • Scene-task association (color vs. visual complexity judgment) (Sharot and Yonelinas, 2008) • Paired scene-location (Mather et al., 2009) **Paired design** • Central neutral word-peripheral emotional/neutral word (Sharot and Phelps, 2004)	

addition, for the purpose of making more nuanced distinctions between the types of contextual/relational information tested, it is important to note that source studies have not differentiated between memory for contextual and relational information (to be discussed below). Retrieval queries in these studies have been limited to the recall or recognition of the source information for cued items; when the source is correctly remembered/ attributed, it simultaneously implies accurate memory for the content of the source itself.

In contrast to source memory studies, there are experiments in which there is a one-to-one relationship between the contextual or relational information and trials. In other words, contextual or relational information is trial-unique and as numerous as the trials. Examples include studies that use visual images as background to items, and other studies that present two items in a pair per trial. Importantly, *two* types of information content can be distinguished and tested to demonstrate memory in these designs. The first is *contextual* information content, such as studied background scenes and objects shown with emotional items. The second is *relational binding* information between the contexts and the items, such as which scene was seen with a particular item, or which two items co-occurred during study as a pair.

When the above distinction between studies is made, a pattern does emerge from the literature in terms of the effect of emotion on contextual and relational information. That is, *enhancements* of memory due to emotion have been from two specific types of source memory studies—those that involve temporal information and visual-perceptual features. For example, emotion enhances the remembering of item order within a list (Schmidt et al., 2011), color source associated with items (Doerksen and Shimamura, 2001; D'Argembeau and Van der Linden, 2005; MacKay and Ahmetzanov, 2005), and location information (Mather and Nesmith, 2008). In contrast, *impairments* of memory due to emotion tend to involve tests for *contextual* information as well as for *relational binding* information between context and items or items pairs. That is, studies consistently demonstrate worse detailed memory for scenes accompanying emotional items (Kensinger et al., 2007, experiments 1–3), and worse recognition memory for the pairing between objects on scenes (Touryan et al., 2007; Rimmele et al., 2011) or item pairs (Mather and Knight, 2008; Pierce and Kensinger, 2011).

RELEVANT THEORIES FROM THE EMOTION LITERATURE

As demonstrated above, the distinctions among source, context, and relational information afford a means of conceptualizing the research findings. The importance of these distinctions is supported by two influential views in the current emotion literature, with one being relevant to studies showing enhancements in visual-perceptual source memory, the other explaining impairments in contextual information.

First, the *object-based framework* holds that arousal enhances within-object perceptual bindings intrinsic to the items which then leads to better memory retention of such bindings (Mather, 2007). This framework readily explains emotional enhancements for source memory studies where perceptual features such as the color or location are spatially proximal or overlapping with the emotional items, and thus benefit from enhanced feature-binding through focused attention attracted by the emotional stimuli (Doerksen and Shimamura, 2001; D'Argembeau and Van der Linden, 2005;

MacKay and Ahmetzanov, 2005; Mather and Nesmith, 2008). Second, another view emphasizes a *trade-off* between enhancement of perceptual details for *central* information and a lack of detailed remembering for *peripheral* elements (Christianson et al., 1991), with the central vs. peripheral distinction being defined both spatially and conceptually (see Levine and Edelstein, 2009, for review). In this way, the central-peripheral trade-off view explains impaired memory for designs that test contextual information, such as scenes that serve as background for centrally presented emotional items (Kensinger et al., 2007, experiments 1–3) or for objects that are peripheral to emotional scenes (Touryan et al., 2007), since memory for central details is enhanced at the cost of peripheral information.

MEMORY REPRESENTATIONS TESTED

Although each of the presented theories accounts for a subset of extant studies, there are findings for which they do not have direct predictions. For example, temporal source information does not have spatial properties to which the object-based framework or the central-peripheral view can apply. This is also the case for studies with paired stimuli where two items of equivalent attentional, spatial, and conceptual status are shown in any given trial. In order to conceptualize the enhancing/impairing results in a way that generalizes across a range of studies, we propose it is necessary to consider the underlying memory representations likely to result from various experimental designs.

A well-established body of research in the memory domain informs a distinction between *item* vs. HC-dependent, *relational* memory representations that support memory for relations among multiple items, and between various items and the larger context involving temporal, spatial, and situational relations (Cohen and Eichenbaum, 1993; Cohen et al., 1999; Konkel and Cohen, 2009). Since there are at least two classes of memory representations involved, it follows that research on the effects of emotion on contextual or relational memory need to consider *if* and *how* emotion may affect these representations differently.

From the pattern of results summarized above, we are proposing that there is correspondence between the subset of source studies that shows enhanced memory by emotion to likely rely on item-only memory representations, and other contextual/relational information that shows emotion-driven impairments to involve HC-dependent relational representations. To further clarify, source information enhanced by emotion tends to involve stimuli properties that are perceptual or conceptual in nature, and can thus be "fused" or "unitized" to tax only HC-independent item-memory representations (Cohen et al., 1997; Diana et al., 2008). This is the case with color or location source information that can be associated with items via a visual "snapshot," and temporal information for multiple items that can be conceptually organized into a single, coherent sequence (as instructed in Schmidt et al., 2011). In contrast, we note that emotion seems to impair information supported by relational memory representations, such as contextual information using complex visual scenes (Kensinger et al., 2007, experiments 1–3) and relational information using item pairs (Mather and Knight, 2008; Pierce and Kensinger, 2011), unless stimulus properties allow encoding of stimuli in a non-relational manner (possibly as internally generated, unitary mental images or concepts for word-word stimuli in Guillet and Arndt, 2009) or that encoding instructions encourage the allocation of attention to visual details of the contextual information (in Kensinger et al., 2007, experiment 4). Lastly, we would further generalize that in instances where temporal, spatial, and situational information cannot be represented in a unitized manner, there would not be an enhancement of such information by emotion.

CONCLUSION

To our knowledge, the proposal to conceptualize experimental designs in terms of item vs. HC-dependent relational memory representations taxed is a novel one yet to be extensively tested in emotion research. However, the interaction between the MTL and AMY during emotional memory processing, as proposed by the modulation hypothesis inspired by animal research (McGaugh, 2000), is well-established and confirmed by research in humans (reviewed in Dolcos et al., 2012). Also, there is evidence that AMY-MTL interaction during stressful events can impair HC functioning while enhancing item processing supported by the perirhinal cortex (in Mather, 2007), thus providing plausible neural mechanisms for the differential impact of emotion on these memory representations. To conclude, we propose that in addition to extant theories that are motivated by attentional biases in perception caused by emotional stimuli, future research would benefit from differentiating between source, contextual, and relational information, as well as from considering the types of memory representations taxed in various designs, as a way to further our understanding of the effects of emotion on all types of memory phenomena.

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Task difficulty modulates the impact of emotional stimuli on neural response in cognitive-control regions

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Both heightened reactivity to emotional stimuli and impaired cognitive control are key aspects of depression, anxiety, and addiction. But the impact of emotion on cognitive-control processes, and the factors that modulate this impact, are still not well understood. We examined the effects of threat and reward distracters on the neural correlates of cognitive control using functional MRI (fMRI) and the Multi-Source Interference Task (MSIT). Behaviorally, subjects were slower and less accurate on the more demanding incongruent trials compared to the easier congruent trials. In addition, both threat and reward distracters significantly impaired the speed of responding on incongruent trials relative to the no-distracter condition. At the neural level, we used the *incongruent – congruent* contrast to functionally define four cognitive-control regions of interest (ROIs): anterior cingulate cortex (ACC), left and right inferior frontal gyrus (IFG)/insula, and right dorsolateral prefrontal cortex (DLPFC). A repeated-measures analysis of variance on the extracted contrast values in these ROIs indicated a significant interaction of stimulus salience and task difficulty on the neural response in cognitive-control regions. Specifically, threat distracters significantly *decreased* the response in cognitive-control regions on incongruent trials, whereas they significantly *increased* that response on congruent trials, relative to the no-distracter condition. Exploratory analyses of the amygdala response showed a similar interaction of stimulus salience and task difficulty: threat distracters significantly *decreased* the amygdala response only on incongruent trials. Overall, our results suggest that the impact of emotional distracters on the neural response in cognitive-control regions as well as in the amygdala is modulated by task difficulty, and add to our understanding of the factors that determine whether emotion enhances or impairs cognition.

Keywords: emotion, cognitive control, executive function, emotion-cognition interactions, fMRI, ACC, DLPFC, IFG

INTRODUCTION

Cognitive control is broadly defined as the ability to carry out a task despite interference from task-irrelevant stimuli, and it is a critical requirement for goal-directed behavior. Theoretical accounts have attributed cognitive-control functions to the prefrontal cortical regions (Miller and Cohen, 2001). More specifically, functional MRI (fMRI) evidence has shown that cognitive-control functions rely on a distributed cortical network, including the anterior cingulate cortex (ACC) extending into the dorsomedial prefrontal cortex (DMPFC) along the medial wall, and the dorsolateral prefrontal cortex (DLPFC) and inferior frontal gyrus (IFG) extending into the insula laterally, as well as parietal regions (for review, see Duncan and Owen, 2000; for meta-analyses, see Nee et al., 2007; Niendam et al., 2012). However, this evidence reflects cognitive-control processes recruited primarily in the absence of emotionally salient stimuli (e.g., the classical Stroop task with emotionally neutral color words), and thus leaves open the question of whether – and how – these cognitive-control processes are modulated by emotional salience.

One approach to investigating the relationship between cognitive control and emotion has been to modify an existing cognitive-control task to include emotionally salient stimuli, for example, as task-irrelevant distracters or task-relevant targets. These emotionally salient stimuli can be either negative (threat-related) or positive (reward-related) in valence; they can vary in modality (e.g., visual or auditory) and form (e.g., images vs. words); and they can be presented simultaneously with, or precede, task targets. Several neuroimaging studies have examined the effects of threat-related negative emotional stimuli on the neural correlates of cognitive control in a variety of interference tasks (Whalen et al., 1998a; Compton et al., 2003; Bishop et al., 2004; Etkin et al., 2006; Blair et al., 2007; Egner et al., 2008; Kanske and Kotz, 2011a,b; Hu et al., 2012), working-memory tasks (Dolcos and McCarthy, 2006; Dolcos et al., 2006, 2008; Anticevic et al., 2010; Shafer and Dolcos, 2012), and categorization tasks (Gu et al., 2012; Shafer et al., 2012). Taken together, these studies support the notion that negative emotional stimuli modulate activity in the cognitive-control network, as well as in the amygdala and ventral ACC, although the magnitude and direction of this modulation differs across studies, tasks, and individuals. Although less studied, modulatory effects of reward-related positive emotional stimuli on the cognitive-control network have also been reported, with

similarly inconclusive results (Blair et al., 2007; Padmala and Pessoa, 2010; Savine and Braver, 2010; Krebs et al., 2011). Finally, at the behavioral level, both positive and negative emotional stimuli have been shown to sometimes enhance (Kanske and Kotz, 2011a,b,c) and sometimes impair (Blair et al., 2007; Gu et al., 2012; Jasinska et al., 2012b) cognitive control. Furthermore, significant behavioral effects of emotional stimuli have been sometimes observed only in the more demanding task conditions (Kanske and Kotz, 2011a,b; Gu et al., 2012) and other times only in the less demanding task conditions (Hu et al., 2012; Shafer et al., 2012). Thus, overall, the existing evidence suggests that the impact of emotionally salient stimuli on cognitive-control processes and on cognitive task performance is modulated by other factors (Cohen and Henik, 2012). But most of these factors and their neural mechanisms of action are still poorly understood.

In our previous behavioral investigation (Jasinska et al., 2012b), we examined *task difficulty* (also referred to as *task load* or *task demands*) as a plausible factor modulating the impact of threat distracters on cognitive task performance (Gu et al., 2012; Hu et al., 2012; Shafer et al., 2012). We used the Multi-Source Interference Task (MSIT; Bush and Shin, 2006), a demanding cognitive interference task with robust neural and behavioral effects, in order to maximize the chances that modulation of these task effects by threat stimuli could be detected. The task included threat distracters (angry and fearful faces) as well as perceptually matched neutral distracters (neutral faces), in addition to the no-distracter condition, and threat distracters were rated as significantly higher in both emotional intensity and distractability than neutral distracters by the subjects. Our behavioral data indicated a significant interaction between stimulus salience and task difficulty (i.e., the easier congruent MSIT condition vs. the more demanding incongruent MSIT condition) in both measures of task performance. In particular, relative to both the neutral-distracter and no-distracter conditions, threat distracters *impaired* task performance on the more demanding incongruent trials, on which a correct response required overcoming interference from a competing response tendency; but threat distracters actually *enhanced* task performance on the easier congruent trials, which relied on a simple stimulus-response mapping.

Having previously demonstrated robust behavioral effects of threat distracters on cognitive task performance, the goal of the current study was to investigate the neural processes that underlie these effects. We employed event-related fMRI, which measures the blood-oxygenation-level-dependant (BOLD) signal considered to be an index of neural activity, and a novel version of the MSIT modified to include both threat and reward distracters. The primary aim of our study was to examine the impact of threat and reward distracters on the neural response of cognitive-control regions (including the ACC, DLPFC, and IFG/insula) during cognitive task performance. Based on the results of our behavioral study (Jasinska et al., 2012b), we expected to observe an interaction of stimulus salience and task difficulty, such that threat distracters should decrease the response in cognitive-control regions in the more demanding incongruent MSIT condition, but increase the response in cognitive-control regions in the easier congruent MSIT condition. We also tentatively hypothesized that a similar interaction of stimulus salience and task difficulty on the response of cognitive-control regions would be observed for reward distracters. The secondary, more exploratory aim of our study was to test whether a similar interaction of stimulus salience and task difficulty would be observed in the amygdala for threat and reward distracters.

MATERIALS AND METHODS

SUBJECTS

Fifteen healthy Caucasian females aged 20 to 31 years (M = 24.4 years, SD = 3.4 years) participated in the study. Due to technical problems and loss of data for two participants, we present the fMRI data from the final sample of 13 participants. All subjects were right-handed and had normal or corrected-to-normal vision. Exclusion criteria included any serious medical condition, head injury or trauma, lifetime diagnosis of psychiatric illness, current use of a psychoactive medication, and cigarette smoking. All subjects had participated in a behavioral investigation using the threat-distracter MSIT approximately 2 years prior to the fMRI experiment (Jasinska et al., 2012b). Only females were included at this stage to maximize statistical power to detect the effects of interest in light of documented sex differences in the processing of emotional stimuli in the brain (Klein et al., 2003; Wrase et al., 2003). The study was approved by the University of Michigan Medical School IRB and all subjects provided written informed consent.

THREAT- AND REWARD-DISTRACTER MSIT

We employed a modified version of the MSIT (Bush et al., 2003; Bush and Shin, 2006). The MSIT combines the sources of interference from Erikson, Stroop, and Simon tasks, and it was designed to elicit activation in the prefrontal cortical regions associated with interference processing, particularly the dorsal ACC, in neuroimaging studies (Bush et al., 2003). On each trial, subjects were presented with a row of three numbers ranging from 0 to 3, and one of the numbers was different from the other two (the oddball number). Subjects were instructed to indicate the identity of the oddball number with a corresponding key press on a scanner-compatible response glove: a key press with the index finger if the oddball number was "1," with the middle finger if the oddball number was "2," and with the ring finger if the oddball number was "3." On congruent trials, the identity of the oddball number corresponded to its location and the other two numbers were 0's, not related to any valid key press response (e.g., "1" on the left and two zeros, or two zeros and "3" on the right). On incongruent trials, the identity of the oddball number was incongruent with its position and the other two numbers were associated with competing key press responses (e.g., "3" on the left" or "1" on the right), resulting in stimulus-response incompatibility and response interference. The incongruent condition vs. congruent condition contrast was used as a measure of interference in reaction times (*incongruent RT – congruent RT*) and in accuracy (*congruent accuracy – incongruent accuracy*). We modified the MSIT to include threat and reward flanker distracters in addition to the no-distracter condition (**Figure 1**). Threat distracters were color images of human faces signaling the presence of a threat (angry or fearful expression). The majority of face stimuli (13 images) were selected from standardized sets (Gur et al., 2002; Tottenham et al., 2009), supplemented with a small number of carefully selected stimuli from

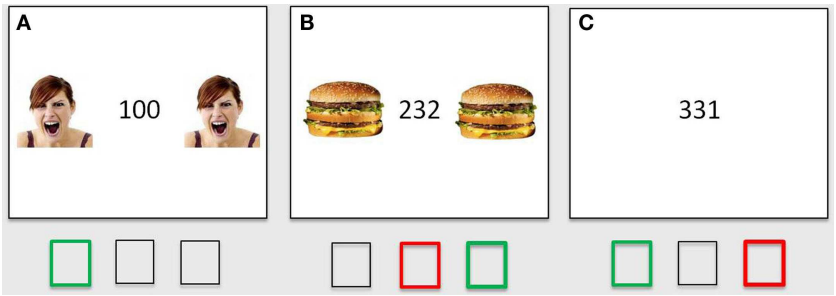

FIGURE 1 | Threat- and reward-distracter MSIT. MSIT congruent trial with flanker threat distracters **(A)**, MSIT incongruent trial with flanker reward distracters **(B)**, and MSIT incongruent trial with no distracters (so only emotionally neutral stimuli; **C**). The correct responses are shown in green; common incorrect responses on incongruent trials (i.e., indicating the position instead of the value of the oddball number) are shown in red.

online sources (three images). Angry and fearful faces displayed intense emotion and showed bared teeth and/or open mouth as an additional perceptual homogeneity criterion. Reward distracters were color images of high-calorie, highly palatable foods selected from online sources. On distracter trials, two identical distracter images flanked the MSIT stimuli on both sides. Neutral distracters were not included in the fMRI paradigm in order to minimize the number of trials and the duration of the scanning protocol in light of documented habituation of the amygdala response to repeated presentation of threat stimuli (Breiter et al., 1996; Whalen et al., 1998b; Wright et al., 2001), which could potentially reduce or even eliminate threat-distracter effects over time; and because our previous behavioral study already established a significant effect of threat distracters (angry or fearful faces) above and beyond that of closely matched neutral distracters (neutral faces; see also the Discussion). Following instructions and a short practice, subjects completed two runs of the MSIT, 60 trials per run, for a total of 120 trials (20 congruent/threat distracters, 20 incongruent/threat distracters, 20 congruent/reward distracters, 20 incongruent/reward distracters, 20 congruent/no distracters, 20 incongruent/no distracters). On each trial, task stimuli together with distracters were presented for 1 s, followed by a white screen for another 1 s, a fixation cross of jittered duration (mean 6 s, range 4–10 s), and another white screen for 300 ms. The total response limit on each trial was 2 s. Including the jitter, the task took approximately 17 min to perform.

fMRI DATA ACQUISITION AND PREPROCESSING

Scanning was performed on a 3T GE Signa Excite 2 scanner (Milwaukee, Wisconsin), beginning with a structural T1-overlay image [repetition time (TR) = 250 ms, echo time (TE) = 5.7 ms, flip angle (FA) = 85°, field of view (FOV) = 220 mm, 43 oblique axial slices, 256 × 256, slice thickness 3.0 mm]. Functional scans were collected using a T2*-weighted spiral-in acquisition sequence (gradient echo, TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 220 mm, 64 × 64, slice thickness 3.0 mm; Noll et al., 1998). High-resolution T1 scans were also obtained for precise anatomical localization [3D spoiled-gradient echo (3D-SPGR) with inversion recovery prep, time of inversion = 400 ms, TR = 9.0 ms, TE = 1.8 ms, FA = 15 degrees, FOV = 260 mm, 128 slices, 256 × 256, 1.2 mm slice]. The functional scans were physio-corrected, slice-time-corrected, and realigned to the first scan using the MCFLIRT program (FSL Analysis Group, FMRIB, Oxford, UK). Subsequent processing was done using SPM 8 (Wellcome Institute of Cognitive Neurology, London, UK). For each subject, the high-resolution 3D-SPGR image was co-registered with a mean functional scan and anatomically normalized to the Montreal Neurological Institute (MNI) 152 template. The resulting transformation parameters were then applied to the co-registered functional volumes. All functional volumes were smoothed with a Gaussian kernel (8 mm^3).

fMRI DATA ANALYSES

After preprocessing, the individual fMRI data were analyzed using a jittered event-related design in the framework of the General Linear Model as implemented in SPM8. Regressors of interest (i.e., vectors of the onset times specific to each trial type) were convolved with a canonical hemodynamic response function (HRF) with a time derivative to account for between-subject and between-voxel variability in the response peak. Six regressors of interest were defined for the MSIT task: MSIT incongruent/threat-distracter trials, MSIT incongruent/reward-distracter trials, MSIT incongruent/no-distracter trials, MSIT congruent/threat-distracter trials, MSIT congruent/reward-distracter trials, and MSIT congruent/no-distracter trials. A number of contrasts were estimated for each individual subject. First, the *incongruent/no distracters – congruent/no-distracters* contrast was used to identify brain regions associated with cognitive control. Significant clusters in the established cognitive-control regions (i.e., ACC, DLPFC, and IFG/insula) were then saved as functionally defined region of interest (ROI) masks. Next, several other contrasts of interests were estimated, including the *incongruent/threat distracters – fixation, incongruent/reward distracters – fixation*, and *incongruent/no distracters – fixation* contrasts. The incongruent condition was compared to a fixation baseline rather than to the congruent condition for two reasons: first, to allow a comparison of incongruent and congruent conditions against a common baseline; and second, to avoid "double-dipping" (i.e., testing the same contrast that was used to define the ROI). Group analyses were then conducted using random-effects models and one-sample *t*-tests in SPM8. Mean contrast values were extracted from each ROI mask for all contrasts of interest for all participants. These values were then analyzed using repeated-measures ANOVAs and *post hoc* tests in

SPSS 19.0, starting with an omnibus ANOVA, in order to test for main and interactive effects of stimulus salience and task difficulty on the BOLD response in cognitive-control regions. Exploratory analyses were also conducted for the amygdala, using anatomically defined left and right amygdala masks. All *t*-tests were two-tailed paired-sample *t*-tests.

RESULTS

BEHAVIORAL RESULTS

The behavioral results from the MSIT are summarized in **Table 1**. We first conducted a 2 × 3 repeated-measures ANOVA with two factors (factor 1: task difficulty: easier/congruent trials or more demanding/incongruent trials; factor 2: stimulus salience: threat distracters, reward distracters or no distracters/neutral stimuli) on correct RTs and accuracy rates. Consistent with previous reports (Bush et al., 2003; Bush and Shin, 2006), we found a significant MSIT interference effect (i.e., main effect of task difficulty or congruency) in both measures of task performance: in RTs, $F(1, 14) = 224.184$, $p < 0.0001$, and in accuracy, $F(1, 14) = 22.232$, $p < 0.0001$ (see **Table 1**). Namely, subjects were significantly slower to respond in the incongruent compared to the congruent condition, $t(14) = 14.966$, $p < 0.0001$, and they were also significantly less accurate in the incongruent compared to the congruent condition, $t(14) = -4.709$, $p < 0.0001$. We also found a significant main effect of stimulus salience in RTs, $F(1, 14) = 12.385$, $p < 0.0001$, but not in accuracy, $F(1, 14) = 0.237$, $p = 0.790$. Collapsing across the MSIT congruent and incongruent trials, subjects were significantly slower to respond in the presence of threat distracters, $t(14) = 3.833$, $p = 0.002$, or reward distracters, $t(14) = 3.436$, $p = 0.004$, compared to the no-distracter condition with only neutral stimuli. Speed of responding in the presence of threat and reward distracters did not differ, $t(14) = 0.812$, $p = 0.43$. Lastly, there was also a significant interaction of task difficulty and stimulus salience in RTs, $F(2, 13) = 7.209$, $p = 0.003$, but not in accuracy, $F(2, 13) = 0.473$, $p = 0.628$. Specifically, the distracter effects were very robust on the more demanding incongruent trials [threat-distracter RT > no-distracter RT, $t(14) = 5.727$, $p < 0.0001$; reward-distracter RT > no-distracter RT, $t(14) = 5.021$, $p < 0.0001$], but were virtually absent on the easier congruent trials ($ps > 0.440$), except for a trend toward significantly higher RTs in the congruent trials with threat distracters compared to the congruent trials with reward distracters, $t(14) = 1.864$, $p = 0.083$. The speed of responding on incongruent trials with threat distracters compared to reward distracters did not significantly differ, $t(14) = -0.456$, $p = 0.655$.

NEUROIMAGING RESULTS

Identifying cognitive-control regions with the incongruent – congruent contrast

In the first step, we identified brain regions associated with cognitive control by directly comparing the response to incongruent and congruent trials in the absence of emotionally salient stimuli (the *incongruent/no distracters – congruent/no distracters* contrast, thresholded at $p < 0.001$, minimum 10 contiguous voxels). This comparison yielded robust activation in regions previously associated with cognitive control, including bilateral anterior cingulate (ACC), left and right IFG/insula, and right DLPFC (**Figure 2**), as well as a number of other cortical and subcortical regions (**Table 2**). Significant clusters in the ACC, left IFG/insula, right IFG/insula, and right DLPFC were saved as functionally defined cognitive-control ROIs. In subsequent analyses, we used contrast values extracted from these four ROIs in order to test for main and interactive effects of stimulus salience and task difficulty on neural correlates of cognitive control.

Interaction of stimulus salience and task difficulty on neural correlates of cognitive control

The omnibus 4 × 2 × 3 repeated-measures ANOVA on extracted contrast values (factor 1, ROI: ACC, left IFG/insula, right IFG/insula, right DLPFC; factor 2, task difficulty: congruent and incongruent; and factor 3, stimulus salience: threat distracters, reward distracters, and no distracters/neutral stimuli) yielded several significant main and interactive effects. The results are shown in **Figure 3**. Consistent with robust behavioral MSIT effects, we observed a significant main effect of task difficulty (i.e., main effect of congruency) on the BOLD response in cognitive-control regions, $F(1, 12) = 30.480$, $p < 0.0001$, with the response to incongruent trials significantly higher than that to congruent trials (**Figure 3A**). There was also a significant main effect of ROI, $F(3, 10) = 11.870$, $p = 0.001$, as well as a significant interaction

Table 1 | Summary of behavioral task results.

Distracter	MSIT condition		*MSIT interference effect*		
	Congruent	Incongruent	*Mean*	*T*	*P value*
RT (ms)					
Threat	647 (109)	857 (105)	210 (72)	−11.266	<0.0001
Reward	632 (98)	861 (118)	229 (63)	−13.989	<0.0001
Null	637 (101)	807 (107)	170 (53)	−12.544	<0.0001
Overall	639 (100)	842 (109)	203 (53)	−14.966	<0.0001
ACCURACY (PROPORTION ACCURATE)					
Threat	0.990 (0.039)	0.913 (0.090)	0.077 (0.062)	4.766	<0.0001
Reward	0.983 (0.052)	0.933 (0.084)	0.050 (0.078)	2.485	0.026
Null	0.990 (0.028)	0.927 (0.116)	0.063 (0.097)	2.523	0.024
Overall	0.988 (0.081)	0.925 (0.081)	0.063 (0.052)	4.709	<0.0001

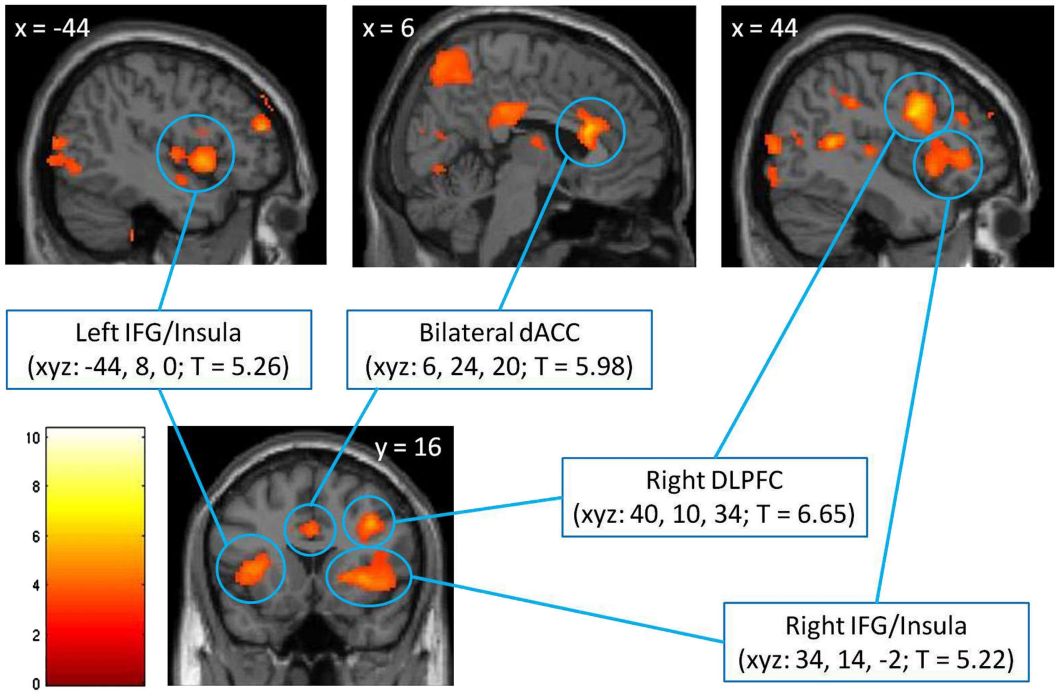

FIGURE 2 | Identification of cognitive-control regions in the brain, as assessed with a comparison of voxel-wise responses to incongruent and congruent MSIT trials in the absence of emotional distracters (the *incongruent/no distracters – congruent/no distracters* contrast), thresholded at $p < 0.001$, minimum 10 contiguous voxels. The significant clusters are localized using Montreal Neurological Institute (MNI) coordinates of left/right (*x*), anterior/posterior (*y*), and superior/inferior (*z*), respectively, and are shown against the MNI anatomical brain template. The scale represents *t* values. dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus.

of ROI and stimulus salience, $F(6, 7) = 11.392$, $p = 0.003$, on the BOLD response in cognitive-control regions. Critically, and consistent with our main hypothesis, we found a significant interaction of task difficulty and stimulus salience on the BOLD response in cognitive-control regions, $F(2, 11) = 4.498$, $p = 0.037$ (**Figure 3B**). Specifically, we found a significant double dissociation with respect to threat-distracter effects on the BOLD response in cognitive-control regions across the two levels of task difficulty: threat distracters significantly *decreased* the BOLD response in cognitive-control regions on the more demanding, incongruent MSIT trials, $t(12) = -2.343$, $p = 0.037$, whereas they significantly *increased* the BOLD response in cognitive-control regions on the easier, congruent MSIT trials, $t(12) = 2.247$, $p = 0.044$, relative to the no-distracter condition. Reward distracters produced levels of response intermediate between threat-distracter and no-distracter conditions, but these effects did not reach significance ($ps > 0.170$). The difference in the BOLD response in cognitive-control regions between threat and reward distracters was also not significant ($ps > 0.173$).

To further investigate the observed effects, separate 2×3 repeated-measures ANOVAs were conducted for each ROI (**Figure 3C**). The ROI-specific ANOVAs confirmed a significant main effect of task difficulty on the BOLD responses in all four cognitive-control ROIs, with a higher response magnitude for incongruent compared to congruent trials in ACC, $F(1, 12) = 16.372$, $p = 0.002$; in right DLPFC, $F(1, 12) = 29.664$, $p < 0.0001$; in left IFG/insula, $F(1, 12) = 15.540$, $p = 0.002$; and in right IFG/insula, $F(1, 12) = 40.427$, $p < 0.0001$. Importantly, the ROI-specific ANOVAs also confirmed a significant interaction of task difficulty and stimulus salience on the BOLD response in ACC, $F(2, 11) = 7.936$, $p = 0.007$, and in left IFG/insula, $F(2, 11) = 4.696$, $p = 0.034$, as well as a trend toward a significant interaction in right DLPFC, $F(2, 11) = 3.786$, $p = 0.056$, and in right IFG/insula, $F(2, 11) = 2.837$, $p = 0.101$. Specifically, threat distracters produced significant decreases in the BOLD response to incongruent trials in ACC, $t(12) = -2.861$, $p = 0.014$, and in left IFG/insula, $t(12) = -2.612$, $p = 0.023$, as well as a trend toward a significant decrease in right IFG/insula, $t(12) = -1.803$, $p = 0.097$, relative to the no-distracter condition. Conversely, threat distracters produced a significant increase in the BOLD response to congruent trials in right DLPFC, $t(12) = 2.699$, $p = 0.019$, as well as a trend toward a significant increase in left IFG/insula, $t(12) = 1.793$, $p = 0.098$, and in right IFG/insula, $t(12) = 1.915$, $p = 0.088$, relative to the no-distracter condition. In addition, reward distracters produced a trend toward a significant decrease in DLPFC response to incongruent trials, $t(12) = -1.888$, $p = 0.083$, as well as a significant increase in left IFG/insula response to congruent trials, $t(12) = 3.494$, $p = 0.004$, relative to no distracters. No other effects of reward-distracters reached statistical significance. Threat distracters and reward distracters generally did not significantly differ in their effects on the BOLD response in cognitive-control regions, except for a trend toward a

Table 2 | Response to incongruent trials relative to congruent trials in the absence of emotionally salient distracters.

Region	BA	*x*	*y*	*z*[a]	*k*[b]	*T*	*Z*[c]
R Precuneus	7	30	−64	26	877	10.32	5.15
R Middle Frontal Gyrus (DLPFC)	9, 6	40	10	34	538	6.65	4.23
L Middle Frontal Gyrus	10	−48	46	20	47	6.49	4.18
Anterior Cingulate (ACC)	24	6	24	20	175	5.98	4.00
L Precentral Gyrus	6	−30	−10	30	145	5.87	3.96
R Superior Temporal Gyrus		46	−50	12	53	5.66	3.88
Middle/Posterior Cingulate	23, 31	−2	−28	32	294	5.61	3.86
L IFG/Insula	13, 47	−44	8	0	159	5.26	3.72
R IFG/Insula	47, 13	34	14	−2	245	5.22	3.70
R Precuneus	7	12	−74	34	28	5.00	3.61
R Superior Frontal Gyrus	9	34	52	36	38	4.89	3.56
L Superior Occipital Gyrus	31	−28	−62	20	30	4.57	3.41
L Thalamus (Pulvinar)		−18	−22	18	31	4.51	3.38
L Middle Occipital Gyrus	19	−26	−88	18	25	4.47	3.37
R Calcarine Sulcus	18	14	−82	16	14	4.44	3.35
R Thalamus (Pulvinar)		18	−28	12	15	4.41	3.33
R Thalamus		14	−10	16	26	4.40	3.33
R Precuneus		24	−58	52	12	4.36	3.31

This contrast was used to functionally identify cognitive-control regions (specifically, the ACC, DLPFC, and IFG/insula, shown in bold) for subsequent analyses.

BA, Brodmann Area; DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

[a] *Stereotactic coordinates of the peak voxel from the Montreal Neurological Institute atlas, left/right (x), anterior/posterior (y), and superior/inferior (z), respectively.*

[b] *Spatial extent of the cluster in voxels (minimum 10 contiguous voxels).*

[c] *Significance threshold of $p < 0.001$.*

significant threat-related increase (i.e., a smaller decrease) in the ACC response to congruent trials relative to reward distracters, $t(12) = 2.155$, $p = 0.052$.

In summary, and consistent with our main hypothesis, we found a significant interaction of task difficulty and stimulus salience on the BOLD response in functionally defined cognitive-control regions. This interaction was driven by threat distracters, which had significant and dissociable effects on the response in cognitive-control regions depending on the level of task difficulty. Specifically, in the more demanding, incongruent MSIT condition, threat distracters acted to decrease the response in cognitive-control regions; in contrast, in the easier, congruent MSIT condition, threat distracters acted to increase the response in cognitive-control regions.

Exploratory analyses of amygdala response

In light of the documented importance of the amygdala in emotion processes and in emotion-cognition interactions, we also conducted exploratory analyses to test for main and interactive effects of stimulus salience and task difficulty on amygdala response. We used a 2 × 2 × 2 repeated-measures ANOVA (factor 1: ROI: left or right amygdala; factor 2: task difficulty: congruent or incongruent; factor 2: stimulus salience: threat distracters or reward distracters). The results are shown in **Figure 4**. There were no significant main effects of ROI and no interactions with ROI ($ps > 0.251$). As expected, the main effect of task difficulty on amygdala response was not significant, $F(1, 12) = 1.091$, $p = 0.317$. The main effect of stimulus salience was also not significant, $F(1, 12) = 0.210$, $p = 0.655$. However, we observed a significant interaction of task difficulty and stimulus salience on amygdala response, $F(1, 12) = 4.992$, $p = 0.045$. Specifically, averaging across left and right amygdala, the amygdala response to threat distracters was significantly reduced in the incongruent MSIT condition compared to the congruent MSIT condition, $t(12) = -2.944$, $p = 0.012$, whereas the amygdala response to reward distracters was not significantly affected by task difficulty, $t(12) = 0.662$, $p = 0.520$. The difference in the average amygdala response between threat distracters and reward distracters was not significant in either congruent or incongruent MSIT condition ($ps > 0.134$). This pattern of results was also observed in the left and right amygdala separately, as signaled by a lack of main or interactive effects of ROI. The left amygdala response to threat distracters on incongruent trials was significantly lower than to threat distracters on congruent trials, $t(12) = -2.683$, $p = 0.020$; and similarly, the right amygdala response to threat distracters on incongruent trials was significantly lower than to threat distracters on congruent trials, $t(12) = -2.553$, $p = 0.025$. In contrast, the responses to reward distracters in left and right amygdala were not significantly modulated by task difficulty ($ps > 0.517$). The responses to threat and reward distracters on either congruent or incongruent trials also did not significantly differ either in the left or right amygdala ($ps > 0.112$). In addition, correlations showed that the amygdala responses to threat and reward distracters were significantly positively correlated in all task conditions (left amygdala: incongruent trials, $r = 0.831$, $p < 0.0001$; congruent trials, $r = 0.612$, $p = 0.026$; right amygdala: incongruent trials, $r = 0.774$, $p = 0.002$; congruent trials, $r = 0.602$, $p = 0.030$).

To further explain this reduction in the amygdala response to threat distracters (but not to reward distracters) during task performance, we tested for correlations between the amygdala

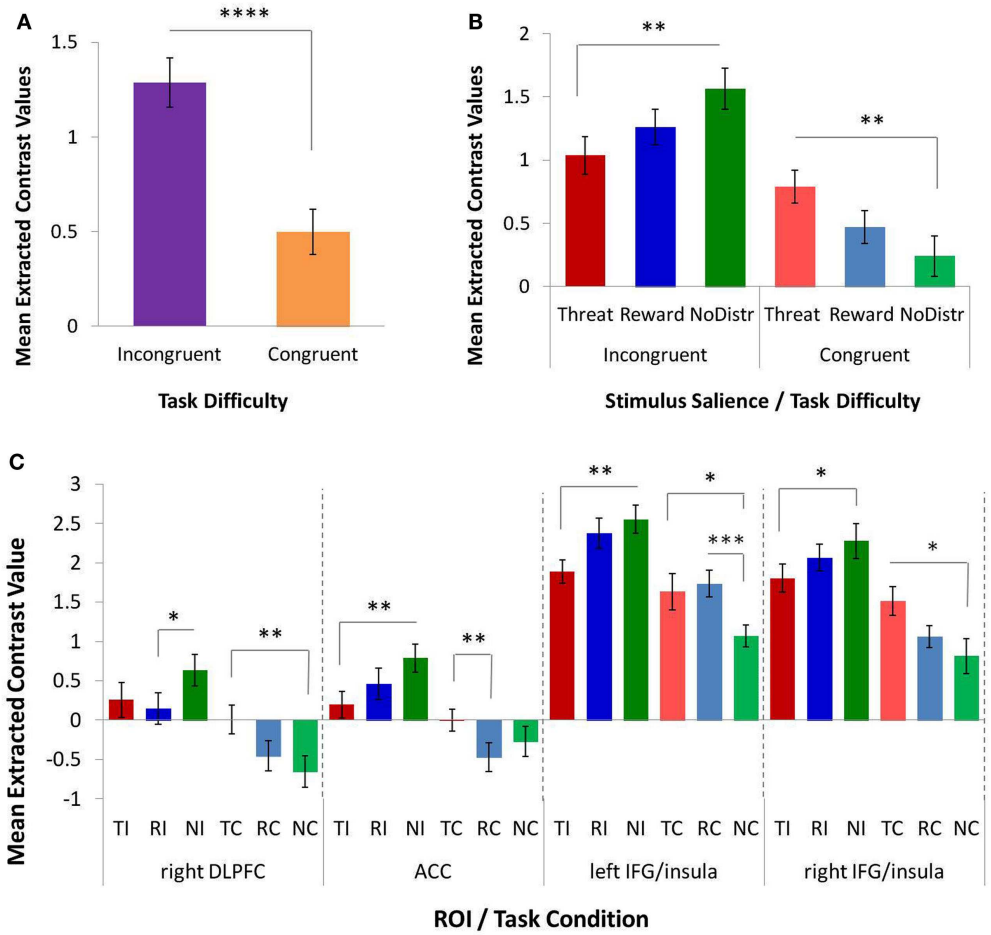

FIGURE 3 | The effects of task difficulty and stimulus salience on the response in functionally defined cognitive-control regions, as assessed with a repeated-measures ANOVA and *post hoc t*-tests on extracted contrast values. (A) A significant main effect of task difficulty (or MSIT condition) on the response in cognitive-control regions. The more demanding incongruent condition elicited a greater response than the easier congruent condition. **(B)** A significant interaction of task difficulty and stimulus salience on the response in cognitive-control regions. Threat distracters reduced the response to incongruent trials, but increased the response to congruent trials, relative to the no-distracter condition. **(C)** Interaction of task difficulty and stimulus salience in individual cognitive-control ROIs: right DLPFC, ACC, left IFG/insula, and right IFG/insula. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MSIT, Multi-Source Interference Task; ROI, region of interest; NC, congruent/no distracters; NI, incongruent/no distracters; RC, congruent/reward distracters; RI, incongruent/reward distracters; TC, congruent/threat distracters; TI, incongruent/threat distracters. $^{*}p < 0.10$; $^{**}p < 0.05$; $^{***}p < 0.01$; $^{****}p < 0.001$.

response and the response in the cognitive-control regions in congruent and incongruent MSIT conditions separately. In the threat-distracter condition, the amygdala response was not significantly correlated with the response in any of the four cognitive-control ROIs in either congruent or incongruent MSIT condition ($ps > 0.148$). However, on incongruent trials with reward distracters, the amygdala response was significantly positively correlated with the right IFG/insula response, $r = 0.553$, $p = 0.050$, and showed a trend toward a positive association with the left IFG/insula response, $r = 0.516$, $p = 0.071$. Interestingly, both reward-related associations were driven by the right amygdala (with left IFG/insula, $r = 0.600$, $p = 0.030$; with right IFG/insula, $r = 0.558$, $p = 0.047$); whereas the left amygdala response showed only a trend toward a positive association with the right IFG/insula response, $r = 0.533$, $p = 0.061$, and was not significantly associated with the left IFG/insula response, $r = 0.444$, $p = 0.129$. In addition, on congruent trials with reward distracters, the amygdala response was significantly negatively correlated with the right DLPFC response, $r = -0.636$, $p = 0.019$. The association with the right DLPFC was driven by the right amygdala, $r = -0.735$, $p = 0.004$, but was also detected at a trend level in the left amygdala, $r = -0.550$, $p = 0.052$.

DISCUSSION

Complex, bidirectional emotion-cognition interactions, including those between emotionally salient stimuli and cognitive-control processes, are crucial to goal-directed behavior and may be impaired in several psychological disorders such as depression, anxiety, and addiction. Although increasingly a research focus in the neurosciences, the neural mechanisms underlying the

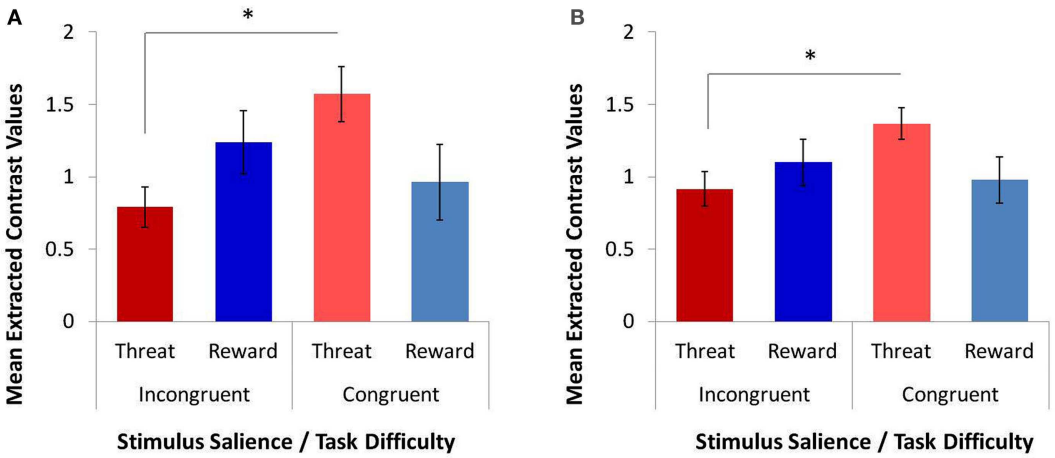

FIGURE 4 | The effects of task difficulty and stimulus salience on the response in anatomically defined left and right amygdala, as assessed with a repeated-measures ANOVA and post hoc *t-tests* on extracted contrast values. We observed a significant interaction of task difficulty and stimulus salience on the response in both left amygdala **(A)** and right amygdala **(B)**. The amygdala response to threat distracters on the more demanding incongruent trials was significantly lower than to threat distracters on the easier congruent trials. In contrast, the amygdala response to reward distracters was not modulated by task difficulty. $^{*}p < 0.05$.

relationships between emotion and cognitive control are still incompletely understood. In particular, evidence suggests that emotionally salient stimuli can sometimes enhance and sometimes impair cognitive task performance, although our understanding of factors that determine which of the two effects occurs is still limited.

In the current fMRI study, building on the evidence from our previous behavioral investigation (Jasinska et al., 2012b) and from other studies (Gu et al., 2012; Hu et al., 2012; Shafer et al., 2012), we focused on *task difficulty* as a plausible factor modulating the impact of emotionally salient distracters on the response in cognitive-control regions and on cognitive task performance. We used an event-related fMRI design and a robust interference task, the MSIT (Bush and Shin, 2006), modified to include both threat and reward distracters. This permitted us to examine the main and interactive effects of stimulus salience (threat, reward, or neutral stimuli) and task difficulty (a demanding incongruent task condition vs. an easier congruent task condition).

As expected, the threat/reward-distracter MSIT produced robust behavioral effects. Consistent with prior studies using the standard MSIT (Bush et al., 2003), we found significant main effects of task difficulty (or congruency) in both RTs and accuracy: subjects were significantly slower and significantly less accurate in the more demanding incongruent condition compared to the easier congruent condition. Furthermore, these interference effects (incongruent vs. congruent contrasts) were present in all distracter conditions, supporting the notion that an additional cognitive-control process was required to overcome the interference on incongruent trials, which was not engaged (or engaged to a lesser degree) on congruent trials. We also found a significant main effect of stimulus salience, as well as a significant interaction of task difficulty and stimulus salience, in RTs but not in accuracy. Subjects were significantly slower in the presence of threat or reward distracters compared to no distracters, and this effect was driven by threat- and reward-distracter-related slowing specific to the incongruent trials but absent from the congruent trials. In contrast to our previous behavioral study (Jasinska et al., 2012b), we failed to observe an enhancing effect of threat distracters on task performance in the congruent condition in the behavioral data collected during fMRI. We also found no significant differences in RTs or accuracy between the threat- and reward-distracter conditions, suggesting comparable effects of both positive and negative emotional distracters on behavioral performance in our paradigm.

At the neural level, also as expected and consistent with previous fMRI studies using the standard MSIT (Bush et al., 2003), the *incongruent – congruent* contrast with no emotional stimuli yielded robust activation in regions associated with cognitive control: the bilateral ACC, left and right IFG/insula, and right DLPFC. We used this contrast to functionally define four cognitive-control ROIs for subsequent analyses, which were performed on extracted contrast values, with all six conditions of interest (incongruent/threat distracters, congruent/threat distracters, incongruent/reward distracters, congruent/reward distracters, incongruent/no distracters, and congruent/no distracters) compared to a common fixation baseline. But the key question addressed by our study was the impact of threat and reward distracters on the response in the cognitive-control ROIs, and whether this impact was modulated by task difficulty. Indeed, consistent with our main hypothesis, we found a significant interaction of stimulus salience and task difficulty on the response in cognitive-control regions. Specifically, and in agreement with our previous behavioral report (Jasinska et al., 2012b), the fMRI data indicated that threat distracters had dissociable and opposite effects on the response in the cognitive-control ROIs in the difficult and easy task conditions. Namely, threat distracters acted to significantly *reduce* the response in cognitive-control regions on the more demanding incongruent MSIT trials, whereas they acted to significantly *enhance* the response in cognitive-control regions on the easier

congruent MSIT trials, relative to the emotionally neutral no-distracter condition. The responses in cognitive-control regions observed in the reward-distracter condition were intermediate between threat-distracter and no-distracter conditions, but these effects did not reach significance in our data. Of note, and consistent with the behavioral results from the scanner, the difference in responses in cognitive-control regions between threat and reward distracters was also not significant.

The results of the current study contribute to a growing body of research aimed at elucidating the factors that modulate the impact of emotional stimuli on cognitive control and cognitive task performance – in other words, the factors that determine whether emotion *impairs* or *enhances* cognition. In particular, our results confirm that *task difficulty* is one factor that modulates the effects of emotional stimuli on cognitive-control processes. We found a significant interaction of task difficulty and stimulus salience, or a trend toward such interaction, in all four cognitive-control ROIs tested (left IFG/insula, ACC, DLPFC, and right IFG/insula). In all four ROIs, threat distracters reduced the response to the more demanding incongruent trials (an effect that reached significance, or a trend to significance, in left IFG/insula, ACC, and right IFG/insula), while they enhanced the response to the easier congruent trials (an effect that reached significance, or a trend to significance, in right DLPFC, left IFG/insula, and right IFG/insula).

Our finding that task difficulty modulates the impact of threat distracters on left IFG/insula response is perhaps the most intriguing. The IFG has been primarily associated with inhibitory control or response inhibition (Aron et al., 2004; Munakata et al., 2011), including inhibitory control over negative emotional stimuli (Ochsner and Gross, 2005), although it is also known to play a role in interference resolution (Nee et al., 2007). A similar pattern of modulation in left IFG was observed by Blair et al. (2007), who reported a reduction in the left IFG response to incongruent trials relative to congruent trials in the presence of threat distracters, to the point that any difference between incongruent and congruent trials was abolished. Also relevant to our study was the result obtained by Gu et al. (2012), who reported an interaction of task difficulty and stimulus salience in the left anterior insula (AI), a region anatomically adjacent to, and connected with, the left IFG. Gu et al. (2012) concluded that the AI is a key region in a network of regions that serve to integrate emotional and cognitive processes in the human brain. However, in that study, threat information increased – rather than decreased – the left AI response to the more demanding task condition (laterality judgment) relative to the easier task condition (body-part judgment). One possible explanation for this reversed direction of modulation is that *goal or task relevance* of negative emotional stimuli is another factor modulating the impact of these stimuli on cognitive-control processes (see Kanske, 2012). Indeed, previous studies suggest that task-irrelevant negative emotional distracters tend to *impair* performance on tasks engaging cognitive control (Blair et al., 2007; Jasinska et al., 2012b), whereas task-relevant negative emotional targets *enhance* performance on such tasks (Kanske and Kotz, 2011a,b). Thus, we may expect that task-irrelevant threat distracters (in the current study) and task-relevant threat targets (Gu et al., 2012) would produce an opposite pattern of modulation at the neural level as well; namely, that if threat distracters decreased the neural response in a specific cognitive-control region, threat targets should increase this neural response, and vice versa. Furthermore, both modulatory factors – task difficulty and goal relevance – may interact with stimulus salience to affect cognitive-control processes and task performance, a three-way interaction that may add further nuance and complexity to a predicted pattern of response in cognitive-control regions. To our knowledge, such three-way interaction has not yet been tested.

We also observed an interaction of task difficulty and stimulus salience in the ACC, specifically the dorsal portion of the ACC (dACC), a region well known to be involved in cognitive control (Carter et al., 1999; Botvinick et al., 2001) but not typically associated with responses to emotional stimuli. This is in contrast to the rostral ACC (rACC), which is believed to play a key role in signaling and resolving emotional conflict (Etkin et al., 2006; Egner et al., 2008), and the ventral ACC (vACC, also referred to as subgenual ACC), which has been implicated in conflict processing in the presence of emotional stimuli (Kanske and Kotz, 2011a,b). However, growing evidence suggests that the dACC, extending into the anterior midcingulate cortex (aMCC), may also be involved in integrating emotion and cognition – specifically, the integration of negative emotion, pain, and cognitive control (for review, see Shackman et al., 2011). Furthermore, the dACC, rACC, and vACC are closely related in terms of phylogeny, cytoarchitecture, and anatomical connections, with the dACC and vACC displaying a comparable high density of connections with the amygdala (Ray and Zald, 2012). Several previous studies failed to detect either main or interactive effects of stimulus salience in the dACC for negative emotional stimuli (Blair et al., 2007; Kanske and Kotz, 2011a,b; Gu et al., 2012). One possible reason is an insufficient intensity of the emotional stimuli used (e.g., a presentation of threat-related images compared to an actual pain induction; Shackman et al., 2011; Gu et al., 2012). We propose that another possible explanation for a failure to observe a main effect of stimulus salience, and particularly an interaction of stimulus salience and task difficulty, is insufficiently high level of task difficulty, which in turns produces only a modest response in the dACC, making subtle effects of modulatory factors difficult to detect.

The third cognitive-control region in which we observed an interaction between task difficulty and stimulus salience was the right DLPFC. The DLPFC is known to play a critical role in working memory (Curtis and D'Esposito, 2003), including the maintenance and updating of goal representations and task sets. A similar interaction in the DLPFC was reported by Gu et al. (2012), but that study found that threat *targets* increased the DLPFC response to the more demanding task condition relative to the easier task condition, whereas we observed that threat *distracters* reduced the DLPFC response to the harder incongruent trials compared to the easier congruent trials. Thus, as discussed above for the IFG/insula, the DLPFC response during task performance may be modulated by a three-way interaction between task difficulty, goal relevance, and stimulus salience, which is yet to be tested. Our DLPFC result also resonates with an earlier report of interactive effects – with no main effects – of induced emotional state (positive, negative, or neutral) and stimulus type (words or faces) on the DLPFC response during a working-memory task (Gray et al., 2002).

Taken together, our results suggest that negative emotional distracters can either impair or enhance cognitive control, depending on the situation, by decreasing or increasing the response in cognitive-control regions. This conclusion fits well with the view that the adaptive function of emotional states is to rapidly and flexibly switch between different modes of responding, in order to best meet the current challenges of the environment (Gray, 2004). In most situations, a goal-directed and rule-guided behavior which engages cognitive control may be most adaptive, ensuring that the organism's needs are met; but in some situations, especially when facing a threat, it may be more adaptive to "switch off" cognitive-control processes and instead rely on fast, automatic responses to fend off danger and ensure survival. Consistent with the latter case, in addition to impairing interference resolution, cues signaling a threat of electric shock have been shown to impair response inhibition (Pessoa et al., 2012) and fearful-face distracters have been found to impair task switching (Zhou et al., 2011). From a researcher's perspective, this generalization of threat effects across different aspects of cognitive-control presents an opportunity: because the neural mechanisms underlying the different cognitive-control processes within and across the ACC, IFG/insula, and DLPFC regions are still not well understood, emotional modulation of these regions may serve as a novel probe for elucidating these mechanisms.

We also report preliminary evidence of an interaction of task difficulty and stimulus salience on the amygdala response. Previous reports have suggested that the amygdala does not respond to cognitive conflict (Kanske and Kotz, 2011a,b) and that the amygdala response to negative emotional stimuli does not change whether these stimuli are attentional targets or distracters (Vuilleumier et al., 2001). However, evidence that the amygdala response to negative emotional stimuli is in fact modulated by attentional focus has also been reported (Pessoa et al., 2002, 2005). Furthermore, and of particular relevance to the current study, Blair et al. (2007) reported that the amygdala response can be modulated by task difficulty; specifically, in the presence of threat distracters, the left and right amygdala responses to incongruent trials were lower than to congruent trials. This is very similar to the result that we obtained in the current study: that the left and right amygdala responses to incongruent trials were lower than to congruent trials in the threat-distracter condition (although not in the reward-distracter condition). The interpretation of this pattern of results in the amygdala is at present unclear, and future studies will be needed to explain the nature and significance of the interaction between stimulus salience, task difficulty, and goal relevance on the amygdala response (for Discussion, see also Jasinska et al., 2012a).

Some limitations of the present study should be acknowledged. The first limitation is a lack of emotionally neutral distracters in our paradigm. We chose not to include such neutral distracters as a control condition, and instead to compare both threat and reward distracters against the no-distracter condition (with only neutral stimuli) and against the fixation baseline, for two reasons. Our previous behavioral study using the MSIT (Jasinska et al., 2012b), which included such closely matched neutral distracters, already established that threat distracters produced significant effects on both RTs and accuracy relative to neutral distracters as well as relative to the no-distracter condition. But the more urgent consideration was that, given a long scanning time, the amygdala response could habituate to the emotional stimuli upon repeated presentation (Breiter et al., 1996; Whalen et al., 1998b; Wright et al., 2001), which would diminish or even abolish the subtle modulation effects that we were trying to detect in the current study. Nevertheless, the lack of such neutral distracters as a control condition warrants caution in interpreting our results. In particular, it is possible that the observed effects of threat and reward distracters reflect simply distracter effects (i.e., added interference) rather than any emotion effects. Without a direct comparison between the emotional-distracter conditions and a neutral-distracter condition, we cannot be sure that the observed effects are due to the emotional salience of the distracters and not to their other attributes. However, it should be noted that if the effect was due simply to increased interference and not to emotional salience of distracters, we would expect an increase – rather than a reduction – in the response of cognitive-control regions. Another limitation of the current study is a relatively small sample size. In addition, we limited the current investigation to female participants, in order to maximize the chance of detecting the effects of interest (i.e., modulation of neural and behavioral correlates of cognitive control by threat and reward distracters) in light of considerable sex differences in emotion processing (Klein et al., 2003; Wrase et al., 2003).

An important goal for future research will be to assess the range and impact of individual differences in susceptibility to emotional distraction, conceptualized as an interplay of emotional reactivity on the one hand and cognitive-control efficiency on the other hand. The same emotional distracters may enhance cognitive control in some individuals but impair cognitive control in others, as shown with opposite patterns of behavioral performance and corresponding brain activity for working memory (Dolcos et al., 2008). Ultimately, such individual neurobiological profiles of emotion-cognition interactions may help us determine the risk of, and select the most effective treatment for, such disorders as depression, anxiety, or addiction (Dolcos et al., 2011).

In conclusion, using fMRI and a robust behavioral paradigm, we demonstrated that task difficulty modulates the impact of emotionally salient distracters on the response in cognitive-control regions, including the ACC, IFG/insula, and DLPFC, during cognitive task performance in healthy females. Specifically, threat distracters decreased the response in cognitive-control regions on the more demanding incongruent trials, whereas they increased the response in cognitive-control regions on the easier congruent trials, relative to the no-distracter condition. A similar effect was also observed in the left and right amygdala: threat distracters produced a decrease in the amygdala response on incongruent trials relative to congruent trials. These results add to our understanding of the neural processes through which emotional distracters affect cognitive control and behavior, and may have implications for the study of psychological disorders in which heightened emotional reactivity and impaired cognitive control interact to undermine normal function.

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Modulation of early and late event-related potentials by emotion

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Although emotionally salient stimuli influence higher order information processing, the relative vulnerability of specific stages of cognitive processing to modulation by emotional input remains elusive. To test the temporal dynamics of emotional interference during executive function, we recorded event-related potentials (ERPs) while participants performed an effortful anticipation task with aversive emotional and neutral distracters. Participants were presented with a modified delayed Stroop task that dissociated the anticipation of an easier or more difficult task (instructional cues to attend to word vs. color) from the response to the Stroop stimulus, while aversive and neutral pictures were displayed during the delay period. Our results indicated a relative decrease in the amplitude of the contingent negative variation (CNV) during aversive trials that was greater during the early anticipatory phase than during the later response preparation phase, and greater during (the more difficult) color than word trials. During the initial stage of cue processing, there was also significant interaction between emotion and anticipatory difficulty on N1 amplitude, where emotional stimuli led to significantly enhanced negativity during color cues relative to word cues. These results suggest that earlier processes of orientation and effortful anticipation may reflect executive engagement that is influenced by emotional interference while later phases of response preparation may be modulated by emotional interference regardless of anticipatory difficulty.

Keywords: contingent negative variation, emotion, anticipation, distraction

INTRODUCTION

The presence of emotionally salient stimuli is known to influence how the brain processes information. Depending upon the specific timing in which emotional and cognitive systems are engaged, input from emotional circuitry can enhance or disrupt neural activity related to higher order executive function. While presentation of negative emotionally salient distracters subsequent to the onset of an executive task can lead to disruption of sustained attention processes (Arnsten and Goldman-Rakic, 1998; Dolcos and McCarthy, 2006), several studies have shown that emotional stimuli presented prior to or concurrent with cognitive processing can also lead to an improvement in performance (Gray et al., 2002; Schupp et al., 2007). Several studies by our group and others have characterized the dynamics of these opposing systems with functional neuroimaging (Blair et al., 2007; Hart et al., 2010). While these studies inform about the global effects of emotional interference, most executive functions rely on a sequence of complex operations, including stimulus selection, rule encoding, anticipation and response preparation, as well as response selection, and execution. By investigating how emotional interference may modulate these specific stages of processing, we may gain a better understanding of the underlying mechanisms of emotional-executive interactions.

Understanding the effects of emotional interference during specific stages of executive function is critical for not only understanding how affective interference modulates cognition in healthy brain development and function, but also for understanding the affective and cognitive dysregulation in a number of brain disorders, including schizophrenia, post-traumatic stress disorder (PTSD), affective disorders, and autism. Dysregulation of these executive-emotional interactions may trigger the onset or exacerbation of cognitive deficits associated with emotional-executive regulation mechanisms. In order to gain a more complete understanding of emotion-cognitive interactions in both the healthy brain and in psychiatric disorders, it is important to investigate how emotion influences cognition at different temporal stages of processing, as well as how it influences cognition in specific neural circuits. Therefore, in the current study we aimed to further elucidate the mechanisms underlying executive-emotional interactions by examining the influence of emotional distracters across different temporal stages of executive processing by using event-related potentials (ERPs). We aimed to investigate how specific stages of cognitive processing, such as the anticipation of cognitive effort and the preparation for a motor response, may differ in their vulnerability to emotional modulation.

The ability to prepare for an upcoming task is a critical aspect of executive function and involves recruitment of several neural circuits across multiple stages of processing (Brass and von Cramon, 2004). Electroencephalographic (EEG) recordings have long been used to study the different processes involved in the coordination of goal-directed behavior by means of slow brain potentials. The best known examples in this regard are

the readiness potential (RP), the stimulus preceding negativity (SPN), and the contingent negative variation (CNV). The RP (Kornhuber and Deecke, 1965) reflects the timing of a future voluntary movement, the SPN (Brunia, 1988; Leynes et al., 1998) reflects anticipatory attention for an upcoming stimulus and the CNV (Walter et al., 1964) reflects the preparation of a signaled movement and the simultaneous anticipatory attention for the imperative stimulus. When a longer period (3–5 s) between a warning/instructional stimulus and an imperative/probe stimulus is used, the CNV can be divided into early and late phases (Brunia and van Boxtel, 2001). The early phase of the CNV primarily reflects orientation and anticipatory cognitive control processes in response to a warning stimulus, and the late phase of the CNV primarily (but not necessarily) reflects preparation for an upcoming motor response (Brunia and van Boxtel, 2001). Many studies have demonstrated that the CNV amplitude is increased during attentional demand and is significantly reduced when a distracting stimulus is present (Teece, 1972; Gontier et al., 2007). The neural generators for the CNV have been reported to include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), premotor cortex and supplementary motor area for the early phase (Gomez et al., 2004; Lutcke et al., 2009), and basal ganglia, prefrontal, pre-motor, and dorsal ACC (Ikeda et al., 1997; Gomez et al., 2003; Lutcke et al., 2009) for the late phase.

Several previous studies have examined the interactions between anticipatory processing and emotion but have primarily focused on the role of cognitive strategies during anticipation of an upcoming task-relevant emotional stimulus, reflecting the modulation of attentional resource allocation. Moser et al. (2009) recently demonstrated that preparation for cognitive reappraisal of an impending negative emotional stimulus modulates the SPN. Greater engagement of cognitive resources during anticipatory processes may therefore suppress the effect of subsequent negative emotional stimuli, as the process of mental preparation for the impending emotional stimulus allows the brain to regulate the degree of emotional processing through increased prefrontal cortical activity (Goldin et al., 2008). Anticipatory processes are also modulated by preparation for emotionally salient inputs, with enhanced amplitudes during anticipation of positive emotional stimuli (Casement et al., 2008).

While these studies have demonstrated that anticipatory processes can influence task-relevant emotional processing, there is a relative lack of knowledge about the opposite effect, that is, how task-*irrelevant* emotional interference may affect anticipatory processes for an upcoming (difficult) cognitive task. Because the direction of attention allocation may influence how emotional and anticipatory processes interact, it is important to understand how each process may impact the other. By using a slow wave ERP paradigm we aimed to address the effect of emotion on anticipatory processing by measuring how the different temporal phases of preparation for goal-directed behavior may be modulated by emotional interference. We chose to use emotional stimuli with negative valence based on a multitude of previous findings showing disruption of prefrontal activity (Dolcos and McCarthy, 2006; Arnsten, 2009; Qin et al., 2009). To test the temporal dynamics of emotional interference, we used a delayed Stroop task that dissociates the instructional cue from the response in order to separately examine anticipatory processes and the executive response. The Stroop task allows for the measurement of cognitive control processes required to suppress an automatic response (reading a word) while identifying the color in which the word is printed. When these stimulus attributes are incongruent with one another (e.g., the word "RED" in green print), it is more difficult to suppress the prepotent response to read the word. In order to assess anticipatory difficulty, we first presented an instructional cue indicating whether the subject should subsequently identify the presented word (the easier reading response) or the print color (requiring more cognitive control). A delay period followed, during which emotional distracter images were presented while participants prepared to respond to an upcoming Stroop stimulus. The delayed Stroop task design allowed for the dissociation of separable cognitive phases so that the effects of emotional interference could be assessed over time. Additionally, the task was previously validated with fMRI (MacDonald et al., 2000) and therefore had the advantage of allowing for inference of the neural circuits likely involved.

We focused our analyses on the ERP components elicited by the presentation of the cue (N1) and during the anticipatory period across the delay (CNV) prior to the executive response to the Stroop stimulus. By presenting emotional stimuli during the delay period, we measured the modulation across the early (cognitive control) and late (motor preparatory) phases of the CNV, and tested how anticipation of increased task demand (with presumed increased PFC engagement) affected this emotional modulation. Furthermore, analysis of the N1 component allowed us to determine whether emotional interference also disrupts attentional processing at the earliest sensory phase, prior to the emergence of the CNV. The N1 has previously been found to be the earliest component modulated by emotional stimuli in a passive viewing task (Foti et al., 2009) and has been associated with increased vigilance for emotionally threatening stimuli (Shackman et al., 2011).

Given previous findings that the PFC is involved in effortful anticipation (MacDonald et al., 2000) and may be disrupted by negative emotional interference (Dolcos and McCarthy, 2006), we predicted that ERP components elicited during the early preparatory task phase would show greater emotional modulation under conditions of increased anticipatory effort than ERP components elicited during the later preparatory phase of the Stroop task. We also expected that participants would be slower to respond during more effortful anticipatory trials, with further decline in performance during aversive emotional interference.

MATERIALS AND METHODS

PARTICIPANTS

We collected EEG data from 12 healthy participants between the ages of 19–34 (mean age = 22.9), including six males and six females. All participants were right-handed, with no current or past history of substance abuse or neurologic/neuropsychiatric disorders, and reported normal or corrected-to-normal vision. Participants gave informed consent as approved by the UNC Institutional Review Board.

EXPERIMENTAL PROCEDURE

Continuous EEG data was recorded during a modified Stroop task designed to temporally dissociate effortful anticipatory processing from the implementation of cognitive control. The classic Stroop task requires participants to respond to a color word (e.g., "RED") by either reading the word or responding to the ink color in which the word is written. The ink color may be congruent (e.g., "RED" in red ink) or incongruent (e.g., "RED" in blue ink), requiring additional cognitive control to suppress the prepotent reading response. To assess the anticipatory phase, we first presented an instructional cue indicating whether the subject should identify the presented word (the prepotent reading response) or the print color (requiring more cognitive control). Following a delay period during which the participants prepared to respond, the Stroop stimulus (probe) was presented. Three possible congruent probes (the word "RED" in red, the word "BLUE" in blue, and the word "GREEN" in green) and six possible incongruent probes (the word "RED" in blue, the word "RED" in green, the word "BLUE" in red, the word "BLUE" in green, the word "GREEN" in red, and the word "GREEN" in blue) were used. The Stroop probe stimuli were randomly varied to be congruent and incongruent (each comprising 50% of the total trials). Participants were directed to respond to the probe as quickly and accurately as possible pressing one out of three buttons. The buttons 7, 8, and 9 on a standard USB keyboard were mapped according to the three colors possible (i.e., red = 7, blue = 8, and green = 9). Participants always responded with their index (button 7), middle (button 8) or ring finger (button 9) to red, blue, or green colors, respectively. The inter-trial interval was randomized between 3 and 6 s at 250 ms intervals. Additionally, prior to beginning the task, all participants performed a practice session with 20 total trials using scrambled images in place of the International Affective Picture System (IAPS) distracter images. This session allowed participants to become familiarized with the button response mappings, and to learn that identification of the word was easier than the print color, without introducing any habituation to the emotional images.

In order to modulate emotional processing, each trial included presentation of a task-irrelevant picture from the IAPS database (Lang et al., 2005). This database includes images that have standardized ratings for arousal and valence on a scale of 1–9, with higher numbers indicating greater arousal and more positive emotional valence. Within the experiment, 50% of the trials were aversive (valence mean = 2.57, $SD = 0.81$; arousal mean = 6.46, $SD = 0.46$) and 50% were neutral (valence mean = 5.27, $SD = 0.8$; arousal mean = 3.27, $SD = 0.62$). The images used in the neutral condition had significantly higher valence [$F_{(1,\ 158)} = 444.34, p < 0.0001$] and lower arousal ratings [$F_{(1,\ 158)} = 1340.83, p < 0.0001$] than the aversive condition.

Each trial began with the presentation of an aversive or neutral IAPS distracter image (**Figure 1**). Beginning at 250 ms after the onset of the trial, a cue was imposed over the IAPS distracter image for 500 ms displaying either "word," instructing the participant to respond to the probe by reading the

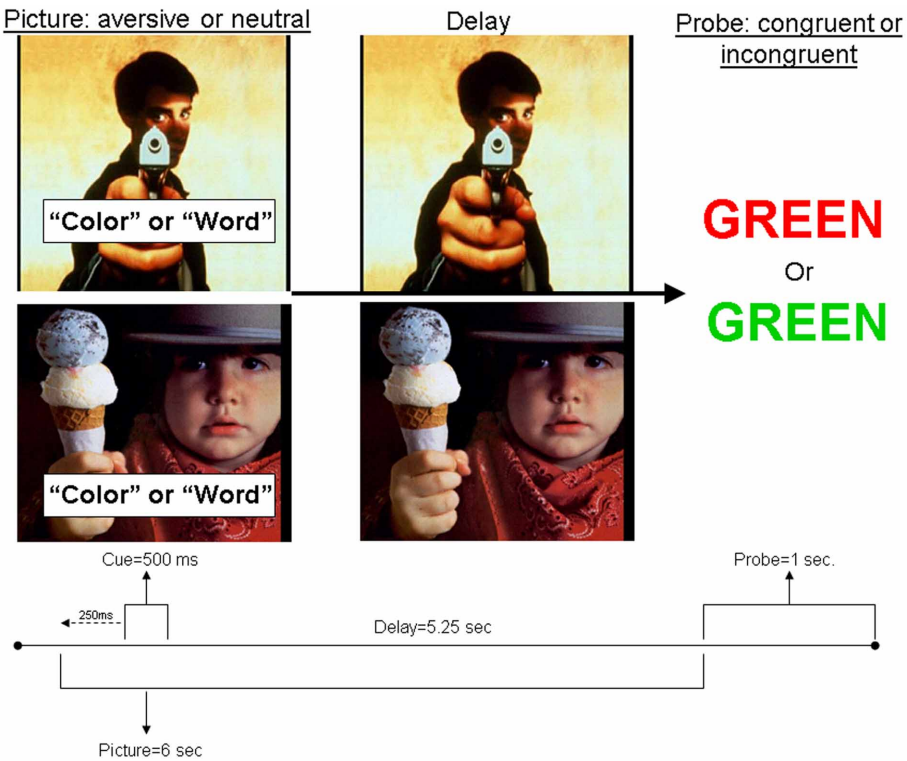

FIGURE 1 | Schematic of task design.

printed word, or "color," instructing the participant to respond to the probe using the color of the text. Each cue type was randomly presented in 50% of the total trials across the experiment. After the cue, there was a 5250 ms delay during which the IAPS distracter image remained on the screen. Following the delay, the IAPS image disappeared and a Stroop probe was displayed for 1 s. There were 160 total trials (each with a unique image) presented across 8 runs, with 20 trials per run.

Electrophysiological recording

Participants were seated comfortably in a sound-attenuated, dimly lit booth. Pictures were displayed at a distance of about 80 cm at eye level on a 19′ Dell flat panel monitor. Stimulus presentation was controlled by Presentation software, version 12.1 (Neurobehavioral Systems, Albany, CA). Continuous EEG data was collected using an elastic cap containing 32 electrodes at frontal (F7, F3, Fz, F4, F8), frontocentral (FT7, FC3, FCz, FC4, FT8), central (T7, C3, Cz, C4, T8), centroparietal (TP7, CP3, CPz, CP4, TP8), and occipital (O1, Oz, O2) scalp locations. The right mastoid served as the reference electrode and AFz as the ground. Bipolar recordings of the vertical and horizontal electro-oculogram (EOG) were obtained by electrodes placed above and below the right eye and on the outer canthus of each eye, respectively. EEG and EOG data were sampled at a rate of 500 Hz and bandpass filtered online between 0.05 and 100 Hz, with a narrow 60 Hz notch filter used to reduce main power frequency interference. Continuous data was collected and analyzed off-line using a NeuroScan 4.4 system (Neurosoft, Inc., Sterling, VA).

DATA PROCESSING

Response latencies and percentage of correct responses were calculated for each subject. All incorrect trials or trials containing responses less than 200 ms and greater than 1000 ms from onset of the probe were excluded from further analyses. Continuous EEG data was filtered offline with a 30 Hz (24 dB/octave) low-pass filter and visually inspected for movement artifacts, and incorrect behavioral responses were removed from the analyses. EEG data sets from each participant were corrected for eye-movements using regression analysis as implemented in Neuroscan Edit 4.4 (Semlitsch et al., 1986).

For analysis of the CNV, continuous data was divided into 8 s long epochs, spanning from 500 ms before the distracter stimulus to 7500 ms thereafter and including a 1500 ms post-probe period. All epochs were baseline corrected using the first 200 ms of the pre-distracter interval, with all conditions using the same averaged baseline. Any epoch containing amplitudes exceeding $\pm 100\mu V$ at any electrode was excluded from further analyses. All remaining epochs were averaged together based on stimulus category.

In order to separately analyze the early and late components of the CNV, average amplitudes were computed for two time windows during the CNV delay period: 250–2250 ms following the cue onset (early CNV) and 3250–5250 ms following cue onset (late CNV). Based on prior findings of the scalp distribution for the two phases of the CNV (Zappoli et al., 2000; Gomez et al., 2001, 2003), the early phase was analyzed at frontal sites (F3, Fz, and F4) and the late CNV at parietal sites (P3, Pz, and P4), with both phases analyzed at electrode Cz. To analyze the response related to the "word" or "color" instructional cue (N1), negative peak amplitude and latency was analyzed from a window between the onset of the cue and 250 ms following cue onset at electrodes Fz and Cz. These electrodes were chosen in order to visualize the experimental effects on the N1 and CNV at the same site. Additionally, we performed the N1 analyses at occipital sites, including O1, Oz, and O2. For statistical analysis, a series of repeated measures ANOVAs were performed with electrode location, cue type and emotion as within-subjects factors. We note that while a P3 component was generated following the Stroop probe stimulus, the analysis of this component was outside the scope of our hypotheses, which focused specifically on emotional modulation of anticipatory processing. Because of our sample size limitation, and because our hypotheses were focused on the role of cue and emotion on behavior and ERP measures, we chose not to include a Three-Way ANOVA integrating the probe condition in our analyses.

RESULTS

BEHAVIORAL DATA

The behavioral findings for accuracy and RT for all conditions are presented in **Table 1**. An ANOVA was performed using RT on correct trials as the dependent variable. Color trials were found to be associated with significantly slower RTs relative to word trials

Table 1 | Behavioral Results.

	Congruent				Incongruent		
	Aversive	**Neutral**	**Average**		**Aversive**	**Neutral**	**Average**
Accuracy (% correct)							
Color: Mean, SD	89.81 (4.82)	94.09 (3.18)	91.95 (4.55)	Color: Mean, SD	87.01 (10.62)	83.1 (9.13)	85.06 (10.62)
Word: Mean, SD	90.05 (4.95)	93.85 (3.24)	91.95 (4.53)	Word: Mean, SD	87.21 (6.04)	77.7 (3.6)	82.46 (6.88)
Average	89.93 (4.78)	93.97 (3.14)	91.95 (4.49)	Average	87.11 (8.45)	80.4 (7.33)	83.76 (8.53)
Reaction time (ms)							
Color: Mean, SD	1001.89 (232.66)	914.59 (272.85)	958.24 (251.96)	Color: Mean, SD	1310.97 (354.2)	1268.18 (313.5)	1289.57 (327.85)
Word: Mean, SD	931.39 (223.39)	961.6 (305.64)	946.5 (262.26)	Word: Mean, SD	1158.47 (322.35)	1142.87 (342.4)	1150.67 (325.31)
Average	966.64 (225.95)	938.1(284.36)	952.37 (254.48)	Average	1234.72 (340.24)	1205.52 (327.37)	1220.12 (330.62)

$[F_{(1,11)} = 4.98, p = 0.05]$. Additionally, aversive emotional trials were associated with significantly slower RTs compared to neutral trials $[F_{(1, 11)} = 4.75, p = 0.05]$. A significant Cue by Emotion interaction $[F_{(1, 11)} = 7.7, p = 0.02]$ indicated that the slowing of RTs during color trials was primarily driven by the emotional interference (**Figure 2A**). *Post-hoc* tests indicated that aversive pictures led to significantly slower RT than neutral pictures on color trials $[F_{(1, 11)} = 13.95, p = 0.003]$, but no significant effect of emotion was found on word trials. Additional analyses of accuracy revealed no significant main effects of cue or emotionality, and no significant cue by emotionality interaction effect.

Additional exploratory analyses were performed to determine how the cue and emotionality conditions affected Stroop probe processing. For the Stroop probe stimuli, incongruent trials were associated with lower percent accuracy $[F_{(1, 11)} = 26.64, p < 0.001]$ and slower RTs $[F_{(1, 11)} = 63.79, p < 0.001]$ than congruent trials. To analyze the behavioral effects of cue type and emotionality on the Stroop effect, a repeated measures ANOVA was performed with Cue (word vs. color) and Emotion (aversive vs. neutral) entered as within subjects factors and Stroop cost (RT difference between incongruent and congruent trials) used as the dependent variable. The results indicated that there were significantly greater Stroop costs on color trials (mean difference = 331.33 ms) than word trials (mean difference = 204.17 ms) $[F_{(1, 11)} = 9.81, p = 0.01]$ (**Figure 2B**). *Post-hoc* analyses indicated that color trials were associated with slower RTs than word trials, both during the incongruent $[F_{(1, 11)} = 17.95, p = 0.001]$ and congruent conditions $[F_{(1, 11)} = 6.18, p = 0.03]$. There was no significant effect of emotionality and no Emotion by Cue interaction on Stroop costs.

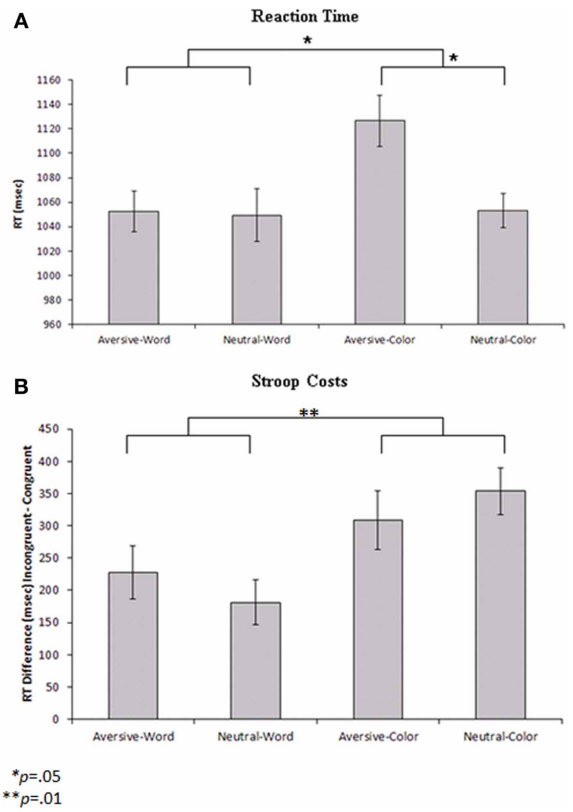

FIGURE 2 | (A) Reaction times to the probe stimuli for each condition with repeated-measures error bars. Color cues led to significantly slower reaction times than word cues ($p = 0.05$), and aversive trials led to slower reaction times than neutral trials within the color condition ($p = 0.05$). **(B)** Reaction time differences between incongruent and congruent probe stimuli (Stroop costs) for each condition with repeated-measures error bars. Color cues led to significantly greater Stroop costs than word cues ($p = 0.01$).

N1 MEASURES

The average ERPs across the entire trial for the neutral-word, neutral-color, aversive-word, and aversive-color conditions are presented from an array of nine electrodes in **Figure 3**. Analyses at electrodes Fz and Cz indicated that aversive trials led to significantly decreased negativity in N1 amplitude relative to neutral trials $[F_{(1, 22)} = 9.59, p = 0.005]$, but no significant effect of Cue was found. A significant Cue by Emotion interaction was found $[F_{(1, 22)} = 14.91, p < 0.001]$, where the relative decrease in N1 amplitude by emotion was significant on color trials $[F_{(1, 22)} = 19.47, p < 0.001]$ (**Figure 4A**), but not word trials (**Figure 4B**). No significant effect of electrode location was found. Analyses at occipital electrodes showed similar effects, with N1 amplitude significantly decreased during aversive trials $[F_{(1, 33)} = 11.26, p = 0.002]$ and a significant Cue by Emotion interaction $[F_{(1, 33)} = 11.79, p = 0.002]$. Analyses of N1 peak latency indicated that word cues showed a trend for slightly faster peak latency than color cues $[F_{(1, 22)} = 3.88, p = 0.06]$, but no effects of Emotion, Emotion by Cue interaction, or electrode location were found.

EARLY AND LATE CNV MEASURES

A repeated measures ANOVA was performed on frontal sites (F3, Fz, and F4) to determine effects of Emotion and Cue on the early CNV average amplitude. The ANOVA revealed that emotional trials led to significantly decreased negativity relative to neutral trials $[F_{(1, 33)} = 20.66, p < 0.001]$, but no significant effect of Cue was found. A significant Emotion by Cue interaction $[F_{(1, 33)} = 12.06, p = 0.002]$ revealed that the early CNV average amplitude was significantly modulated by Emotion during the processing of the color trials $[F_{(1, 33)} = 24.72, p < 0.001]$, but not the word trials[1] (**Figures 3**, **4**). Additionally, no significant effects of electrode location were found.

Another repeated measures ANOVA was performed on parietal sites (P3, Pz, and P4) to determine effects of emotion and cue on late CNV average amplitude. The ANOVA revealed that aversive trials led to significantly decreased negativity compared to neutral trials $[F_{(1, 33)} = 5.96, p = 0.02]$, but no significant main effect of Cue was found. Additionally, no significant Cue by

[1]What we describe in this section as a relative "decrease in negativity" could also be described as a relative "increase in positivity." However, even if we follow the latter line of reasoning—in that the aversive figure triggers a large positive component in the color condition but fails to do so in the word condition—we would still reach the same conclusion. That is: early orienting and effortful anticipation are significantly reduced in the presence of emotional interference, but only when preparation for greater cognitive control is required.

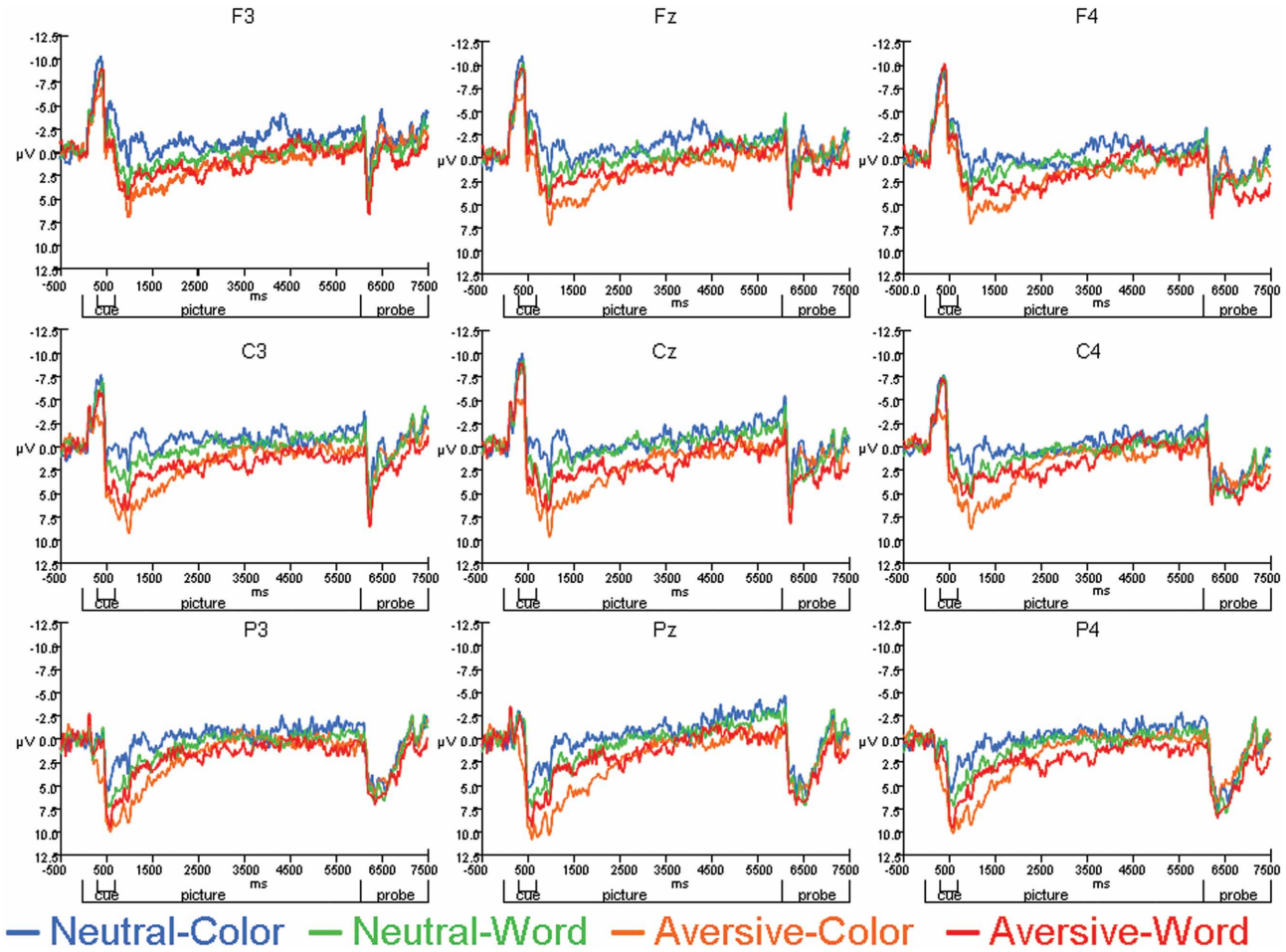

FIGURE 3 | Average ERPs for Neutral-Color, Neutral-Word, Aversive-Color, and Aversive-Word conditions across individual electrode sites.

Emotion interaction was found, nor was there a significant effect of electrode location.

DISCUSSION

The overall goal of this study was to examine the temporal characteristics of emotional interference and modulation of executive anticipatory processes. Our results indicated that N1 and early CNV amplitudes during early orienting and anticipatory processing were significantly reduced in the presence of emotional interference, but only when preparation for greater cognitive control was required. These results were consistent with the reaction time data, indicating that the process of anticipating a cognitively demanding task is more vulnerable to disruption from emotionally salient information than a less demanding task. In contrast, for the late CNV component associated with preparation for a motor response, aversive images led to a significant reduction in negative going amplitude regardless of anticipatory effort. These results suggest that while the N1 and early CNV may provide markers of executive engagement that are sensitive to emotional modulation, motor preparatory processes indexed by the late CNV are affected in general by emotional interference but are not differentially engaged by anticipatory difficulty. Emotional input may therefore lead to disruption of activity across the entire phase of anticipatory processing, but the engagement of additional cognitive control mechanisms leads to additional modulation by emotional interference. These findings reveal differential effects of emotional interference on specific sequential operations of executive processing and suggest potential implications for psychiatric disorders that are characterized by dysfunction in these mechanisms. Indeed, individual differences in salience attribution to emotional cues, or increased attention allocation due to "perceived" task complexity may alter early response preparation and anticipation during higher order executive tasks.

As the interpretation of ERPs is limited by poor spatial resolution, the integration of complementary measures that identify the underlying neural circuits will allow for improved characterization of how emotional interference affects anticipatory processing. Because our task was modeled on the delayed Stroop paradigm used in the fMRI study by MacDonald et al. (2000), it allows us to infer the specific neural circuits that may be recruited by the task while gaining temporal information from ERP recording. MacDonald et al. (2000) reported a double dissociation in

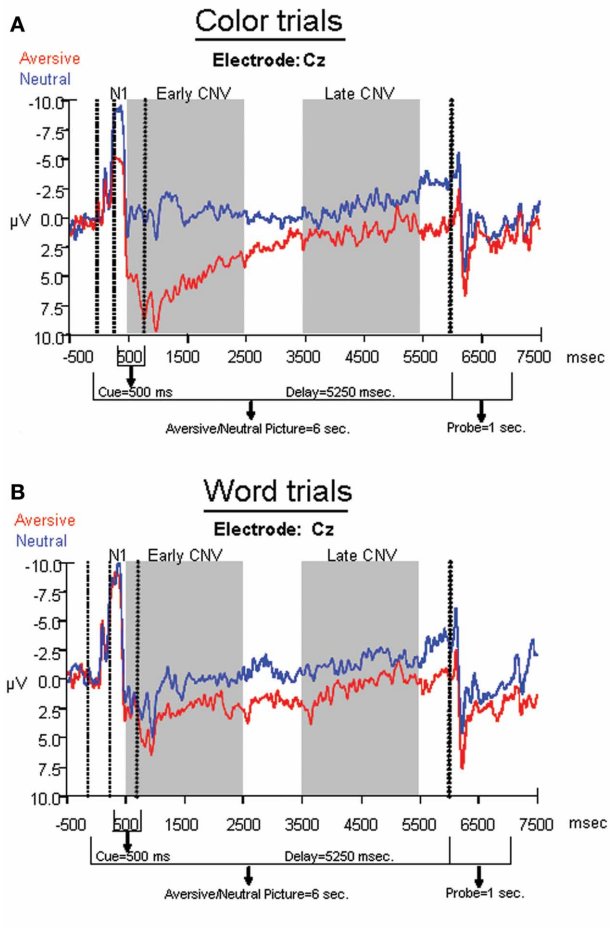

FIGURE 4 | Average ERPs for aversive and neutral conditions within (A) color trials and (B) word trials. Electrode Cz was chosen for display purposes, as it was analyzed across the N1, early, and late CNV components.

that anticipation of a more difficult task (color trials) recruited the dorsolateral PFC (dlPFC) to a greater degree, while response conflict at the Stroop probe was associated with greater anterior cingulate activity. These regions were interpreted to potentially comprise a feedback loop in which top-down control (dlPFC) and evaluative processes (ACC) interact to maintain optimal task performance. Based on these findings, the results of the current study suggest that the emotional modulation we observed in the ERP data was likely related to disruption of the engagement of the PFC early in the trial during effortful anticipation. Although the anterior cingulate has been implicated as a source for the early CNV (Gomez et al., 2004) and is engaged during anticipation and performance monitoring in general (MacDonald et al., 2000), the previous fMRI findings suggest that it was likely not engaged to a greater degree during the more difficult anticipation condition in our task until the Stroop probe stimulus occurred.

The CNV was found in the current study to be modulated in an interactive way by both attentional demand and emotional interference. It has been classically described as reflecting the amount of attention allocated to an impending subsequent stimulus, which requires a response from the subject (Teece, 1972). Many additional studies have demonstrated that the CNV amplitude is increased during attentional demand, and is significantly reduced when a distracting stimulus is present (Teece, 1972; Gontier et al., 2007). The CNV has also been found to be sensitive to arousal effects. A study using similar emotional stimuli as the current design demonstrated modulation of the CNV in individuals with PTSD, with greater arousal to negative IAPS pictures associated with larger CNV amplitudes (Wessa and Flor, 2007). Increased CNV amplitudes have also been found after administration of amphetamine, and decreased amplitude following administration of barbiturates, which lead to enhanced or suppressed arousal, respectively (Kopell et al., 1974). As behavioral performance is also improved by pharmacologically-induced arousal, the concomitant CNV amplitude changes have been interpreted to reflect increased ability to attend to task-relevant features and resist distraction (Teece, 1972; Kopell et al., 1974). The current study's findings differ in that task-irrelevant emotionally arousing stimuli led to behavioral interference and decreased CNV amplitude on cognitively demanding trials. Our results reflect the role of emotional arousal as a distracter that likely inhibits the prefrontal-mediated processes underlying the CNV (as in Dolcos and McCarthy, 2006), but modulation of the task relevance or timing in which emotionally arousing stimuli are presented may differentially affect CNV amplitude and performance.

The timing of the emotional and executive requirements of the task may be particularly critical in determining how these processes interact over time. The current study's findings are consistent with the idea that more difficult cognitive processing may be impaired by emotional interference due to competition for resources (Pessoa, 2009). Therefore, the earlier phase of anticipatory processing, likely reflecting greater engagement of PFC, may also reflect relatively increased competition for attention from emotional stimuli. However, a previous study from our group showed that when emotional interference is presented immediately prior to the engagement of a Stroop task, the need for greater executive function overrides the emotional attenuation effect (Hart et al., 2010). Executive function engagement is therefore likely to be modulated differently depending on the relative timing of emotional inputs and task goals, which may determine whether emotion has an enhancing or impairing impact on cognition. The current study's results suggest that emotional interference during anticipatory processing has an impairing effect during specific early phases of processing, when prefrontal mechanisms are likely more engaged.

Several limitations should be considered when interpreting the current study. Our study design lacked sufficient power to allow for the assessment of how the ERP response to the Stroop probe conditions (congruent vs. incongruent) interacted with cue difficulty and emotionality of the pictures. While our behavioral data indicated that Stroop costs were affected by cue difficulty but not emotional interference, it is possible that increased engagement of the ACC during response to conflicting Stroop probes could be differentially modulated by prior emotional distraction and increased preparatory difficulty. Additionally, our study design did not allow us to make a direct comparison between

emotional effects on the early and late phases of the CNV. By manipulating the interval between the emotional stimuli and the subsequent Stroop probe, it would be possible to directly investigate the effects of the onset of emotional stimuli on different phases of the trial. A third limitation of the current study is the possibility of habituation effects to the emotional pictures, over the course of a single trial or the experiment as a whole. Within-trial habituation effects could potentially differentially influence the early and late phases of the CNV. However, our results showed that the aversive condition still led to a decrease in the late CNV during the less-demanding word trials, with the decrease being more pronounced on more difficult color trials. These results are consistent with findings indicating that differential emotional modulation of other ERP components are resistant to time-on-task effects (Olofsson and Polich, 2007). Finally, our design did not distinguish between positive and negative emotional modulation of the CNV. The relationship between positive emotion and distractibility is unclear, but a recent study showed that the CNV was not modulated by induced positive mood prior to a cognitive control task (van Wouwe et al., 2011). Future studies that directly compare positive and negative distracters during the CNV delay interval may address the potential differing roles of stimulus valence in CNV modulation.

An additional consideration is that the current study's design cannot directly address whether the emotional interference effect could have been specific to color processing compared to semantic processing, as opposed to attributing it to task difficulty. While we believe that participants did likely anticipate a more difficult task during color trials as a result of the training period prior to the study, our design cannot determine whether there may be some specificity about anticipation of color processing that would be more vulnerable to emotional interference. However, given that prior findings have shown PFC engagement in the same task (MacDonald et al., 2000) and as emotional interference has been found to disrupt the PFC (Dolcos and McCarthy, 2006), we believe that our results suggest that greater need for cognitive control likely accounted for the interactions between emotion and cue.

The current findings may be particularly relevant for several psychiatric disorders that are characterized by changes in prefrontal-limbic interactions, such as schizophrenia, autism, and PTSD. Recent studies have reported alterations in CNV amplitudes in control subjects but not schizophrenia patients in response to sensory cue processing (Dias et al., 2011; Bickel et al., 2012) as well as anticipation of upcoming target events (Ford et al., 2010). Given these observations, it is important to elucidate factors that may contribute to a reduced early CNV attenuation. The current data suggest that emotional context differentially affects the early phases of the CNV, and suggest that disorders where prefrontal pathophysiology has been implicated may lead to greater susceptibility to emotional interference, particularly during earlier phases of the CNV generation and response preparation when executive and attentional mechanisms are more engaged. The future use of a similar study design that allows for temporal dissociation between phases of processing may be helpful for directly investigating potential patterns of neural dysfunction in executive-emotional interactions that characterize these disorders.

Overall, the current study's findings help to elucidate the temporal dynamics of emotional-executive interactions by showing that emotional distracters can be shown to elicit differential effects depending on the phase of processing. By segregating different phases of neural activity involved in anticipatory processing, emotional distracters can be found to selectively depress both early orienting and anticipatory processing only under conditions where cognitive control mechanisms are more engaged. The later phase of motor preparatory activity, in contrast, may be more generally affected by emotional interference without being dependent on increased preparatory activity for a more difficult task. It may be that the later phase engages prefrontal and premotor mechanisms that are functionally affected by emotional input, but are not engaged by greater need for executive control. In contrast, the need for greater executive engagement at an earlier stage of processing may exacerbate the effect of emotion. Future studies that directly manipulate task difficulty within a sensory domain may rule out whether the current study's effects are specific to differences between color and word processing. Further studies may focus on combining these approaches with fMRI to better localize the neural sources of the dynamic changes in cognitive-emotional interactions, and manipulating the context in which emotional stimuli may interfere with or potentiate executive functions.

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Influence of threat and serotonin transporter genotype on interference effects

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Emotion-cognition interactions are critical in goal-directed behavior and may be disrupted in psychopathology. Growing evidence also suggests that emotion-cognition interactions are modulated by genetic variation, including genetic variation in the serotonin system. The goal of the current study was to examine the impact of threat-related distracters and serotonin transporter promoter polymorphism (5-HTTLPR/rs25531) on cognitive task performance in healthy females. Using a novel threat-distracter version of the Multi-Source Interference Task specifically designed to probe emotion-cognition interactions, we demonstrate a robust and temporally dynamic modulation of cognitive interference effects by threat-related distracters relative to other distracter types and relative to no-distracter condition. We further show that threat-related distracters have dissociable and opposite effects on cognitive task performance in easy and difficult task conditions, operationalized as the level of response interference that has to be surmounted to produce a correct response. Finally, we present evidence that the 5-HTTLPR/rs25531 genotype in females modulates susceptibility to cognitive interference in a global fashion, across all distracter conditions, and irrespective of the emotional salience of distracters, rather than specifically in the presence of threat-related distracters. Taken together, these results add to our understanding of the processes through which threat-related distracters affect cognitive processing, and have implications for our understanding of disorders in which threat signals have a detrimental effect on cognition, including depression and anxiety disorders.

Keywords: cognition, emotion, interference resolution, threat, serotonin transporter gene, 5-HTTLPR, MSIT

INTRODUCTION

The ability to successfully carry out a task despite interference from task-irrelevant stimuli is a crucial requirement for goal-directed behavior. According to accepted models of selective attention and cognitive-control, task-irrelevant stimuli interfere with cognitive task performance by competing with task-relevant stimuli for attentional and response-selection resources (Desimone and Duncan, 1995; Miller and Cohen, 2001). However, the impact of distracters on task performance – or conversely, our ability to resist interference from these distracters – can vary considerably, depending on the attributes of the distracters and the attributes of the task itself (Lavie, 2005), as well as on individual differences in susceptibility to various distracters.

Critically, with respect to distracter attributes, such interference can come from both neutral and emotionally salient stimuli, highlighting the fact that emotional and cognitive processes are closely interrelated, giving rise to complex and bidirectional emotion-cognition interactions (Davidson, 2003; Blair et al., 2007). In particular, if neutral distracters impair task performance, threat-related distracters should be even more effective in high-jacking attention and interfering with the task at hand due to the preferential processing of threat stimuli over non-threat stimuli in the brain. This rapid and automatic processing of threat signals is possible because the amygdala receives threat-related information through a fast subcortical pathway as well as through a slower cortical route (Romanski and LeDoux, 1992; Morris et al., 1999), a finding supported by functional neuroimaging studies showing that the amygdala responds to threat stimuli that are outside of attentional focus or conscious awareness (Whalen et al., 1998; Vuilleumier et al., 2001). From an evolutionary perspective, in humans as in many other species, such preferential processing of potential threat signals serves the adaptive function of facilitating rapid threat detection and fight-or-flight responses essential for survival (Ohman and Mineka, 2001). However, although supported by some studies (Vuilleumier et al., 2001; Dolcos and McCarthy, 2006; Blair et al., 2007; Mitchell et al., 2008), such increased distractability by threat-related distracters relative to neutral distracters in behavioral measures has not been consistently demonstrated in healthy subjects (Bar-Haim et al., 2007), suggesting that additional modulatory factors may be at play.

Neuroimaging evidence also suggests that the effects of threat distracters on interference processing may dynamically change

over the time-course of the task, because the amygdala response to threat stimuli is temporally dynamic due to both habituation and regulation processes. Salient or novel stimuli initially elicit a strong neural and behavioral response, because they may signal threat or reward, and are thus potentially important to the organism's survival. Habituation refers to a diminished reactivity to a specific stimulus or stimulus class following repeated presentation with no important consequences for the organism, and it is believed to serve an adaptive function of preserving cognitive and behavioral resources and allowing continuous vigilance (Wright et al., 2001). Growing evidence from neuroimaging studies in humans shows that the amygdala habituates to repeatedly presented threat stimuli both in healthy individuals (Breiter et al., 1996; Whalen et al., 1998; Wright et al., 2001) and in patients with anxiety disorders such as post-traumatic stress disorder (Shin et al., 2005). In addition, neuroimaging studies of emotion regulation show a decrease in amygdala response to threat-related stimuli when human subjects actively regulate their emotional response using cognitive-control strategies such as reappraisal, distraction, or suppression (Ochsner et al., 2002; Phan et al., 2005; Eippert et al., 2007; Kim and Hamann, 2007; Wager et al., 2008; McRae et al., 2010), and convergent results have been obtained in animals in the context of fear extinction (Quirk and Beer, 2006; Hartley and Phelps, 2010). This temporally dynamic character of amygdala response to threat stimuli may also be a factor modulating threat-distracter effects on cognitive task performance.

Another important factor that may modulate – or obscure – threat-distracter effects on cognitive task performance is the difficulty level of the task itself. For instance, high perceptual load has been shown to decrease distracter effects relative to low perceptual load for neutral distracters (Rees et al., 1997), although salient distracters such as images of human faces appear to escape this modulation (Lavie et al., 2003). In contrast, high cognitive load increases distracter effects relative to low cognitive load (Lavie, 2005). In particular, a task that is too easy to perform may not allow detection of threat-distracter effects due to ceiling effects in performance, an issue particularly relevant to studies of healthy adults. Ideally, therefore, the impact of threat distracters should be investigated and compared in two different task conditions varying in difficulty, or in the level of cognitive demand required to successfully perform the task.

Finally, growing evidence suggests that common genetic variation in the serotonin system modulates both emotional reactivity and cognitive processing in the human brain, and may also modulate the impact of threat distracters on cognitive task performance. Serotonin, or 5-hydroxytryptamine (5-HT), is known to be involved in a range of behavioral control processes (Cools et al., 2008, 2011; Dayan and Huys, 2009). Serotonergic neurons densely innervate the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (VMPFC), and the amygdala (Hensler, 2006), the key brain circuits involved in resolving interference (Carter et al., 1999) as well as integrating emotional and cognitive influences on behavior (Barbas, 2000; Bechara et al., 2000). Importantly, the serotonin transporter gene (*SLC6A4*) contains a well-studied promoter polymorphism (5-HTT-linked polymorphic region, or 5-HTTLPR; Heils et al., 1996). The short (S) allele, consisting of 14 repeats, has been associated with decreased transporter expression and decreased 5-HT uptake *in vitro*, compared to the long (L) allele with 16 repeats (Heils et al., 1996; Lesch et al., 1996). In addition, an A → G single nucleotide polymorphism (SNP) within the 5-HTTLPR (rs25531) produces L_A and L_G alleles, with the L_G allele being functionally equivalent to the S allele (Hu et al., 2006). With respect to emotional and stressor reactivity, the S allele has been associated with higher measures of anxiety-related personality traits such as neuroticism (Lesch et al., 1996; Sen et al., 2004) and with an increased attentional bias to negative emotional stimuli such as images of spiders (Osinsky et al., 2008) relative to the L allele. The S allele has also been linked to a greater susceptibility to depression, depressive symptoms and suicide following adverse early-life experiences or stressful life events in adulthood (Caspi et al., 2003; Eley et al., 2004; Kendler et al., 2005; Taylor et al., 2006; Zalsman et al., 2006), findings supported by a recent meta-analysis (Karg et al., 2011, although see Risch et al., 2009). Converging evidence from neuroimaging studies shows that the S or L_G allele carriers display a heightened amygdala response to threat stimuli (Hariri et al., 2002, 2005; Dannlowski et al., 2007, 2010; Munafo et al., 2008) and an increased functional connectivity between the amygdala and VMPFC during the processing of threat stimuli (Heinz et al., 2005; Pezawas et al., 2005; Friedel et al., 2009), relative to the L/L or L_A/L_A group.

Growing evidence also suggests that the 5-HTTLPR/rs25531 modulation extends to cognitive processes (Homberg and Lesch, 2010). Although improved cognitive function in the S or L_G allele carriers relative to L/L or L_A/L_A homozygotes has also been reported (Roiser et al., 2007; Borg et al., 2009), a majority of studies have shown that the S or L_G allele is associated with a relative impairment in cognitive task performance relative to the L or L_A allele (da Rocha et al., 2008; Holmes et al., 2010), including dose effects of the SL_G allele on disadvantageous choices in the Iowa Gambling Task (Homberg et al., 2008) and on impulsive responding in the Continuous Performance Task (Walderhaug et al., 2010, although see Lage et al., 2011). Studies of 5-HTTLPR/rs25531 modulation of cognitive interference effects remain few in number. Using a simple flanker interference task, one group (Holmes et al., 2010) reported altered post-error behavioral adjustments in the S or L_G carriers relative to the L_A/L_A group, while another larger study (Olvet et al., 2010) found no effect of 5-HTTLPR/rs25531 genotype on task performance. However, both studies may have been hindered by ceiling effects in task performance, making subtle genetic effects difficult to detect.

In the current study, we employed a novel and demanding threat-distracter version of the Multi-Source Interference Task (MSIT; Bush and Shin, 2006) in healthy females genotyped for the 5-HTTLPR/rs25531 promoter polymorphism, in order to examine the impact of threat-related distracters and 5-HTTLPR/rs25531 genotype on cognitive task performance. Based on previous studies (Vuilleumier et al., 2001; Dolcos and McCarthy, 2006; Blair et al., 2007; Mitchell et al., 2008, although see Bar-Haim et al., 2007), we hypothesized that threat distracters would potentiate interference effects relative to other distracter types and relative to a no-distracter condition. With respect to genetic effects, the simplest model is that functional variants affect gene transcription and protein function in a dose-dependent manner, without dominance, and this model is supported by some evidence

for additive effects of the SL_G allele on cognitive task performance (Homberg et al., 2008; Walderhaug et al., 2010) as well as on reactivity to environmental adversity (Caspi et al., 2003). Although non-additive effects have also been reported (Kendler et al., 2005), these reports have not been consistent and may be due to ceiling effects in measurement. Therefore, we expected that the SL_G allele of 5-HTTLPR/rs25531 would increase interference effects in a dose-dependent or additive manner, such that the effect of genotype on interference would follow a specific order: $L_A/L_A < L_A/SL_G < SL_G/SL_G$. We further tested two competing hypotheses about the scope of 5-HTTLPR/rs25531 effects on cognitive task performance. Specifically, genetic effects could be present exclusively in the threat-distracter condition, or alternatively, genetic effects could extend to all distracter conditions, irrespective of emotional salience of distracters. We also tested whether the effects of threat distracters change over the time-course of the task, and whether these effects are modulated by task difficulty. We expected that threat distracter effects would decrease over time due to habituation and regulation processes, and that the effects of threat distracters would be greater in the more difficult incongruent task condition compared to the easier congruent task condition.

MATERIALS AND METHODS

SUBJECTS

Seventy-one healthy, right-handed Caucasian females aged 18–34 years ($M = 23.0$ years, $SD = 4.0$ years) participated in the study. All subjects had normal or corrected-to-normal vision. Exclusion criteria included any serious medical condition, head injury or trauma, lifetime diagnosis of psychiatric illness, current use of a psychoactive medication, and smoking. Only females were studied at this stage, in order to maximize the power to detect genetic modulation of threat-distracter effects in light of prior evidence of interactions between sex hormones and serotonin transporter gene variation on threat reactivity (Josephs et al., 2012), as well as sex differences in the serotonin system (Jovanovic et al., 2008) and in the processing of emotional stimuli in the brain (Klein et al., 2003; Wrase et al., 2003). The study was approved by the University of Michigan Medical School IRB and all subjects provided written informed consent.

TASK: THREAT-DISTRACTER MSIT

We employed a modified version of the MSIT (Bush et al., 2003; Bush and Shin, 2006). The MSIT is a validated response-interference paradigm which combines the sources of interference from Erikson, Stroop, and Simon tasks, in order to maximally tax the interference processing associated with the ACC (Bush et al., 2003). The MSIT has been shown to produce a robust and temporally stable *interference effect* both in reaction times (RTs) and in accuracy (Bush et al., 2003).

In the MSIT, subjects were presented with a set of three numbers from 0 to 3, one of which was different from the other two (the oddball number). Subjects were instructed to indicate the identity of the oddball number with a corresponding key press: a key press with the index finger if the oddball number was "1," with the middle finger if the oddball number was "2," and with the ring finger if the oddball number was "3." On *congruent* trials, the identity of the oddball number corresponds to its location and the other two numbers are 0's, not related to any valid key press response. On *incongruent* trials, the identity of the oddball number is incongruent with its position and the other two numbers are related to competing key press responses, resulting in stimulus-response incompatibility and response interference. The *incongruent condition* vs. *congruent condition* contrast yields the interference effect in RTs (*Incongruent RT – Congruent RT*) and interference effect in accuracy (*Congruent Accuracy – Incongruent Accuracy*).

We modified the MSIT to include three categories of task-irrelevant flanker distracters, threat, neutral, and scrambled, in addition to the null distracter condition. Threat distracters were images of human faces signaling the presence of a threat (angry or fearful expression). To isolate the effects specific to emotionally salient stimuli, we included neutral distracters (images of human faces with neutral expression), and scrambled distracters (images retaining the basic oval shape of a face but no facial features). Face stimuli were carefully selected from standardized sets (Ekman and Friesen, 1976; Gur et al., 2002; Tottenham et al., 2009). Angry and fearful faces displayed intense emotion and showed bared teeth and/or open mouth as an additional perceptual homogeneity criterion. In contrast, all neutral faces had closed mouths. All faces were Caucasian, to optimally control for potential sources of variability in emotional responses. All images were presented in grayscale, with hair and background cropped to yield an oval shape. Scrambled distracters were generated from the human face stimuli used in the other two distracter conditions by randomly rearranging the pixels within the oval while preserving the brightness of the image.

EXPERIMENTAL PROTOCOL

A timeline of events in a single trial is shown in **Figure 1**. The MSIT stimuli and two identical flanking distracter images were presented simultaneously for 500 ms, followed by a black screen for 1000 ms, and then a fixation cross for another 500 ms. The durations of these three events added up to the overall response limit of 2000 ms. A black screen presented for 100 ms separated two consecutive trials. Subjects were instructed to respond as fast and as accurately as they could. The task stimuli were presented and the key press responses collected using E-Prime 2.0.

After a self-timed tutorial in the task and a short practice run, subjects completed a total of 640 trials, divided into 2 runs, four blocks per run, 80 trials per block. A short intermission separated run 1 (blocks 1–4, a total of 320 trials) from run 2 (blocks 5–8, a total of 320 trials). The order of the trials was pseudo-randomized within each block, with the provision that no two consecutive trials (1) had the same correct response or (2) both included threat distracters. Each block lasted approximately 3 min and consisted of 40 congruent and 40 incongruent trials. Within the sets of 40 congruent and 40 incongruent trials, 10 trials included threat distracters (five angry faces, three female, two male or two female, three male; and five fearful faces, three female, two male or two female, three male), 10 trials included neutral distracters (five female, five male), 10 trials included scrambled distracters, and 10 trials were no-distracter trials (i.e., with MSIT stimuli only). The whole experiment lasted approximately 30 min.

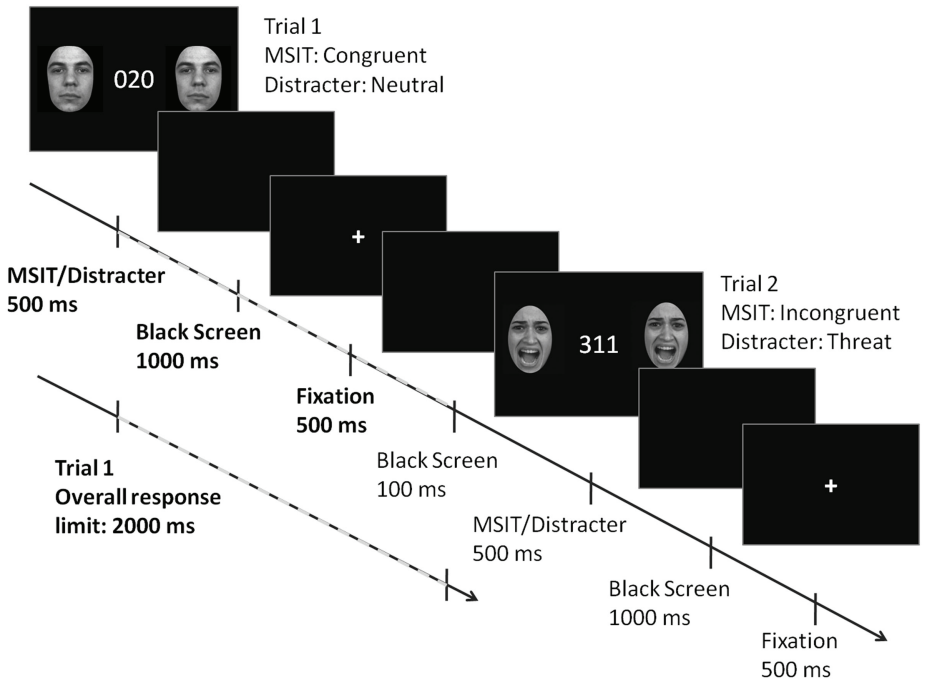

FIGURE 1 | The anatomy of a trial in threat-distracter MSIT. The MSIT stimuli and two identical flanking distracter images were presented simultaneously for 500 ms, followed by a black screen for 1000 ms, and then a fixation cross for another 500 ms. The durations of these three events added up to the overall response limit of 2000 ms. A black screen (100 ms) separated two consecutive trials. Face images reproduced with permission from Gur et al. (2002).

GENOTYPING OF 5-HTTLPR/rs25531

Genomic DNA was obtained from saliva using the Oragene saliva collection system and extracted using the protocol provided (Genotek, Ontario, Canada). The extracted DNA samples were genotyped for 5-HTTLPR and rs25531 in two steps, according to Wendland et al. (2006). In the first step, the 5-HTTLPR was amplified via polymerase-chain reaction (PCR) using site-specific forward and reverse primers, yielding "short" (14-repeat, 375 bp) and "long" (16-repeat, 419 bp) products. In the second step, the PCR product from the first step was digested with *Hpa* II restriction enzyme to genotype the A → G SNP (rs25531) by identifying L_G (305 bp) and L_A alleles. All PCR products were visualized via gel electrophoresis on a 3% agarose gel using ethidium bromide under ultraviolet (UV) light.

STATISTICAL ANALYSES

The data were analyzed in a series of steps using repeated-measures Analysis of Variance (ANOVA), correlations, and *t*-tests as implemented in SPSS 19.0. We used two behavioral indices of task performance as dependent variables, RTs on correct trials and accuracy rates. The MSIT interference effects (congruent vs. incongruent) in RTs and in accuracy were used as a global measure of the efficiency of interference processing, with greater interference effects indicating less efficient interference resolution. We conducted two separate 4 × 2 × 3 repeated-measures ANOVAs – one on interference effects in accuracy and one on interference effects in RTs – with distracter type (four levels: threat-related, neutral, scrambled, or null) and run (two levels: pre-intermission run 1 or post-intermission run 2) as within-subject factors, and 5-HTTLPR/rs25531 genotype (three levels: 0 SL_G alleles, 1 SL_G alleles, or 2 SL_G alleles) as a between-subject factor. Because we conducted two separate ANOVAs, we used a Bonferroni-corrected *p* value of 0.025 as our statistical threshold for the ANOVA results. The *t*-tests and Pearson's correlations are two-tailed unless stated otherwise.

RESULTS

FINAL SAMPLE

Out of the 71 healthy female subjects who participated in the study, the data from the final sample of 69 subjects were analyzed and are reported below. The data from two subjects were excluded from analysis due to concerns about task compliance and performance accuracy. One subject did not follow the task instructions and responded to the position of the oddball number rather than to its identity ($M = 0.05$ accuracy on incongruent trials), an occurrence reported in approximately 5% of participants in prior work using the original version of the MSIT (Bush and Shin, 2006). Another subject had a mean accuracy of 0.34 on incongruent trials, corresponding to a chance level of responding in a three-choice task.

GENOTYPING RESULTS

We observed the following 5-HTTLPR genotype counts (and frequencies): 25 (0.35) L/L homozygotes, 35 (0.49) L/S heterozygotes, and 11 (0.16) S/S homozygotes (**Table 1**). The observed genotype frequencies did not deviate from the

Table 1 | Distribution of 5-HTTLPR and 5-HTTLPR/rs25531 alleles and genotypes.

5-HTTLPR genotype count (frequency)						5-HTTLPR allele count (frequency)		
L/L		**L/S**		**S/S**		**L**		**S**
25 (0.35)		35 (0.49)		11 (0.16)		85 (0.60)		57 (0.40)
5-HTTLPR/rs25531 genotype count (frequency)						**5-HTTLPR/rs25531 allele count (frequency)**		
Func L/L		**Func L/S**		**Func S/S**		**Func L**		**Func S**
23 (0.32)		36 (0.51)		12 (0.17)		82 (0.58)		60 (0.42)
L_A/L_A	**L_A/L_G**	**L_A/S**	**L_G/L_G**	**L_G/S**	**S/S**	**L_A**	**L_G**	**S**
23 (0.32)	2 (0.03)	34 (0.48)	0	1 (0.01)	11 (0.16)	82 (0.58)	3 (0.02)	57 (0.40)

S allele and L_G allele are denoted as functional S alleles.

Hardy–Weinberg Equilibrium ($\chi^2 = 0.047$, $p = 0.828$). The combined 5-HTTLPR/rs25531 functional genotypes were grouped as follows: 23 (0.32) subjects were L_A/L_A, 36 (0.51) subjects were L_A/L_GS (2 L_A/L_G and 34 L_A/S_A), and 12 (0.17) subjects were S/S (1 L_G/S and 11 S/S). SL_G denoted S or L_G allele (**Table 1**). Neither the 5-HTTLPR genotype groups nor the 5-HTTLPR/rs25531 genotype groups differed in age, education, or socio-economic status (**Table 2**).

Table 2 | Demographic profiles of the 5-HTTLPR and 5-HTTLPR/sr25531 genotype groups.

	S/S ($n = 11$)	**S/L ($n = 33$)**	**L/L ($n = 25$)**	**χ^2 (p value)**
5-HTTLPR GENOTYPE				
Age (years)	22.36 ± 3.50	22.39 ± 4.10	24.08 ± 4.18	19.97 (0.793)
Education (years)	15.64 ± 2.20	15.55 ± 2.60	15.96 ± 1.93	19.51 (0.361)
SES	2.18 ± 0.60	2.30 ± 0.53	2.24 ± 0.44	6.56 (0.363)
	SL_G/SL_G ($n = 12$)	**SL_G/L_A ($n = 34$)**	**L_A/L_A ($n = 23$)**	**χ^2 (p value)**
5-HTTLPR/rs25531 GENOTYPE				
Age (years)	22.17 ± 3.41	22.38 ± 4.02	24.35 ± 4.25	17.67 (0.887)
Education (years)	15.50 ± 2.15	15.56 ± 2.56	16.04 ± 2.00	18.64 (0.415)
SES	2.17 ± 0.58	2.29 ± 0.52	2.26 ± 0.45	5.88 (0.436)

Means and standard deviations are given. No group differences in age, education, or socio-economic status (SES) were found, as assessed with a chi-square (χ^2) test.

BEHAVIORAL RESULTS

Robust MSIT interference effects across all distracter conditions

Consistent with previous reports (Bush et al., 2003; Bush and Shin, 2006), we observed a robust and highly significant MSIT interference effect (i.e., a main effect of congruency) in both measures of task performance. Overall, subjects were significantly less accurate in the incongruent condition compared to the congruent condition (congruent accuracy, $M = 0.993$, SE = 0.001; incongruent accuracy, $M = 0.838$, SE = 0.016; interference effect in accuracy, $M = 0.158$, SE = 0.015; $F(1, 66) = 107.290$, $p < 0.0001$, partial eta squared = 0.619), and they were also significantly slower to correctly respond in the incongruent condition compared to the congruent condition (congruent RT, $M = 492$ ms, SE = 11 ms; incongruent RT, $M = 710$ ms, SE = 16 ms; interference effect in RT, $M = 218$ ms, SE = 9 ms; $F(1, 66) = 579.179$, $p < 0.0001$, partial eta squared = 0.898).

The interference effects were robust and highly significant in all four distracter conditions (all p's < 0.0001, paired-sample t-tests). The accuracy results per distracter condition are summarized in **Table 3** and the RT results per distracter condition are summarized in **Table 4**. In addition, the interference effect on accuracy was significant in both runs (run 1, $M = 0.192$, SE = 0.017; $t(68) = 11.077$, $p < 0.0001$; run 2, $M = 0.124$, SE = 0.013; $t(68) = 9.993$, $p < 0.0001$), although it significantly diminished from run 1 to run 2, $t(68) = 7.319$, $p < 0.0001$, as also indicated by a significant two-way interaction between congruency and run on accuracy, $F(1, 66) = 72.882$, $p < 0.0001$, partial eta squared = 0.525. The interference effect in RTs was also significant in both runs (run 1, $M = 221$ ms, SE = 9 ms; $t(68) = 26.795$, $p < 0.0001$; run 2, $M = 216$ ms, SE = 9 ms; $t(68) = 25.463$, $p < 0.0001$), and did not change significantly from run 1 to run 2, $t(68) = 1.496$, $p = 0.139$. These results confirmed that MSIT produced a robust behavioral difference between the easier congruent condition and the more difficult incongruent condition, which persisted across all distracter conditions and across time.

Threat distracters potentiate MSIT interference effects

Next, we examined whether threat-related distracters potentiated MSIT interference effects. As hypothesized, the ANOVA on interference effects yielded robust and significant main effects of distracter type on interference effects both in accuracy, $F(3, 64) = 7.803$, $p < 0.0001$, partial eta squared = 0.268, and

Table 3 | Summary of accuracy data.

Distracter type	Accuracy (proportion accurate)				
	MSIT condition		MSIT interference effect		
	Congruent	Incongruent	Mean	*t*	*p* value
Threat	0.995 (0.013)	0.839 (0.121)	0.156 (0.117)	11.002	<0.0001
Neutral	0.993 (0.014)	0.844 (0.126)	0.149 (0.121)	10.297	<0.0001
Scrambled	0.996 (0.009)	0.834 (0.125)	0.161 (0.120)	11.193	<0.0001
Null	0.990 (0.015)	0.856 (0.117)	0.134 (0.110)	10.177	<0.0001

Means and standard deviations (in parentheses) are given, together with t statistics and p values for paired-sample t-tests (n = 69).

Table 4 | Summary of RT data.

Distracter type	RT (ms)				
	MSIT condition		MSIT interference effect		
	Congruent	Incongruent	Mean	*t*	*p* value
Threat	486 (82)	710 (116)	224 (72)	26.048	<0.0001
Neutral	489 (81)	711 (118)	222 (70)	26.272	<0.0001
Scrambled	489 (87)	714 (117)	225 (71)	26.236	<0.0001
Null	495 (84)	701 (116)	205 (64)	26.781	<0.0001

Means and standard deviations (in parentheses) are given, together with t statistics and p values for paired-sample t-tests (n = 69).

in RTs, $F(3, 64) = 6.309$, $p = 0.001$, partial eta squared = 0.228. Convergent results were obtained from the ANOVA on accuracy and RTs, which indicated a significant two-way interaction between congruency and distracter type both on accuracy, $F(3, 64) = 6.465$, $p = 0.001$, partial eta squared = 0.233, and on RTs, $F(3, 64) = 8.030$, $p < 0.0001$, partial eta squared = 0.273. The overall interference effects in accuracy per distracter condition are given in **Table 3** and the overall interference effects in RTs per distracter condition are given in **Table 4**. The interference effects in accuracy in the threat-distracter condition were significantly greater than in the no-distracter condition, $t(68) = 3.415$, $p = 0.001$, but not significantly greater than in the neutral-distracter condition, $t(68) = 0.964$, $p = 0.338$, or in the scrambled-distracter condition, $t(68) = 1.017$, $p = 0.313$. Similarly, the interference effects in RTs were significantly greater with threat distracters present compared to with no distracters present, $t(68) = 6.308$, $p < 0.0001$, but not significantly different compared to neutral distracters, $t(68) = 0.710$, $p = 0.480$, or scrambled distracters, $t(68) = 0.211$, $p = 0.833$. Overall, interference effects in accuracy were significantly greater in the presence of distracters compared to the no-distracter condition (with distracters: $M = 0.155$, SE = 0.014; no distracters: $M = 0.134$, SE = 0.013; $t(68) = 4.056$, $p < 0.0001$). Similarly, interference effects in RTs were significantly greater in the presence of distracters compared to the no-distracter condition (with distracters: $M = 220$ ms, SE = 8 ms; no distracters: $M = 205$ ms, SE = 8 ms; $t(68) = 5.390$, $p < 0.0001$).

Threat-distracter effects on MSIT interference effects are transient

Overall, there was a robust and highly significant main effect of run both on accuracy [$F(1, 66) = 68.309$, $p < 0.0001$, partial eta squared = 0.509] and on RTs [$F(1, 66) = 104.982$, $p < 0.0001$, partial eta squared = 0.614]. The overall accuracy in run 1 was $M = 0.903$, SE = 0.009, whereas in run 2 it significantly increased to $M = 0.936$, SE = 0.006, $t(68) = 7.249$, $p < 0.0001$. The overall RT in run 1 was $M = 625$ ms, SE = 13 ms, whereas in run 2 it significantly decreased to $M = 574$ ms, SE = 10 ms, $t(68) = 11.708$, $p < 0.0001$. In addition, there was a significant two-way interaction between distracter type and run on interference effects in accuracy, $F(3, 64) = 4.290$, $p = 0.008$, partial eta squared = 0.167, and in RTs, $F(3, 64) = 11.932$, $p < 0.0001$, partial eta squared = 0.359. These data are summarized in **Table 5** (accuracy) and **Table 6** (RTs) and graphically shown in **Figure 2A** (accuracy) and **Figure 2B** (RTs).

We also examined how the effects of threat distracters on MSIT interference effects changed over time. In run 1, threat distracters potentiated the interference effects in accuracy relative to neutral distracters, $t(68) = 3.03$, $p = 0.004$, scrambled distracters, $t(68) = 1.74$, $p = 0.09$, and no distracters, $t(68) = 3.73$, $p < 0.0001$ (**Figure 2A**). In contrast, in run 2 (following the intermission), the interference effects in accuracy elicited by threat distracters appeared to be lower than those elicited by neutral distracters, $t(68) = -1.78$, $p = 0.08$, or scrambled distracters, $t(68) = -3.24$, $p = 0.002$, and comparable to the interference effects observed in the no-distracter condition. Interestingly, examining congruent and incongruent trials separately revealed that threat distracters had dissociable and opposite effects on

Table 5 | Summary of accuracy data (in proportion accurate) in run 1 and run 2.

Distracter type	Run 1			Run 2		
	MSIT condition		MSIT interference effect	MSIT condition		MSIT interference effect
	Congruent	Incongruent		Congruent	Incongruent	
Threat	0.996 (0.002)	0.788 (0.021)	0.213 (0.020)	0.994 (0.002)	0.884 (0.013)	0.113 (0.013)
Neutral	0.991 (0.002)	0.808 (0.020)	0.184 (0.019)	0.996 (0.002)	0.865 (0.015)	0.136 (0.015)
Scrambled	0.993 (0.002)	0.798 (0.019)	0.196 (0.018)	0.997 (0.001)	0.860 (0.016)	0.141 (0.015)
Null	0.982 (0.004)	0.809 (0.020)	0.173 (0.018)	0.997 (0.001)	0.895 (0.014)	0.103 (0.014)

Means and standard errors (in parentheses) are given.

Table 6 | Summary of RT data (in ms) in run 1 and run 2.

Distracter type	Run 1			Run 2		
	MSIT condition		MSIT interference effect	MSIT condition		MSIT interference effect
	Congruent	Incongruent		Congruent	Incongruent	
Threat	502 (12)	739 (18)	238 (11)	474 (10)	682 (14)	208 (10)
Neutral	516 (13)	734 (17)	217 (10)	465 (9)	689 (15)	224 (10)
Scrambled	513 (13)	737 (17)	224 (10)	471 (10)	689 (15)	219 (10)
Null	528 (13)	733 (17)	204 (8)	682 (14)	674 (15)	211 (10)

Means and standard errors (in parentheses) are given.

accuracy in congruent and incongruent trials across time. As expected, in run 1, subjects were less accurate on the more difficult incongruent trials in the presence of threat distracters than in the presence of neutral distracters, $t(68) = -2.231$, $p = 0.029$, or null distracters, $t(68) = -2.379$, $p = 0.020$, although not relative to scrambled distracters, $t(68) = -1.203$, $p = 0.233$. However, this relationship was reversed in run 2, and subjects appeared more accurate on incongruent trials with threat distracters relative to neutral distracters, $t(68) = 1.615$, $p = 0.111$, or scrambled distracters, $t(68) = 3.010$, $p = 0.004$, although not different in accuracy compared to incongruent trials with no distracters present, $t(68) = -0.967$, $p = 0.337$. In addition, and unexpectedly, in run 1, subjects were actually more accurate on the easy congruent trials in the presence of threat distracters relative to neutral distracters, $t(68) = 2.013$, $p = 0.048$, and relative to no distracters, $t(68) = 3.570$, $p = 0.001$, although not relative to scrambled distracters, $t(68) = 0.479$, $p = 0.638$. In run 2, these apparent performance-enhancing effects of threat distracters were abolished, and subjects' accuracy on congruent trials in the presence of threat distracters did not significantly differ from their accuracy in the presence of neutral distracters, $t(68) = -0.397$, $p = 0.693$, scrambled distracters, $t(68) = -1.413$, $p = 0.162$, or no distracters, $t(68) = -1.383$, $p = 0.171$.

The results were similar for RTs (**Figure 2B**). In run 1, threat distracters potentiated the interference effects in RTs relative to neutral distracters, $t(68) = 4.31$, $p < 0.0001$, scrambled distracters, $t(68) = 2.38$, $p = 0.020$, and no distracters, $t(68) = 7.36$, $p < 0.0001$. In contrast, in run 2 (following the intermission), the interference effects in RTs observed in the threat-distracter condition were lower than in the presence of neutral distracters, $t(68) = -3.87$, $p < 0.0001$, or scrambled distracters, $t(68) = -3.28$, $p = 0.002$, and comparable to the no-distracter condition. As described above for accuracy, threat distracters appeared to have dissociable and opposite effects on the speed of correct responses in congruent and incongruent trials across time. As might be expected, in run 1, subjects were somewhat slower to correctly respond on the more difficult incongruent trials in the presence of threat distracters than in the presence of neutral distracters, $t(68) = 1.626$, $p = 0.108$, or no distracters, $t(68) = 2.595$, $p = 0.012$, although not relative to scrambled distracters, $t(68) = 0.407$, $p = 0.685$. This relationship was reversed in run 2, in which subjects were somewhat faster to correctly respond on incongruent trials with threat distracters relative to neutral distracters, $t(68) = -1.987$, $p = 0.051$, or scrambled distracters, $t(68) = -2.776$, $p = 0.007$, although still somewhat slower to correctly respond than on incongruent trials with no distracters present, $t(68) = 1.847$, $p = 0.069$. In addition, and again unexpectedly, in run 1, subjects were actually faster to accurately respond on the easy congruent trials in the presence of threat distracters relative to neutral distracters, $t(68) = -5.702$, $p < 0.0001$, scrambled distracters, $t(68) = -3.848$, $p < 0.0001$, or no distracters, $t(68) = -8.615$, $p < 0.0001$. This performance-enhancing effect of threat distracters was again transient, as seen above for accuracy. In run 2, the relationship was reversed and subjects were slower to correctly respond on congruent trials with threat distracters relative to neutral distracters, $t(68) = 4.482$, $p < 0.0001$,

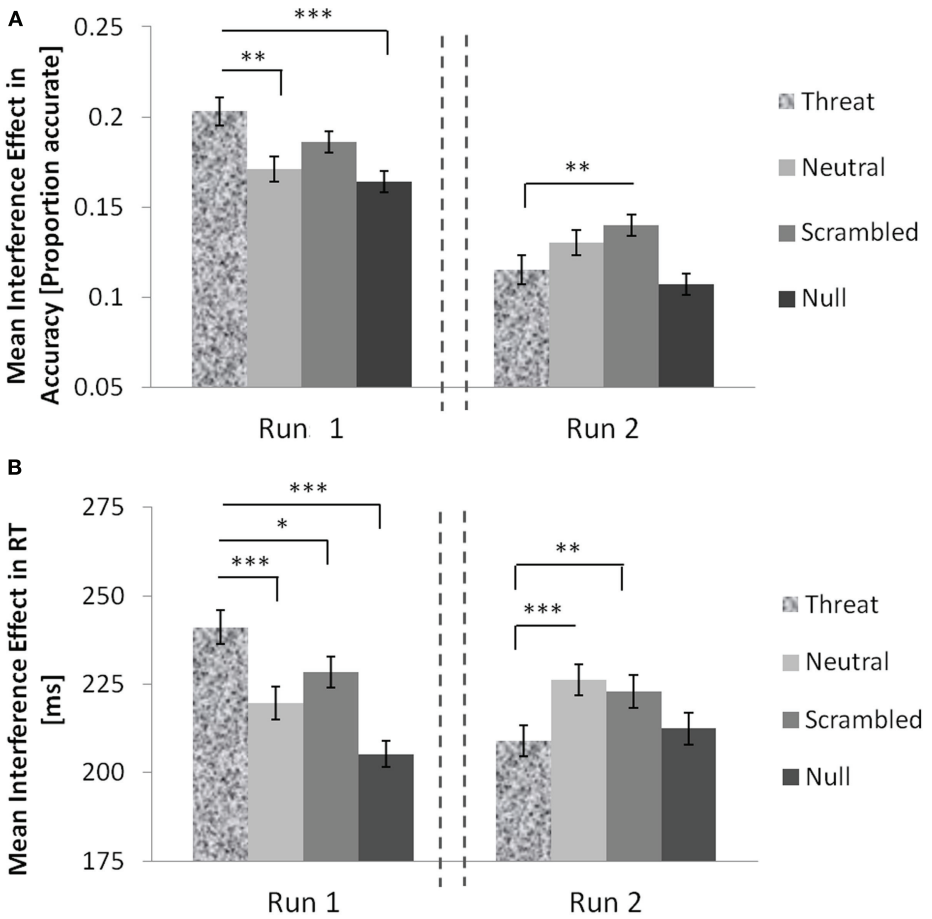

FIGURE 2 | The interaction of threat distracters and time on MSIT interference effects in healthy females. Threat distracters potentiated interference effects in RTs **(A)** and in accuracy **(B)** relative to other distracter conditions in run 1 but these effects were abolished in run 2. Error bars show standard errors of the mean. The dashed lines denote an intermission. Significant two-tailed *t*-tests: $*p < 0.05$; $**p < 0.01$; $***p < 0.0001$.

scrambled distracters, $t(68) = 1.613$, $p = 0.111$, or no distracters, $t(68) = 5.925$, $p < 0.0001$.

In sum, threat distracters increased the interference effect in accuracy and in RTs compared with neutral or scrambled distracters in the first half of the experiment, but these effects were reversed in the second half, following an intermission. In addition, this transient increase in interference effects in the presence of threat distracters was driven both by a threat-distracter-related impairment in performance on the more difficult incongruent trials, and, unexpectedly, by a threat-distracter-related enhancement in performance on the easy congruent trials.

5-HTTLPR/rs25531 genotype modulates interference effects irrespective of emotional salience of distracters

Next, we tested whether the 5-HTTLPR/rs25531 genotype modulated the impact of threat-related distracters on cognitive task performance. Collapsing across both runs and across distracter conditions, genotype did not have a significant effect on interference effects either in accuracy, $F(2, 66) = 0.983$, $p = 0.379$, or in RTs. $F(2, 66) = 0.399$, $p = 0.673$. But there was a significant two-way interaction between genotype and run on interference effects in accuracy, $F(2, 66) = 5.111$, $p = 0.009$, partial eta squared $= 0.134$. These results were confirmed by the ANOVA on accuracy, which produced a significant two-way interaction between genotype and run on accuracy, $F(2, 66) = 4.082$, $p = 0.021$, partial eta squared $= 0.110$.

Specifically, there was an increase in interference effects in accuracy with the number of the SL_G alleles, which was significant in run 1 (L_A/L_A: 0.156 ± 0.027; SL_G/L_A: 0.176 ± 0.021; SL_G/SL_G: 0.243 ± 0.046; $r = 0.207$, $p = 0.044$, one-tailed correlation) but did not reach significance in run 2 (L_A/L_A: 0.107 ± 0.021; SL_G/L_A: 0.130 ± 0.016; SL_G/SL_G: 0.133 ± 0.036; $r = 0.103$, $p = 0.201$, one-tailed correlation). A comparison of the 5-HTTLPR/rs25531 genotype groups on interference effects in accuracy separately for each distracter condition is given in **Figure 3**. The increase in interference effects in accuracy with the number of the SL_G alleles was also significant or marginally significant in all four distracter conditions in run1 (threat: $r = 0.195$, $p = 0.054$; neutral: $r = 0.170$, $p = 0.082$; scrambled: $r = 0.192$, $p = 0.057$; null: $r = 0.218$, $p = 0.036$; all one-tailed correlations).

There were no comparable effects of genotype on interference effects in RTs. The magnitude of interference effects in RTs was

not significantly associated with the number of SL_G alleles either in run 1 (L_A/L_A: 230 ± 14 ms; SL_G/L_A: 225 ± 12.2 ms; SL_G/SL_G: 207 ± 20 ms; $r = -0.103$, $p = 0.201$, one-tailed correlation) or in run 2 (L_A/L_A: 226 ± 13 ms; SL_G/L_A: 217 ± 13 ms; SL_G/SL_G: 204 ± 24 ms; $r = -0.107$, $p = 0.192$, one-tailed correlation). A comparison of the 5-HTTLPR/rs25531 genotype groups on interference effects in RTs separately for each distracter condition is given in **Figure 4**.

DISCUSSION

Our data demonstrate that threat-related distracters robustly modulate cognitive interference effects but the modulation dynamically changes over time. Threat-related distracters potentiated interference effects in both accuracy and in RTs relative to non-threat-related distracter types and relative to the no-distracter condition in the first half of the experiment, prior to the intermission. However, these effects were reversed in the second half of the experiment, in which the interference effects in accuracy and in RTs in the presence of threat distracters decreased below the interference effects seen in other distracter conditions, to the level observed when no distracters were present. Furthermore, by examining the congruent and incongruent conditions separately, we were able to show that this transient potentiation of interference effects by threat distracters had a dual source: on the one hand, it was due to a predicted threat-related impairment in task performance in the more difficult incongruent condition

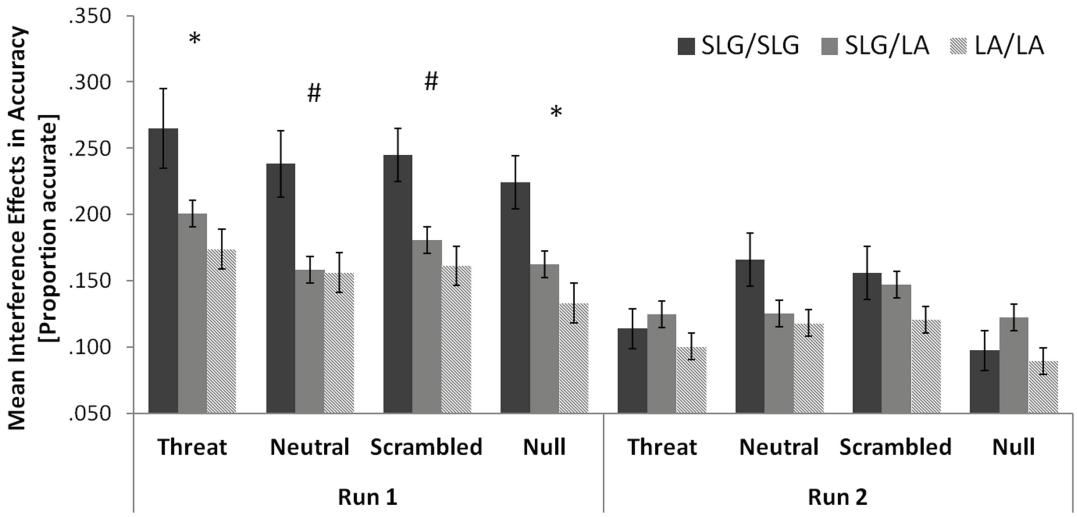

FIGURE 3 | The 5-HTTLPR/rs25531 genotype marginally modulates interference effects in accuracy across all distracter conditions in healthy females. Error bars show standard errors of the mean. Significant or approaching significance one-tailed correlations: *p < 0.05; #p < .10.

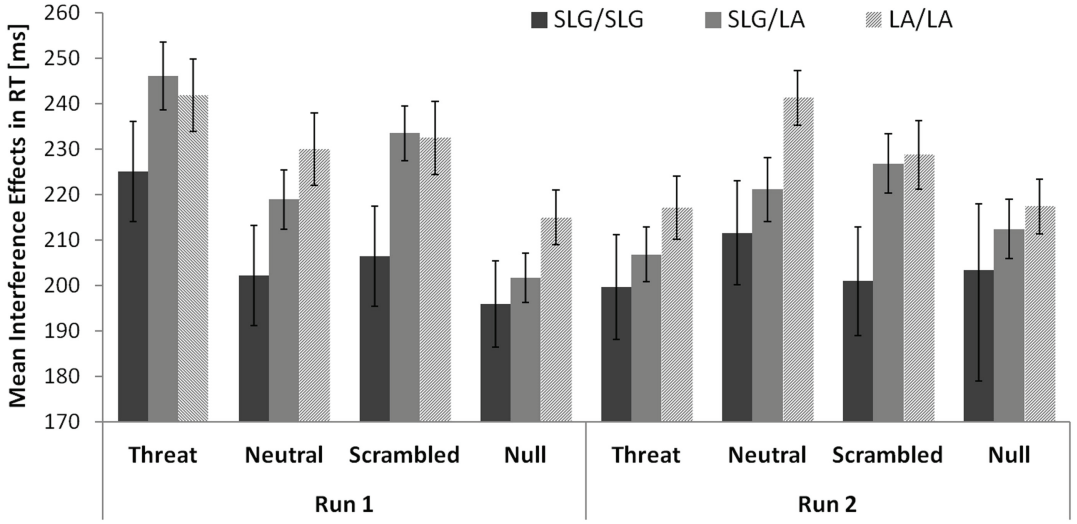

FIGURE 4 | No evidence that the 5-HTTLPR/rs25531 genotype modulates interference effects in RTs in healthy females. Error bars show standard errors of the mean.

(i.e., subjects were less accurate and slower to correctly respond on incongruent trials in the presence of threat distracters relative to other distracter conditions), but on the other hand, it was also due to an unexpected threat-related enhancement of task performance in the easy congruent condition (i.e., subjects were actually more accurate and faster to correctly respond on congruent trials in the presence of threat distracters compared to other distracter conditions).

We propose that the temporally dynamic character of threat-distracter effects may be due to both habituation and regulation of amygdala response to threat stimuli. Both habitation and regulation would result in diminished amygdala reactivity. Amygdala habituation to threat stimuli has been demonstrated in neuroimaging studies involving both healthy individuals (Breiter et al., 1996; Whalen et al., 1998; Wright et al., 2001) and patients with anxiety disorders such as post-traumatic stress disorder (Shin et al., 2005). A separate line of neuroimaging evidence also shows a decrease in amygdala response to threat-related stimuli when people actively regulate their emotional response using cognitive-control strategies such as reappraisal, distraction, or suppression (Ochsner et al., 2002; Phan et al., 2005; Eippert et al., 2007; Kim and Hamann, 2007; Wager et al., 2008; McRae et al., 2010), with convergent evidence coming from animal studies of fear extinction (Quirk and Beer, 2006; Hartley and Phelps, 2010). We propose that both processes – habituation and regulation of amygdala response to threat stimuli – may be at work in our study. Habituation may be gradually produced by repeated harmless presentation of threat stimuli over the time-course of the task, whereas regulation may be triggered specifically by the intermission separating run 1 from run 2, giving subjects a short reprise from the demands of the task and permitting them to "take stock" and adjust their emotional response to the threat stimuli in run 2. Unfortunately, we are unable to fully dissociate the role of these two processes in the observed decrease in threat-distracter effects on cognitive performance over time using the current study design.

An intriguing finding in our study is the dissociable and opposite character of threat effects on task performance in congruent vs. incongruent task conditions. The transient increase in interference effects in the presence of threat distracters was driven both by threat-distracter-related impairment in performance on the more difficult incongruent trials, and by threat-distracter-related enhancement in performance on the easier congruent trials. Threat-related impairment in task performance has been documented before (Vuilleumier et al., 2001; Dolcos and McCarthy, 2006; Blair et al., 2007; Mitchell et al., 2008), although the findings have been inconsistent (Bar-Haim et al., 2007). Our data suggest that the inconsistencies may come from variable level of task difficulty, with more robust threat-related impairment observed in more difficult task conditions requiring additional time and processing steps to resolve cognitive interference arising from competing stimulus-to-response goal representations, as compared to easier task conditions involving one simple stimulus-to-response mapping.

In this respect, our finding of threat-related enhancement of task performance specific to the easier congruent task condition is informative. We speculate that this threat-related enhancement of both accuracy and speed of correct responding in the easier task condition may reflect a general priming of the motor system in response to threat signals. Our findings resonate with previous reports of enhanced response speed and force due to exposure to unpleasant stimuli during a preparation of a simple motor response (Coombes et al., 2005, 2009). Consistent with the adaptive function of rapid behavioral response to potential threat signals in the environment, threat-related stimuli may act to prime the motor system for action (Coombes et al., 2005) regardless of their status as task-relevant targets or task-irrelevant distracters. Therefore, both threat-related *enhancement* of task performance in the absence of cognitive interference (easier task condition) and threat-related *impairment* of task performance when the task requires resolution of cognitive interference (more difficult task condition) would reflect the priming of the simple, prepotent motor response – but the primed response itself would be correct in the former case and incorrect in the latter case. We further speculate that the impact of threat distracters on task performance may be mediated primarily through the effects of threat stimuli on the selection and execution of the motor response within broadly defined attentional control processes. Specifically, the detection of a potential threat signal and the subsequent activation of the threat-processing pathway could act either to directly facilitate the execution of the prepotent motor response, or to remove the inhibition of this prepotent response. In either case, performance would be expected to improve when the prepotent response is desired (e.g., in the easier congruent task condition), but suffer when the inhibition of a prepotent response in required for the selection and execution of a correct response (e.g., in the more difficult incongruent task condition). Thus, one possible strategy to reduce threat-related impairment may be to automatize the performance of a given task (i.e., to render the desired task response the prepotent response) through intense practice and habit formation, consistent with the theory of Norman and Shallice (1986).

We also report evidence that the serotonin transporter promoter polymorphism (5-HTTLPR/rs25531) modulates cognitive task performance in healthy female subjects in a global fashion, irrespective of the presence or emotional salience of distracters. Specifically, we observed dose effects of the SL_G allele on interference effects in accuracy (but not in RTs) in the expected direction: L_A/L_A interference effects < SL_G/L_A interference effects < SL_G/SL_G interference effects. In addition, the modulation of interference effects by 5-HTTLPR/rs25531 genotype was not specific to threat distracters, but instead extended to all four distracter conditions, including threat, neutral, scrambled, and no distracters. Furthermore, the genetic modulation of interference effects was observed exclusively in the first half of the experiment, prior to the intermission, and was abolished in the second half of the experiment.

This pattern of genetic results is particularly intriguing in light of the robust (if transient) potentiation of the interference effects by threat-related distracters observed in the whole sample, collapsing across genotypes. The pattern strongly suggests that the 5-HTTLPR/rs25531 genotype modulates susceptibility to cognitive interference in healthy females in general, rather than to cognitive interference produced specifically by threat-related distracters. In this respect, our results are broadly consistent with the view that the 5-HTTLPR genotype may affect susceptibility

to environmental influences in general rather than modulating specifically the impact of adverse stimuli (Uher, 2008; Belsky and Pluess, 2009), a trait described as *hypervigilance* (Homberg and Lesch, 2010). Thus, the S or L_G allele is associated with worse behavioral and clinical outcomes in the context of adverse environmental conditions, such as childhood maltreatment or stressful life events, but it can also lead to more favorable outcomes in protective, nurturing environments, relative to the L allele (Caspi et al., 2003; Eley et al., 2004; Taylor et al., 2006). Indeed, Roiser et al. (2009) provided elegant evidence for such increased "framing effects" during decision-making, as well as for the corresponding changes in the amygdala-PFC circuitry, in S/S homozygotes compared to L_A/L_A homozygotes. Although the neurobiological mechanisms involved are likely to be highly complex and thus challenging to fully elucidate, we recently proposed one possible molecular mechanism underlying the interaction of stressors and 5-HTTLPR/rs25531 genotype on the amygdala-VMPFC-dorsal raphe nucleus circuitry and the risk of depression (Jasinska et al., 2012).

Some limitations of the current study should be acknowledged. Although our sample size was sufficiently large to give us high statistical power to detect main and interactive effects of the task, it was relatively small to detect genetic effects. The genetic effects in particular should therefore be considered preliminary until replicated in a larger independent sample. It will also be important to replicate the results in both sexes. Furthermore, cognitive function may also be modulated by other functional variants in the serotonin transporter gene (e.g., serotonin transporter intron 2 polymorphism, STin2; Payton et al., 2005; Sarosi et al., 2008), in other serotonergic genes (e.g., *TPH2*; Strobel et al., 2007), or in genes involved in gene-gene interactions with the serotonin transporter gene (e.g., *BDNF*), either in isolation or in interaction with the 5-HTTLPR/rs25531. These effects were unmeasured in our study. Finally, the level of emotion regulation exerted by subjects while performing the task may also modulate performance on tasks which engage emotion-cognition interactions by altering the activity and functional connectivity within the amygdala-PFC circuitry, consistent with recent reports (Schardt et al., 2010; Enge et al., 2011; Lemogne et al., 2011). Therefore, an important goal of future studies will be to measure and manipulate emotion regulation, particularly with respect to serotonin transporter gene effects, to determine to what degree it alters task performance and can compensate for genetic vulnerability to threat reactivity and to cognitive interference.

In conclusion, using a novel threat-distracter MSIT, we demonstrated that threat distracters robustly but transiently potentiate cognitive interference effects, and that 5-HTTLPR/rs25531 genotype modulation of these cognitive interference effects extends to all distracter conditions, irrespective of emotional salience of distracters, in healthy female subjects. These results add to our understanding of the processes through which threat-related distracters affect cognitive processing, and have implications for our understanding of disorders in which threat signals have a detrimental effect on cognition, including depression and anxiety disorders.

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Dissociation of the role of the prelimbic cortex in interval timing and resource allocation: beneficial effect of norepinephrine and dopamine reuptake inhibitor nomifensine on anxiety-inducing distraction

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Emotional distracters impair cognitive function. Emotional processing is dysregulated in affective disorders such as depression, phobias, schizophrenia, and post-traumatic stress disorder (PTSD). Among the processes impaired by emotional distracters, and whose dysregulation is documented in affective disorders, is the ability to time in the seconds-to-minutes range, i.e., interval timing. Presentation of task-irrelevant distracters during a timing task results in a delay in responding suggesting a failure to maintain subjective time in working memory, possibly due to attentional and working memory resources being diverted away from timing, as proposed by the Relative Time-Sharing (RTS) model. We investigated the role of the prelimbic cortex in the detrimental effect of anxiety-inducing task-irrelevant distracters on the cognitive ability to keep track of time, using local infusions of norepinephrine and dopamine reuptake inhibitor (NDRI) nomifensine in a modified peak-interval procedure with neutral and anxiety-inducing distracters. Given that some anti-depressants have beneficial effects on attention and working memory, e.g., decreasing emotional response to negative events, we hypothesized that nomifensine would improve maintenance of information in working memory in trials with distracters, resulting in a decrease of the disruptive effect of emotional events on the timekeeping abilities. Our results revealed a dissociation of the effects of nomifensine infusion in prelimbic cortex between interval timing and resource allocation, and between neutral and anxiety-inducing distraction. Nomifensine was effective only during trials with distracters, but not during trials without distracters. Nomifensine reduced the detrimental effect of the distracters only when the distracters were anxiety-inducing, but not when they were neutral. Results are discussed in relation to the brain circuits involved in RTS of resources, and the pharmacological management of affective disorders.

Keywords: affective disorder, dopamine, interval timing, nomifensine, norepinephrine

INTRODUCTION

Attentional and working memory resources are crucial for the ability to keep track of time in the seconds-to-minutes range, i.e., interval timing (Buhusi and Meck, 2009a). The time keeping ability, and the effect of distracters on timing, can be tested within the Peak Interval (PI) procedure. Within the internal clock paradigm (Gibbon et al., 1984) (**Figure 1**, left panel), regular pulses emitted by a pacemaker, accumulate and are temporarily stored in working memory. Upon the subject being rewarded at the criterion (objective) time, the number of pulses in working memory (subjective time) is stored in reference memory. Responses are generated based on the ratio comparison between the number of pulses in working and reference memory. In trained subjects, responding is low at the beginning of the trial, reaches its peak about the time subjects are rewarded, and decreases afterward, when the current time (in working memory) is much larger than the criterion time (stored in reference memory). However, presentation of task-irrelevant distracters during the PI procedure results in a delay in responding (Buhusi and Meck, 2009a; Buhusi, 2012), suggesting a failure to maintain subjective time in working memory, possibly due to the attentional and working memory resources being diverted away from timing toward processing the distracter (**Figure 1**). According to this Relative Time-Sharing (RTS) model (Buhusi, 2003; Buhusi and Meck, 2009a), distracters result in a difference between the subjective (perceived) time and the objective time, thus explaining why "time flies when you are having fun," but also how food gets burnt when little attention is paid to cooking.

Resource re-allocation is exacerbated by anxiety-inducing task-irrelevant distracters, resulting in impairing effects. For

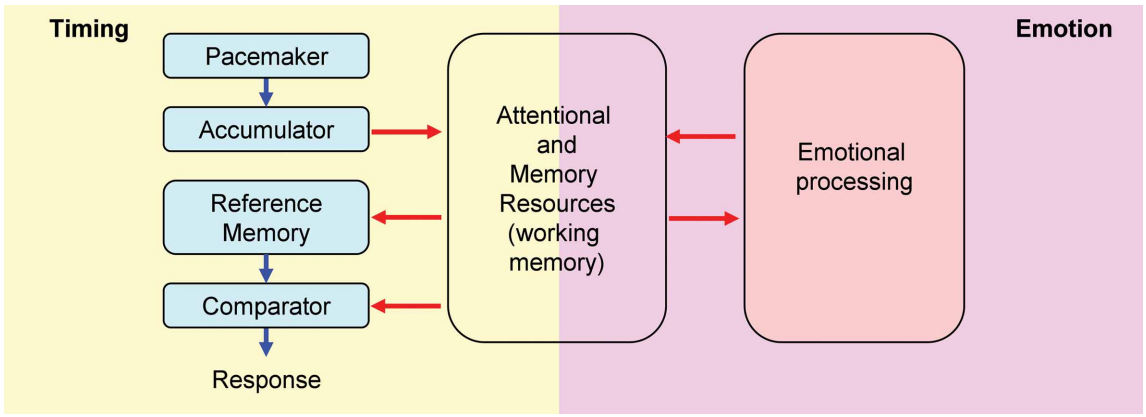

FIGURE 1 | Relative Time-Sharing model. The Relative Time-Sharing model assumes that timing and emotional processing are concurrent processes which share working memory and attentional resources. Task-irrelevant emotional events are assumed to take away working memory and attentional resources from timing; without resources, timing is delayed. Since emotional events seem to have a sustained (long-lasting) effect on resource allocation, interval timing could be delayed considerably by emotional events (modified from Buhusi, 2012).

example, when asked to keep a face in working memory (primary task), the presentation of emotional faces (secondary task) impaired recognition memory (Dolcos and McCarthy, 2006). Indeed, the amygdala is strongly activated during emotional distracters and the dorso-lateral prefrontal cortex (dlPFC) is deactivated during emotional distracters (Dolcos and McCarthy, 2006; Pessoa, 2008; Denkova et al., 2010), thus decreasing resources allotted to the primary task. Similarly, the presentation of emotionally charged distracters during the uninterrupted to-be-timed signal results in a considerable delay in responding relative to neutral distracters (Aum et al., 2004; Brown et al., 2007). According to the RTS model, anxiety-inducing distracters divert attentional and working memory resources away from timing (**Figure 1**, left panel) to emotional processing (**Figure 1**, right panel) (Schirmer, 2011), thus reducing the ability to maintain the subjective time in working memory (Buhusi, 2003; Buhusi and Meck, 2009a). These task-irrelevant emotionally charged distracters would effectively keep timing "shut off" (time not stored in working memory) until emotional processing ceases (Schirmer, 2011), thus delaying timing for considerably longer durations than neutral distracters (Aum et al., 2004; Brown et al., 2007).

Conversely, when the emotional variable is embedded within the primary task, emotion enhances processing of the primary task. For example, when asked to discriminate between a long or a short presentation of an (emotional) face, human participants perceive angry emotional faces as being of longer duration than neutral faces (Droit-Volet and Meck, 2007), possibly due to re-allocation of resources toward the timed emotional stimulus: angry-looking faces increase amygdalar activation compared to happy faces (Davidson and Irwin, 1999), and may increase attention to the timed stimulus, thus facilitating time accumulation. In turn, selective attention to anxiety-inducing stimuli is abolished by inactivation of the amygdala, particularly baso-lateral amygdala (BLA), and may enhance time processing. For example, BLA lesions enhance the ability of rats to simultaneously time an aversive and an appetitive stimulus, due to the reduced fear disruption of dividing attention (Meck and Macdonald, 2007). Thus, emotion may have both impairing and enhancing effects on time processing (Macdonald and Meck, 2004; Droit-Volet and Meck, 2007; Etkin and Wager, 2007; Meck and Macdonald, 2007).

Learning and memory abilities are altered in patients with depression, PTSD, schizophrenia, and phobias (Davidson and Irwin, 1999; Rose and Ebmeier, 2006; Etkin and Wager, 2007; Gohier et al., 2009; Amir and Bomyea, 2011). A recent line of pharmacological treatment for these disorders involves norepinephrine and dopamine reuptake inhibitors (NDRIs), which indirectly increase neurotransmission in the noradrenergic (NE) and dopaminergic (DA) pathways. In turn, both DA and NE modulate the internal clock (Buhusi and Meck, 2010). DA agonists speed-up, and DA antagonists slow-down timing (Buhusi and Meck, 2002, 2005; Matell et al., 2004, 2006; Taylor et al., 2007; Coull et al., 2011). Moreover, NE modulates interval timing in both human participants (Rammsayer et al., 2001) and rodents (Penney et al., 1996). Nevertheless, the specific roles of DA and NE in interval timing at various brain sites are less understood.

Here we investigate the role of the prelimbic cortex in the detrimental effect of anxiety-inducing task-irrelevant distracters on the cognitive ability to keep track of time, in a modified version of the PI procedure with distracters (Buhusi and Meck, 2006), where emotionally charged auditory distracters were presented during the uninterrupted to-be-timed visual signal (Brown et al., 2007). As in previous studies (Aum et al., 2004; Brown et al., 2007), we expected the anxiety-inducing distracters to have detrimental effects on timing, and to delay responding much longer than when the distracters were neutral (Buhusi, 2012). We also hypothesized that interval timing and working memory for time depend on the NE and DA systems (Buhusi and Meck, 2002, 2005, 2009a; Coull et al., 2011). Therefore, local infusions of NDRI nomifensine in prelimbic cortex were expected to alter NE and DA transmission (Robinson and Wightman, 2004; Masana

et al., 2011), and affect both clock speed (in trials without distracters) and maintenance of working memory for time (in trials with distracters). Given that some anti-depressants have beneficial effects on attention and working memory (Rammsayer et al., 2001), e.g., decreasing emotional response to negative events (Masana et al., 2011), we anticipated that nomifensine would improve maintenance of information in working memory in trials with distracters, resulting in a decrease in the disruptive effect of emotional events on the cognitive ability of timekeeping.

MATERIALS AND METHODS

SUBJECTS

Twenty-two naïve Sprague-Dawley male rats, 300–350 g (3 months old at the beginning of the experiment) were housed individually in a temperature-controlled room, under a 12/12 h light-dark cycle, with water given *ad libitum*. Rats were maintained at 85% of their *ad libitum* weight by restricting access to food (Rodent Diet 5001, PMI Nutrition International, Inc., Brentwood, MO). All experimental procedures were conducted in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (1996).

APPARATUS

The apparatus consisted of 12 standard rat operant chambers (MED Associates, St. Albans, VT) housed in sound attenuating cubicles, of which four were used for fear conditioning and the other eight for interval timing. An auditory stimulus was first used during fear conditioning in the fear conditioning chambers, then later used as an anxiety-inducing distracter during the timing task in the timing chambers. The fear conditioning chambers and the interval timing chambers were made distinctive as follows: the fear conditioning chambers contained a dipper entry space for a liquid dipper (not used in the experiment); no lever was inserted in the boxes at any time; no food was given inside these chambers; pine pellets (Feline Pine Cat Litter, West Palm Beach, FL) were placed in the waste pan. In contrast, the interval timing chambers contained four nose pokes (not used in the experiment) and a lever; food was provided for lever-pressing at the right time; the bedding used in these boxes was cedar shavings (Grreat Choice, Phoenix, AZ).

In the fear conditioning chambers the grid floor was connected to shockers and scramblers controlled by a Med Associates interface, generating a 1 s 0.85 mA foot shock. The fear conditioning stimulus was an 85 dB white noise produced by a white-noise generator (MED Associates, St. Albans, VT). The intensity of the distracter was measured with a sound-level meter (Realistic Radio Shack, Model 33–2050) from the center of the silent box.

The interval timing chambers were equipped with a single fixed lever situated on the front wall of the chamber. According to the schedule, 45 mg precision food pellets (PMI Nutrition International, Inc., Brentwood, MO) were delivered in a food cup situated on the front wall, 1 cm above the grid floor, under the center lever, by a pellet dispenser. The to-be-timed visual stimulus was a 28 V 100 mA house light mounted at the center-top of the front wall. The auditory distracter was an 85 dB white noise produced by a white-noise generator (MED Associates, St. Albans, VT) mounted on the opposite wall from the response levers. A 66 dB background sound produced by a ventilation fan was present throughout the session.

BEHAVIORAL TRAINING

For details of training and testing in the peak-interval timing procedure with distracters, see Buhusi and Meck (2006). For details of training and testing with emotional distracters in the peak-interval timing procedure, see Brown et al. (2007). Relevant details are given below.

FIXED-INTERVAL (FI) TRAINING

All timing sessions were conducted in the eight timing chambers. After being shaped to lever press, rats received five daily sessions of fixed-interval (FI) training, during which the first lever press 40 s after the onset of the visual signal was reinforced by the delivery of a food pellet and turned off the house light for the duration of a random 120 $\pm$ 30 s inter-trial interval (ITI).

PEAK–INTERVAL (PI) TRAINING

Afterward, rats received five sessions of peak-interval training during which FI trials were randomly intermixed with non-reinforced PI trials in which the visual signal was presented for a duration three times longer than the FI, before being terminated irrespective of responding. Trials were separated by a 120 $\pm$ 30 s random ITIs.

FEAR CONDITIONING

Rats were randomly assigned to two groups. Rats in the FEAR group were placed in the fear conditioning chambers, where they received six pairings of a 5 s white noise and a 1 s 0.85 mA foot shock, separated by random intervals (2–6 min long). Rats in the CTRL group were placed in the fear conditioning chambers for an equivalent amount of time, where they received six presentations of the 5 s white noise separated by random intervals (2–6 min long) (no foot shock). Rats received two 30 min sessions of fear conditioning, one before and one after the surgery (Brown et al., 2007).

SURGERY

During aseptic surgery under isoflurane anaesthesia, 26-gauge bilateral cannula guides (PlasticsOne, Roanoke, VA) were implanted aiming at the prelimbic cortex (AP 2.5 mm, ML $\pm$ 0.6 mm, DV $-$3.5 mm) (Paxinos and Watson, 1998) and embedded in dental cement. Rats were given at least 3 days to recover from surgery before retraining began again. Data (available, but not shown) indicated that rats responded reasonably well post-recovery. Rats were given six sessions of PI re-training before any local infusions began.

FREEZING BEHAVIOR TESTING AND RE-TRAINING

Rats in the FEAR group were placed in the fear conditioning chambers where they received two presentations of the noise in extinction followed by two noise-shock pairings, at 4 min intervals. The session lasted 20 min. For rats in the CTRL group, the white noise stimulus was not paired with the foot shock. Behavior was recorded and freezing behavior was scored by

two-independent observers in 2.5 s bins. The percent agreement score between the two observers was 89.64 ± 1.25 percent. Fear conditioning testing and re-training was followed by one session of PI re-training, as described above.

LOCAL INFUSIONS

Cannulae injectors aiming at mPFC were lowered into the cannula guides, extending 1 mm below the guides. Rats received intracranial injections of either saline or norepinephrine and dopamine reuptake inhibitor (NDRI) nomifensine (nomifensine maleate salt, Sigma Aldrich, St. Louis, MO), dissolved in 45% cyclodextrin (methyl-beta-cyclodextrin, Sigma Aldrich, St. Louis, MO). Rats received microinjections of 0.5 μL nomifensine solution (4 μg/side) or saline, bilaterally, at a rate of 0.25 μL/min, over 2 min, followed by a 2 min interval to allow the drug to infuse the tissue. Five minutes afterward, rats were placed into the timing chambers for testing in a timing sessions with noise (see next paragraph). Infusion sessions were separated by three no-drug sessions as follows: one post-drug PI re-training session, one fear conditioning testing and re-training session, and one post-fear conditioning PI re-training session. The order of drug infusion (saline or nomifensine) was counterbalanced between animals.

TIMING SESSIONS WITH NOISE AND DRUG INFUSION

Five minutes after drug infusion, rats received two consecutive 1.5 h sessions of interval timing testing, during which rats received 20 FI and 14 PI trials randomly intermixed with 6 PI trials with noise (PI + N). PI + N trials were similar to PI trials, except that the 5 s white noise was presented (during the uninterrupted visual to-be-timed stimulus), 5 s from the onset of the trial.

HISTOLOGY

Rats were anesthetized with isoflurane overdose and transcardially perfused with formalin; their brains were collected and sectioned on a vibratome. Sixty-micron sections were placed on slides and stained with sky-blue for histological analyses. Three rats were eliminated due to incorrect cannula placement; two rats lost their cannulae before testing was completed and were eliminated from the study (CTRL $n = 6$, FEAR $n = 11$) (**Figure 2**).

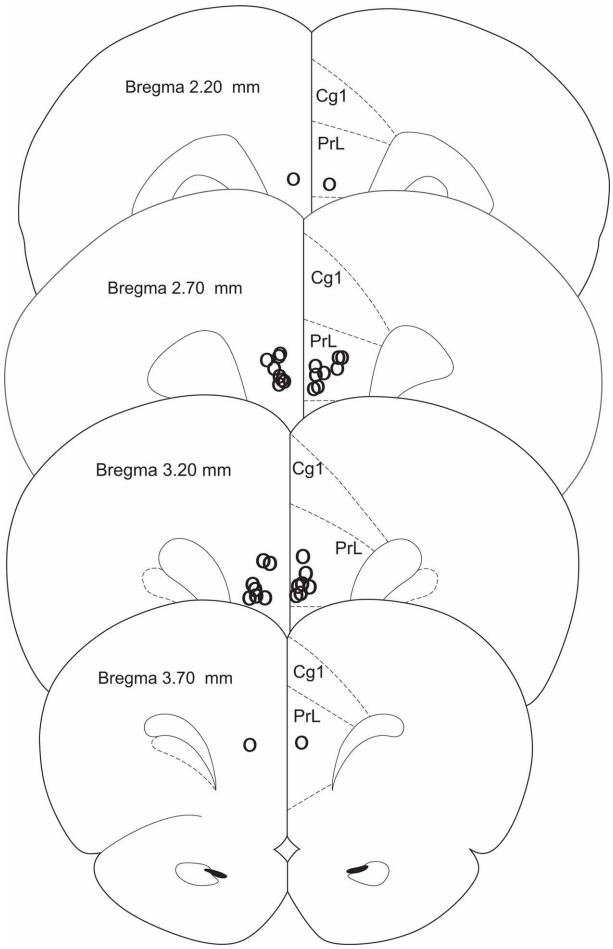

FIGURE 2 | Histology. Cannula placements in the present experiment. Only rats with injections in the prelimbic cortex were used in the experiment (CTRL $n = 6$, FEAR $n = 11$).

DATA COLLECTION AND ANALYSIS

The experimental procedures were controlled through a MED Associates interface connected to an IBM-PC compatible computer running a MED-PC software system (MED Associates, 1999). Lever presses were recorded in real time. Lever presses from PI and PI + N trials from the first 1.5 h test session with drug infusion were used to estimate the peak time, peak rate, and precision of timing (width of the response functions) for each rat. The number of responses (in 4 s bins) was averaged daily over trials, to obtain a mean response rate function for each rat. Analyses were conducted on the data from a 100 s interval-of-interest starting at the onset (for PI trials) or 20 s from the onset of the to-be-timed signal (for PI + N trials). The average response rate in the interval-of-interest was fit using the Marquardt-Levenberg iterative algorithm (Marquardt, 1963) to find the coefficients (parameters) of a Gaussian + linear equation that gave the best fit (least squares minimization) between the equation and the data (Buhusi and Meck, 2000). The algorithm provided the following parameters of the response curve: the accuracy of timing (peak time), precision of timing (width of response function), and peak rate of response (for details see Buhusi and Meck, 2000).

To further investigate the effect of the presentation of the noise and the effect of the drug on the dynamics of timing behavior, individual-trial analyses were performed as described in (Church et al., 1994; Swearingen and Buhusi, 2010). Briefly, during individual trials, the distribution of lever presses can be approximated by a low-high-low function. Analysis algorithms described in (Swearingen and Buhusi, 2010) were used to extract the *start* and *stop* times during individual trials. The *start* time is the time point at which there is a significant increase in response rate during the trial (at the transition from the low to high states). The *stop* time is the point during the trial at which there is a significant decrease in response rate (at the transition from the high to low states). Trials without temporal control (about 20% of total trials) were eliminated from individual-trial analyses based on the

very conservative criteria defined in (Church et al., 1994), except for PI + N trials in the FEAR group: to accommodate for the disruption in response caused by the presentation of the noise, in PI + N trials in the FEAR group analyses were conducted on data after the noise [in the interval-of-interest (20–120 s), same interval as for the curve fitting analysis, see above] and there were no exclusion criteria for *start* time.

The dependent variables *peak time*, *width of function*, *start time*, *stop time*, and *the coefficient of variation (CV) of the start and stop times* were submitted to mixed ANOVAs with independent between-subject variable *group* (FEAR, CTRL) and within-subject variables *trial type* (PI, PI + N) and *drug* (SAL, NOM), followed by planned comparisons. Statistical tests were evaluated at a significance level of 0.05.

RESULTS

LONG-LASTING EMOTIONAL RESPONSE TO THE FEAR-INDUCING EVENT

Rats' emotional response in the fear context before and after the noise was measured during freezing behavior testing and re-training sessions, as shown in **Figure 3**. Before the noise occurred, both the CTRL and FEAR groups show similar low levels of freezing, all $ts_{(15)} < 1.62$, $p > 0.12$. Moreover, no freezing behavior was shown after the noise when the noise was not paired with the foot-shock (CTRL rats), all $ts_{(5)} < 1.19$, $p > 0.14$. In contrast, when the noise was emotionally charged by being paired with foot shock (FEAR group), rats showed reliable freezing behavior following the presentation of the noise in extinction (without shock presentation), all $ts_{(15)} > 3.98$, $p < 0.001$. Interestingly, the strong levels of freezing (e.g., 87.5% during the noise) lasted for several minutes after the noise ended (see **Figure 3**), and decreased slowly to baseline levels before the next presentation of the noise. This long-lasting effect of the presentation of the emotionally charged event (FEAR group), explains the considerable delay in timing by the presentation of the same fear-inducing event in the timing context, see below.

NO EFFECT OF TREATMENT ON VARIABILITY OF TIMING (WIDTH OF THE RESPONSE FUNCTION)

The average maximum percent response rate functions in PI and PI + N trials, with and without auditory distracter are shown in **Figure 4**. These results suggest that, the variability in timing (width of the timing function) is not affected by either treatment. Indeed, a mixed ANOVA of the width of the timing functions with between-subject variable group (FEAR, CTRL) and within-group variables drug (SAL, NOM) and trial type (PI, PI + N), failed to indicate any reliable main effects or interactions, all $Fs_{(1, 15)} < 0.95$, $p > 0.35$, suggesting that neither nomifensine nor the distracter had any reliable effects on variability of response in either group. In short, the treatments simply shifted the timing functions without changing their width. Therefore, for the remainder of the paper, we will focus only on the effect of treatment on timing (i.e., on the peak time).

NO EFFECT OF NOMIFENSINE ON TIMING IN PI TRIALS (WITHOUT DISTRACTER)

The average maximum percent response rate functions in PI trials (without auditory distracter) are shown in the left panels of **Figure 4**. Under saline, the PI timing functions peaked at 36.51 ± 2.21 s in FEAR rats, and at 35.25 ± 1.46 s in CTRL rats. Under nomifensine, the PI timing functions peaked at 34.69 ± 1.39 s in FEAR rats, and at 36.92 ± 2.34 s in CTRL rats,

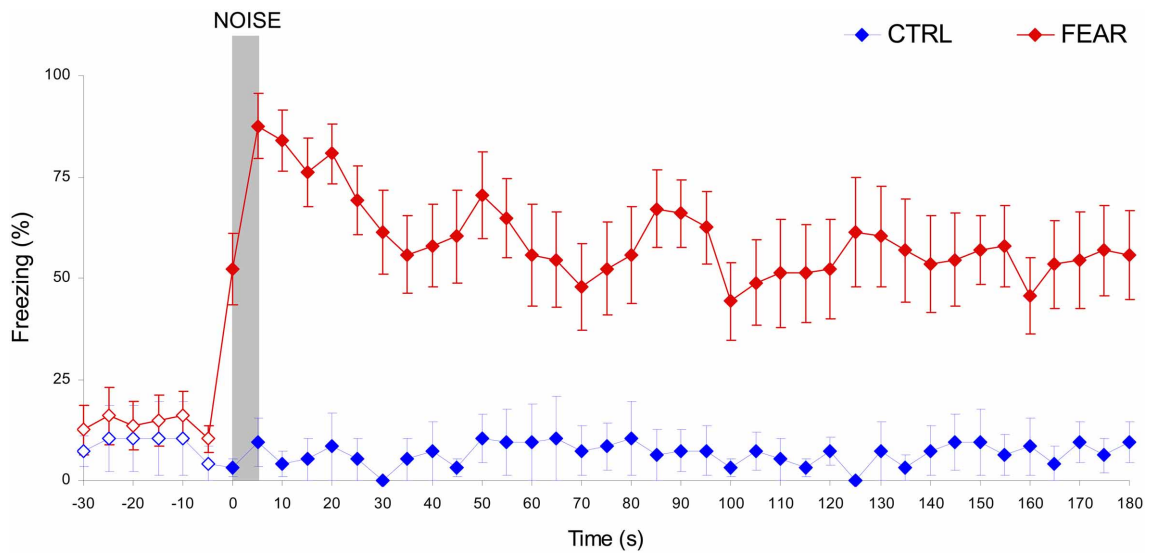

FIGURE 3 | Long-lasting freezing behavior following the presentation of the auditory distracter in the FEAR, but not CTRL rats. Average percent freezing behavior (±SEM) in the fear conditioning context during freezing behavior testing and re-training sessions, before, during, and after the presentation of the noise (in extinction, no shock). Unlike CTRL rats, FEAR rats show reliable, long-lasting freezing behavior after, but not before the presentation of the noise. Empty symbols show time where emotional response (freezing behavior) did not differ reliably between FEAR and CTRL rats, $p > 0.05$. The gray bar indicates the presentation of the auditory distracter.

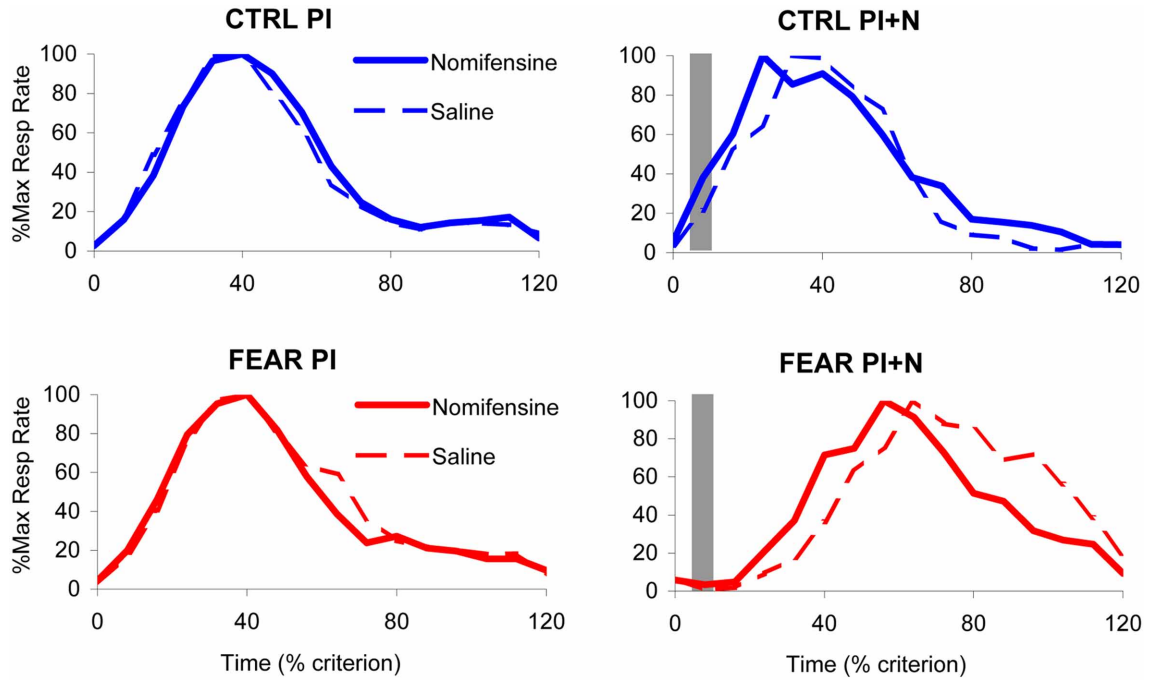

FIGURE 4 | Effect of nomifensine infusion on average timing functions. Average maximum percent response (lever pressing) rate in rats trained to time a 40 s criterion signaled by a visual stimulus when presented with a neutral distracter (CTRL group, *upper panels*) or an emotionally charged distracter (noise previously paired with foot shock, FEAR group, *lower panels*). *Left panels*: Peak interval (PI) trials (without noise): nomifensine has no reliable effects in either group. *Right panels*: Peak interval with noise (PI + N) trials (with noise): when emotionally charged (FEAR group), the distracter shifts the response function rightward considerably relative to neutral events (CTRL); nomifensine reduces the delaying effect of the distracter only when the distracter is emotionally charged (FEAR group). The gray bars indicate the presentation of the auditory distracters.

suggesting that nomifensine had no specific effects relative to saline. Although reliably lower than 40 s for both saline and nomifensine, all $ts > 2.63$, $p < 0.05$, the estimated peak times were relatively close to the criterion time, indicating that rats acquired the timing task. Indeed, a mixed ANOVA of peak time with between-subject variable group (FEAR, CTRL) and within-group variable drug (SAL, NOM) failed to indicate reliable effects of group, drug, or interactions, all $Fs_{(1,\ 15)} < 0.73$, $p > 0.41$, suggesting that nomifensine had no reliable effects in trials without noise distracter (PI trials) in either group.

THE AUDITORY DISTRACTER DELAYS TIMING ONLY WHEN IT IS FEAR-INDUCING

The top-right panel of **Figure 4** indicates that the presentation of the noise has no effect on timing when the distracter was neutral (CTRL group). The PI + N timing functions peaked at 38.42 ± 3.38 s under saline, and at 32.44 ± 3.61 s under nomifensine, not significantly different from the 40 s criterion, all $ts < 2.09$, $p > 0.05$. In contrast, as seen in the bottom-right panel of **Figure 4**, responding was considerably delayed by the presentation of the fear-inducing distracter under both saline and nomifensine, relative to trials without the distracter. In the FEAR group, the PI + N timing functions peaked at 69.77 ± 5.50 s under saline, and at 56.83 ± 3.19 s, under nomifensine. The difference between groups was confirmed by a mixed ANOVA of peak time in PI + N trials, with between-subject variable group (FEAR, CTRL) and within-group variable drug (SAL, NOM) which indicated a reliable main effect of group, $F_{(1,\ 15)} = 38.0$, $p < 0.001$, suggesting that the distracter has a reliably different effect when it is emotionally charged or neutral.

To further investigate the differential effect of nomifensine in the two groups in trials with distracters, relative to trials without distracters, we computed and analyzed a delay in peak time between the two trial types, as shown in **Figure 5**. Should the distracter have no effect, the rats would continue to time (run, delay = 0 s). Should rats stop timing during the distracter, the delay would be equal to the duration of the noise (stop, delay = 5 s). Should rats restart timing after the distracter, the delay would be approximately equal to the duration of the noise, 5 s, plus the duration of the pre-distracter interval, 5 s (reset, delay = 10 s). Results indicate no delay (run) in the CTRL group, $t_{(5)} = 1.01$, $p > 0.36$, but a considerable delay by an emotionally charged noise (FEAR group), beyond a full reset of timing. Indeed, a mixed ANOVA with between-subject variable group (FEAR, CTRL) and within-subject variable drug (SAL, NOM) indicated a reliable effect of group, $F_{(1,\ 15)} = 43.88$, $p < 0.001$, drug $F_{(1,\ 15)} = 5.83$, $p < 0.03$, but no drug × group interaction $F_{(1,\ 15)} = 0.20$, $p < 0.66$. In the CTRL group, the neutral noise had no effect on delay (run), $t_{(5)} = 2.01$, $p > 0.1$. In contrast, in the FEAR group, the emotionally charged noise significant delayed timing more than the reset (over-reset), $t_{(10)} = 5.52$, $p < 0.001$. These results are consistent

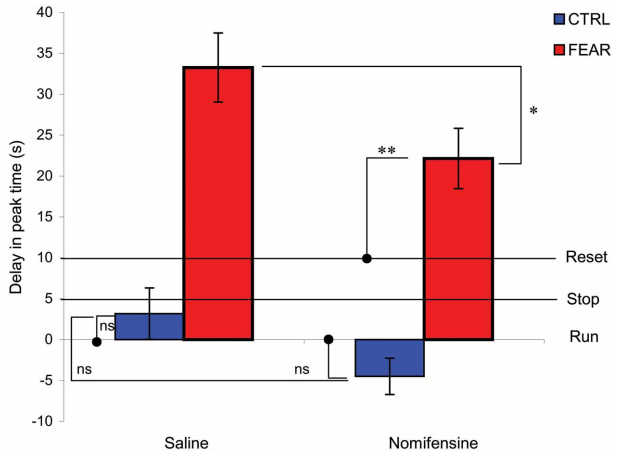

FIGURE 5 | Average delay for trials with and without noise distracter. Average peak time delay (±SEM) in trials with distracters (PI + N) relative to trials without distracters (PI). Should the distracter have no effect, the clock would continue to time (run, delay = 0 s). Should the clock stop timing during the distracter, the delay would be equal to the duration of the noise (stop, delay = 5 s). Should the clock restart timing after the distracter, the delay would be equal to the duration of the noise, 5 s, plus the duration of the pre-distracter interval, 5 s (reset, delay = 10 s). Rats ignored a neutral distracter (CTRL). In contrast, rats over-reset when the distracter is emotionally charged (FEAR). Nomifensine reliably reduces the time delay. $^{*}p < 0.05$; $^{**}p < 0.01$; ns, $p > 0.05$.

with those of Brown et al. (2007) and Aum et al. (2004), where an emotionally charged distracter resulted in an over-reset of timing.

NOMIFENSINE INFUSION REDUCES THE DELAY IN RESPONDING FOR FEAR-INDUCING DISTRACTERS, BUT NOT FOR NEUTRAL DISTRACTERS

The data from **Figure 5** also indicates that nomifensine reduces the delay in peak time only when the noise is emotionally charged (FEAR group). A mixed ANOVA of the delay time between PI + N and PI trials with between-subject variable group (FEAR, CTRL) and within-subject variable drug (SAL, NOM), indicated a reliable effect of drug, $F_{(1,\ 15)} = 5.83$, $p < 0.05$ (see **Figure 5**). Planned comparisons indicated that in PI + N trials, nomifensine reliably decreases the delay in timing for the FEAR group, $F_{(1,\ 15)} = 5.80$, $p < 0.05$, but not in the CTRL group, $F_{(1,\ 15)} = 1.49$, $p > 0.05$. Moreover, in the FEAR group, the delay under nomifensine is reliably smaller than under saline, yet larger than reset, $t_{(10)} = 3.29$, $p < 0.01$.

NO EFFECT OF NOMIFENSINE ON START AND STOP TIMES IN PI TRIALS (WITHOUT DISTRACTER)

To further investigate the effect of nomifensine on the dynamics of responding (lever pressing) in trials with and without noise, we followed the observation that during individual trials the rate of lever pressing has a low-high-low profile (Church et al., 1994). Using algorithms described in Swearingen and Buhusi (2010), we extracted and analyzed the *start* and *stop* times during individual trials. Briefly, the *start* time is the time of transitioning between the low and high state, and the *stop* time is the time of transitioning between the high and low state, in that individual trial. The start and stop times in PI trials (without noise) are shown in the left panels of **Figure 6**, suggesting that there was no effect of nomifensine on start and stop times in PI trials. The lack of effect of nomifensine on start and stop times is PI trials was confirmed by mixed ANOVAs with between-subject variable group (FEAR, CTRL), and within-subject variable drug (SAL, NOM), which failed to indicate reliable effects of group, drug, or interactions, all $Fs_{(1,\ 15)} < 1.73$, $p > 0.21$ (see **Figure 6**, left panels).

The lack of effect of nomifensine in trials without noise (PI) may have been due to large variations in response, for example, in trials before and after trials with auditory distracter (PI + N). Considering the relatively long-lasting freezing behavior following the presentation of the noise (see **Figure 3**), rats were expected to have large disruptions in response immediately after a PI + N trial, but recover before the next PI + N trial. These differences in responding before and after a PI + N trial may have resulted in large variations in response, which may have obscured the effect of the drug in PI trials. Therefore, we extracted and contrasted the start and stop times in PI trials before and after PI + N trials, and their coefficients of variation. However, analyses of start and stop times and their coefficients of variation failed to indicate main effects of the group, all $Fs_{(1,\ 15)} < 2.31$, $p > 0.15$, the before-after condition, all $Fs_{(1,\ 15)} < 3.24$, $p > 0.11$, drug, all $Fs_{(1,\ 15)} < 0.45$, $p > 0.51$, or interactions, all $Fs_{(1,\ 15)} < 2.54$, $p > 0.13$, suggesting that the response in PI trials were relatively stable before and after a PI + N trial. Thus, the lack of effect of nomifensine in PI trials does not seem to be due to interference from trials with distracters.

NOMIFENSINE SHORTENS BOTH START AND STOP TIMES AFTER FEAR-INDUCING DISTRACTERS, BUT NOT AFTER NEUTRAL DISTRACTERS

Mixed ANOVAs of start and stop times with between-subject variable group (FEAR, CTRL), and within-subject variable drug (SAL, NOM), indicated a reliable main effect of group, $Fs_{(1,\ 15)} > 58.49$, $p < 0.001$. Planned comparisons indicated a reliable effect of nomifensine on the start and stop times in the FEAR group, $Fs_{(1,\ 15)} > 6.66$, $p < 0.02$, but not in the CTRL group, $Fs_{(1,\ 15)} < 0.09$, $p > 0.77$, suggesting that infusion of nomifensine resulted in a reliable decrease in both start and stop times only in FEAR rats (see **Figure 6**, right panels).

DISCUSSION

This study was aimed at elucidating both the impact of fear-inducing task-irrelevant distracters on interval timing, and the role of the NE and DA modulation of the prelimbic cortex in emotional processing of timed events. Our results suggest a dissociation of the effects of nomifensine in the prelimbic cortex on interval timing, explained by resource allocation (Relative Time-Sharing), after fear-inducing distraction, but not after neutral distraction. Rats ignore low-salience neutral distracters (run), stop timing during the medium-salience neutral distracters, and reset (restart timing from the beginning) after high-salience neutral distracters (Buhusi and Meck, 2000, 2006; Buhusi, 2012). Accordingly, the RTS model proposes that during

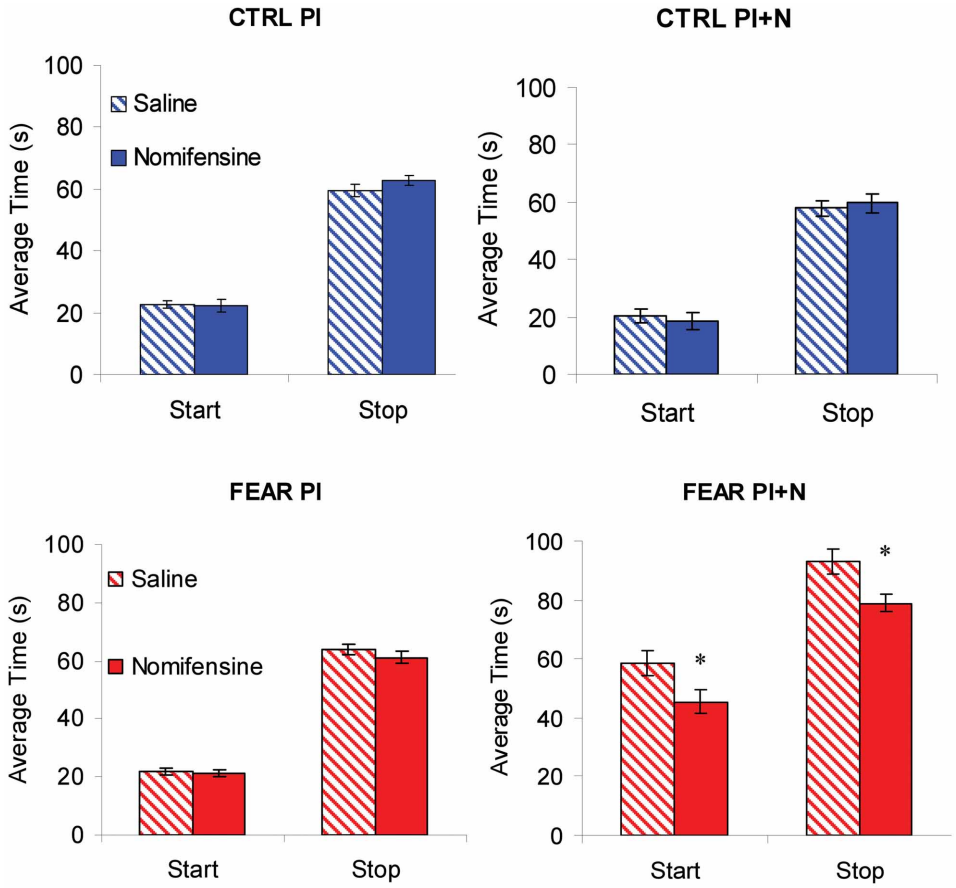

FIGURE 6 | Individual-trial dynamics. Average estimated start and stop times (±SEM) in individual trials. Nomifensine reliably reduced both start and stop times only in trials with distracter (PI + N) and only when the noise distracter is emotionally charged (FEAR rats). *$p < 0.05$.

neutral distracters, working memory for time decreases at a rate proportional to the salience of the distracter (Buhusi, 2003, 2012; Buhusi and Meck, 2009a). While some emotional distracters have transient (short-lived) effects, like neutral distracters (Droit-Volet and Meck, 2007), in our setting, the fear-inducing distracters may have been very salient, because they considerably delayed responding, beyond the reset (Aum et al., 2004; Brown et al., 2007), suggesting that resources are not returned back to timing until long after the distracter has ended. This "post-cue" effect (Aum et al., 2004; Brown et al., 2007) is consistent with our finding that rats in the FEAR group show a long-lasting emotional response long after the offset of the auditory distracter. However, under nomifensine, the delay in responding was shortened, and rats started and stopped timing earlier, suggesting that nomifensine decreased the fear-inducing effect of the distracter, and facilitated the return of resources from emotional processing back to interval timing.

Interestingly, nomifensine was effective only during trials with distracters (PI + N), but not during trials without distracters (PI trials), suggesting that at the current dose (4 μg/side) the drug does not change the speed of an internal clock. This finding is rather surprising, considering the strong DA modulation by nomifensine, and the putative role of DA in the control of the speed of an internal clock (Buhusi and Meck, 2010). Striatal infusion of nomifensine elevates DA release, with effects on operant behavior (Robinson and Wightman, 2004). Also, NE drugs are thought to selectively enhance mesocortical DA, due to the co-release of NE and DA at NE terminals (Masana et al., 2011). In addition, NE transporter (NET) is not specific for NE, and allows reuptake of DA as well. Therefore, blockage of both DAT and NET by NDRIs allows for a much higher amount of DA and NE to be released in medial prefrontal cortex (mPFC) (Masana et al., 2011). Since systemic administration of DA drugs alters the speed of an internal clock (Buhusi and Meck, 2005; Coull et al., 2011), we expected that increasing DA availability by nomifensine infusion to speed-up timing in PI trials, but this was not the case in our study.

One possible explanation for the ineffectiveness of nomifensine on the speed of an internal clock (in PI trials) is the increased variation in response. For example, considering the relatively long-lasting emotional response following the presentation of the noise, rats could have had large disruptions in response in PI trials that immediately follow a PI + N trial, but may have recovered before the next PI + N trial. This hypothesis was not supported

by individual-trial analyses which failed to indicate differences in start and stop times, and in their CVs, in PI trials before and after PI + N trials. This finding mirrors that of Brown et al. (2007), which found that the delaying effect of the distracter is limited to trials with distracters, and does not "spill" into PI trials.

Nomifensine administration in mPFC was only effective in distracter (PI + N) trials, and only when the distracter was fear-inducing. Indeed, fear-inducing events have detrimental effects on cognition, in accord with reallocation of resources between the task at hand (e.g., interval timing) and emotional processing. Emotionally charged events create a markedly different pattern of activation within the ventral "emotional" and dorsal "executive" systems (Davidson and Irwin, 1999; Dolcos and McCarthy, 2006; Pessoa, 2008; Etkin et al., 2011; Johnson et al., 2011). Both fMRI studies in human participants and lesion studies in rodents indicate that emotional distracters produce working memory deficits by altering the relative activity of the dorsal and ventral systems (Dolcos and McCarthy, 2006; Denkova et al., 2010). The dorsal executive system is activated in working memory tasks (such as interval timing) (Buhusi and Meck, 2005; Pessoa, 2008). Impairing the function of the dorsal executive system results in working memory deficits in both human participants (Dolcos and McCarthy, 2006) and rodents (Kim et al., 2009). For example, working memory performance is hindered in human participants with decreased activation in dorsomedial and dorsolateral PFC (Pessoa, 2008; Denkova et al., 2010). Similarly, deficits in interval timing (which relies on working memory) have been reported in rodents following temporary inactivation of mPFC (Kim et al., 2009).

The dlPFC/mPFC is a "connectivity hub" which integrates motivation and cognitive executive functions (Chiew and Braver, 2011), and where cognition and emotion interact (Pessoa, 2008). Lesion studies indicate the importance of the frontal cortex for both interval timing (Kim et al., 2009) and emotion (Sierra-Mercado et al., 2011): rats with cortical lesions are unable to simultaneously attend to two concurrent intervals being timed (Olton et al., 1988). A similar effect was seen in rats presented with emotional stimuli during timing; the disruption was blocked by bilateral lesions of the amygdala (Meck and Macdonald, 2007). On the other hand, emotional information reaches amygdala by two pathways, a rapid but imprecise subcortical "low road," and a slower cortical "high road" which provides more elaborate cognitive influences to be placed over emotional action (Ledoux, 2007; Johnson et al., 2011). The two tracts would act as two different mechanisms differentially activated by the particular arousal level (Droit-Volet and Meck, 2007; Chiew and Braver, 2011). A low arousal level would indicate attentional control; a high arousal level would indicate that motivational-survival systems are controlling behavior automatically. A high arousal level would increase the activation of the autonomic nervous system, which is associated with increases in clock speed (Droit-Volet and Meck, 2007). The two parallel tracts allow for the modulation of activity in the amygdala and allow cognitive influences to be placed over emotional action. The dlPFC/mPFC might work as a mediator between the frontal executive functions and the amygdalar emotional responses (Pessoa, 2008; Etkin et al., 2011).

Norepinephrine and dopamine may shift the balance between the cortical "high road" and the subcortical "low road," by acting both in the amygdala and at cortical level, in opposite directions. Fear conditioning generates stress and is associated with NE reduction in the amygdala. NE reduction reduces the feedback within the amygdala and creates an overactive fear response (Johnson et al., 2011). In contrast, combined systemic administration of NET blocker reboxetine and NE alpha-2 blocker mirtazapine decrease fear and increase DA release in mPFC, thus providing a balancing mechanism to exert cognitive influences over emotional responses (Masana et al., 2012) ... Similarly, DA receptor activation in amygdala removes its mPFC suppression (i.e., hypoactivity) (Rosenkranz and Grace, 2002), which increases the emotional response. In contrast, mPFC 6-OHDA lesions delayed extinction of fear, suggesting that mPFC DA modulates the response to fear-inducing cues, as in our experimental setting (Morrow et al., 1999). Therefore, the "high" pathway creates the ability to overcome emotional memories and to consciously balance the emotional response to the "low" pathway (Rosenkranz and Grace, 2002; Meck and Macdonald, 2007). Indeed, our experiment indicates that nomifensine's modulation of NE and DA cortical activity could offset the increased fear caused by the distracter, possibly by activating the cortical "high" road and reducing fear, thus decreasing both the start and stop in responding.

Nomifensine within the prelimbic cortex may have altered the sharing of resources between timing and emotional processing. Recent explanations of attentional effects in interval timing, particularly in regard to the effect of task-irrelevant distracters (either neutral or emotionally charged), are done within the framework of the RTS model (Buhusi and Meck, 2006, 2009a; Buhusi, 2012) which assumes that distracters result in the reallocation of the limited pool of attentional and working memory resources from timing toward other processes (e.g., emotional processing) (Buhusi and Meck, 2009b; Schirmer, 2011; Buhusi, 2012). The model is compatible with the current understanding of the circuits involved in interval timing and emotional processing, and involves homologous relationships in humans and rodents (Uylings et al., 2003; Vertes, 2004) (**Figure 7**). Interval timing engages fronto-striatal functional circuits (Buhusi and Meck, 2005, 2009a) dependent on brain regions known to be involved in working memory, such as dlPFC in human participants (Stevens et al., 2007), and the mPFC in rodents (Kim et al., 2009) (**Figure 7**, left panel). Homologous relationships between the primate dlPFC and rodent mPFC have been also shown in regard to amygdalar connectivity, which is crucial for emotional processing (Sierra-Mercado et al., 2011) (**Figure 7**, right panel). The sharing of brain regions involved in working memory, between the circuits involved in timing (**Figure 7**, left) and emotional processing (**Figure 7**, right) provides support for a neurobiological RTS model, by which resource allocation is dependent on the modulation of activity in brain regions dealing with working memory (dlPFC for humans, mPFC for rodents) by both the circuits involved in timing and other processing (e.g., emotional). During timing, fronto-striatal circuits would engage working memory (dlPFC/mPFC). However, presentation of an emotionally charged distracter would also activate

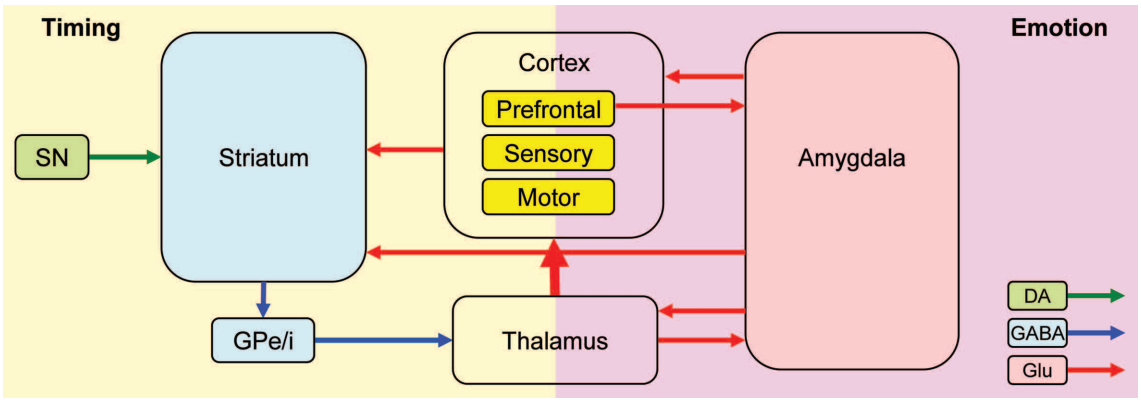

FIGURE 7 | A neurobiological RTS model: Interactions between timing and emotion circuits. Interval timing relies on fronto-striatal circuits and cortical regions involved in attention and working memory. Emotional processing relies on direct thalamo-amygdalar projections (low road), and indirect thalamo-cortico-amygdalar projections (high road). Interactions between the timing and emotion circuits may occur at cortical level, or through direct amygdala-striatum projections. SNc, substantia nigra pars compacta; GPe/i, globus pallidus external/internal; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; DA, dopamine; Glu, glutamate; GABA, gamma-aminobutyric acid. This simplified model of the timing–emotion interaction has been modified from Buhusi and Meck (2005) and Rosenkranz and Grace (2002).

the amygdala, which would engage the dlPFC/mPFC in emotional processing, thus decreasing the relative activation on the fronto-striatal timing circuits. When emotional processing ceases (which could be long after the offset of the distracter), the activation of dlPFC/mPFC by (emotional) amygdalar circuits would decrease relative to their activation by fronto-striatal (timing) circuits, thus re-starting the timing process. In this framework, nomifensine would modulate activity within mPFC, to either decrease the fear-inducing effect of the distracter, and/or to reallocate resources toward timing, e.g., by increasing maintenance of temporal information in working memory. This may explain the "over-resetting" effect of the distracter, and the fact that nomifensine was effective only in PI + N trials, and only when distracters were fear-inducing.

On the other hand, results are inconsistent with an "attentional switch" or "flickering switch" (FS) model (Gibbon et al., 1984). Early explanations of attentional effects on interval timing have suggested an attentional switch in between the pacemaker and the accumulator, controlled by the presence and the salience of the to-be-timed signal (Gibbon et al., 1984), and dependent on the DA (Buhusi, 2003) and NE systems (Penney et al., 1996). Manipulations that affect the attention paid to timing were assumed to affect the latency to open/close the (flickering) switch, such that pulses from the pacemaker do not reach the accumulator, resulting in delayed responding (Lejeune, 1998; Zakay, 2000; Buhusi and Meck, 2002, 2005, 2009b). The FS model cannot address our findings. First, the switch is supposed to be closed during the uninterrupted presentation of the to-be-timed signal (Church, 1978, 1984), such that it cannot address the delaying of timing in our study (since the to-be-timed visual signal was not interrupted in PI + N trials), let alone the "over-reset" seen under saline in FEAR rats. Second, FS and RTS differ on both the location of the putative mechanism, before and after the accumulator respectively, and on the duration of action, either strictly during the interrupting event or throughout the task (see Buhusi and Meck, 2006). The FS switch is flickering only during the interrupting event, and is located before the accumulator; therefore, it would at best predict a stop (no pulses accumulated.) On the other hand, RTS is active throughout the task, not only during the noise but possibly after the noise as well, and it is located after the accumulator, at the level of working memory; therefore, RTS can explain the over-reset behavior in the present experiment. Thirdly, RTS is concurrent with timing (involves competition between the timer and other processes outside of the timer) while FS is a process inside the timer. Therefore, FS cannot predict an over-reset (since the timer itself cannot over-reset) while RTS is free from this restriction.

Moreover, while FS is a cognitive construct, RTS can been applied (as done in this paper) to neurobiological data (e.g., Buhusi and Meck, 2002, 2009a), as follows: first, past studies using retention intervals (gaps) indicated that DA has dissociable effects on the clock speed (in PI trials) and RTS (in trials with distracters) (Buhusi and Meck, 2002, 2007): systemic administration of DA agonists increases clock speed in PI trials and delays timing in trials with gaps; In contrast, despite being an indirect DA agonist, nomifensine had no effects in PI trials, and reduced the delay in timing in trials with distracters, suggesting that nomifensine infusions into mPFC affect RTS, but not clock speed, and that clock speed may rely on DA flow in other brain regions beside mPFC. Second, systemic administration of clonidine, an NE α2 agonist, results in delayed responding in PI trials (Penney et al., 1996), consistent with an increase in the latency of the FS to open. In contrast, in our study, nomifensine, an indirect NE agonist had no effects in PI trials, suggesting that Penney et al.'s FS interpretation of NE results is questionable. Finally, in our study nomifensine was effective only in trials with an fear-inducing distracter, but not when the distracter was neutral, which is consistent with the use of nomifensine in the treatment of depression and anxiety (Tejani-Butt et al., 2003; Jiao et al., 2006). These results can be easily addressed by the RTS model

(Buhusi and Meck, 2006, 2009a; Buhusi, 2012), in that nomifensine decreases the fear-inducing effect of the distracter, and/or affects reallocation of resources toward timing, e.g., by increasing maintenance of temporal information in working memory. Therefore, nomifensine treatment may be beneficial in disorders characterized by impaired working memory processing, especially in affective disorders.

Indeed, emotional processing is dysregulated—either impaired or enhanced—in disorders such as schizophrenia, depression, phobias, and post-traumatic stress disorder (PTSD) (DSM-IV-TR, 2000). Alterations in the dorsal system involved in executive processing and ventral systems involved in emotional processing are reported in patients diagnosed as being depressed (Dolcos and McCarthy, 2006). Damage to the left dlPFC increases the likelihood of becoming depressed, while damage to the right dlPFC is linked to working memory impairments (Davidson and Irwin, 1999). Anxiety disorders, such as PTSD, are characterized by a specific deficiency in the ability to extinguish fear responses (Droit-Volet and Meck, 2007; Denkova et al., 2010; Sierra-Mercado et al., 2011), and by reoccurring and intrusive memories of the traumatic event. Extinction learning is hindered if the fronto-amygdalar circuit is dysregulated. PFC hypoactivity (Etkin and Wager, 2007; Etkin et al., 2011), and significant amygdalar activation (Davidson and Irwin, 1999) contribute to the emotional dysregulation in PTSD. Amygdalar hyperactivity is also seen in patients with social anxiety disorder and specific phobias (Rosenkranz and Grace, 2002). Moreover, heightened amygdalar activity can result in emotional responses to non-salient sensory stimuli, which in the absence of PFC-suppression, might lead to paranoia-like feelings (Rosenkranz and Grace, 2002). The dorsal system could modulate activity between emotional judgment and attention (Johnson et al., 2011). Greater control over fear and anxiety could be obtained in patients by increasing the PFC regulation of emotional events, for example, by reappraisal treatment, shown to activate the mPFC and to decrease negative emotions (Etkin et al., 2011). Solutions that allow for coping with emotional distractions in the executive and cognitively controlled frontal regions of the brain can help control emotional distraction (Denkova et al., 2010). Controlling mPFC activity, for example by NRDI antidepressants like nomifensine, may regulate working memory, and increase the quality of life for patients with affective disorders (Etkin and Wager, 2007).

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"Distracters" do not always distract: visual working memory for angry faces is enhanced by incidental emotional words

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We are often required to filter out distraction in order to focus on a primary task during which working memory (WM) is engaged. Previous research has shown that negative versus neutral distracters presented during a visual WM maintenance period significantly impair memory for neutral information. However, the contents of WM are often also emotional in nature. The question we address here is how incidental information might impact upon visual WM when both this and the memory items contain emotional information. We presented emotional versus neutral words during the maintenance interval of an emotional visual WM faces task. Participants encoded two angry or happy faces into WM, and several seconds into a 9 s maintenance period a negative, positive, or neutral word was flashed on the screen three times. A single neutral test face was presented for retrieval with a face identity that was either present or absent in the preceding study array. WM for angry face identities was significantly better when an emotional (negative or positive) versus neutral (or no) word was presented. In contrast, WM for happy face identities was not significantly affected by word valence. These findings suggest that the presence of emotion within an intervening stimulus boosts the emotional value of threat-related information maintained in visual WM and thus improves performance. In addition, we show that incidental events that are emotional in nature do not always distract from an ongoing WM task.

Keywords: emotion, working memory, distraction, faces, facilitation, angry face, threat

INTRODUCTION

During social interaction we often have to assimilate multiple pieces of incoming information in any given moment. To achieve this we use attention systems to filter relevant from irrelevant information, and working memory (WM) to monitor, update, and integrate ongoing current events. This enables us to forecast others' intentions and plan one's own behavior fluently and efficiently.

Social encounters are often rich with emotion. The presence of emotion during attention and WM tasks has been shown to strongly influence how we in turn perceive and process a situation, and there is evidence that particular emotions can both facilitate and impair performance, depending on the task at hand. Numerous studies report that attention is rapidly oriented and biased toward faces displaying fear or anger (Eastwood et al., 2003; Fenske and Eastwood, 2003; Fox and Damjanovic, 2006; Hahn et al., 2006; Horstmann et al., 2006; Bannerman et al., 2010; Feldmann-Wüstefeld et al., 2011; Huang et al., 2011) and toward threatening words and scenes (Fox et al., 2001; Yiend and Mathews, 2001; Koster et al., 2004). Within the normal human population this attentional threat bias is considered to be facilitatory in that it engages a primitive survival response to locate and process danger swiftly and effectively. There is also evidence that the presence of task-irrelevant threat can enhance the allocation of attention to a separate, unrelated task. For example, contrast discrimination is shown to be more sensitive when preceded by a fearful face (Phelps et al., 2006), and visual search efficiency for a prepotent target increases when preceded by a fearful face (Becker, 2009) or an emotional scene (Kristjánsson et al., 2012). Such knock-on effects of negative emotional stimuli on attention are widely considered to result from activation of amygdala and its associated networks (e.g., Phelps et al., 2006). In contrast, negative emotions have also been shown to impair rather than facilitate attention processes. Among anxious people, for whom the threat bias is particularly pronounced (e.g., Mogg and Bradley, 1998; Bradley et al., 2000; Fox et al., 2001), attention to threatening stimuli is associated with the inability to disengage from the threat item (Fox et al., 2001, 2002; Yiend and Mathews, 2001; Koster et al., 2004), a detrimental effect which may disrupt attention to other ongoing tasks. A disadvantageous bias to threat within the normal adult population is reported in a phenomenon called emotion-induced blindness, which describes impaired awareness of stimuli that follow in close temporal and spatial proximity to a negative emotional item (Most et al., 2005). A possible mechanism for these effects is that limited attention resources for high-level visual processing are directed toward irrelevant emotional stimuli and away from task relevant ones, thus impairing performance.

A smaller number of studies have asked whether emotionally positive stimuli have effects similar to those reported for negative

stimuli. The general finding is that when stimuli are associated with reward and are therefore positive, they are highly effective at attracting attention. These effects have been found with a range of different stimuli including sexual stimuli (Arnell et al., 2007; van Hoof et al., 2010), drug related stimuli for addicted individuals (e.g., Bradley et al., 2004), and for arbitrary stimuli that have been associated with reward via conditioning (Raymond and O'Brien, 2009; Anderson et al., 2011). Other work suggests that arousal level of stimuli, positive or negative, determines their effect on attention (Anderson, 2005; Schimmack, 2005). Higher-level cognitive tasks are also affected by emotion, and again both facilitatory and detrimental effects of threat are reported. Complementing the advantageous threat bias in the attention literature, visual WM for the identity of faces is significantly better for faces bearing an angry (Jackson et al., 2009) or fearful (Sessa et al., 2010) expression than for faces bearing a positive or neutral expression. The ability to accurately maintain the identity of angry and fearful individuals in visual WM is likely to have evolved from the need to respond rapidly and appropriately to social threat cues. Note that the angry and happy faces used in our previous studies (and also used here) were rated very similar in arousal levels (see Jackson et al., 2009), therefore differences in arousal are unlikely to account for the finding of enhanced WM for angry faces.

Conversely, there are also disadvantageous effects of attention to negatively valenced information on separate, concurrent WM tasks. Task-irrelevant negative stimuli that are presented during a WM task have been shown to impair memory for neutral items, termed a distraction effect. For example, negative distracter words presented during the serial presentation of word memoranda impaired serial recall relative to positive and neutral words (Buchner et al., 2004). Similarly, Dolcos and McCarthy (2006) found that visual WM for neutral faces was significantly impaired when negative versus neutral or scrambled scenes were inserted as distracters into the WM maintenance period (see Dolcos et al., 2011, for a review of the neural correlates of such emotion-cognition interactions). These findings suggest that negative information although incidental detracts attention from an ongoing neutral task in which WM is engaged [see also the review by Cohen and Henik (2012) which outlines evidence that irrelevant emotional stimuli can both impair and enhance executive control].

What is unknown at present, however, is how task-irrelevant emotional information might impact upon a separate WM task when the memoranda themselves are emotional. Effective social engagement relies heavily on WM processes to maintain and update relevant person information, and this rarely occurs in an emotional vacuum. Facial expressions of emotion are crucial for rapidly communicating one's own state of mind, and the ability to monitor others' emotions over time is fundamental for normal human social interaction. With this in mind, in the current study we measured visual WM for angry and happy faces and assessed the impact of incidental negative, positive, and neutral words presented during a 9 s maintenance interval. We chose to use verbal rather than visual stimuli to act as intervening distracters because this study is a precursor to an fMRI investigation. This is the first use of emotional distracters in a WM task that also involves emotional items, therefore in using fMRI we want to be able to more clearly separate and examine brain activity in regions associated with the emotional faces (visual) compared to the emotional words (verbal).

Importantly, in the WM task two angry or happy faces were presented for encoding but the single test face presented at retrieval was always neutral. The task was to state whether the test person was present or absent at encoding and emotional expression was task-irrelevant. This design ensured that any effects of word valence on WM for emotional faces could be directly attributed to the presence of facial expression information at encoding and thus maintained during the retention interval, rather than a feedforward effect of word valence on retrieval processes if facial expression were also present at retrieval (as was the case in the original studies that first reported the angry face benefit in WM; Jackson et al., 2008, 2009).

First, we assessed whether intervening words intended to distract from the WM task would interfere with memory for emotional faces at all. Dolcos and McCarthy (2006) found that neutral distracters impaired WM for neutral stimuli relative to a condition in which a scrambled distracter was presented, indicating that incidental non-emotional information, when meaningful, can interfere with WM maintenance processes. It is possible that emotional information held in WM is protected from such distraction in a way that neutral information is not, perhaps as a result of increased salience or enhanced motivational value. To test this, in Experiment 1 we directly compared the effect of intervening neutral words versus no words on WM for angry and happy faces. We favored a no-distraction condition over a scrambled word condition in order to provide a pure baseline measure of WM performance using a maintenance interval here (9000 ms) that is nine times longer than that used in the original studies of WM for emotional faces (1000 ms; Jackson et al., 2008, 2009). We used a particularly long delay interval because in the intended follow-up fMRI experiment we aim to measure brain activity during WM maintenance. Furthermore, comparing some versus no-distraction enhances the real-life validity of the test. To anticipate, we found no difference in WM performance between the two conditions for both angry and happy faces. On the one hand, it is possible that the absence of a distracter effect resulted from the relatively long maintenance interval and/or the neutral words used in the present study. On the other hand, this result also raises the interesting possibility that, when the contents of WM are emotional, some form of protection from distraction is afforded.

In Experiment 2, we again measured WM for angry and happy faces but this time directly compared the influence of negative, positive, and neutral intervening words. With this design we can predict several possible outcomes. If attention is biased to negative words, we would expect impaired WM for both angry and happy faces when negative versus both positive and neutral words are presented during WM maintenance, an effect that should result in a main effect of word valence. There is also reason to predict an interaction between word valence and facial expression on WM performance. Negative words might impair WM for happy faces to a greater degree than WM for angry faces (and vice versa: positive words might impair WM for angry faces to a greater degree that WM for happy faces) by virtue of incompatible valence interference. Alternatively, because WM has been found to be superior for angry versus happy faces (Jackson et al., 2008, 2009), suggesting

enhanced maintenance of threat information, WM for angry faces in the current task might be protected from any distraction and remain unaffected by the valence of intervening words, while WM for happy faces might suffer from negative distraction. To anticipate, none of the above predictions were borne out, making our results both surprising and interesting. We found that emotional words (regardless of whether negative or positive) actually boosted WM for angry faces relative to the neutral word condition, whereas WM for happy faces was not significantly affected by word valence. The current study adds some interesting substance to the literature concerning the ability of emotion to enhance or impair cognition. Our findings call attention to the fact that information intended to distract from an ongoing task does not always serve to impair performance; incidental emotional material can facilitate WM when the memoranda signal threat.

MATERIALS AND METHODS

PARTICIPANTS

Students from Bangor University took part in return for tokens for use of university printers or money. All had normal or corrected-to-normal vision and were fluent in English. None were dyslexic (self-report). Twenty-five (20 females, 5 males; mean age 20 years) took part in Experiment 1; a different 27 (18 females, 9 males; mean age 20 years) participated in Experiment 2.

STIMULI

We used a set of 18 male Ekman and Friesen (1976) face images, comprising six individuals each with an angry, happy, and neutral expression. Faces were grayscale with hair removed by cropping each face into an oval that when presented in the experiments at a viewing distance of 60 cm subtended approximately $3.3 \times 1.9^{\circ}$ of visual angles. It is preferable to use a small number of faces for a WM task, rather than a large stimulus set, in order to ensure that long-term memory does not encroach on any retrieval decisions. For example, if a large selection of faces were used, every time a new individual is presented at retrieval on non-match trials, participants could notice that this face had not been seen before and thus make a correct non-match judgment that is based on long-term memory rather than WM. We also chose to use only male faces for this reason, and because of the possibility that a mix of male and female faces could elicit differential responses to the emotions portrayed (a separate study is required to determine whether enhanced WM for angry faces is gender-specific).

Twenty-four words (eight negative, eight positive, eight neutral) were selected from the Affective Norms for English Words (ANEW; Bradley and Lang, 1999) database for use as distracter items presented during the WM maintenance period. Experiment 2 used all negative, positive, and neutral words while Experiment 1 used only the neutral words. Research has shown that the attention-grabbing quality of distracter words is particularly strong if the words are characterized as "other-relevant" (Wentura et al., 2000), which in turn can have social consequences for the observer/participant (Peeters, 1983). Therefore, the words used here were explicitly selected to denote person-related traits in order to strengthen the relationship between distracter items and the faces held in memory, and thus maximize the potential for distraction effects (see **Table 1**). Using the data provided by

Table 1 | Negative, positive, and neutral words used as distracter items, selected from the ANEW database.

Negative	Positive	Neutral
Aggressive	Elated	Coarse
Brutal	Friendly	Detached
Cruel	Handsome	Indifferent
Evil	Honest	Listless
Hostile	Joyful	Skeptical
Ugly	Romantic	Serious
Violent	Sexy	Solemn
Wicked	Thoughtful	Weary
MEANS		
Valence = 2.94 (0.34)	Valence = 7.97 (0.12)	Valence = 4.36 (0.15)
Arousal = 6.16 (0.18)	Arousal = 6.16 (0.32)	Arousal = 3.63 (0.42)
Frequency = 24.13 (7.40)	Frequency = 24.63 (8.28)	Frequency = 23.25 (13.35)
Length = 6.13 (0.69)	Length = 6.88 (0.64)	Length = 7.38 (0.68)

ANEW provides ratings of valence, arousal, frequency, and length for each word, and the means (standard errors in brackets) for each word valence category are reported here. All words were used in Experiment 2; only neutral words were used in Experiment 1.

ANEW, the three negative, positive, and neutral word lists were matched for average word frequency and length (independent t-tests revealed all comparison $ps > 0.23$); positive and negative word lists were matched for arousal ratings [$t(14) = 0.02, p = 0.98$] but differed significantly on valence [$t(14) = 13.94, p < 0.001$]; the neutral list differed significantly in valence from both the negative [$t(14) = 3.82$, $p = 0.002$] and positive [$t(14) = 18.54$, $p < 0.001$] lists, and in arousal from both negative [$t(14) = 5.58$, $p < 0.001$] and positive [$t(14) = 4.83$, $p < 0.001$] lists. Words were presented in bold capital letters using Courier New font size 18. Stimuli were presented on a 22-inch Mitsubishi Diamond-Pro 2060u monitor (32-bit true color; resolution 1280×1024 pixels) using E-Prime 1.1 (Schneider et al., 2002).

PROCEDURE AND DESIGN

In summary, each trial comprised a 2000 ms WM encoding phase, a 9000 ms WM maintenance phase, and a 3000 ms WM retrieval phase. On no-distracter trials (Experiment 1 only) participants simply viewed a central fixation cross during the 9000 ms maintenance phase. On trials in which a word was presented, within the maintenance phase there was a 3000 ms "distraction" period. A trial example is provided in **Figure 1**. The beginning of each trial was indicated by a fixation cross that temporarily grew in size. Two faces (both angry or both happy) were then presented on either side of fixation for 2000 ms for encoding into WM. The horizontal distance between the center of each face was 3.5 cm (approximately 3.3° of visual angle). The WM maintenance period began when the faces disappeared. For the first 3000–5000 ms of the maintenance period participants simply viewed the fixation cross in the center of the screen (this variable duration was selected at random to be 3000, 3500, 4000, 4500, or 5000 ms). Then a word was flashed in the center a total of three times; each word flash was visible on the screen for 500 ms, totaling a presentation duration of

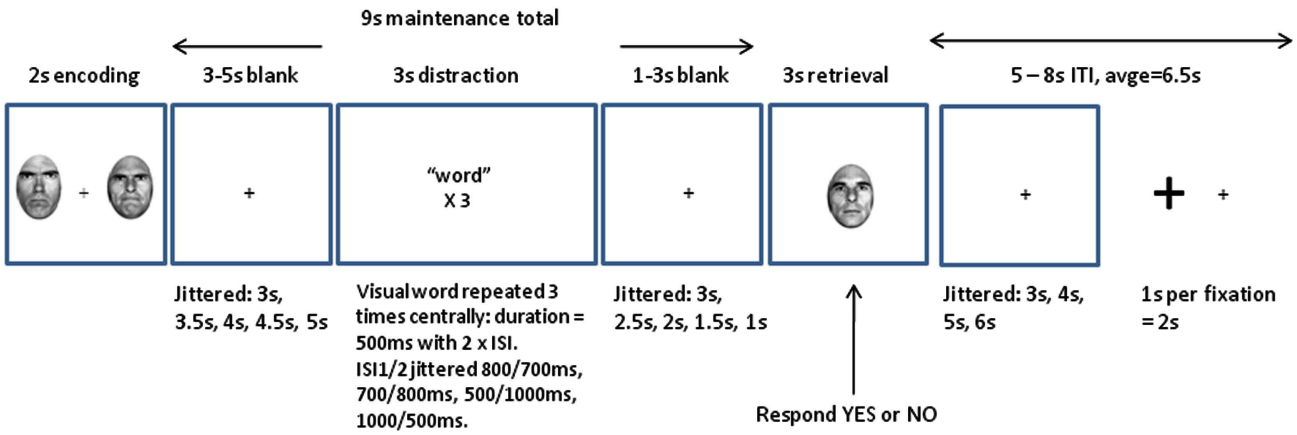

FIGURE 1 | Example trial in the "distraction" conditions. Two angry or two happy faces were presented for encoding for 2000 ms, and 3000–5000 ms into the WM maintenance period a "distracter" word was flashed three times for 500 ms each time. Following a further 1000–3000 ms blank interval, a single neutral face was presented for retrieval. The task was to state whether the single neutral face shared identity with one of the faces present at encoding.

1500 ms. There was a variable delay between the first and second and between the second and third word presentations (each delay was selected to be 500, 700, 800, or 1000 ms, with the sum of the two delays totaling 1500 ms each time). This variable word gap delay was designed to reduce predictability of distracter onset and thus maximize attention to the word. Participants were instructed to simply look at the words presented. A further 1000–3000 ms variable delay period comprising only the central fixation cross (selected from 1000, 1500, 2000, 2500, or 3000 ms to always sum with the first delay period to 6000 ms) completed the 9000 ms WM maintenance interval. Finally, a single probe face that held a neutral expression was presented for retrieval from WM for 3000 ms. Participants responded "yes" if they thought the identity of the probe face matched one of the faces held in WM, and "no" if it did not match. Emotional expression was irrelevant to the task with participants required only to retain person identity information in WM. Each trial was separated by an interval comprising a single fixation cross, that varied in duration between 5000 and 8000 ms (selected at random to be 5000, 6000, 7000, or 8000 ms).

In Experiments 1 and 2, half the trials comprised angry faces and the other half happy faces. Within each face emotion condition there were equal numbers of distracter conditions (neutral versus no-distracter trials in Experiment 1; negative versus positive versus neutral trials in Experiment 2). In Experiment 1, face emotion (angry, happy) and distracter (neutral, no-distracter) conditions were pseudo-randomized with 16 trials in each condition, yielding 64 trials in total. The presentation of each face identity and word was randomized, but these factors were not fully counterbalanced with face emotion and word valence conditions as this would render the experiment too long. Each neutral word was presented four times within each condition to yield a total of 16 repetitions per word. In Experiment 2, face emotion (angry, happy) and word valence (negative, positive, neutral) conditions were also pseudo-randomized with 16 trials in each, yielding 96 trials in total. Each word was presented 4 times within each condition to yield a total of 24 repetitions per word. In both experiments, on half of trials the probe face at retrieval matched in identity to one of the faces at encoding, and on the other half it did not match, counterbalanced across face emotion and distracter conditions.

On completion of the WM task, participants rated each of the distracter words for valence and arousal using the Self Assessment Manikin (Bradley and Lang, 1994). They also rated how distracting each word seemed using a four point scale (1 = Not distracting at all; 2 = Just a little distracting; 3 = Fairly distracting; 4 = Very distracting). In support of the valence ratings provided by the ANEW database, the current sample of participants in Experiment 2 rated the negative words (mean valence = −2.59) as significantly more unpleasant than the positive words (mean valence = 2.76; $t(26) = 18.46$, $p < 0.001$) and the neutral words (mean = −0.91; $t(26) = 8.69$, $p < 0.001$). The positive words were rated as significantly more pleasant than the neutral words [$t(26) = 19.45$, $p < 0.001$]. In support of the arousal ratings provided by the ANEW database, the current sample of participants in Experiment 2 rated the negative words (mean arousal = 0.03) as similarly arousing as the positive words (mean arousal = 0.30; $t(26) = 0.57$, $p = 0.57$); the negative words as significantly more arousing than the neutral words (mean arousal = −1.68; $t(26) = 5.76$, $p < 0.001$); and the positive words as significantly more arousing than the neutral words [$t(26) = 5.70$, $p < 0.001$]. In terms of distractibility, participants from Experiment 2 rated the negative words (mean = 2.81) as significantly more distracting than the positive words (mean = 1.97; $t(26) = 5.56$, $p > 0.001$), and the neutral words (mean = 1.85; $t(26) = 6.19$, $p < 0.001$). There was a non-significant difference in distracter ratings between the positive and neutral words [$t(26) = 1.0$, $p = 0.33$].

DATA ANALYSIS

Hit rates (the proportion of trials on which participants correctly responded "yes" when the probe face matched one of the faces presented at encoding) and False Alarm rates (the proportion of trials on which participants incorrectly responded "yes" when the

probe face did not match one of the faces presented at encoding) were converted into d' values ($d' = \text{zHits} - \text{zFalse Alarms}$) and submitted to statistical analysis. Reaction times (RTs), filtered to exclude responses less than than 200 ms, were analyzed on correct trials only.

EXPERIMENT 1

In Experiment 1 we aimed to determine whether the presence of an intervening word had a distracting effect on WM for emotional faces relative to when no-distracter was present.

RESULTS

A repeated-measures ANOVA on d' using face emotion (angry, happy) and distracter condition (neutral, none) as within-subject factors was conducted. Group means for each condition are plotted in **Figure 2**. Group mean proportion correct scores are reported in **Table 2**. There were non-significant main effects of face emotion and distracter condition, and these two factors did not significantly interact (all F's < 1.0). These results indicate that a neutral word presented during the maintenance period had no measurable impact on WM for face identity, regardless of whether the faces in memory had angry or happy expressions, relative to when no word was present. Furthermore, it is interesting to note that enhanced WM for angry versus happy faces observed in the original studies using a 1000 ms maintenance period was not replicated here (no-distracter condition) using a 9000 ms retention period.

A repeated-measures ANOVA on RTs, with face emotion (angry, happy) and distracter condition (neutral, none) as within factors, revealed a significant main effect of distracter condition, $F(1, 24) = 9.53$, $p = 0.005$. Responses were faster when a neutral word (mean = 1274.90 ms, SE = 46.34 ms) was presented compared to when no stimuli intervened during the retention interval (mean = 1340.34 ms, SE = 54.34 ms). It is possible that the appearance of a neutral word served to help sustain attention to the task and participants were thus perhaps better prepared to make a retrieval response, whereas when nothing happened during the long retention interval participants' attention may have drifted and thus responses were slowed when the probe face appeared. The main effect of face emotion and its interaction with distracter condition were non-significant (both Fs < 1.0).

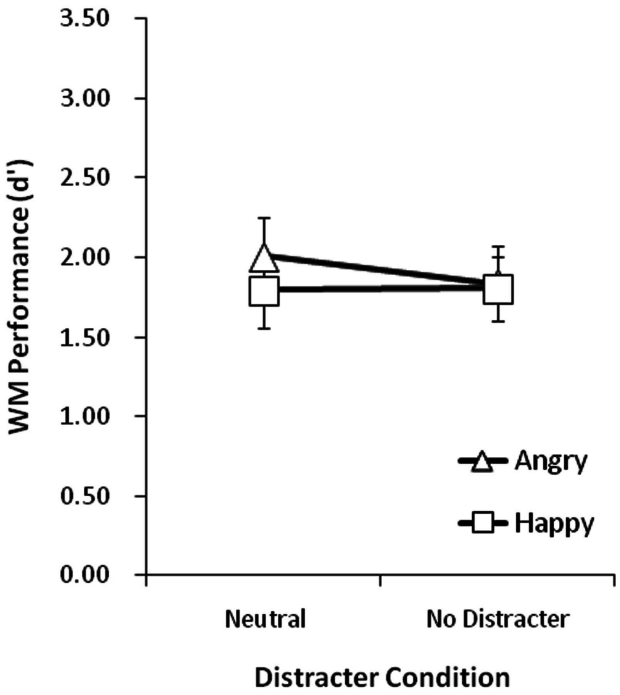

FIGURE 2 | Group mean WM performance measured in d' when all WM memoranda faces had happy or angry expressions and either neutral words or no-distracter were presented during the retention interval. Vertical lines represent ±1 SE.

Table 2 | Group mean proportion correct scores for each experiment.

WM Condition	Distracter	Experiment 1	Experiment 2
WM Angry	Emotional		0.85 (0.02)
	Neutral	0.77 (0.02)	0.80 (0.02)
	None	0.76 (0.03)	
WM Happy	Emotional		0.81 (0.02)
	Neutral	0.76 (0.03)	0.82 (0.03)
	None	0.77 (0.02)	

Numbers in parentheses indicate the standard error.

EXPERIMENT 2

In Experiment 2 we aimed to determine whether WM for angry and happy faces was differentially affected by the valence of intervening words (negative, positive, neutral) presented during maintenance.

RESULTS

A repeated-measures ANOVA on d' using face emotion (angry, happy) and word valence (negative, positive, neutral) as within factors was conducted to determine distracter effects on WM for faces. Group means for each condition are plotted in **Figure 3** and group mean proportion correct scores are reported in **Table 2**. There were non-significant main effects of face emotion [$F(1, 26) = 1.23$, $p = 0.28$] and word valence ($F < 1.0$). However, the interaction between face emotion and word valence was significant [$F(2, 52) = 4.18$, $p = 0.02$]. To explore this interaction we first examined the effects of word valence for each face emotion separately. When faces held in WM were angry, there was a significant main effect of word valence [$F(2, 52) = 4.57$, $p = 0.02$]. Paired t-tests revealed that WM for angry faces was significantly better when a positive ($d' = 2.89$) versus neutral ($d' = 2.30$) intervening word was presented, $t(26) = 3.28$, $p = 0.003$. Although WM was also better when a negative ($d' = 2.71$) versus neutral word was presented, this difference did not reach significance, $t(26) = 1.57$, $p = 0.13$. The difference between positive and negative word conditions was non-significant, $t(26) = 1.35$, $p = 0.19$. When faces held in WM were happy, the main effect of word valence was non-significant, $F(2, 52) = 1.14$, $p = 0.33$. We

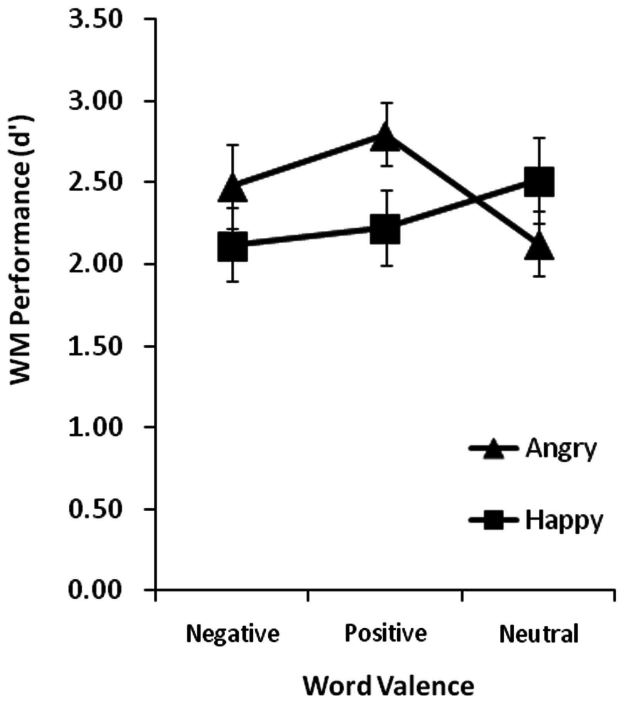

FIGURE 3 | Group mean WM performance measured in d' when all WM memoranda faces had happy or angry expressions and the incidental words presented during the retention interval were negative, positive, or neutral. Vertical lines represent ±1 SE.

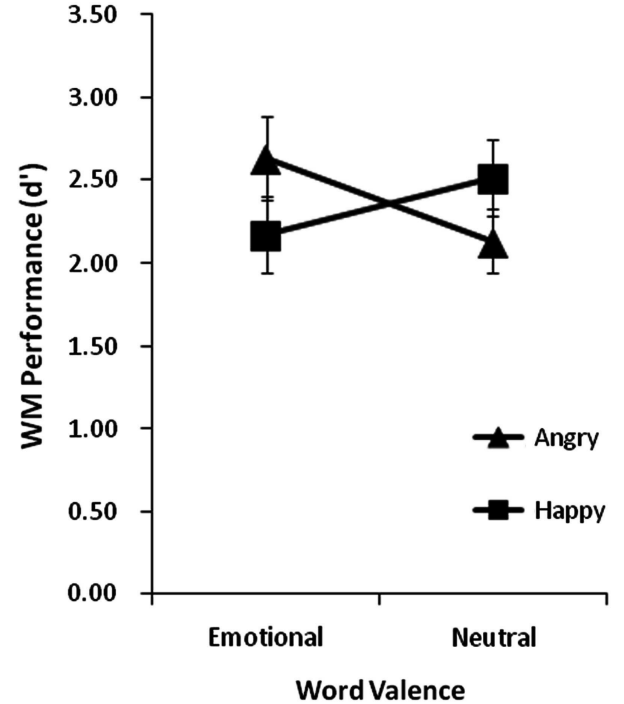

FIGURE 4 | Group mean WM performance measured in d' when all WM memoranda faces had happy or angry expressions and the incidental words presented during the retention interval were emotional or neutral. Vertical lines represent ±1 SE.

also examined the presence or absence of the angry face benefit in each word valence condition. Paired *t*-tests showed that WM was significantly better for angry than happy faces when the intervening word was positive, $t(26) = 2.44$, $p = 0.02$, but the corresponding difference was non-significant when the word was negative [$t(26) = 1.41$, $p = 0.17$] or neutral [$t(26) = 1.36$, $p = 0.19$].

Because there was no measurable effect of positive versus negative distracters on the recall of angry faces, and also no effect on the recall of happy faces, we combined data from these two word valence conditions to compare WM when the distracter was emotional versus neutral. This data is plotted in **Figure 4**. A repeated-measures ANOVA with face emotion (angry, happy) and word valence (emotional, neutral) as within factors revealed a significant interaction, $F(1, 26) = 9.14$, $p = 0.006$. Main effects of face emotion and word valence were non-significant (both Fs < 1). This interaction reflects significantly better WM for angry faces when the word was emotional ($d' = 2.68$) versus neutral ($d' = 2.06$) [$t(26) = 2.85$, $p = 0.01$] and a non-significant effect of word emotionality on WM for happy faces [neutral $d' = 2.50$; emotional $d' = 2.13$, $t(26) = 1.56$, $p = 0.13$]. Furthermore, WM was significantly better for angry than happy faces when the word was emotional [angry benefit; $t(26) = 2.89$, $p = 0.01$], but the difference in WM between angry and happy faces when the word was neutral was non-significant, $t(26) = 1.36$, $p = 0.19$.

The lack of a significant difference between WM for angry and happy faces when a neutral word was presented replicates the results of Experiment 1, and a repeated-measures ANOVA on neutral word data with face emotion as a within factor and experiment as a between factor confirmed this [non-significant face emotion × experiment interaction, $F(1, 50) = 2.01$, $p = 0.16$]. This lack of interaction also indicates that the two different participant groups performed at a similar level on the WM task in general.

Importantly, the angry face benefit in WM that we observe in Experiment 2 when an emotional word was presented during maintenance is not evident when there is no intervening word (Experiment 1). This result is particularly enlightening to the effects seen in this second experiment, as it indicates that an emotional word serves to specifically boost WM for angry faces (rather than a neutral word impairing WM), relative to the no-distracter baseline condition. WM for happy faces is less susceptible to modulation by the presence or absence of a concurrent emotional or non-emotional event. In support of these observations, independent samples *t*-tests comparing Experiments 1 and 2 revealed that when angry faces were held in WM, performance was significantly better when an emotional versus no word was presented, $t(50) = 2.69$, $p = 0.01$. When happy faces were held in memory the difference between emotional versus no word conditions was non-significant, $t(50) = 1.43$, $p = 0.16$.

A repeated-measures ANOVA on RTs, with face emotion (angry, happy) and distracter condition (negative, positive, neutral) as within factors, revealed non-significant main effects and interaction (all Fs < 1.0).

DISCUSSION

The current study reveals some interesting and perhaps unexpected effects of intervening emotional stimuli on WM for emotional faces. In contrast to previous research that showed impaired WM for neutral items when a negative versus neutral distracter is presented during maintenance (Dolcos and McCarthy, 2006), here we show that emotional versus neutral words presented during the maintenance period can boost WM performance, but only when items held in WM are negative in valence (angry faces). When items held in WM are positive (happy faces), there is little evidence that the emotionality of intervening words impacts on memory performance. However, a direct comparison of our findings with those of Dolcos and McCarthy (2006) is limited because we did not include a condition with neutral WM memoranda (see Caveats section at the end).

We also found that WM for expressive (angry or happy) face identities was not significantly affected by the presentation of neutral words during the retention interval relative to when the retention interval was devoid of new stimulation, a finding that raises the possibility that emotional content in WM may afford some form of protection from distraction. Future studies can verify this possibility by confirming that distracters impair WM for neutral faces, even when using a long maintenance interval and word distracters as in the present paradigm. Alternatively, it is possible that increased task difficulty afforded by the long retention interval served to modulate the distractibility of the words. Other work in this special issue shows that task difficulty can modulate the impact of emotional distracters (Jasinska et al., 2012).

There are two possible explanations for these effects. One possibility is that when angry faces are represented in WM, their emotional significance and valence leads to a state of heightened vigilance (over and above that afforded by happy face representations) for other potentially significant emotional events, a notion consistent with the theories regarding attention biases to threat stimuli (Öhman et al., 2001). Heightened vigilance could facilitate the ability of the emotional words to compete for selection to awareness, allowing them to elaborate the face representations already in WM and thereby improve performance in the task. Although WM for angry faces did not differ significantly between positive and negative word conditions, the elevation of WM for angry compared to happy faces was driven more by positive than negative words (**Figure 3**). If angry faces were already deemed threatening by virtue of their expression, then negative emotional words appearing during the retention interval would be less surprising, whereas positive words would present a contradiction that could have sparked greater elaborative thought and therefore better consolidation. It is also possible that our results are due to differences in arousal levels elicited by positive and negative words. For example, the theory of *arousal-biased competition* (ABC) proposes that arousal enhances memory for items that successfully compete for selective attention (Mather and Sutherland, 2011). Despite the fact that positive and negative words were rated as equally arousing when presented outside of the WM task (and that the angry and happy faces used here were rated as equally arousing; see Jackson et al., 2009), an ABC account might suggest that angry face representations maintained in WM received a greater arousal boost when a positive word appeared than when a negative word was presented (if attention were heightened by the contradiction in valence between the face and word). However, we can only speculate about such possibilities because the same cannot be said for happy faces followed by a negative word, and we did not measure attention to the word stimuli. It is possible that in this task (which depends on WM for face identity) the task-irrelevant expression information is discarded when the to-be-remembered faces are happy but retained when they are angry. Binding expression and identity may be more imperative with negative than positive expressions because the former more typically signal a need for an immediate change in action plans, whereas the latter do not. In this view, retaining the identity of happy faces may be unaffected by word valence simply because there is no emotional information being held in WM with which the word stimuli can interact. Other work in our lab, in which we probed the emotional contents of face WM by asking participants to categorize the valence of congruent or incongruently valenced stimuli during the retention interval, suggests that this indeed might be the case (unpublished data).

Of relevance to this explanation is another interesting aspect of our results, namely that the angry face benefit to WM found in our previous work using short (1000 ms) retention intervals (Jackson et al., 2008, 2009) is not observed when the retention interval is long (9000 ms) and either lacks additional stimulation or involves the presentation of neutral words (Experiment 1). During a longer WM retention interval there is greater scope for both visual face representations and the strength of associated emotional information to fade, and this might explain why we do not find the angry face benefit here. When, as in Experiment 2, another emotional event occurs during the longer retention interval, the fading angry memory trace may be reactivated and thus enable improved performance. However, it is important to note that there are other procedural differences between the current experiment and our previous work. Here, WM load was not varied and the probe face was always neutral, making the task more difficult.

Our main result was a facilitatory effect of incidental information (the emotional words) on WM performance for face identity. This facilitatory effect conforms to a growing body of literature showing that incidental information is not necessarily distracting, but can boost performance on a range of different tasks, including WM tasks. Several studies have now shown such effects with neutrally valenced but arousing (e.g., novel or otherwise salient) stimuli. SanMiguel et al. (2010) found that whether an unexpected sound led to impaired or improved WM for neutral faces depended on trial duration. They suggested that the orienting response induced by the unexpected sound can help to refocus attention in states of unfocused attention (longer trials) whereas it may distract from the task at hand in states of more focused attention (shorter trials). Similar facilitatory effects of

novel sounds were found for a visual discrimination task by Wetzel et al. (2012). Using emotional stimuli as incidental distracters, Sutherland and Mather (2012) showed that negatively arousing sounds boosted WM for perceptually salient stimuli. Additionally, positive and negative visual scenes inserted into the WM maintenance period of a delayed discrimination task for letters have been shown to support memory performance while neutral distracter scenes impaired performance, relative to a no-distracter condition (Erk et al., 2007). Taken together these findings provide an emerging picture of how incidental emotional information can support rather than hinder online processing of other information.

The novel and important finding in our study is that the facilitatory effect of incidental emotional distracters on WM for face identity was confined to the condition involving social threat in the WM memoranda. Although we previously reported a benefit for angry faces in WM without the use of incidental distracters and with a brief retention interval (1000 ms; Jackson et al., 2008, 2009), here, using a long retention interval, we found this effect only when emotional words were presented during maintenance. This suggests that an additional "boost" from incidental emotional information is needed to support the advantage of threat-related information in WM over longer intervals. Other studies have shown that emotional (versus neutral) information presented during WM retention enhances activity in "hot" emotion areas and decreases activity in "cold" executive areas during a WM maintenance period (Dolcos and McCarthy, 2006; Wong et al., 2012). While such enhanced recruitment of emotion processing areas has been shown to impair WM for neutral items, it may conversely support the consolidation of emotionally salient information, such as threat cues, into WM.

In conclusion, we find facilitatory effects of incidental information with emotional content specifically on the retention of threat-related information in WM. Our previous work had shown that angry faces are particularly well retained in WM (Jackson et al., 2008, 2009), but the present results suggest that further WM consolidation over longer periods of time relies on an added boost of activation from emotion networks. Functional imaging work is required to directly assess the impact of these results on brain activity within hot emotion and cold executive regions.

CAVEATS

It is necessary to address particular aspects of our design that may raise questions in our readers. Our original findings (Jackson et al., 2009) were elicited using a paradigm which differed in several ways to the current design: (1) faces were emotional versus neutral at encoding, (2) the expression displayed at retrieval always matched the expression displayed at encoding (so on match trials at retrieval the exact same face image matched in both identity and expression was shown), and (3) a shorter retention interval of 1000 ms was used. We addressed this third point earlier in the paper and do not revisit it here, but it is important to expand upon the first two points. The original design has two disadvantages: (1) we cannot tell whether the impact of the presence of an angry expression upon WM for face identity was elicited at encoding or retrieval, (2) results may have simply been due to some sort of low level perceptual advantage in image matching afforded by angry faces, rather than a higher-level response to the presence of anger. To disentangle these issues and improve the design, we conducted a further study using angry versus happy faces at encoding but neutral faces at retrieval (with a 1000 ms retention interval). We replicated the original findings in that WM was significantly better for angry than happy faces, despite the absence of emotion at retrieval and the fact that participants were now forced to actively extract face identity from emotional expression in order to successfully perform the task (unpublished data).

We chose to use this "neutral probe" design in the current paper rather than display the same expression at encoding and retrieval as in the original study for two reasons. First, we wanted to isolate any effects of distracter word valence on WM for emotional faces to the presence of facial expression information at encoding, and avoid contamination from a possible feed-forward effect of word valence on emotion-related retrieval processes. Second, we intend to repeat the current study using fMRI to measure brain responses to emotional memoranda during the retention/distraction interval. If we were to use a design in which emotion was present in the facial memoranda during both encoding and retrieval, as well as in distracter words during the maintenance interval, this would complicate things greatly in terms of separating the brain's response to emotional stimuli across time and context. However, we acknowledge that using the "neutral probe" design in the current paradigm carries a disadvantage in that it does not allow for a direct measure of the effect of distraction on WM for emotional versus neutral memoranda. If we were to use neutral faces at encoding (and thus neutral faces at retrieval) this introduces fundamental differences between emotion conditions in how faces are matched and retrieval decisions made, thus rendering impossible any direct comparison of the effects of distraction on emotional versus neutral faces. While our current design also limits the comparisons that can be made between our study and that of Dolcos and McCarthy (2006) in which neutral memoranda were used, we feel that our results provide valuable information on how the valence of intervening stimuli can impact differentially upon WM for positive versus negative stimuli.

It is also worth re-iterating here that our original, and other, studies showed that the presence of only specific facial emotional expressions alters how we remember non-emotion-related person information: WM for face identity was significantly better when the faces portrayed anger (versus happiness or a neutral expression; Jackson et al., 2008, 2009) or fear (versus neutral expression; Sessa et al., 2010). Importantly, our previous work showed that there was no significant difference between WM for happy and neutral faces, suggesting that it is not the presence of emotion *per se* that interacts with the WM task, but rather a specific response to threatening/negative emotions.

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Negative emotion does not modulate rapid feature integration effects

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Emotional arousal at encoding is known to facilitate later memory recall. In the present study, we asked whether this emotion-modulation of episodic memory is also evident at very short time scales, as measured by "feature integration effects," the moment-by-moment binding of relevant stimulus and response features in episodic memory. This question was motivated by recent findings that negative emotion appears to potentiate first-order trial sequence effects in classic conflict tasks, which has been attributed to emotion-modulation of conflict-driven cognitive control processes. However, these effects could equally well have been carried by emotion-modulation of mnemonic feature binding processes, which were perfectly confounded with putative control processes in these studies. In the present experiments, we tried to shed light on this question by testing explicitly whether feature integration processes, assessed in isolation of conflict–control, are in fact susceptible to negative emotion-modulation. For this purpose, we adopted a standard protocol for assessing the rapid binding of stimulus and response features in episodic memory (Experiment 1) and paired it with the presentation of either neutral or fearful background face stimuli, shown either at encoding only (Experiment 2), or at both encoding and retrieval (Experiment 3). Whereas reliable feature integration effects were observed in all three experiments, no evidence for emotion-modulation of these effects was detected, in spite of significant effects of emotion on response times. These findings suggest that rapid feature integration of foreground stimulus and response features is not subject to modulation by negative emotional background stimuli and further suggest that previous reports of emotion-modulated trial–transition effects are likely attributable to the effects of emotion on cognitive control processes.

Keywords: feature integration, emotion, cognitive control, event files, binding

INTRODUCTION

Affectively salient stimuli have been found to impact cognitive processing in a variety of ways. For instance, a survival-relevant stimulus, such as a fearful face, can exert a powerful exogenous pull on attention (LeDoux, 2000; Ohman et al., 2001), even if it is irrelevant to the task at hand (Mathews and MacLeod, 1985; McKenna, 1986; Isenberg et al., 1999; Phelps et al., 2006; Reeck and Egner, 2011). In addition to attentional effects, a rich animal and human research literature has documented that affectively salient stimuli or situations also modulate episodic memory processes. Specifically, it is well-established that emotional arousal at the time of encoding enhances long-term memory consolidation in comparison to emotionally neutral conditions (McGaugh and Roozendaal, 2002; McGaugh, 2004; for reviews, see Hamann, 2001; LaBar and Cabeza, 2006). Other studies have shown that emotional stimuli also have more immediate effects on memory encoding, which are likely attention-mediated and may enhance episodic memory in the short-term (that is, prior to consolidation into long-term memory) as well as in the long term (Hamann et al., 1999; Hamann, 2001; Tabert et al., 2001).

In the latter work, an important distinction has been drawn between the recall of a specific object that carries emotional salience (item memory) and the binding of that item and its context (source memory). Specifically, a number of studies suggest that emotional arousal facilitates the recall of emotional stimuli themselves but either does not enhance (Mather and Nesmith, 2008) or is detrimental to the recall of contextual features that are not part of the salient object, resulting in poor context or source memory (Mather et al., 2006; Mitchell et al., 2006). These effects have been theorized to reflect the fact that emotionally arousing stimuli attract attention at the expense of other, co-occurring stimuli, which results in a boost to emotional item memory but poorer mnemonic integration of incidental, non-emotional stimuli into episodic memory (Mather, 2007; but see Hadley and Mackay, 2006). In the current study, we sought to further elucidate the interplay between (negative) emotional stimuli and mnemonic feature binding processes, but with a focus on immediate (or very fast) binding effects, which occur at a time-scale that has been largely ignored in the previous literature.

The temporal lag between memory encoding and retrieval in studies that assessed emotion effects on short-term memory is

typically in the range of several minutes (LaBar and Phelps, 1998; Hamann et al., 1999; Tabert et al., 2001; Sharot and Phelps, 2004), and at the least in the range of 7–8 s (Mather et al., 2006; Mitchell et al., 2006). By contrast, in the present study, we sought to evaluate the influence of emotional stimuli on very fast-acting processes in episodic memory associated with "feature integration," the seemingly obligatory moment-by-moment binding of stimulus and response features into compound episodic memory traces referred to as "event files" (Hommel, 1998). These binding processes appear to take effect almost instantaneously, as their consequences can be observed at a time-scale of less than 1 s (Hommel, 1998) and they last at least several seconds (Hommel et al., 2004). Note that this type of feature integration involves not only the binding of different perceptual features, which has typically been the focus of previous emotional memory studies (see Mather, 2007), but also the integration of these stimulus features with a motor action on the part of the subject (Hommel, 1998).

Specifically, building on the notion of "object files" – the momentary binding of object features at attended locations into a cohesive percept and memory representation (Kahneman et al., 1992) – Hommel has shown convincingly that both task-relevant (and sometimes task-irrelevant) stimulus and response features comprising an "event" appear to be integrated into a common short-term memory trace, such that processing costs are incurred when this integrated memory has to be bypassed or "unbound" subsequently (e.g., Hommel, 1998, 2004; Hommel et al., 2004). For instance, if a participant performs a right-hand button-press response that temporally coincides with the presentation of a particular visual stimulus (e.g., a blue square), the stimulus and response features are thought to be bound together into an episodic event file. If, shortly afterward, the subject has to perform a left-hand button-press in the presence of the same stimulus features (a "partial repetition" of the previous event), the response will be slowed in comparison to conditions in which either all response/stimulus features repeat or they all change. This is argued to reflect the fact that the reoccurring stimulus features will reactivate (or retrieve) the strongest or most recent memory trace involving those features, including their associated response, which now conflicts with the required response; this conflict has to be overcome for the correct response to be selected, resulting in slower response times (RT; for a similar scheme, see Logan, 1988). These *partial repetition costs* incurred on partial repetition trials as compared to complete repetitions or alternations can therefore serve as a behavioral index of feature integration in short-term episodic memory, and they will be employed as the dependent variable for testing the effects of emotional stimuli on fast short-term memory binding processes in the present study.

The major motivation for assessing the impact of (negative) emotion on these feature integration processes in the current study stems from the fact that this type of feature binding represents a well-known confound in many studies investigating trial–transition effects in traditional conflict tasks (like Stroop and Simon tasks; Hommel et al., 2004; for review see Egner, 2007). Here, conflict (or interference) effects are typically reduced following an incongruent, high-conflict trial compared to a congruent, low-conflict trial, because performance on successive incongruent and successive congruent trials tends to be faster than performance on incongruent trials following a congruent trial and on congruent trials following an incongruent trial, respectively (Gratton et al., 1992). These inter-trial dependencies in behavioral performance are typically attributed to the operation of a conflict-driven cognitive control mechanism that enhances the selection of task-relevant stimulus information following an incongruent trial, thus reducing the performance difference between congruent and incongruent trials under these conditions (Botvinick et al., 2001; Egner and Hirsch, 2005). However, this sequence effect can often equally well be interpreted in terms of feature integration processes, because in conflict tasks with small stimulus sets, successive congruent and incongruent trials tend to be associated with either an exact repetition of all stimulus and response features or a complete change of these features, whereas congruent trials following an incongruent trial and incongruent trials following a congruent trial tend to be partial repetition trials (Hommel et al., 2004; Egner, 2007).

Importantly, recent studies have suggested that emotional states modulate these trial–transition effects (van Steenbergen et al., 2009, 2010; but see Stürmer et al., 2011), whereby negative emotion is held to potentiate inter-trial dependencies, and these effects have been interpreted as reflecting the modulation of conflict-driven cognitive control by emotion (van Steenbergen et al., 2009, 2010). However, the designs of these studies did not allow for segregating the effects of conflict-driven control from those of feature integration, such that it is presently not clear whether the emotion effects observed were carried by modulation of conflict-driven control or by modulation of feature integration processes. Here, we sought to clarify this issue by assessing the impact of negative emotion-evoking stimuli on a pure measure of feature integration, outside of the context of a conflict task: if negative emotion were to potentiate feature binding, the previously reported effects might be attributable to this type of modulation, whereas if there were no evidence for emotion-modulation of feature integration, the potentiating effects of negative emotion on trial–transition effects in previous studies are likely attributable to the modulation of conflict-driven control processes.

Given this particular perspective on emotion–memory interactions, our design entailed an additional distinction from many previous studies of emotional memory, in that we did not assess memory for the emotional stimulus itself, but rather whether the mere presence of a (task-irrelevant) background stimulus thought to evoke emotional arousal would modulate episodic binding processes concerning task-relevant foreground stimuli and responses. This approach mimics more closely the type of designs used in investigating emotion-modulation of cognitive control processes (Dreisbach and Goschke, 2004; van Steenbergen et al., 2009, 2010; Stürmer et al., 2011). From the item vs. context perspective in the emotional memory literature highlighted above, this design could be cast as assessing whether emotional arousal modulates fast binding processes of contextual stimuli that are task-relevant but not part of the emotional stimulus itself. In sum, our goal was to gauge whether threat-related emotional (as compared to neutral) background stimuli would influence the short-term episodic binding phenomena underlying

the moment-by-moment integration of stimulus and response features.

THE PRESENT EXPERIMENTS

We approached the question of whether emotional stimuli modulate feature integration by adopting the basic task design developed by Hommel (1998). Specifically, in each trial, a multi-featured stimulus (a colored shape) was first paired with a pre-cued response in an arbitrary manner (i.e., the response was not determined by the stimulus features), followed by a second stimulus presentation where the task-relevant stimulus feature (color) determined which one of two possible responses to perform. This design allows one to independently vary repetitions vs. changes in the task-relevant stimulus feature (color), the irrelevant stimulus feature (shape), and the response (left vs. right) from the first to the second stimulus presentation. Consequently, the degree of integration between the response and the relevant and irrelevant stimulus features can be gauged via the respective partial repetition costs (i.e., the relative increase in RT in partial repetition trials as compared to complete repetitions and alternations). In Experiment 1, we simply aimed at replicating the basic stimulus–response feature integration effects reported by Hommel (1998) in the absence of any additional stimuli. In the second and third experiments, we then tested whether presenting additional task-irrelevant background stimuli of varying emotional valence (face stimuli with neutral vs. fearful expressions) either at encoding (Experiment 2) or at encoding and retrieval (Experiment 3) would differentially modulate the episodic binding between the foreground stimulus features and the response. For a different approach to investigating emotional modulation of feature integration effects, see Colzato et al. (2007), which will be addressed in detail in the Section "General Discussion."

EXPERIMENT 1

Our first experiment simply served to ascertain that we could replicate the standard feature integration effects reported by Hommel (1998) in a simple task where the task-relevant stimulus feature consisted of stimulus color and the task-irrelevant feature consisted of stimulus shape. We anticipated observing reliable binding effects between stimulus color and response and weaker (if any) binding effects between stimulus shape and response.

METHODS

Subjects

Twenty healthy college student volunteers ($M_{age} = 19.15$ years, SD = 1.1, eight women) participated in this study for course credit. All participants were fluent in English and had normal or corrected-to-normal vision. Prior to study participation, written informed consent was obtained from each participant in accordance with institutional guidelines.

Stimuli and procedure

The experiment was programmed and presented using Presentation software (Neurobehavioral Systems, http://nbs.neuro-bs.com), with stimuli displayed on a 19″ Dell Flat Panel 1907FPVt monitor that was controlled by a Dell Optiplex 960 computer. Stimuli consisted of luminance-equated blue and green circles and squares; response cues were the words "left" and "right," printed in black uppercase letters. Both stimuli and response cues always appeared in the center of the screen on a gray background (see **Figure 1A**). Participants were seated approximately 60 cm from the screen. The colored shape stimuli subtended approximately 5 (height) × 5 (width) degrees of visual angle and the response cues subtended approximately 2 (height) × 3 (width) degrees of visual angle. Responses were made by pressing the "N" and "J" keys of a standard QWERTY keyboard with the index and middle finger of the right hand, respectively.

The task was modeled after Hommel's (1998) feature integration experiments: in a given trial, participants first performed a delayed simple reaction task (T1), followed by a binary-choice reaction task (T2). For T1, responses (R1) had to be performed in accordance with the content of a preceding response cue (i.e.,

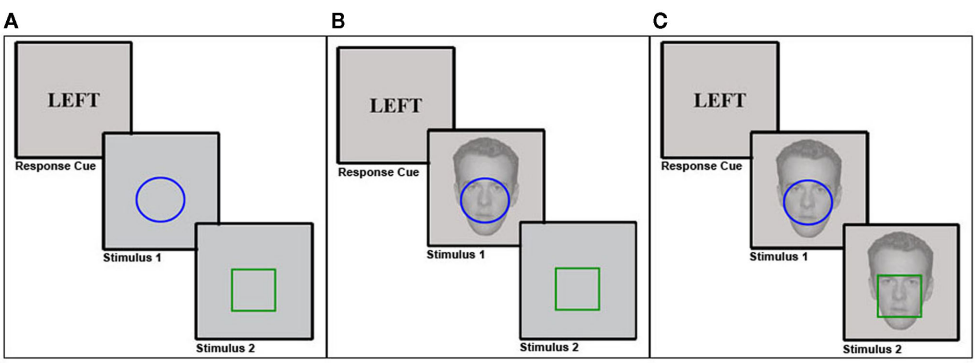

FIGURE 1 | Experimental protocols. In each experiment, participants first performed a delayed simple reaction task, where a response cue pre-determined the response (left vs. right) subjects had to execute upon presentation of stimulus 1 (S1), regardless of the particular S1 stimulus features. This was followed by a binary-choice reaction task upon presentation of stimulus 2 (S2), where subjects had to respond in accordance with the color of a colored shape stimulus (e.g., blue = left response, green = right response, counterbalanced across subjects). In Experiment 1 **(A)**, this task was performed without any background stimuli. In Experiment 2 **(B)**, a task-irrelevant face stimulus that could display either a neutral or a fearful expression was shown in the background during S1 presentation. In Experiment 3 **(C)**, a task-irrelevant face stimulus that could display either a neutral or a fearful expression was shown in the background during both S1 and S2 presentation.

"left," "right") as soon as the stimulus (S1) appeared on the screen. Importantly, S1 only served as a generic "go" signal for the execution of the pre-cued response, such that the S1 stimulus features did not determine which response had to be selected. For T2, the color (i.e., blue vs. green) of the second stimulus (S2) had to be identified by pressing the left or right response button (R2). Color-to-button response mappings were counterbalanced across participants.

The timing of events in each trial was adopted from Hommel (1998) and was as follows: a fixation cross was presented for 2,000 ms, after which the response cue was shown for 1,500 ms. The fixation cross reappeared for 1,000 ms, followed by S1 presentation for 500 ms. Following S1, there was another fixation interval of 500 ms before S2 was displayed for 2,000 ms. Trials were presented to each participant in one of five pseudo-random orders, generated to satisfy the criterion of equal numbers of occurrences of the possible S2 color (blue vs. green) and shape (circle vs. square) combinations, as well as the possible transition relationships between S1 and S2 regarding color and shape (i.e., repetition vs. alternation), and the two possible relationships between R1 and R2 (repetition vs. alternation). Moreover, the stimulus sequences did not include any direct repetitions of trial types. The experimental session consisted of 4 blocks of 48 trials each, preceded by 20 practice trials. Participants were instructed to respond as fast as possible while maintaining accuracy and they were allowed to take short breaks between blocks.

Analyses

The analyses focused on R2 RT. Only trials where both R1 and R2 had been performed correctly were considered correct trials. All error and post-error trials, as well as outlier RT values of more than 2 SDs from subject-specific grand means were excluded from the analysis. Accuracy was at ceiling (mean = 97.3%, SD = 3.2) and was not considered for statistical analysis. We analyzed R2 RT data as a function of the transition relationship between S2 stimulus and R2 response features and S1 and R1 features (i.e., repetition vs. alternation of features). Specifically, the data were submitted to a 2 (color: repetition vs. alternation) × 2 (shape: repetition vs. alternation) × 2 (response: repetition vs. alternation) repeated-measures ANOVA.

RESULTS

The R2 RT data (**Table 1**) displayed no main effects of the color, shape, or response transition factors but, as expected, response and color transitions interacted [$F(1, 19) = 43.9$, $P < 0.001$], as response repetitions were faster than response changes when they were accompanied by color feature repetitions (518 vs. 557 ms), but slower when they were accompanied by color feature changes (564 vs. 518 ms; **Figure 2A**). Shape transitions also interacted with response transitions [$F(1, 19) = 6.5$, $P < 0.05$], as response repetitions were faster than response changes when accompanied by a shape feature repetition (533 vs. 543 ms) but slower when accompanied by a shape feature change (548 vs. 532 ms; **Figure 2B**). No other main or interaction effects were obtained. A direct comparison between the respective color–response and shape–response binding effects revealed that the former were significantly larger than the latter [$t(19) = 5.0$, $P < 0.001$]. In order to facilitate comparison with results from Experiments 2 and 3, **Figure 3A** plots the two-way interactions between response and stimulus features as single values that capture the degree of binding between response and stimulus features by indicating the RT cost of having to overcome conflicting bindings (partial repetition costs), using the formula [(feature repetition, response change + feature change, response repetition)/2 − (feature repetition, response repetition + feature change, response change)/2]. Thus, positive RT values reflect the relative slow-down in responses when the response repeats but a given stimulus feature changes (and vice versa), compared to when both the response and stimulus feature repeat or alternate in concert (cf. Hommel, 2005).

Table 1 | Descriptive statistics for mean R2 response times.

	Emotion	Response repetition	Response change
EXPERIMENT 1			
Color repetition		518 (124)	557 (130)
Color change		564 (138)	518 (117)
Shape repetition		533 (121)	543 (126)
Shape change		548 (141)	532 (120)
EXPERIMENT 2			
Color repetition	Neutral	508 (106)	529 (113)
Color change	Neutral	544 (125)	498 (105)
Shape repetition	Neutral	523 (111)	514 (110)
Shape change	Neutral	529 (117)	513 (107)
Color repetition	Fearful	500 (110)	519 (111)
Color change	Fearful	536 (112)	502 (109)
Shape repetition	Fearful	517 (111)	509 (107)
Shape change	Fearful	519 (109)	512 (113)
EXPERIMENT 3			
Color repetition	Neutral	529 (148)	551 (145)
Color change	Neutral	574 (150)	520 (127)
Shape repetition	Neutral	546 (144)	536 (131)
Shape change	Neutral	557 (154)	535 (140)
Color repetition	Fearful	520 (138)	556 (141)
Color change	Fearful	566 (144)	524 (135)
Shape repetition	Fearful	539 (140)	538 (132)
Shape change	Fearful	547 (142)	542 (142)

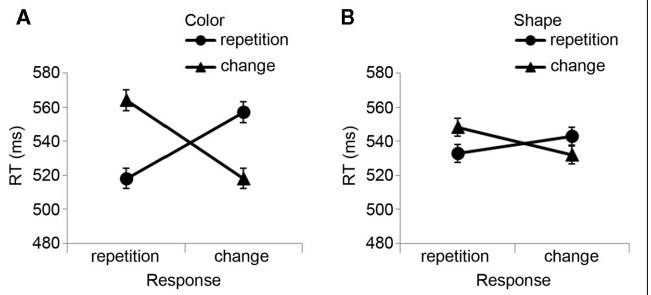

FIGURE 2 | Experiment 1 feature integration effects. Mean R2 response times (±SEM) in Experiment 1 are displayed as a function of **(A)** stimulus color and response transitions, and **(B)** stimulus shape and response transitions.

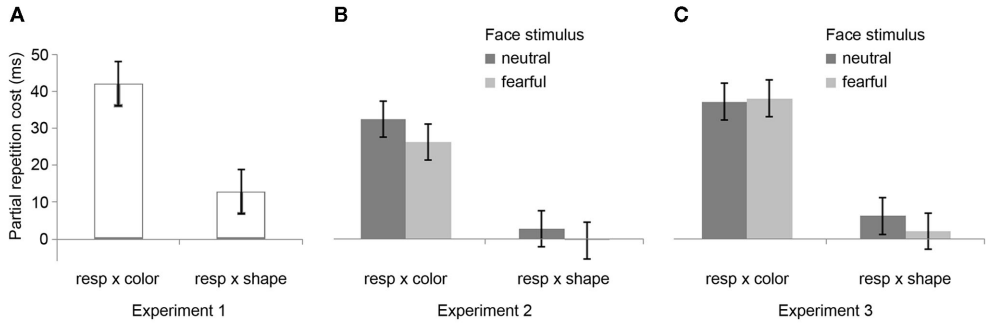

FIGURE 3 | Feature integration effects across Experiments 1–3. Bar graphs summarize mean partial repetition costs (±SEM) involving the task-relevant foreground feature (color) and responses, and the task-irrelevant foreground feature (shape) and responses for Experiments 1 **(A)**, 2 **(B)**, and 3 **(C)**, as well as the modulation of these effects by the affective expression of background face stimuli (neutral vs. fearful) for Experiments 2 **(B)** and 3 **(C)**. Note that there were no background face stimuli (and thus no modulation thereby) in Experiment 1. Each bar represents the two-way interaction between response and stimulus features as a single value that captures the degree of binding between response and stimulus features by indicating the RT cost of partial repetitions [(feature repetition, response change + feature change, response repetition)/2 − (feature repetition, response repetition + feature change, response change)/2]. In other words, positive RT values reflect the relative slow-down in responses when the response repeats but a given stimulus feature changes (and vice versa), compared to when both the response and stimulus feature repeat or alternate in concert (cf. Hommel, 2005).

DISCUSSION

The data obtained in Experiment 1 represent a successful replication of the key feature integration results obtained by Hommel (1998): substantial costs are incurred when a response has to be repeated in the presence of a stimulus feature change, and vice versa, compared to complete repetition and complete alternation conditions. Moreover, the binding effect is much more pronounced for the task-relevant stimulus feature (color) than for the task-irrelevant one (shape) (Hommel, 1998, 2005). In the subsequent experiments, we sought to test whether either one of these indices of fast episodic stimulus–response binding processes would be modulated by the presence of a (task-irrelevant) emotionally salient stimulus of negative valence.

EXPERIMENT 2

Our basic research question concerned the impact of emotion on the short-term episodic memory phenomenon of feature integration. In Experiment 1, we established the basic procedure for obtaining reliable feature integration effects. In Experiment 2, we aimed at adding a manipulation of emotion to that procedure. As emotion-provoking stimuli, we chose photographs of male faces with fearful expressions, to be contrasted with the same individuals' faces posing neutral expressions. A large literature has established that fearful face stimuli are potent emotional stimuli that evoke heightened arousal (as measured by galvanic skin response; e.g., Williams et al., 2001), trigger strong responses in neural fear circuits centering on the amygdala (e.g. Breiter et al., 1996), and can have immediate effects on perceptual and cognitive processing (e.g., Phelps et al., 2006; Reeck and Egner, 2011). In order to assess the effects of threat-related, negative emotion on feature integration, in Experiment 2 we therefore simply added a task-irrelevant background face stimulus (neutral vs. fearful) during the encoding phase (that is, at S1) of the feature integration task we had employed in Experiment 1 (see **Figure 1B**).

METHODS

Subjects

Twenty-one healthy college student volunteers ($M_{age} = 19.33$ years, SD = 1.4, eight women) participated in this study for course credit. All participants were fluent in English and had normal or corrected-to-normal vision. Prior to study participation, written informed consent was obtained from each participant in accordance with institutional guidelines.

Stimuli and procedure

The stimuli and procedure were identical to the ones in Experiment 1, with the following modification: for the S1 stimuli, the colored shapes were now overlaid on semi-transparent, gray-scale photographs of male faces (40% opacity), tightly surrounding the eye- and mouth-region of any given face (see **Figure 1B**). The face stimuli subtended approximately 10 (height) × 8 (width) degrees of visual angle. The faces stemmed from the NimStim Set of Facial Expressions (Tottenham et al., 2009) and consisted of six male actors posing neutral and fearful facial expressions. Thus, a given S1 could have either a neutral or fearful face displayed in the background. The faces (and their expressions) were irrelevant to the subjects' task. The experimental session was composed of 1 practice block of 20 trials followed by 8 experimental blocks of 48 trials each.

Analyses

The analyses focused on R2 RT. Only trials where both R1 and R2 had been performed correctly were considered correct trials. All error and post-error trials, as well as outlier RT values of more than 2 SDs from subject-specific grand means were excluded from the analysis. Accuracy was at ceiling (mean = 97.8%, SD = 2.0) and was not considered for statistical analysis. We analyzed R2 RT data as a function of the transition relationship between S2/R2 and S1/R1 features as well as the affect of the facial expression during S1. Specifically, the data were submitted to a 2 (color: repetition vs. alternation) × 2 (shape: repetition vs. alternation) × 2 (response:

repetition vs. alternation) × 2 (facial affect: neutral vs. fearful) repeated-measures ANOVA.

RESULTS

In the R2 RT data (**Table 1**), a main effect of emotion was evident [$F(1, 20) = 7.6$, $P < 0.05$], as responses were generally a little faster following the presentation of a fearful background face (514 ms) than following an emotionally neutral face stimulus (520 ms). There was also a trend toward a main effect of response transition [$F(1, 20) = 3.7$, $P = 0.069$], with responses tending to be generally slower on response repetition (522 ms) than response change trials (513 ms). More importantly, the standard feature integration interaction effect between response and color transitions was obtained [$F(1, 20) = 26.3$, $P < 0.001$], as response repetitions were faster than response changes when they were accompanied by color feature repetitions (504 vs. 524 ms), but slower when they were accompanied by color feature changes (540 vs. 500 ms). No significant interaction was observed between response and shape transitions. However, most pertinent to our current concerns, as can be seen in **Figure 3B**, the emotional expression of the background face in S1 did not have any impact on the foreground stimulus–response binding effects, as neither the three-way interaction involving emotion, shape, and response transitions [$F(1, 20) = 0.4$, $P = 0.55$], nor that involving emotion, color, and response transitions [$F(1, 23) = 2.0$, $P = 0.17$] were significant.

DISCUSSION

The data obtained in Experiment 2 replicated the basic partial repetition costs associated with episodic stimulus–response integration, though that effect was only significant for the task-relevant color feature. Importantly, we observed no interaction of this feature integration effect with the emotionality of the background face stimulus presented at encoding, suggesting that emotional responses do not modulate the fast-acting short-term binding of foreground stimulus and response features in episodic memory. It is important to note that the emotion manipulation as such did have an impact on performance, as expressed in a main effect of facial affect at S1 on R2 RT, where responses were found to be faster following a fearful background face stimulus than a neutral one. This general speed-up of RT suggests that the fearful face stimuli indeed triggered an increase in threat-related arousal, but that this emotional response had no effect on the foreground feature binding. Crucially, this finding documents that the lack of an emotion-modulation effect on feature integration cannot be attributed to a weak or ineffective manipulation of emotion. It also demonstrates that, even though the face stimuli were irrelevant to the subjects' task, subjects did not manage to avoid processing of those stimuli. In Experiment 3, we sought to replicate these findings while controlling for a possible confound stemming from the fact that faces were presented only at S1 but not at S2.

EXPERIMENT 3

One aspect of the design of Experiment 2 that may have impeded the expression of emotion-modulation of feature integration is that the background face stimuli were shown at encoding (S1) but were not displayed at S2. While this approach makes intuitive sense when one is interested in how emotion impacts encoding processes, the fact that there was a major feature change in the stimulus display between S1 and S2 could have feasibly confounded the results. Specifically, it is likely that the face stimuli themselves will form part of the event file that is encoded at S1, such that the non-appearance of faces at S2 would essentially render every trial a partial repetition trial, in that even if all other S1 and R1 features repeat, one salient aspect of the stimulus display does not repeat. In order to avoid any possible confounds stemming from the non-repetition of the background face stimuli, in Experiment 3 we simply added the background faces both to S1 and S2, such that on each trial, the exact same face (identity and expression) was shown both at encoding and during S2/R2 (see **Figure 1C**).

METHODS

Subjects

Twenty-four healthy college student volunteers ($M_{age} = 21.08$ years, SD = 4.9, 14 women) participated in this study for course credit. All participants were fluent in English and had normal or corrected-to-normal vision. Prior to study participation, written informed consent was obtained from each participant in accordance with institutional guidelines.

Stimuli and procedure

Stimuli and procedure were identical to Experiment 2, with the only exception that the background faces shown during S1 were now also present during S2. Specifically, the exact same face stimulus (identity plus expression) shown in S1 was repeated in S2 on each trial (see **Figure 1C**).

Analyses

The analyses focused on R2 RT. Only trials where both R1 and R2 had been performed correctly were considered correct trials. All error and post-error trials, as well as outlier RT values of more than 2 SDs from subject-specific grand means were excluded from the analysis. Accuracy was at ceiling (mean = 96.8%, SD = 2.8) and was not considered for statistical analysis. We analyzed R2 RT data as a function of the transition relationship between S2/R2 and S1/R1 features as well as the affect of the facial expression of the background stimulus. Specifically, the data were submitted to a 2 (color: repetition vs. alternation) × 2 (shape: repetition vs. alternation) × 2 (response: repetition vs. alternation) × 2 (facial affect: neutral vs. fearful) repeated-measures ANOVA.

RESULTS

In the R2 RT data (**Table 1**), we observed a trend toward a main effect of response transition [$F(1, 23) = 4.0$, $P = 0.057$], due to a tendency for slower responses on response repetition (547 ms) as compared to response change trials (538 ms). A trend toward a main effect of color transitions [$F(1, 23) = 3.7$, $P = 0.066$] was characterized by a tendency for faster responses on color repetition (539 ms) than color change trials (546 ms). Moreover, a trend toward a main effect of shape transitions [$F(1, 23) = 4.1$, $P = 0.054$] was characterized by a tendency for faster responses on shape repetition (540 ms) than shape change trials (545 ms). More importantly, the standard feature integration interaction effect between response and color transitions was obtained [$F(1, 23) = 77.3$, $P < 0.001$], as response repetitions were faster than

response changes when they were accompanied by color feature repetitions (525 vs. 554 ms), but slower when they were accompanied by color feature changes (570 vs. 522 ms). No significant interaction was observed between response and shape transitions but, interestingly, response transitions interacted with the emotional expression of the background face stimulus [$F(1, 23) = 7.2$, $P < 0.05$], as response repetitions were slower than response changes in the presence of a neutral face stimulus (551 vs. 535 ms), but of similar speed in the presence of a fearful face (543 vs. 540 ms). Most importantly, as can be observed in **Figure 3C**, the emotional expression of the background face stimulus again did not modulate the standard feature integration effect(s), as neither the three-way interaction involving emotion, shape, and response transitions [$F(1, 23) = 0.3$, $P = 0.58$], nor that involving emotion, color, and response transitions [$F(1, 23) = 0.1$, $P = 0.81$] were significant.

DISCUSSION

Akin to Experiments 1 and 2, Experiment 3 reproduced the basic feature integration effect of binding costs associated with the relevant stimulus feature and the response. However, we again did not obtain any evidence for this effect being susceptible to modulation by a threat-related emotional background stimulus, thus suggesting that feature integration is not affected by negative emotional states. In contrast to Experiment 2, these results were obtained in the presence of (constant) background stimuli during both S1 and S2, thus preempting the possibility that an additional stimulus feature change between S1 and S2 that was present in Experiment 2 could somehow have masked an emotion-modulation effect on feature integration. Importantly, just as in Experiment 2, the emotion manipulation as such did produce an effect on behavior. Whereas in Experiment 2 there was a main effect of emotion on R2 RT, in Experiment 3 the emotional expression of the face stimulus interacted with the response transition factor in influencing R2 RT. This finding rules out the possibility that a lack of emotion-modulation of the feature integration effect was due to an ineffective manipulation of emotion, or that subjects somehow managed to ignore the irrelevant face stimuli.

GENERAL DISCUSSION

We adopted Hommel's (1998) experimental set-up for gauging rapid episodic memory integration effects of stimulus and response features (Experiment 1) and tested whether such feature binding was susceptible to modulation by emotional arousal, as evoked by background fearful (vs. neutral) face stimuli (Experiments 2 and 3). The results were clear-cut, in that we reliably reproduced the behavioral signature of the basic feature integration effect (partial repetition costs) (see **Table 2**) but were unable to detect any evidence for emotional modulation of this effect, regardless of whether threat-related background stimuli were displayed at encoding (S1) or at both encoding and retrieval (S1 and S2). In fact, a direct comparison of feature integration effects across Experiments 1–3 (with experiment serving as a between-subjects factor) reveals that the two-way interaction between the relevant stimulus feature (color) and response transitions (that is, the standard feature integration effect) did not differ across the experiments [three-way interaction of color × response × experiment, $F(2, 62) = 0.5$, $P = 0.61$].

Table 2 | Significant main and interaction effects on R2 response time.

	F	*P*-value
EXPERIMENT 1		
Response × color transition	43.9	<0.001
Response × shape transition	6.5	<0.05
EXPERIMENT 2		
Emotion	7.6	<0.05
Response × color transition	26.3	<0.001
EXPERIMENT 3		
Response × color transition	77.3	<0.001
Response transition × emotion	7.2	<0.05

Moreover, a between-experiment analysis involving only Experiments 2 and 3, which included two subtly different emotion manipulations, revealed no effect of experiment on the relationship between emotion and color/response transitions [four-way interaction of emotion × color × response × experiment, $F(1, 43) = 1.7$, $P = 0.20$]. Thus, feature integration between the relevant stimulus feature and response was entirely unaffected by the emotion manipulations, both within and across experiments.

In the context of these null-effects, it is crucial to note, however, that the emotion manipulation *per se* was nevertheless found to be effective, as the expression of the background face stimulus did significantly affect R2 performance in both Experiments 2 and 3. In Experiment 2, fearful facial expressions in S1 sped up R2 RT compared to neutral expressions, and in Experiment 3, the emotional face expression interacted with the response transition factor, due to slower R2 RT for response repetitions than response changes in the presence of neutral faces, but similar RT for response changes and repetitions in the presence of fearful faces. These data allow us to rule out a number of alternative reasons for not obtaining emotion-modulation effects on feature integration. First, the fact that R2 RT in both Experiments 2 and 3 were significantly modulated by the emotional expression of the task-irrelevant face stimuli clearly shows that these stimuli effectively influenced information processing, thus ruling out the possibility that our manipulation of emotion was too weak to affect subjects' behavior. Second, these significant effects demonstrate that our design was sensitive enough to detect the influences of facial expressions on behavior. Finally, these findings also rule out the possibility that subjects were able to somehow filter out the task-irrelevant emotional face stimuli. Given these data, it can be concluded that our study should have been able to detect negative emotion-modulation of short-term feature binding processes if such effects existed, unless those bindings were, for some unknown reason, subject to a substantially higher threshold for emotion-modulation than response selection and transition effects.

As noted above, the emotion manipulations in Experiment 2 and 3 had qualitatively different effects on behavior. Recall that in Experiment 2, face stimuli were shown only at encoding (S1) whereas in Experiment 3 they were shown both during encoding and retrieval. This change in procedure could evidently be responsible for the differential effects. Alternatively, these distinct effects could in theory have stemmed from a difference in how the face stimuli were processed during S1/R1. Accordingly, we analyzed mean R1 RT as a function of facial affect and experiment.

However, no differences in the response to neutral vs. emotional face stimuli was observed across experiments [$F(1, 43) = 0.34$, $P = 0.56$]. Thus, it appears that the procedural differences between the two experiments were responsible for the distinct effects of emotion. However, we remain ignorant (and agnostic) about the exact reasons for this differential impact of emotion as well as the specifics of its interaction with the response transition factor in Experiment 3.

Our main motivation for assessing the effect of emotion on rapid feature integration processes stemmed from recent reports of emotion-modulation concerning trial-by-trial effects of conflict-driven control in experiments that did not tease apart pure conflict–control effects from possible feature integration effects (van Steenbergen et al., 2009, 2010). Specifically, these studies documented that negative emotional states potentiate trial–transition effects in conflict tasks, and the present experiments were geared at testing whether these findings may have been mediated by potentiation of feature integration rather than cognitive control processes. We observed no evidence of emotion modulating feature integration processes. *Vis-à-vis* these and other previous studies of emotion manipulations on trial–transition effects (e.g., Dreisbach and Goschke, 2004; Stürmer et al., 2011), the current results therefore suggest that it is unlikely such effects are carried by emotion-modulation of rapid feature integration, and are thus probably reflective of emotion-modulation of cognitive control processes. A feasible avenue for the rapid modulation of cognitive control processes by positive or negative emotional stimuli is provided by the well-known interactions between the midbrain dopamine system and the prefrontal cortex (e.g., Braver and Cohen, 2000). An important caveat concerning the current conclusions, however, is that we only assessed the effects of a negative, threat-related emotion manipulation (in comparison to neutral stimuli), from which one cannot necessarily extrapolate to effects of positive emotional stimuli or rewards. Thus, it remains a possibility that feature integration effects of the type we investigated here are susceptible to modulation by positive emotional states.

Some suggestive evidence for this possibility has been supplied by a study on feature integration and emotion by Colzato et al. (2007). In a similar protocol to the current study, these authors presented either negative or positive task-irrelevant emotional picture stimuli not during encoding of S1/R1 but just prior to the retrieval of these S–R ensembles. Specifically, emotional stimuli were displayed 1,000 ms after S1 offset, starting from 200 ms before and lasting until the presentation of S2 (and execution of R2). Thus, this study likely gauged the effects of emotion on the retrieval of recent S–R bindings, in contrast to the present study's focus on the encoding of S–R bindings. Colzato et al. (2007) found some evidence for feature integration effects following negative stimuli to be less pronounced than following positive stimuli, though this effect was only observed when the task-relevant S2 feature was stimulus shape but not when it was stimulus location or color. The authors interpreted the latter effect by suggesting that the processing of positive/negative picture stimuli would require the processing of shape but not of color or location information. Given that the Colzato et al. (2007) study did not include an emotionally neutral baseline comparison, it is impossible to tell to which degree this modulation was carried by the positive or negative stimuli. But, considering the present findings of a lack of differential feature integration effects when comparing negative and neutral stimuli, it could be speculated that the Colzato et al. (2007) results were likely driven by the positive emotional stimuli modulating the retrieval of recently formed S–R bindings.

However, given the considerable differences in study design between the present experiments and those of Colzato et al. (2007), any conclusions drawn from contrasting their respective results must be regarded as very tentative at best. In addition to the use of positive and negative stimuli in Colzato et al. (2007) as opposed to negative and neutral stimuli in the present study, differences in results could also stem from the fact that the two studies targeted different time points in the binding process (encoding vs. retrieval) and/or due to the use of different task-relevant stimulus features. Specifically, unlike Colzato et al. (2007), the present study only employed color as the task-relevant stimulus feature, such that it is in principle not certain whether our findings can be generalized to contexts where other stimulus features are task-relevant. In any case, however, even though there is thus some evidence for (positive) emotion-modulation of feature integration (Colzato et al., 2007), the direction of this effect (positive emotional stimuli enhancing feature integration) is precisely opposite to the effects of emotion manipulations in cognitive control tasks, where it is negative emotional states that appear to potentiate trial-by-trial performance dependencies and positive states that appear to loosen these dependencies (Dreisbach and Goschke, 2004; van Steenbergen et al., 2009, 2010). Thus, our conclusion that the previously observed effects of emotion on trial–transition metrics of cognitive control are unlikely to have been mediated by emotion-modulated feature integration effects is actually supported by this prior study (Colzato et al., 2007).

From the perspective of the emotional memory literature, the current data could be argued to provide support for the "object-based" framework of emotional arousal put forward by Mather (2007), which holds that emotional arousal benefits the recall of an emotional item itself but not that of other stimuli providing the context to that item. The present results demonstrate the latter, namely, that the presence of emotional stimuli does not confer any memory advantage (or disadvantage) on other non-emotional stimuli presented concurrently (see also Mather and Nesmith, 2008; Mather et al., 2009). Moreover, the current data extend this notion to a shorter time-scale than has been investigated in previous studies, and to the binding of concurrent stimulus and responses features rather than of stimulus features alone. While the present results are thus in principle in line with an object-based binding framework of emotional arousal, additional experiments would be required to determine whether memory for the emotional stimuli themselves would actually be enhanced in the type of protocol we employed here, as would be predicted by this theory (Mather, 2007).

CONCLUSION

In sum, the rapid integration of task-relevant stimulus and response features into episodic "event files" is not modulated by concurrent presentation of threat-related negative emotional stimuli at encoding and/or retrieval. This finding is concordant with the proposal that emotional arousal facilitates emotional

item memory but does not extend this mnemonic benefit to other concurrent stimulus or response features. Moreover, this lack of emotion-modulation of feature integration effects has important implications for the interpretation of emotion-modulated trial–transition effects in studies of cognitive control, in that the latter effects are unlikely to be mediated by the influence of emotion on feature integration effects that are commonly confounded with the effects of cognitive control.

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Neural correlates of opposing effects of emotional distraction on perception and episodic memory: an event-related fMRI investigation

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A main question in emotion and memory literature concerns the relationship between the immediate impact of emotional distraction on perception and the long-term impact of emotion on memory. While previous research shows both automatic and resource-mediated mechanisms to be involved in initial emotion processing and memory, it remains unclear what the exact relationship between the immediate and long-term effects is, and how this relationship may change as a function of manipulations at perception favoring the engagement of either more automatic or mediated mechanisms. Using event-related functional magnetic resonance imaging, we varied the degree of resource availability for processing task-irrelevant emotional information, to determine how the initial (impairing) impact of emotional distraction related to the long-term (enhancing) impact of emotion on memory. Results showed that a direct relationship between emotional distraction and memory was dependent on automatic mechanisms, as this was found only under conditions of limited resource availability and engagement of amygdala (AMY)-hippocampal (HC) mechanisms to both impairing and enhancing effects. A hemispheric disassociation was also identified in AMY-HC, where while both sides were associated with emotional distraction and left AMY and anterior HC were linked to emotional memory, functional asymmetry was only identified in the posterior HC, with only the left side contributing to emotional memory. Finally, areas dissociating between the two opposing effects included the medial frontal, precentral, superior temporal, and middle occipital gyri (linked to emotional distraction), and the superior parietal cortex (linked to emotional memory). These findings demonstrate the relationship between emotional distraction and memory is context dependent and that specific brain regions may be more or less susceptible to the direction of emotional modulation (increased or decreased), depending on the task manipulation, and processes investigated.

Keywords: affect, emotional automaticity, emotional distraction, emotional memory, encoding success

INTRODUCTION

An important question in the emotion literature concerns the relationship between the immediate impact of emotional distraction on perception and the long-term impact of emotion on memory. Typically, in the context of distraction and dual task paradigms, task-concurrent emotional distraction impairs task-relevant performance as the emotional information tends to capture and reallocate cognitive resources (Vuilleumier et al., 2001; Kensinger and Corkin, 2003; Mitchell et al., 2007; Talmi et al., 2007; Hodsoll et al., 2011; Pottage and Schaefer, 2012). This has been thought to occur as a result of privileged processing for emotional information, due to its increased relevance for survival. It is not clear, however, how this initial processing of distracting emotional information influences memory for the distracters themselves, and what the neural mechanisms linking the immediate and long-term effects of distracting emotions are. The present study addressed this issue using functional magnetic resonance imaging (fMRI) and an experimental design that assessed both the immediate (*impairing*) and long-term (*enhancing*) effects of task-irrelevant emotional distraction.

The severity by which emotional distraction impacts perception has been shown to be influenced by two factors: the degree of cognitive demand or attentional resources required to perform the main task, and the degree of emotional challenge (Vuilleumier et al., 2001; Pessoa et al., 2002, 2005; Anderson et al., 2003; Vuilleumier, 2005; Mitchell et al., 2007; Silvert et al., 2007; Shafer et al., 2012). Previous research investigating these factors yielded mixed findings, consistent either with the view that emotion processing is automatic and independent of attentional resources (*traditional* view), or consistent with the view that emotion processing depends on manipulations that affect the availability of processing resources (*competing view*), linked to the demands/difficulty of the main task. However, these studies have not involved systematic manipulations of both task difficulty and emotional challenge. A

recent study investigating this issue in a "lower-level" perceptual task that manipulated both of these factors provided evidence that processing of emotional distraction is both automatic and modulated by attention (Shafer et al., 2012), which is consistent with both views. Specifically, consistent with the traditional view, we found that overall emotional distraction impacted task performance regardless of the attentional demands necessary to perform the main task. However, consistent with the competing view, we also found that the highest level of disruption by emotional distraction occurred when most resources were available for distraction. These results suggest that two mechanisms contribute to the immediate impact of emotional distraction on perception: one rooted in automaticity and the other modulated by attention. What remains unclear is how these manipulations at perception affecting the immediate impact of emotion may also influence the long-term effects of emotion on memory.

Regarding the long-term impact of emotion on memory, extant evidence also suggests the existence of two routes contributing to the memory-enhancing effect of emotion (Dolcos et al., 2004a,b, 2011; Kensinger and Corkin, 2004; LaBar and Cabeza, 2006). One route, consisting of medial temporal lobe (MTL) structures comprised of emotion-based (amygdala, AMY) and memory-based (hippocampal structures, HC) regions, is thought to operate more automatically and largely independently of resources at the time of encoding. The other route, involving prefrontal and parietal cortices, is thought to depend on the contribution of other processes to the memory-enhancing effect of emotion, such as working memory, semantic memory, and attention. Evidence supporting the dissociation between the automatic and mediated routes has shown, for instance, that the AMY-HC engagement is associated with emotional memory following a shallow level of processing during encoding, whereas areas previously shown to be modulated by attention were more sensitive to emotional memory under a deep level of processing (Dolcos et al., 2004a,b, 2011; Ritchey et al., 2011). Overall, these results lend support to the idea that the memory-enhancing effect of emotion can result from both automatic and mediated/attention-dependent mechanisms.

A main open question concerns the relationship between the immediate and long-term effects of emotion in conditions where emotional information is presented as task-irrelevant distraction, especially given that both effects seem to engage automatic and mediated/attention-dependent mechanisms. Specifically, it is not clear whether there is a one-to-one relationship between the two opposing effects of task-irrelevant information on perception and memory – i.e., is there a direct link between the immediate (*impairing*) and long-term (*enhancing*) impact, such that the conditions in which emotional distraction produces the strongest immediate impact will also be translated in the strongest long-term impact on memory? If so, this would suggest that reallocation of processing resources by emotional distraction, overlapping with the initiation of processing leading to better memory for the distracters themselves, is the main mechanism linking the immediate/impairing and long-term/enhancing effects of task-irrelevant emotional information. Alternatively, it is possible that the link between the impairing and enhancing effects does not occur when the former effect is maximized, and hence would likely involve slightly different mechanisms.

Previous research investigating how immediate resource allocation relates to long-term memory via manipulations of the amount of resources allocated toward the to-be-remembered items has shown that divided attention at the time of encoding negatively influences how well those items will be remembered compared to items encoded with full/non-divided attention (Hicks and Marsh, 2000; Craik, 2001; Uncapher and Rugg, 2005, 2008). However, similar manipulations with emotional stimuli have shown smaller decrements in memory performance when attention was divided, although this resilience in memory came at a cost, as performance on the primary task was disrupted by the presence of emotional distraction (Kensinger and Corkin, 2003; Talmi et al., 2007; Pottage and Schaefer, 2012). Overall, these findings suggest a direct relationship between the immediate and long-term impact of emotional distraction, possibly involving automatic mechanisms, although a role of mediated attention-related mechanisms is also implied. It is not clear, however, what the circumstances are in which a direct link between the immediate (impairing) and long-term (enhancing) impact of emotion can be found, what the neural correlates of the link between these opposing effects are, and how they are distinguished from those involved in one (immediate/impairing) or the other (long-term/enhancing) of these effects.

The overarching goal of the current study was to investigate the relationship between the immediate (impairing) and long-term (enhancing) effects of emotion by (i) examining how emotionally distracting information at perception influences the memory-enhancing effect of emotion, and by (ii) identifying common and dissociable neural correlates of emotional distraction on perception and encoding success, thus linking the behavioral effects of emotional distraction and memory. These issues were investigated using a perception task involving manipulation of cognitive demand of goal-relevant processing in the presence of emotional distraction, followed by a surprise memory task for the distracters themselves, while event-related fMRI data were recorded.

Based on the extant evidence suggesting possible relationships between the immediate and long-term impact of emotional distraction, we made the following conditional predictions. First, regarding the behavioral effects, if there is a one-to-one relationship between the immediate/impairing and long-term/enhancing impact of emotion, we predict that the condition with the strongest immediate impact of emotion will produce the strongest long-term impact. Alternatively, if other factors also contribute to one or the other of these opposing effects, conditions where the immediate impact of emotion is present may not necessarily lead to a long-term impact of the same extent, and vice-versa. Regarding the neural correlates of these effects, if the same automatic and attention-mediated processes are involved in both the immediate and long-term effects and there is a one-to-one relationship between the two effects in the behavioral data, then we predict an overlap in the responses to the immediate and long-term impact of emotion in the same areas of the emotion network (e.g., AMY). However, if dissociable processes are involved in the immediate and long-term effects and there is no one-to-one relationship between the two effects, then we predict largely dissociable regions associated with the immediate and long-term effects of emotional distraction.

MATERIALS AND METHODS

PARTICIPANTS

The present investigation involved analyses on data from 16 (seven males) healthy right-handed young adults (19–34 years), recruited from the University of Alberta and Edmonton City area. Participants signed an informed consent form before participating, and were reimbursed for their participation. The experimental protocol was approved for ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

TASKS AND STIMULI

Participants completed two tasks, both performed in the scanner: a perceptual orientation discrimination task with distraction and an episodic memory task (see task diagram illustrated in **Figure 1**). In the perception task, participants made decisions on the orientation of vertical and horizontal pictures with negative and neutral content, and in the memory task they made decisions about whether emotional and neutral pictures were presented during the perception task or not. Since the focus of the current paper is on encoding success only fMRI data from the perception task were analyzed.

Perception task

The stimuli and design of the perception task were described in a previous report focusing on the perceptual task (Shafer et al., 2012). Briefly, the task used pictures selected from the International Affective Pictures System (Lang et al., 2008), based on their normative scores for arousal and valence and was supplemented with in-house pictures used in previous studies (Yamasaki et al., 2002; Dolcos and McCarthy, 2006). Distraction type was manipulated by the emotional content (negative vs. neutral) of the rectangular pictures. Attentional demand was manipulated by varying the presentation time of the stimuli (Short Dur = 250 ms vs. Long Dur = 1000 ms) and by varying the ratio of the horizontal vs. vertical sides of the rectangles (Lo-Load = clearly rectangles vs. Hi-Load = closer to squares). These two manipulations were chosen because both are considered manipulations of task demand (Grill-Spector and Kanwisher, 2005; LaBar and Cabeza, 2006), and to be consistent with research from both perception and memory domains. Specifically, a shorter presentation time (i.e., 250 ms) is consistent with investigations of the effect of processing load in studies of perception (e.g, Pessoa et al., 2002, 2005), while a longer presentation time (i.e., 1000 ms) is more consistent with paradigms investigating emotional memory (e.g., Ritchey et al., 2008). Participants were instructed to maintain focus on the orientation task and determine the orientation of the rectangular shapes (1 = horizontal; 2 = vertical).

Recognition task

Following the perception task, participants performed a recognition memory task for a sub-set of the pictures presented in the perception task. Of the total of 224 emotional (112) and neutral (112) pictures presented during the perception task, 160 (80 emotional and 80 neutral) were pseudo-randomly selected for the recognition memory task. Half of the 160 selected were Lo-Load and half were Hi-Load, and half were Short Dur and half Long Dur. This resulted in 20 emotional, Lo-Load, Short Dur; 20 emotional, Hi-Load, Short Dur; 20 emotional, Lo-Load, Long Dur; 20 emotional, Hi-Load, Long Dur; 20 neutral, Lo-Load, Short Dur; 20 neutral, Hi-Load, Short Dur; 20 neutral, Lo-Load, Long Dur; 20 neutral, Hi-Load, Long Dur. The 160 old images were pseudo-randomized with 80 new images selected from the same original picture databases and were selected on arousal and valence scores as well as similar semantic content. Averaged normative arousal and valence scores for Old and New emotional and neutral items, respectively, were as follows: 5.93/2.63 for Emotional old pictures; 5.95/2.66 for Emotional new pictures; 3.41/5.04, for Neutral old

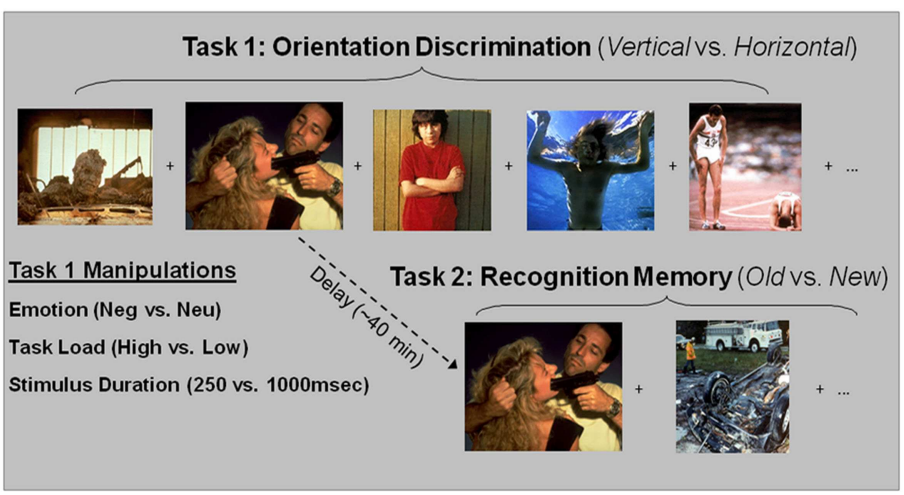

FIGURE 1 | Diagrams of perception and memory tasks. Trial type during the orientation discrimination task was defined by the type of distraction in the rectangular picture (Emo, Neu), the duration of the stimulus (250, 1000 ms), and the perceptual load necessary to perform the task (High, Low). Participants were instructed to determine the orientation of the shape. Following the perception task, participants were given a surprise recognition memory task for a sub-set of the distracters presented in the perception task. Participants were instructed to determine if the pictures were from the perception task "Old" or were "New," not presented during the perception task. Emo, Emotional; Neu, Neutral.

pictures; and 3.41/5.02 for Neutral new pictures. Arousal and valence scores were assessed using nine-point Likert scales, as follows: Arousal (1 = Lowest/9 = Highest), Valence (1 = Very Negative, 5 = Neutral, and 9 = Very Positive). Pairwise comparisons showed that emotional pictures had significantly greater arousal scores and lower valence scores than the neutral pictures, but there were no differences between the scores for emotional or neutral pictures from different categories.

EXPERIMENTAL PROCEDURES

The 240 trials were divided into five runs of 48 trials (16 Emotional old, 16 Neutral old, 8 Emotional new, 8 Neutral new). Old stimuli were pseudo-randomized based on when they appeared in the perception task to ensure that a delay of approximately 40 min occurred between the encoding and retrieval of a stimulus. For example, if a picture was presented in the first run of the perception task, then it would be presented in either the first or second run of the recognition task. Likewise, if a stimulus was presented in the last run of the perception task then it was presented in the last run of the recognition task. To avoid induction of longer-lasting mood states, the trials within each run were pseudo-randomized, so that no more than two trials of the same valence type were consecutively presented. Each picture was displayed for 2000 ms during which the participant had to indicate with a button press whether it was an "*Old*" or a "*New*" image. Immediately following this 2000 ms response window a confidence rating screen appeared for 2000 ms asking the participant to rate the confidence of their decision on a three-point Likert scale (1 = lowest, 3 = highest). Each trial was followed by a jittered fixation interval drawn from an exponential distribution with a median of 6 s and a range from 4 to 12 s. Participants were not aware that a memory task would come following the perceptual task – they were told that the perception task would last for the entire time they were in the scanner. However, the perception task lasted approximately 55 min after which the experimenter instructed them that they would be performing a memory task for items that were presented in the perception task. The memory task did not begin until the participants confirmed that they understood the instructions for the task.

IMAGING PROTOCOL

Collection of MRI data was conducted on a 1.5-T Siemens Sonata scanner. After the sagittal localizer and the 3-D magnetization prepared rapid acquisition gradient-echo anatomical series [field of view (FOV) = 256 mm × 256 mm, repetition time (TR) = 1600 ms, echo time (TE) = 3.82 ms, number of slices = 112, voxel size = 1 mm^3), a series of functional volumes allowing for full-brain coverage were acquired axially, using an echoplanar sequence (FOV = 256 mm × 256 mm, TR = 2000 ms, TE = 40 ms, number of slices = 28, voxel size = 4 mm × 4 mm × 4 mm, flip angle = 90°).

BEHAVIORAL DATA ANALYSIS

The immediate impact of emotion on perception was measured as reaction time (RT) to making orientation (vertical vs. horizontal) discrimination decisions to the rectangular pictures. An initial analysis was performed similar to that from the report focusing on the immediate effect of emotional distraction (Shafer et al., 2012), and involved a repeated measures ANOVA with three within subjects variables [Emotion (Emo, Neu); Load (Lo, Hi); Duration (Short, Long)]. However, to establish the link between the immediate and long-term effects of emotion, the present focus was on items that were both correct in the perception task and also later remembered in the memory task (Hits), and involved data from subjects that had at least four trials per condition (11 subjects met this criterion). This analysis was done to ensure that similar behavioral effects existed for the perception task after reducing the number of subjects and trials per subject as only items from the perception task that were also in the memory task were assessed. The long-term impact of emotion on memory was assessed as corrected recognition scores [% Hits – % False Alarms (FA)], using repeated measures ANOVA with the same three variables. Corrected recognition scores were involved because their calculation is a common and stringent technique of assessing accuracy in memory tasks, as it considers responses to both *Old* (Hits and Misses) and *New*/foil (Correct Rejections and False Alarms) items. Even though confidence ratings were acquired during the recognition task, they were collapsed for analyses in order to increase statistical power.

Following these initial assessments on 11 subjects, to increase statistical power for both behavioral and fMRI analyses, data for the Load condition were collapsed together to maximize the possibility of comparing both the immediate and long-term effects of emotional distraction on perception and memory. In considering the main goal of the study (i.e., identification of common neural correlates of the opposing effects of emotional distraction), it was necessary to focus on conditions where the opposing effects of emotion were seen behaviorally, as this was the basis of our fMRI investigation. These opposing effects were identified in only one condition (i.e., Short Dur Hi-Load – see the third set of bars from left in the top and bottom panels of **Figure 2**). While, ideally, would have been to investigate the neural correlates of these opposing effects in the Hi-Load condition only, separation according to all conditions was possible only in data from 11 subjects. Hence, to increase the statistical power for brain imaging analyses, it was necessary to collapse the Load condition. This was the most valid choice for further analyses, as collapsing Load maintained the opposing effects (see first set of bars in **Figure 3**), and thus allowed us to perform the fMRI analyses corresponding to these behavioral effects on data from 16 subjects. Although collapsing Load might have overall weakened the effects observed in the fMRI data, seemingly driven by the Hi-Load condition (compare **Figures 2** and **3**), this was a necessary and advantageous trade-off, as it allowed for investigation of data from more subjects, although our sample size in this follow-up investigation ($N = 16$) was slightly smaller than what is suggested for the use of brain-behavior relationships (Lieberman et al., 2009), which we employed in the original report ($N = 18$; Shafer et al., 2012). Furthermore, collapsing Load conditions was critical, as also described below, to identify brain activity associated with the impact of emotion on memory using the subsequent memory paradigm (Dolcos et al., 2004b, 2011; Shafer et al., 2011), because it allowed analysis of data when considering Emotion (Emo vs. Neu), Duration (Short vs. Long), and Memory (Remembered vs. Forgotten) variables.

Again, when analyzing data from the larger sample ($N = 16$), to establish the link between the immediate and long-term effects

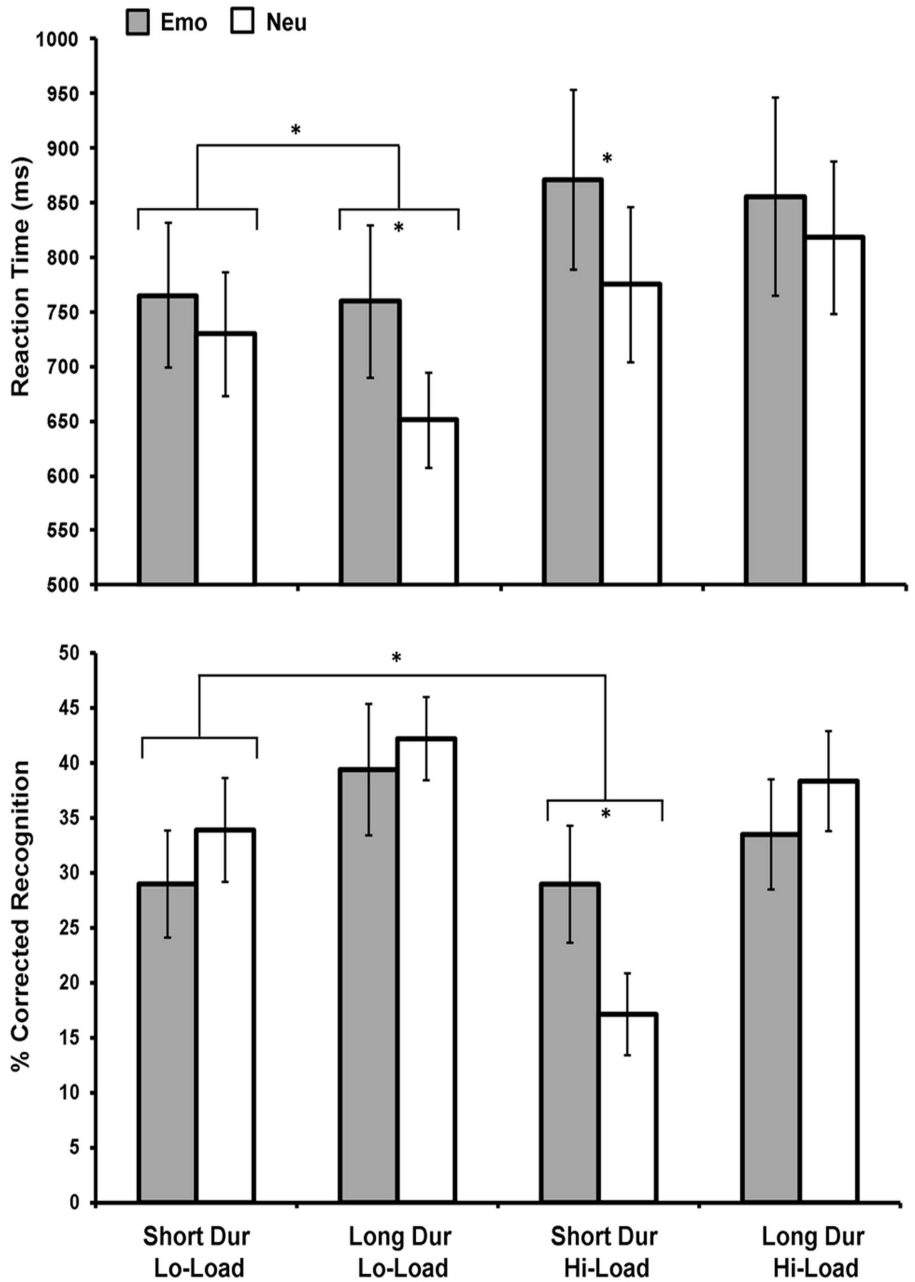

FIGURE 2 | Emotional distraction impaired perceptual performance under increased availability of processing resources while enhanced memory for task-irrelevant emotional distraction occurred only under limited processing resources. Figure shows average reaction time (top panel) and corrected recognition data (bottom panel) for correctly identified rectangles during the perception task for 11 participants. Impaired perceptual task performance for Emo distracters was greatest when resources were most available (under conditions of Lo-Load and Long Dur). Instead, enhanced memory for Emo distracters was found only when resources were the most limited (for Hi-Load and Short Dur trials). An interaction was also found between emotion and load under short stimulus duration due to decreased memory for Neu distracters under conditions of limited resources, while memory for Emo distracters remained unaffected. Emo, Emotional; Neu, Neutral; Lo-Load, Low Perceptual Load; Hi-Load, High Perceptual Load; Dur, Stimulus Duration. *Significant at $p \leq 0.05$, two-tailed.

of emotion in the behavioral data, the immediate impact of emotion was calculated on the items that were also later remembered in the memory task (Hits). The immediate and long-term effects of emotion were examined by performing a repeated measures ANOVA [Emotion (Emo, Neu); Duration (Short, Long)] on RT and corrected recognition data, respectively. Importantly, these analyses allowed us to examine how manipulations of attentional demand at encoding for task-irrelevant emotional items

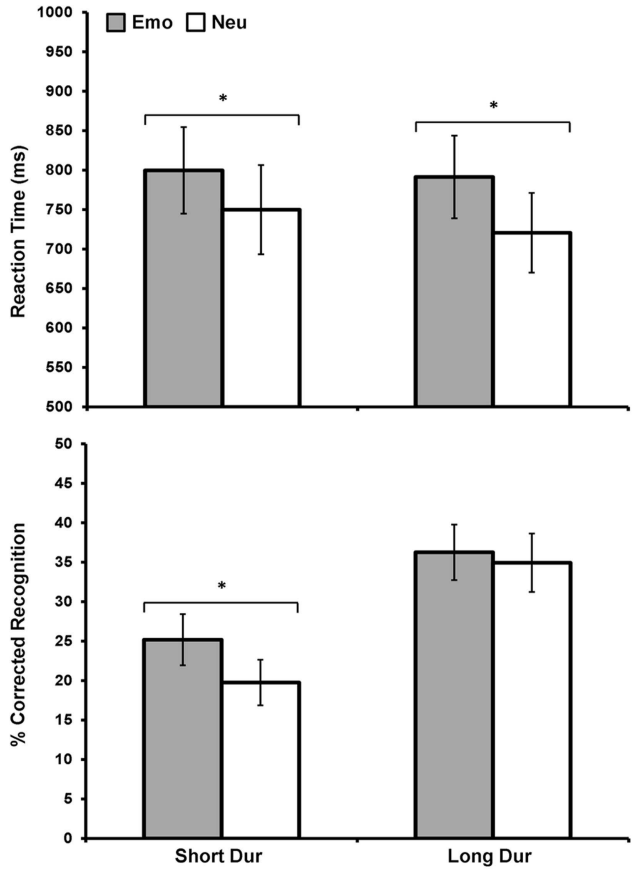

FIGURE 3 | Direct relationship between emotional distraction and memory, under limited resource availability. Figure shows the item categories meeting both criteria – impaired perception and enhanced memory – for 16 subjects, after collapsing the Load variable. Top panel shows average response latency data for correctly identified rectangles that were later remembered. Bottom panel shows average corrected recognition data for the same items. As illustrated, the left side of the two graphs shows the direct relationship between emotional distraction and memory under limited resources during encoding, by identifying the items for which the opposing immediate/impairing vs. long-term/enhancing effects co-occur. Although these opposing effects are driven by the Hi-Load condition (as evident in **Figure 2**), it was necessary to collapse Load to increase power for analyses of brain imaging data using the subsequent memory paradigm. Emo, Emotional; Neu, Neutral; Dur, Stimulus Duration. *Significant at $p \leq 0.05$, two-tailed.

influenced emotion's long-term impact on memory. Pairwise comparisons were Bonferroni corrected.

fMRI DATA ANALYSIS

Imaging data analyses were performed on data from 16 participants, using SPM in conjunction with in-house custom Matlab scripts. Statistical analyses were preceded by the following preprocessing steps: quality assurance, TR alignment, motion correction, coregistration, normalization, and smoothing (8 mm^3 Kernel). For individual analyses, task-related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM2, was used to model the effects of interests and other confounding effects (e.g., session effects and magnetic field drift). There were 14 first-level regressors: eight task variables (Emo Long Dur Hits, Emo Short Dur Hits, Neu Long Dur Hits, Neu Short Dur Hits, Emo Long Dur Misses, Emo Short Dur Misses, Neu Long Dur Misses, Neu Short Dur Misses) +6 motion regressors (three translations, three rotations). Group analyses were conducted using random-effects models to assess the effect of distracter content and stimulus duration on perception and memory processes. Based on the behavioral results and to increase statistical power, as mentioned above, the analyses of fMRI data assessed emotion's interaction with stimulus duration (Short vs. Long), which yielded the strongest effects of emotion on both perception and memory. Furthermore, to ensure that subjects had maintained focus on the primary task and also in accordance with the behavioral data where Hits were driving the main effect of emotion on perceptual performance, the fMRI data analyses for the immediate effect of emotion were performed on items presented during the perception task that were performed correctly in the perception task and that were later remembered (Hits). For the analyses of the long-term impact, subsequent memory effects were calculated for emotional and neutral items and then compared to each other (Dolcos et al., 2004b, 2011; Shafer et al., 2011). As with the analyses concerning the immediate effect of emotion, fMRI data analyses for the long-term effect only included items were correct in the perception task.

The main goal of fMRI data analyses was to identify the neural correlates linking the immediate impact of emotional distraction on perception and the long-term impact of emotion on memory, and to identify the neural correlates specific to one or the other of these effects. To accomplish this goal, we compared activity in brain regions specifically sensitive to the presence of emotional distraction and activity in brain regions sensitive to the emotional enhancement of memory. First, paralleling the behavioral data, we investigated areas associated with emotional distraction for the short duration condition. A *t*-map was computed contrasting short emotional (Emo Short Dur Hits) vs. short neutral (Neu Short Dur Hits) items.

Next, we investigated areas associated with the emotional enhancement of memory. Areas of brain activity reflecting the emotional enhancement of memory during encoding found for the short duration condition in the behavioral data were examined by employing subtraction analysis looking at differences in activity between remembered (Hits) and forgotten (Misses) items (Dm/Subsequent Memory Effect) for Emo Short Dur compared to Neu Short Dur stimuli. First we computed *t*-maps for differences in activity due to memory for Emo and Neu Short Dur items separately [Emo Short Dur Dm = (Emo Short Dur Hits−Emo Short Dur Misses), Neu Short Dur Dm = (Neu Short Dur Hits−Neu Short Dur Misses)]. Then, to identify activity associated with the emotional enhancement of memory, we employed subtraction analysis where the individual *t*-map for Neu Short Dur Dm was subtracted from the individual *t*-map for Emo Short Dur Dm. To make sure that these differences were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition, this interaction was then inclusively masked by Emo Short Dur Dm [(Emo Short Dur Dm−Neu

Short Dur Dm) ∩ (Emo Short Dur Dm)]. Lastly, to ensure that activity was unique to the behavioral effects found in the Short Dm condition, we exclusively masked the above resulting contrast with activity that was present when assessing emotional memory for the long duration condition [(Emo Long Dur Dm−Neu Long Dur Dm) ∩ (Emo Long Dur Dm)]. As with the behavioral data, we collapsed confidence ratings in the fMRI analyses in order to increase statistical power. While this prevented us from disentangling similarities and differences between emotional distraction on recollection vs. familiarity memory processes, by separately examining high vs. low confidence responses (Daselaar et al., 2006; Hayes et al., 2011), we did find the majority of responses to be high in confidence and therefore our data may be more indicative of recollection processes (confidence ratings distribution: high = 71%, medium = 20%, low = 9%).

After separately identifying the neural correlates of the immediate and long-term effects of emotion, we investigated brain regions that contribute both to emotion's initial impact on perception and attention and to emotion's enhancement of memory. To identify brain regions responsible for both effects, we examined overlapping areas of activation between the immediate and long-term impact of emotion using a conjunction analysis. This was performed using the contrast for the effect of emotion during perception for the Short Dur condition and the contrast for the emotional enhancement of memory during the Short Dur condition (Emo Short Dur Hits > Neu Short Dur Hits) ∩ {[(Emo Short Dur Dm − Neu Short Dur Dm) ∩ (Emo Short Dur Dm)], exclusively masked by [Emo Long Dur Dm − Neu Long Dur Dm) ∩ (Emo Long Dur Dm)]}.

Finally, to dissociate areas that showed specificity only to immediate or long-term effects of emotion, we exclusively masked the contrasts computed above. For example, to identify activity associated only with the long-term effect of emotion, we exclusive masked the contrast associated with the long-term effect with that of the immediate effect and vice-versa when identifying activity unique to the immediate effect. Also, to investigate the significance of overlapping or dissociating activations, brain-behavioral relationships were investigated by correlating brain activity with indices of performance (RTs for the immediate and Corrected Recognition scores for the long-term effects). These latter analyses targeted MTL emotion (AMY) and memory (HC) structures.

Cortical structures were assessed with a threshold of $p \leq 0.005$, uncorrected, and *a priori* MTL areas of interest were assessed with a threshold of $p \leq 0.05$; in addition, for all interaction analyses an intensity threshold of $p \leq 0.05$ was employed. These thresholds were selected to stay consistent with our previous report using the same task (Shafer et al., 2012), so that similar inferences could be made across reports. It should also be noted that the interactions were masked by specific main effects using an intensity threshold of $p \leq 0.005$. Hence, the joint probability of the resulting conjunction maps was of $p \leq 0.00025$, which is the product of their independent probabilities (0.05×0.005; Fisher, 1950). Similarly, for all interaction analyses examining MTL regions (i.e., AMY and HC) an intensity threshold of $p \leq 0.05$ was employed for the interaction, which was then masked by a specific effect using an intensity threshold of $p \leq 0.05$. Hence, the joint probability of the resulting conjunction map was of $p \leq 0.0025$. Finally, for correlation analyses in MTL emotion- and memory-related regions a threshold of $p \leq 0.05$ was used and all correlation maps were also masked by the statistical map that they were being correlated with. For example, in MTL regions for the immediate effect of emotion, a double conjunction was used where the correlation map ($p \leq 0.05$) was inclusively masked by the effect of emotion for the Short Dur condition ($p \leq 0.05$), resulting in a joint probability of $p \leq 0.0025$. Similarly, for the long-term effect of emotion a triple conjunction was used $p \leq 0.05$ for the correlation map, $p \leq 0.05$ for the interaction, and $p \leq 0.05$ for the Emo Short Dm, thus the resulting probability was $p \leq 0.000125$. Details about the joint thresholds are provided in the legend of each figure and table. An extent threshold of five contiguous voxels was used in all analyses.

RESULTS

BEHAVIORAL RESULTS

Direct relationship between immediate and long-term impact of emotional distraction, in the context of overall dissociating impairing vs. enhancing effects

Unlike the immediate impact of emotional distraction on perceptual processing, which was greatest when processing resources were most available (easy task and long presentation time), the long-term impact of emotion on memory was the strongest when processing resources were least available (difficult task and short presentation time). Initial analysis ($n = 11$) on RT data for the immediate impairing effect of emotional distraction on perception showed a main effect of Emotion, $F(1, 10) = 10$, $p = 0.01$, Load, $F(1, 10) = 8.03$, $p = 0.02$, and an Emotion × Load × Duration interaction, $F(1, 10) = 5.34$, $p = 0.04$. As previously found with a larger sample (Shafer et al., 2012), trials with negative distracters took longer to respond to than those with neutral distracters and Hi-Load trials took longer to respond to than Lo-Load trials. Furthermore, the three-way interaction was driven by an Emotion × Duration when Load was low, $F(1, 10) = 5.59$, $p = 0.04$, but not high, $F(1, 10) = 0.629$, $p = 0.45$ (see **Figure 2**, top panel). Analysis on corrected recognition data ($n = 11$) revealed a main effect of Load, $F(1, 10) = 5.39$, $p = 0.04$, and Duration, $F(1, 10) = 23.34$, $p \leq 0.001$, but no main effect of Emotion. However, a marginally significant Emotion × Load × Duration interaction was present, $F(1, 10) = 3.82$, $p = 0.08$, and *post hoc* analyses showed that this interaction was driven by an Emotion × Load interaction for short duration items, $F(1, 10) = 7.84$, $p = 0.02$. Specifically, emotion significantly affected memory in the Hi-Load, $t(10) = 2.31$, $p = 0.04$, but not in the Lo-Load, $t(10) = 0.976$, $p = 0.35$, condition for Short Dur items (see **Figure 2**, bottom panel).

As mentioned in Section "Materials and Methods," to increase statistical power for both behavioral and fMRI analyses, data for the Load condition were collapsed together to maximize the possibility of comparing both the immediate and long-term effects of emotional distraction on perception and memory, respectively. This was critical to identify brain activity associated with the impact of emotion on memory using the subsequent memory paradigm (Dolcos et al., 2004b, 2011; Shafer et al., 2011). Collapsing load allowed us to include 16 subjects in our behavioral and imaging analysis for the memory data.

Importantly, collapsing load allowed for identification with increased statistical power of common effects for the immediate (impairing) and long-term (enhancing) impact of emotion, which occurred for the short presentation time (250 ms; see **Figure 3**). Emotional distracters that were later remembered had a significant effect on discrimination performance such that there was delayed RT when distracters were emotional compared to neutral, $F(1, 15) = 9.99$, $p = 0.006$. This effect of emotion was found for both short, $t(15) = -2.15$, $p = 0.05$, and long, $t(15) = -2.56$, $p = 0.02$, duration conditions (**Figure 3**, top panel). Examination of corrected recognition scores also with load conditions collapsed together, for the items that were presented previously as distracters during the perception task, revealed an effect of emotion only for the short condition $t(15) = 2.1$, $p = 0.05$ (**Figure 3**, bottom panel). Analyses also identified a significant main effect of duration, $F(1, 15) = 26.06$, $p \leq 0.001$, with memory performance being overall better for long vs. short duration items.

In summary, the behavioral data showed that the long-term impact of emotion on memory was the strongest when processing resources were least available, and both the immediate and long-term effects of emotion (albeit opposing) occurred for the short duration items. Hence, the fMRI analyses focused on identifying common and dissociable neural correlates associated with those items.

fMRI RESULTS

Common brain regions for the immediate and long-term impact of emotion

Investigation of overlapping effects of emotion on perception and memory in the Short Dur condition identified common areas of activation in ventrolateral PFC (vlPFC), temporal occipital cortex, in the left angular gyrus (AG), precuneus, and left AMY and hippocampus (HC; see **Figure 4** and **Table 1**).

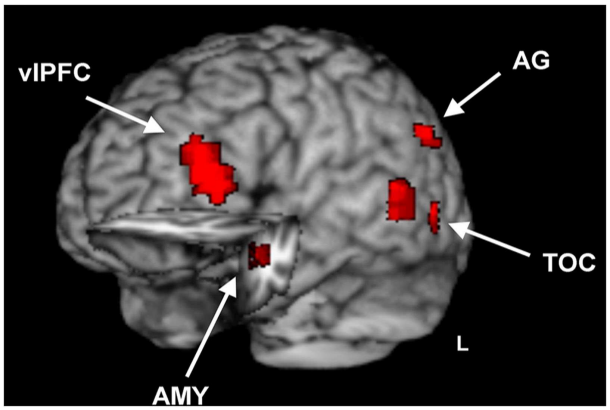

FIGURE 4 | Brain regions sensitive to opposing emotional modulation during emotional distraction vs. memory. Image shows common regions of response to the impairing effect of emotional distraction and the enhancing effect of emotional memory, superimposed on a high resolution brain image displayed in a tridimensional view using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Cut-out in the left hemisphere also reveals similar response to emotional distraction and memory in the left AMY and anterior HC. The conjunction activation maps contributing to the overlap were identified separately for immediate/distraction and long-term/enhanced memory for the short Dur condition. The maps contributing to the final conjunction map were separately created for the immediate and long-term impact, which each resulted from maps with $p < 0.005$, $p < 0.05$, $p < 0.005$ for the main effect of emotion, interaction, and mask maps, respectively, for areas outside of the MTL, and $p < 0.05$, $p < 0.05$, and $p < 0.05$ for the main effect of emotion, interaction, and mask maps, respectively, for areas within the MTL (AMY, HC); see Section "Materials and Methods" for details. vlPFC, ventrolateral Prefrontal Cortex; TOC, Temporal Occipital Cortex; AG, Angular Gyrus; AMY, Amygdala; HC, Hippocampus; L, Left.

Hemispheric disassociation in the amygdala and hippocampus linked to emotional distraction and memory

In addition to identifying brain regions associated with both the immediate and long-term effects of emotion on perception and memory, areas that dissociated between these effects were also identified. This analysis identified a hemispheric disassociation in the AMY and HC, which although showed bilateral activation in response to emotional distraction, showed memory-related activity only in the left hemisphere (see **Figure 5**). To further explore whether this disassociation was indicative of functional asymmetry, we extracted functional regions of interest (ROI) for the three clusters of activity identified in these regions for the long-term effect (i.e., left AMY, anterior HC, and posterior HC) and their homologous counterparts in the right hemisphere. Each functional ROI was comprised of the peak voxel of each cluster along with its neighboring voxels. We then conducted a repeated measures ANOVA with Emotion and Hemisphere as within subject variables for each of the three clusters. Results for the AMY and anterior HC clusters were similar and showed a main effect of Emotion [AMY, $F(1, 15) = 6.39$, $p = 0.02$; anterior HC, $F(1,15) = 8.39$, $p = 0.01$], but no effect of Hemisphere or interaction between Emotion and Hemisphere. However, the posterior HC cluster, not only showed a main effect of Emotion, $F(1, 15) = 5.63$, $p = 0.03$, but also an Emotion × Hemisphere interaction, $F(1, 15) = 7.75$, $p = 0.02$). *Post hoc* analysis revealed that differences between emotional and neutral short Dm were significant in the left, $t(15) = 3.96$, $p = 0.001$, but not right hemisphere $t(15) = 0.18$, $p = 0.86$. While the Emotion × Hemisphere interaction in the AMY and anterior HC clusters was not significant, *post hoc* examination showed the left hemisphere to indeed have stronger statistical difference between emotional and neutral short Dm compared to the right hemisphere; L. AMY, $t(15) = 2.87$, $p = 0.01$; R. AMY, $t(15) = 1.89$, $p = 0.08$; L. anterior HC, $t(15) = 2.81$, $p = 0.01$; R. anterior HC, $t(15) = 2.01$, $p = 0.06$.

Further investigation of activity in these regions using brain-behavior correlations revealed that the left AMY activity identified for the long-term effect of emotion on memory was correlated with the corresponding behavioral difference in memory performance, $r = 0.57$ $p \leq 0.05$ (**Figure 5**); activity in the left anterior HC (Talairach coordinates: $x = -30$, $y = -7$, $z = -15$) also correlated with memory performance, $r = 0.55$, $p \leq 0.05$, but the cluster size was less than five voxels. In addition, a positive brain-behavior covariation was also identified between activity in the left entorhinal cortex (Talairach coordinates: $x = -16$, $y = 4$, $y = -17$) and RT during the perceptual task, but this effect was not specific to emotional distraction ($r = 0.7$, $p \leq 0.05$), as the same relationship was found for the neutral items ($r = 0.69$, $p \leq 0.05$).

Table 1 | Common areas of activation for the immediate and long-term effects of emotion.

Brain regions		Talairach coordinates				*T* values		Cluster size
		BA	*x*	*y*	*z*	Immediate	Long term interaction/mask	
lPFC	R. Middle frontal gyrus	9	43	18	28	4.2	2.64/3.17	20
vlPFC	L. Inferior frontal gyrus	45	−45	28	13	5.08	5.6/3.63	49
	R. Inferior frontal gyrus	45	47	20	14	4.56	3.44/3.04	20
PoCG	R. Post central gyrus	43	54	−11	15	3.47	3.28/3.38	6
PC	L. Angular gyrus	39	−50	−68	29	4.45	4.65/4.62	6
	L. Precuneus	7	−2	−57	35	3.68	3.23/3.47	7
TOC	l. Middle temporal gyrus	21	−57	−47	6	4.02	3.28/3.68	15
	R. Middle temporal gyrus	19	39	−75	19	4.29	3.09/3.19	19
	L. Inferior temporal gyrus	37	−46	−65	1	4.15	1.91/3.53	5
	R. Inferior temporal gyrus	19	40	−65	−5	4.32	2.78/3.91	26
	L. Fusiform Gyrus	37	−42	−50	−5	4.75	2.52/3.14	12
	R. Fusiform Gyrus	37	36	−49	−14	3.78	2.06/3.46	14
	R. Superior occipital gyrus	19	35	−76	27	3.53	2.77/3.31	19
MTL	L. Amygdala		−27	−4	−15	3.05	2.49/1.82	21
	L. Hippocampus		−27	−39	−3	3.5	3.13/2.56	18
	L. Uncus	28	−23	8	−21	4.08	2.65/2.34	32
	L. Parahippocampus	34	−27	4	−14	4.5	3.37/1.87	32
		36	−34	−34	−14	3.65	2.32/2.41	18
Midbrain	L. Substania nigra		−8	−12	−11	4.08	3.69/3.28	8

Table identifies brain regions associated with the both the immediate (impairing) and long-term (enhancing) effects of emotion. Regions were identified by a conjunction map between separately identified regions for immediate and long-term effects. To make sure differences for the long-term effect of emotion were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition, the long-term interaction was inclusively masked by Emo Short Dur Dm = (Emo Short Hits > Emo Short Misses). To ensure activity for the long-term effect of emotion was associated only with the behavioral effect seen for the Short Dur condition, the t-map for long-term effect of emotion for Short Dur was exclusively masked by the long-term effect of emotion for the Long Dur. Conjunction map = Immediate map (Emo Short Dur Hits > Neu Short Dur Hits) ∩ Long-term map {[(Emo Short Dm) vs. (Neu Short Dm) ∩ (Emo Short Dm)], exclusively masked by [(Emo Long Dm) vs. (Neu Long Dm) ∩ (Emo Long Dm)]}. lPFC, lateral Prefrontal Cortex; vlPFC, Ventral Lateral Prefrontal Cortex; PoCG, Post Central Gyrus; PC, Parietal Cortex; TOC, Temporal Occipital Cortex; MTL, Medial Temporal Lobe. T values reported for cortical regions met the criteria of $p < 0.005$, $p < 0.05$, and $p < 0.005$, for the immediate effect, long-term interaction and long-term mask, respectively; values reported for the MTL regions met the criteria of $p < 0.05$ for all effects.

Emotional distraction vs. memory-specific brain activity

Analysis investigating specific response to the immediate vs. long-term impact also identified activity linked only to the immediate impact of emotional distraction. This analysis identified a number of brain areas to have regional or sub-regional specificity, with areas being only involved in the immediate impact of emotional distraction or contributing to both immediate and long-term effects, respectively. Sub-regional specificity was found in the superior frontal gyrus, AG, inferior frontal gyrus, post central gyrus, precuneus, cingulate gyrus, fusiform gyrus, inferior and middle temporal gyri, as well as left AMY, HC, and paraHC regions. For example, inferior frontal gyrus (Brodmann Area 45) was identified for the immediate and long-term impact, whereas Brodmann Area 47 was associated with only the immediate impact of emotional distraction on perception. Regions that exhibited specificity to the immediate effect of emotional distraction included, medial frontal gyrus, precentral gyrus, superior temporal gyrus, and middle occipital gyrus (see **Tables 1** and **2**).

Analyses investigating specific response to the immediate vs. long-term impact also identified activity linked only to the memory-enhancing effect of emotion. Again, as with the immediate impact reported above, sub-regional and regional specificity were found. Sub-regional specificity was identified in the superior frontal gyrus, cingulate gyrus, and precuneus. Of the activity identified as being unique to the long-term impact of emotion on memory only one region, the superior parietal lobe was solely specific to emotional memory.

Collectively, the analyses of fMRI data targeting activity associated with the conditions that had opposing effects of emotional distraction on immediate and long-term processing identified both areas of overlap and areas dissociating these two effects. The overlapping areas are involved in the mechanisms responsible for both the immediate/impairing impact of emotional distraction on perception and for the long-term/enhancing impact on memory for the distracters themselves. Areas dissociating between these two effects were found to do so with either regional or sub-regional specificity. These findings will be discussed in detail below.

DISCUSSION

The present study used an experimental paradigm that manipulated the degree of resource availability for processing task-irrelevant emotional distraction, to determine how the initial

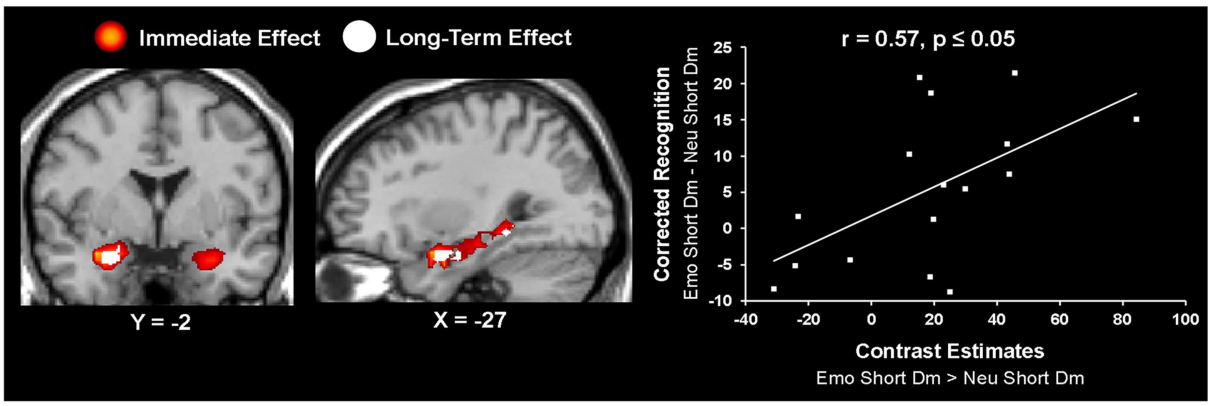

FIGURE 5 | Hemispheric dissociation linked the immediate vs. long-term effects of emotion in the amygdala and hippocampus. Left panel shows a coronal view of the AMY, highlighting the lateralization effect showing the bilateral immediate effect of emotion (in red) and the left-lateralized long-term effect of emotion (in white). The middle panel shows a sagittal view of the three left hemisphere AMY-HC areas identified for the long-term effect of emotion. These activations are overlapped on the activity identified for the immediate effect of emotion. The right panel shows a scatterplot illustrating the results from the peak voxel of the correlation calculated on the contrast estimates from the long-term effect of emotion during the short Dur condition and the corresponding behavioral data, as extracted from left AMY (Talairach coordinates: $x = -27$, $y = -4$, $z = -15$). The contrast used for creating the correlation t-maps was [(Emo Short Dm vs. Neu Short Dm) ∩ (Emo Short Dm)]. The resulting joint probability for the correlation t-map is $p < 0.000125$; see Section "Materials and Methods" for details. Emo, Emotional; Neu, Neutral; Dur, Stimulus Duration; Dm, Difference due to memory; AMY, Amygdala; HC, Hippocampus.

impact of emotional distraction is related to the long-term impact on memory for the distracters themselves. Our study yielded three main findings. First, we observed a direct relationship between the immediate (impairing) and long-term (enhancing) impact of emotion, only under conditions of limited resources during encoding. Second, linked to this behavioral effect, we identified a number of brain regions of the emotion network that were involved in both the immediate and long-term impact of emotion, including AMY-HC regions, the ventrolateral prefrontal, temporal occipital, and inferior parietal cortices. Third, responses in specific regions and sub-regions differentiated between immediate and long-term effects of emotion, both in terms of overall activation and co-variation with performance. Medial frontal, precentral, superior temporal, and middle occipital gyri activity was specifically associated with the immediate impact of emotion, whereas activity in superior parietal cortex was specifically associated with the long-term impact of emotion on memory. Furthermore, left AMY co-variation with subsequent memory performance and a hemispheric asymmetry of posterior HC activity in contributing to subsequent memory performance suggest a disassociation in the hemispheric contribution of these regions to the impact of emotional distraction on perception and memory.

DIRECT RELATIONSHIP BETWEEN IMMEDIATE AND LONG-TERM IMPACT OF EMOTIONAL DISTRACTION, IN THE CONTEXT OF OVERALL DISSOCIATING IMPAIRING vs. ENHANCING EFFECTS

The fact that a direct relationship between the immediate (impairing) and long-term (enhancing) impact of emotion only occurred under conditions of limited processing resources during encoding suggest that the immediate impact of emotional distraction does not translate into long-term effects in a one-to-one fashion. Thus, the conditions in which emotional distraction produces the strongest initial impact on perception do not necessarily lead to the strongest long-term impressions on memory for the distracters themselves. In other words, the aspects that we may remember most may not necessarily be those that initially distracted us while trying to perform a perceptual task. Instead, emotional distraction also produced a boost in long-term memory only under conditions of limited processing resources, which as also discussed below suggest that the direct link between opposing immediate (impairing) and long-term (enhancing) effects of emotional distraction under these circumstances involves automatic mechanisms. The engagement of such mechanisms to process task-irrelevant emotional information presented concurrently with a perceptual task led to reallocation of processing resources by emotional distraction, which in turn initiated processing that also resulted in better memory for the distracters themselves.

The absence of a direct link between the two opposing effects when more processing resources are available does not exclude the possibility that automatic mechanisms of emotion processing are also involved in circumstances that do not lead to a long-term memory advantage for emotional distraction. It is possible that, when more resources are available for processing during encoding, there is more opportunity for the mediated mechanisms to come "online" and influence memory for both emotional and neutral items, and hence the benefit that both emotional and neutral information receives from the mediated influences overshadows the memory boost produced for the emotional information by the automatic mechanisms alone. As a result, emotion's impact on memory is diminished, although overall the memory performance is enhanced in conditions of increased engagement of mediated mechanisms at encoding (e.g., longer processing time). Although the effect of stimulus duration on memory is consistent with findings from research investigating the role of stimulus durations around this range (i.e., 250–1000 ms) on memory performance (Hulme and Merikle, 1976; Christianson and Fallman, 1990; Clark-Foos and Marsh, 2008), the absence of an

Table 2 | Dissociable areas of activation for the immediate and long-term effects of emotion.

Brain regions		Talairach coordinates				*T* values		Cluster Size
		BA	*x*	*y*	*z*	Immediate	Long-term interaction/mask	
IMMEDIATE								
mPFC	L. Superior frontal gyrus	8	−9	39	47	6.66		83
	R. Superior frontal gyrus	8	6	27	54	4.66		
	L. Medial frontal gyrus	10	−5	51	5	6.31		6
lPFC	L. Middle frontal gyrus	6/8	−39	10	44	3.95		13
vlPFC	L. Inferior frontal gyrus	47	−41	26	−8	4.12		6
		46	−42	40	4	5.6		29
	R. Inferior frontal gyrus	47	40	36	−2	3.96		43
Insula	L. Insula	13	−34	8	−14	5.30		83
PrCG	R. Precentral gyrus	4	50	−6	44	3.89		7
PoCG	R. Postcentral gyrus	3	28	−33	49	3.33		5
Cingulate	L. Cingulate gyrus	31	−13	−25	45	4.86		20
PC	L. Inferior parietal lobe	40	−54	−39	43	3.6		7
	L. Precuneus	7	−35	−73	44	4.55		75
	R. Precuneus	7	17	−73	44	3.59		8
	L. Angular gyrus	39	−53	−64	30	4		75
	R. Angular gyrus	39	39	−76	30	3.51		5
TOC	L. Fusiform gyrus	37	−49	−45	−12	4.80		80
		20	−34	−37	−18	4.72		
	L. Middle temporal gyrus	21	−49	9	−28	3.51		7
		37	−49	−66	4	4.65		47
	L. Inferior temporal gyrus	20	−49	−7	−19	3.76		13
	L. Superior temporal Gyrus	22	−64	−36	7	3.93		16
	R. Middle occipital gyrus	18	28	−92	3	4.03		7
MTL	L. Amygdala		−19	−4	−14	2.85		30
	R. Amygdala		21	0	−17	3.21		41
	L. Hippocampus		−27	−19	−12	3.59		76
	R. Hippocampus		29	−23	−12	2.88		65
	R. Parahippocampus	28	25	−23	−12	3.72		8
		30	14	−35	−2	3.21		10
		34	25	4	−17	3.59		5
Subcortical	R. Thalamus-Pulvinar		17	−32	5	3.91		10
Midbrain	R. Substania nigra		10	−23	−9	3.55		9
	R. Red nucleus		6	−16	8	3.74		
Cerebellum	L. Culmen		−8	−46	−7	3.47		10
LONG-TERM								
mPFC	L. Superior frontal gyrus	9	−5	56	24		2.85/4.13	6
Insula	R. Posterior insula		32	−29	13		2.33/3.37	5
Cingulate	L. Anterior cingulate	32	−1	30	22		3.83/3.2	5
		24	−8	43	12		3.06/3.9	6
	R. Anterior cingulate	32	3	42	16		2.9/3.03	6
PC	R. Precuneus	7	5	−74	55		3.17/3.25	8
	R. Superior parietal lobe	7	24	−65	35		3.04/3.32	7
	L. Superior parietal lobe	7	−17	−59	52		2.94/3.64	5
Subcortical	L. Putamen		−23	1	11		3.22/3.58	7

Table identifies brain regions associated with the either the immediate or long-term effect of emotion. Immediate effect = (Emo Short Dur Hits > Neu Short Dur Hits), exclusively masked by the long-term effect of emotion at $p < 0.05$. The long-term effect of emotion was found by calculating the interaction between Emo Short Dm vs. Neu Short Dm. This interaction was then inclusively masked by Emo Short Dur Dm, to make sure the differences were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition. To ensure activity for the long-term effect of emotion was associated only with the behavioral effect seen for the Short Dur condition, the t-map for long-term effect of emotion for Short Dur was exclusively masked by the long-term effect of emotion for the Long Dur. Long-term effect = {[(Emo Short Dm) vs. (Neu Short Dm)∩(Emo Short Dm)], exclusively masked by [(Emo Long Dm) vs. (Neu Long Dm)∩(Emo Long Dm)]}. Lastly, the entire long-term effect was exclusively masked by the immediate effect of emotion at $p < 0.05$. mPFC, Medial Prefrontal Cortex; lPFC, lateral Prefrontal Cortex; vlPFC, Ventral Lateral Prefrontal Cortex; PrCG, Precentral Gyrus; PoCG, Post Central Gyrus; PC, Parietal Cortex; TOC, Temporal Occipital Cortex; MTL, Medial Temporal Lobe. Significance threshold for the immediate effect of emotion is $p < 0.005$ and $p < 0.05$, for cortical and MTL regions, respectively. Significance threshold for the long-term effect of emotion is $p < 0.005$ for the mask for cortical regions and $p < 0.05$ for targeted MTL regions and $p < 0.05$ for the interaction for both cortical and MTL regions.

emotion advantage is inconsistent with previous findings identifying such an effect within divided attention paradigms (Kern et al., 2005; Talmi et al., 2007; Pottage and Schaefer, 2012); it is consistent, however, with previous studies using level of processing paradigms where memory for neutral items may be on par with that of emotional items for deep levels of processing (Reber et al., 1994; Jay et al., 2008).

Elimination of the memory advantage for the emotional stimuli encoded in conditions of enhanced contribution of the mediated mechanisms may be due to a similar boost in memory performance for the neutral items or due to the engagement of mechanisms that diminished the impact of emotion on memory. Regarding the first possibility discussed earlier, with more resources available for distraction it is possible that the addition of mediated processes may have also benefited the neutral items, for instance, due to the engagement of working memory, semantic processing, and attentional processing (Dolcos et al., 2011). Regarding the alternative possibility, given our experimental design in which emotional information was task-irrelevant and participants were instructed to focus on the main perception task, it may be the case that under long stimulus duration, participants engaged processing to diminish the impact of emotional distraction. Thus, while they could not avoid being initially distracted by them (as indicated by the RT data in the perception task), trying to diminish their initial impact might have interfered with the mechanisms necessary for the emotional boost in memory performance. Importantly, however, we did observe a one-to-one relationship when only limited resources were available during the initial processing of emotional distraction.

COMMON AND DISSOCIABLE BRAIN REGIONS FOR THE IMMEDIATE AND LONG-TERM IMPACT OF EMOTION

Turning to the neural correlates of the link between the initial and long-term effects of emotional distraction on perception and memory, analyses of fMRI data identified a number of brain regions of the emotion processing network whose activity was linked to both the immediate/impairing and long-term/enhancing impact of emotion. Consistent with the engagement of automatic mechanisms linking the two opposing effects, we identified overlapping activity in AMY-HC regions, which have been linked to both emotion perception (Sergerie et al., 2008) and emotional memory (Dolcos et al., 2004b).

Hemispheric disassociation in the amygdala and hippocampus linked to emotional distraction and memory

Even though the functional ROI analysis did not confirm our impression of a hemisphere effect in the left AMY and anterior HC for the memory-enhancing effect of emotion, it did identify a hemisphere effect in the posterior HC. The general increased Emo Dm in the AMY and anterior HC is consistent with previous research (Dolcos et al., 2004b), and although there was no hemisphere effect in these two regions for the long-term effect, the increased statistical strength due to decreased variance in Emo Dm response observed in the left hemisphere comparisons, along with the left AMY brain-behavior co-variation, suggest a more consistent left hemisphere involvement in emotional memory for this task. This is consistent with findings from several studies of emotional memory (Canli et al., 2000; Mickley and Kensinger, 2008; Talmi et al., 2008; Mickley Steinmetz and Kensinger, 2009), although it is not consistent with findings of recent meta-analyses (Murty et al., 2010; Kim, 2011), which did not identify patterns of lateralization in the AMY linked to memory. One possibility is that in conditions of processing emotional information as task-irrelevant distraction the right AMY engages rapidly, producing a phasic response to the global arousal properties of the stimulus, thus extracting only crude information to prepare for immediate action. On the other hand, the engagement of the left AMY is associated with a tonic response reflecting the extraction of more specific information and elaborative processing of the emotional qualities of the stimuli, which also contributes to enhanced memory (Markowitsch, 1998; Phelps et al., 2001; Glascher and Adolphs, 2003; Sergerie et al., 2008). Furthermore, and as suggested by the increased variance in the right AMY and anterior HC for Emo Dm, the lack of right hemisphere involvement in emotional memory in these regions might be due to increased susceptibility of their right hemisphere response to individual differences.

Emotional distraction and memory-specific brain activity: increased medial frontal, precentral, superior temporal, and middle occipital activation linked to enhanced emotional distraction and increased parietal activation linked to enhanced emotional memory

Brain regions found to have specificity in response to emotional distraction or memory dissociate between areas that are susceptible to immediate emotional modulation from those that are susceptible to long-term emotional modulation. Importantly, these regions identify unique relationships that are specific to different points along the information processing timeline (i.e., more immediate relationships between emotion and perception and longer-term relationships between emotion and memory). While there were several areas that exhibited sub-regional specificity for these effects, further investigations using a more rigorous approach (e.g., anatomical ROIs) is necessary to draw strong interpretations about these findings. As such, the current discussion will focus on identified regional specificity – i.e., activity in the medial frontal, precentral, superior temporal, and middle occipital gyri, associated only with emotional distraction, and activity in the superior parietal cortex, associated only with emotional memory.

Increased activation in the medial frontal gyrus (BA 10) linked to the immediate impact of emotional distraction on perception is consistent with a large body of research showing sensitivity of this region in response to emotional stimuli (Keightley et al., 2003; Scheuerecker et al., 2007), possibly reflecting increased motivational significance of emotional stimuli (Dolcos et al., 2004a). Activity in the precentral gyrus has been reported in a number of studies of emotion processing (e.g., LaBar et al., 1998; Morris et al., 1998; Canli et al., 2002; Keightley et al., 2003; Wicker et al., 2003; Scheuerecker et al., 2007) although in most investigations this area was not the main the focus of investigation and hence typically was left out of discussion. Studies discussing its role, though, have suggested the involvement of this region is due to the motor control/imagery associated with viewing emotionally arousing stimuli (Canli et al., 2002; de Gelder et al., 2004) or with imitating emotional expressions (Lee et al., 2006). Although the superior temporal gyrus activity identified here is too inferior to be

included in the temporal parietal junction (TPJ), its involvement is consistent with evidence linking activity in this region with attentional re-orienting associated with processing task-irrelevant emotional distraction(Corbetta and Shulman, 2002; Vuilleumier and Driver, 2007; Frank and Sabatinelli, 2012), and with evidence linking TPJ activity with sustained visual spatial attention (Thakral and Slotnick, 2009) toward the emotionally distracting stimuli. Lastly, increased middle occipital activity likely reflects a boost in visual processing received by emotional items linked to increased extrastriate processing mediated by both cortical-cortical and subcortical-cortical mechanisms (Vuilleumier and Huang, 2009).

Turning to the area associated only with emotional memory, it is interesting to note the effect observed in the superior parietal cortex dissociated from that identified in the inferior parietal lobe, which was present in both the immediate and long-term effects of emotional distraction. Considering these results in the framework of stimulus-driven vs. goal-directed attention networks (Corbetta and Shulman, 2002), the present results are consistent with the idea that memory benefits from both increased bottom-up contributions through inferior parietal activation (possibly reflecting capture of attentional resources) and top-down involvement from superior parietal cortex (possibly indicative of goal-relevant processing). Given that the target and distracter were contiguous and presented simultaneously, the superior parietal activity for items that were later remembered may be the result of goal-relevant processing resources being allocated to the item as a whole, and thus the emotional distracters benefited under conditions where an increase in goal-relevant resources was needed to successfully perform the task (i.e., short stimulus duration). The contribution of the superior parietal cortex to the long-term effect of emotional distraction is also consistent with event-related potential evidence that encoding processes contributing to enhanced memory for emotional events occur faster than for neutral events (Dolcos and Cabeza, 2002), presumably within a time window consistent with the present short duration. This evidence along with our findings suggest that parietal contribution to emotional memory may, in fact, be optimized under shorter exposure durations, perhaps indicating that its contribution can be more automatic than previously thought.

CONCLUSION

In summary, this study provided initial evidence for a direct link between the immediate and long-term impact of emotional distraction during a lower-level perceptual task in which the to-be-remembered items were task-irrelevant. First, a direct relationship between the immediate and long-term effects of emotional distraction was identified only under conditions of limited processing resources available at encoding. Also, the engagement of mediated mechanisms, once additional resources were available, diminished the effect of the automatic mechanisms on memory. Second, consistent with a role of automatic mechanisms linking these opposing effect, AMY-HC activity was common to both the immediate/impairing effect of emotional distraction and the long-term/enhancing impact of emotion on memory. Furthermore, whereas a hemispheric disassociation was identified in AMY and HC, with both sides associated with emotional distraction and left AMY and anterior HC linked to emotional memory, a clear asymmetry was identified in the posterior HC, with only the left side contributing to successful encoding of emotional items. Third, brain regions were identified as being specifically susceptible to emotional modulation during distraction or memory formation, with activity in the medial frontal, precentral, superior temporal, and medial occipital gyri being linked to increased impact of emotional distraction, and activity in the superior parietal cortex being linked to better memory for emotional distracters. These findings demonstrate that the relationship between emotional distraction and memory is context dependent and that specific brain regions may be more or less susceptible to the direction of emotional modulation (*increased* or *decreased*), depending on the task manipulation and processes investigated. Understanding the mechanisms linking emotional distraction and memory offers important insight into clinical conditions, such as depression and anxiety, where both of these effects are dysfunctionally exacerbated.

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Neural correlates of opposing effects of emotional distraction on working memory and episodic memory: an event-related fMRI investigation

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A fundamental question in the emotional memory literature is why emotion enhances memory in some conditions but disrupts memory in other conditions. For example, separate studies have shown that emotional stimuli tend to be better remembered in long-term episodic memory (EM), whereas emotional distracters tend to impair working memory (WM) maintenance. The first goal of this study was to directly compare the neural correlates of EM enhancement (EME) and WM impairing (WMI) effects, and the second goal was to explore individual differences in these mechanisms. During event-related functional magnetic resonance imaging (fMRI), participants maintained faces in WM while being distracted by emotional or neutral pictures presented during the delay period. EM for the distracting pictures was tested after scanning and was used to identify successful encoding activity for the picture distracters. The first goal yielded two findings: (1) emotional pictures that disrupted face WM but enhanced subsequent EM were associated with increased amygdala (AMY) and hippocampal activity (ventral system) coupled with reduced dorsolateral PFC (dlPFC) activity (dorsal system); (2) trials in which emotion enhanced EM without disrupting WM were associated with increased ventrolateral PFC activity. The ventral-dorsal switch can explain EME and WMI, while the ventrolateral PFC effect suggests a coping mechanism. The second goal yielded two additional findings: (3) participants who were more susceptible to WMI showed greater amygdala increases and PFC reductions; (4) AMY activity increased and dlPFC activity decreased with measures of attentional impulsivity. Taken together, these results clarify the mechanisms linking the enhancing and impairing effects of emotion on memory, and provide insights into the role of individual differences in the impact of emotional distraction.

Keywords: emotional interference, emotional control, emotional memory, AMY, HC, vlPFC, dlPFC

INTRODUCTION

Emotion is a "double-edged sword" that can either enhance or hinder various aspects of our cognition and behavior. For instance, the emotional charge of an event can lead to better episodic memory (EM) for that event, whereas task-irrelevant emotional distraction can impair working memory (WM), if presented concurrently with goal-relevant information (reviewed in Dolcos et al., 2011; Dolcos et al., 2012; Iordan et al., 2013b; also see Cohen and Henik, 2012 in the present research topic). Although previous research has independently investigated these two opposing effects of emotion on EM and WM, very little is known about their interactions and the associated neural mechanisms. Concomitant investigation of enhancing and impairing effects of emotion and of their interaction is important because they tend to co-occur. For instance, hearing a gunshot may enhance memory for central aspects of what was happening at the time, while impairing memory for peripheral details (Christianson and Loftus, 1991; Kensinger et al., 2007; also see Chiu et al., 2013 in the present research topic). On the other hand, increased distraction from ongoing goals produced by task-irrelevant emotional stimuli may also lead to better memory for the distracting information. The present study directly compared the neural mechanisms of EM enhancing (EME) and WM impairing (WMI) effects of emotion, by using a novel paradigm that measured both the initial impact of emotional distraction on WM and the long-term EM for the distracters themselves. The study also investigated the role of

individual differences in these effects. Below, we briefly review the available evidence concerning the EME and WMI effects of emotion, as derived from their separate investigation, and introduce the rationale for the present approach.

THE LINK BETWEEN OPPOSING EFFECTS OF EMOTIONAL DISTRACTION ON WM AND EM

In both EM and WM literatures, emotion effects have been interpreted in terms of bottom-up and top-down systems. Bottom-up systems are assumed to be relatively automatic and guided by the stimuli, whereas top-down systems are assumed to be controlled and guided by task goals. In the EM literature, the bottom-up and top-down systems have been described as direct vs. indirect and a collaborative relationship has been emphasized, whereas in the WM literature, the bottom-up and top-down systems have been described as *hot* vs. *cold* and the findings have shown an opposing relationship. Importantly, these dissociations also map onto similar ventral and dorsal neural systems, but it is unclear to what extent they overlap or are dissociable.

Available evidence from us and others regarding the EME effect of emotion suggests the existence of two neural routes (reviewed in LaBar and Cabeza, 2006; Dolcos et al., 2011, 2012). Briefly, one route (direct/bottom-up), consisting of emotion-based (amygdala, AMY) and memory-based (hippocampus, HC) medial-temporal lobe (MTL) structures, is thought to operate more automatically and largely independently of resources at the time of encoding (Dolcos et al., 2004b; Shafer and Dolcos, 2012). The other route (indirect/top-down), involving prefrontal and parietal cortices (PFC and PC, respectively), is thought to depend on the contribution of other processes to the memory-enhancing effect of emotion, such as semantic memory, executive control, and attention (Dolcos et al., 2004a). Of note, the evidence supporting the dissociation between these two routes also maps onto a ventral/dorsal location of the associated neural correlates – AMY-HC vs. PFC/PC, respectively. Consistent with this dissociation, recent evidence identified AMY-HC contribution (bottom-up/ventral) to emotional EME following a shallow level of processing during encoding, and the engagement of cognitive control areas (top-down/dorsal) under a deep level of processing (Ritchey et al., 2011). Similarly, evidence from a recent study by Shafer and Dolcos (2012), investigating the link between the immediate and long-term impact of emotional distraction, identified bottom-up/ventral (AMY-HC) mechanisms contributing to EME by emotion, in conditions of limited resources available during encoding. Overall, the available evidence concerning the EME effect points to contributions of both direct/bottom-up/ventral and indirect/top-down/dorsal mechanisms.

Turning to the WMI effect of emotional distraction, a series of functional magnetic resonance imaging (fMRI) studies by Dolcos et al. and studies by others (Dolcos and McCarthy, 2006; Dolcos et al., 2006, 2008; Anticevic et al., 2010; Chuah et al., 2010; Denkova et al., 2010; Iordan et al., 2013a; reviewed in Iordan et al., 2013b) shed light on the neural mechanisms underlying the impact of transient emotional distraction on WM maintenance. Interestingly, similar to the EME effect of emotion, these studies also identified a ventral-dorsal dissociation in the neural correlates of the WMI effect of emotional distraction. Using an experimental design where task-irrelevant emotional distracters were presented during the delay interval of a WM task, these studies demonstrated that the impairing effect of emotional distraction was linked to opposing patterns of activity in brain regions associated with a ventral neural system involved in *hot* emotional processing (*HotEmo* system) and a dorsal neural system associated with *cold* executive processing (*ColdEx* system) (reviewed in Dolcos et al., 2011). Specifically, emotional distraction enhanced activity in ventral-affective regions, such as the AMY, while disrupting delay activity in dorsal-executive regions, such as the dorsolateral PFC (dlPFC) and the lateral parietal cortex (LPC). Given the role of the latter brain regions in attentional processes and active maintenance of goal-relevant information in WM (D'Esposito et al., 2000; Hopfinger et al., 2000; Levy and Goldman-Rakic, 2000; Miller and Cohen, 2001), these findings suggest that activity in the affective and executive neural systems is strongly interconnected, such that increased activity in the ventral-affective regions disrupts activity in the dorsal-executive system and results in WM impairment, possibly as a result of a re-allocation of processing resources by emotional distraction (Dolcos and McCarthy, 2006). Noteworthy, the studies investigating the WMI effect of emotion also identified the neural correlates of coping with emotional distraction (Dolcos and McCarthy, 2006; Dolcos et al., 2006, 2008; Chuah et al., 2010; Denkova et al., 2010; Iordan et al., 2013a; reviewed in Iordan et al., 2013b), and highlighted the role of both basic emotion processing regions (AMY) and regions involved in cognitive control (PFC). In this network, AMY presumably signals PFC regions about the presence of emotional, potentially distracting, stimuli, and thus the need to engage cognitive control mechanisms to cope with emotional distraction (Dolcos et al., 2006, 2008; Chuah et al., 2010; Denkova et al., 2010).

Given the lack of evidence linking these opposing effects of emotion, the first goal of the present study was to directly compare the neural mechanisms of EME and WMI effects. The evidence discussed above identified the involvement of both bottom-up/ventral and top-down/dorsal mechanisms involved in the EME and WMI effects of emotion. What remains unclear, however, is the link between these two opposing effects and the role of the associated neural correlates. Specifically, it is unclear how the initial response to emotional distraction, leading either to impairment or to coping in the presence of task-irrelevant emotional stimuli, influences the long-term memory for this potentially distracting information, and what the neural mechanisms linking the immediate and long-term effects of distracting emotions are. Of particular importance is identification of the role of both ventral and dorsal brain areas that have been commonly identified by the separate investigations of the EME and WMI effects of emotion – i.e., AMY-MTL and PFC.

THE ROLE OF INDIVIDUAL DIFFERENCES IN THE IMPACT OF EMOTIONAL DISTRACTION

The second goal of the present investigation concerns the role of individual differences in the relationship between the enhancing and impairing effects of emotion. This is justified by evidence that, in addition to general emotion processing, both EME and WMI effects of emotion, along and with the engagement of coping strategies are susceptible to individual variations (Canli et al.,

2002; Hamann and Canli, 2004; Touryan et al., 2007; Dolcos et al., 2008; Hooker et al., 2008; Iordan et al., 2013a). This suggests that differences that affect both ventral/bottom-up and dorsal/top-down mechanisms, involved in emotional and cognitive/executive processing, can influence the initial impact of emotional distraction on WM (Dolcos et al., 2008; Iordan et al., 2013a) and possibly the relationships between the WMI and EME effects. Of particular relevance for the present investigation is evidence from a recent study showing that, while in most participants emotional distraction impaired WM performance, in some subjects it did not have a detrimental effect (Dolcos et al., 2008), thus pointing to individual variation in the susceptibility to emotional distraction. However, because that study did not involve assessments of participants in cognitive and emotional domains other than related to the WM task and emotional ratings, it is not clear why some participants were more susceptible to transient task-irrelevant emotional distraction than others.

APPROACH, EXPERIMENTAL DESIGN, AND PREDICTIONS

These issues were investigated using fMRI recording in conjunction with a novel experimental design that assessed both the EME and WMI effects of emotion, within the same participants. In a previous investigation, we examined similar issues by measuring the initial impact of emotional distraction on lower-level perceptual processing and the long-term EME effect (see Shafer and Dolcos, 2012 in the present research topic). Here, we investigated the link between these opposing effects by measuring the initial impact of emotional distraction on higher-level cognitive processes (i.e., WM), which may be differentially affected by distraction (Lavie, 2005). Specifically, we used an adapted version of our WM task with distraction (Dolcos and McCarthy, 2006), to assess not only the initial impact of emotional distraction on WM but also the long-term impact on EM for the distracters themselves (**Figure 1**). To investigate the role of individual differences, aspects of processing in both affective and cognitive domains where measured and investigated linked to differential emotional sensitivity and susceptibility to emotional distraction.

Based on the extant evidence concerning the enhancing and impairing effects of emotion discussed above, we made the following predictions. Regarding the first goal, we predicted that (1) if resource re-allocation by emotional distraction during the WM task coincides with the initiation of processing that also leads to enhanced EM for the distracters themselves, the same AMY regions should play a key role in both of these opposing effects. However, this would produce different effects in brain areas linked to initial WMI (reduced dlPFC activity) vs. long-term EME (increased MTL activity) effects, respectively; (2) coping with emotional distraction would be associated with increased activity in PFC regions. Regarding the second goal, we predicted that individual variations in the susceptibility to emotional distraction would differentially affect the response in emotion and cognitive/executive control brain areas. Specifically, participants with increased susceptibility to WMI would show (3) greater AMY increases and PFC reductions to emotional distraction, and (4) increased AMY activity and decreased PFC activity linked to measures indexing enhanced susceptibility to distraction and impaired executive control.

MATERIALS AND METHODS

SUBJECTS

Analyses were performed on data from 17 young (19–35 years of age) healthy right-handed female participants, recruited from Duke University community. We restricted our study to female participants in order to maintain homogeneity of the subject sample, as evidence shows that women and men differ in terms of general emotional reactivity (Shields, 1991; Lang et al., 1993; Hamann and Canli, 2004), response to emotional distraction (Iordan et al., 2013a), and emotion regulation (Thayer et al., 2003; Matud, 2004; McRae et al., 2008; Mak et al., 2009; Domes et al., 2010; Denkova et al., 2012). Also, this allowed a more direct comparison with findings from similar previous investigations (Dolcos

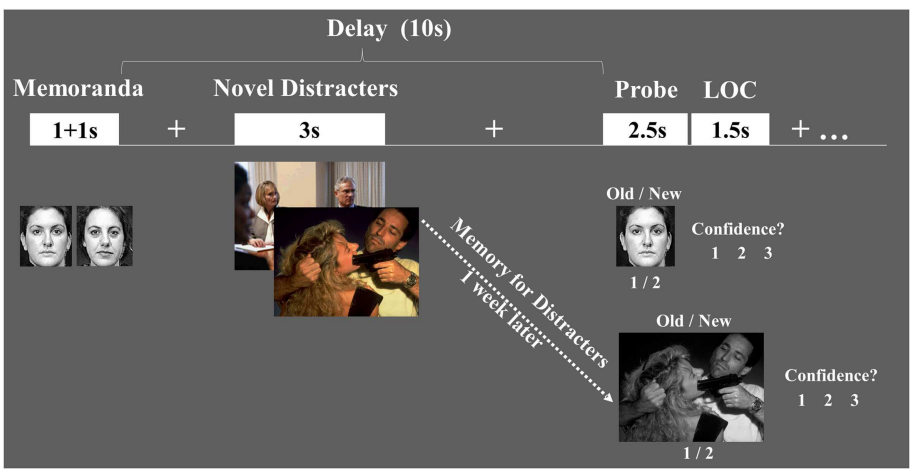

FIGURE 1 | Diagram of the combined WM-EM task. Functional magnetic resonance imaging (fMRI) data were recorded while subjects performed a working memory (WM) task with distraction. WM performance was measured using an *Old/New* recognition memory task, followed by a level of confidence (LOC) task (1 = Low, 2 = Medium, 3 = High). EM for the distracters themselves was measured 1-week later, outside the scanner, and also involved *Old/New* and LOC assessments.

and McCarthy, 2006; Dolcos et al., 2006, 2008). The experimental protocol was approved by the Institutional Review Board at Duke University Medical Center and all subjects provided informed consent.

EXPERIMENTAL PROCEDURES

Subjects performed a combined WM-EM task measuring both the immediate impact of emotion on WM and the long-term impact on EM for the distracters themselves.

Working memory task

Subjects were scanned while performing a delayed-response WM task with novel distracters presented during the delay interval between memoranda and probes (Dolcos and McCarthy, 2006). The memoranda consisted of pairs of human faces (50% females/50% males) presented successively one at a time, that were masked to exclude non-facial features and displayed in black-and-white for increased task difficulty. The distracters consisted of highly arousing, negative emotional scenes (e.g., mutilations, aggressive behaviors) and low arousing neutral scenes (e.g., mundane activities), selected from the International Affective Picture System (IAPS, Lang et al., 2008) and supplemented with in-house pictures used in previous studies (Dolcos and McCarthy, 2006), to equate for complexity and human presence across conditions. The average IAPS arousal/valence ratings for the emotional and neutral scenes, respectively, were 5.91/2.32 and 3.53/5.32. To maximize their impact, distracters were presented in color.

Eight sets of 16 trials (8 emotional and 8 neutral distracters per set) were created and randomly assigned to 8 experimental blocks/runs. To avoid induction of longer-lasting effects, the trials within each run were pseudo-randomized, so that no more than two consecutive trials of the same type were presented. To prevent possible biases resulted from using the same run order, participants were assigned different run orders; a total of 8 different run orders were involved. Each trial started with the presentation of face memoranda (1 s + 1 s), which subjects were instructed to encode and maintain in WM during the delay interval (10 s) between the offset of the second memoranda and the onset of the memory probe. Presentation of the novel picture distracter started 4 s after the offset of the memoranda, and occurred for a total time of 3 s. Participants were instructed to look at the distracters but maintain focus on the WM task, and when the single face probe appeared they had to indicate by a button press whether the face was part of the current memorandum (*Old*) or not (*New*); 50% of the probes were *Old* and 50% were *New*. Subjects were instructed to make quick and accurate responses while the probes were on the screen, and then they also rated the level of confidence (LOC) of their responses, using a 3-point Likert scale (1 = *lowest*, 3 = *highest*). The LOC rating was followed by a 10 s inter-trial interval (ITI), to allow the hemodynamic response to return to baseline. The total length of each trial was 26 s.

Episodic memory task

One week following scanning, subjects performed a surprise memory task that tested EM for the emotional and neutral pictures previously presented as distracters during the WM task. The test included 192 pictures (96 emotional) out of which ∼2/3 were old pictures. Old and new pictures did not reliably differ in normative intensity scores. All pictures were displayed in black-and-white for increased task difficulty. Trials within each block were pseudo-randomized, so that no more than two consecutive trials of the same type were presented, and participants were assigned different run orders. Each picture was displayed for 3 s and subjects had to indicate by a button press whether the picture was previously seen during the WM task (*Old*) or not (*New*). Participants were encouraged to make quick and accurate responses while the picture was on the screen, and then they also rated the LOC of their responses, using a 3-point Likert scale (2 s); the LOC rating was followed by a 2 s ITI.

ADDITIONAL BEHAVIORAL AND PERSONALITY MEASURES

These measures aimed at assessing aspects related to both emotion and executive processing. Following scanning, subjects rated the emotional intensity of the emotional and neutral distracters using a 9-point Likert scale (1 = *lowest*; 9 = *highest*). These ratings were assessed to confirm that the negative distracters were perceived as more emotional than the neutral distracters, and to calculate individual indices of emotional sensitivity to the distracters (see Behavioral Data Analyses). Given the possibility that differences in both emotional and cognitive control/executive processing can modulate the relationships between the immediate and long-term impact of emotion, measures indexing general emotion and executive processing were also assessed in participants. Aspects related to general emotional state were assessed using the Positive and Negative Affective Schedule (PANAS-S; Watson et al., 1988), both at the beginning and at the end of both parts of the study; repeated PANAS measures were involved to make sure that subjects' emotional state did not dramatically change as a result of participating in the study. Aspects related to executive processing were assessed using the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995; Spinella, 2007), which measures a trait that has been consistently linked to impaired executive performance (Enticott et al., 2006; Pietrzak et al., 2008; Kam et al., 2012). This scale yields 3 second-order factors: attentional impulsiveness (AI), motor impulsiveness (MI), and non-planning impulsiveness (NpI).

IMAGING PROTOCOL

Scanning was conducted on a 4T GE scanner (General Electric, Milwaukee, WI, USA). After localizer, anatomical series, and high-order shimming, functional volumes were acquired using an inverse-spiral pulse sequence (echo time: 31 ms; field of view: 25.6 cm × 25.6 cm; repetition time: 2000 ms). Each volume consisted of 30 functional slices acquired axially (voxels size: 4 mm × 4 mm × 4 mm), thus allowing full-brain coverage. Anatomical scans consisted of high-resolution three-dimensional spin-echo structural images, which were acquired coplanar with the functional slices (1 mm × 1 mm × 1 mm; anatomical-functional ratio = 4:1).

BEHAVIORAL DATA ANALYSES

Responses in the WM task were classified in one of the four categories derived from signal detection theory (Macmillian and Creelman, 1991): (1) *Hits* = Probes from memoranda (*Old*) correctly classified as *Old*, (2) *Misses* = Probes from

memoranda incorrectly classified as *New*, (3) *Correct Rejections* (CRs) = New probes correctly classified as *New*, and (4) *False Alarms* (FAs) = New probes incorrectly classified as *Old*. For the EM task, the probes were subsets of the distracters used in the WM task, supplemented with new pictures as foils. Responses in the EM task were classified similarly to the WM task into Hits, Misses, CRs, and FAs. Percentages of probes correctly identified as being *Old* or *New* were also calculated for each participant [% Correct = (% Hits + % CR)/2]. Although based on previous studies (Dolcos and McCarthy, 2006; Dolcos et al., 2008; Anticevic et al., 2010; Denkova et al., 2010) we expected that most participants would show impaired WM performance to emotional distraction, we also expected that this effect would not be consistent across all subjects (Dolcos et al., 2008). Hence, participants who showed the expected pattern of lower WM performance to emotional than to neutral distraction were assigned to the WMI subgroup, while the rest were assigned to the Non-WMI subgroup (see the Results for the average WM performance scores and the number of subjects in the WMI and Non-WMI subgroups). The dependent variables for the behavioral performance analyses were the percentage of correct scores in the WM and EM tasks. The independent variables for the same analyses were trial type (emotional vs. neutral) and subgroup (WMI vs. Non-WMI). Differences in performance between the two trial types (emotional vs. neutral) were assessed separately for the WM and EM tasks, using *t* statistics. Differences between the two subgroups (WMI vs. Non-WMI) were assessed using *t* statistics and mixed-model ANOVAs. Based on the subjects' ratings of the emotional intensity of the distracters, individual indices of emotional sensitivity to the present distracters were calculated separately for each subject by subtracting the average of their own ratings for the neutral distracters from the average of their ratings for the emotional distracters. Finally, to assess the role of individual differences in the relationships between behavioral performance and personality, correlations between WM/EM performance and affective/executive measures were also calculated.

fMRI DATA ANALYSES

Imaging data analyses were performed using SPM2 in conjunction with in-house custom MATLAB scripts. Statistical analyses were preceded by the following preprocessing steps: quality assurance, TR alignment, motion correction, coregistration, normalization, and smoothing (8 mm^3 Kernel). For individual analyses, task-related activity was identified by convolving a vector of the onset times of the distracters with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM2, was used to model the effects of interests and other confounding effects (e.g., session effects and magnetic field drift). There were 14 first-level regressors: eight task variables (Emo *WM-R and EM-R*, Emo *WM-F and EM-R*, Emo *WM-R and EM-F*, Emo *WM-F and EM-F*, Neu *WM-R and EM-R*, Neu *WM-F and EM-R*, Neu *WM-R and EM-F*, Neu *WM-F and EM-F*) and six motion regressors (three translations, three rotations). Group analyses were conducted using random-effects models to assess the effect of distracter content. The following contrast images were taken to the second level: (1) contrasts linking WM impairment due to emotion and EM for the distracters themselves (i.e., Emo *WM-F and EM-R* > Neu *WM-F and EM-R*, and the reverse), (2) contrasts linking WM success in the face of emotional distraction and subsequent EM for the distracters themselves (i.e., Emo *WM-R and EM-R* > Neu *WM-R and EM-R*, and the reverse), (3) contrasts linking both WM and EM success, calculated separately for trials with emotional and neutral distracters that were subsequently remembered in the EM task (i.e., Emo *WM-R and EM-R* > Emo *WM-F and EM-R*, and Neu *WM-R and EM-R* > Neu *WM-F and EM-R*).

The main goals of fMRI data analyses were to (i) identify the neural mechanisms linking the immediate impact of emotional distraction on WM and the EM for the distracters themselves, and to (ii) investigate the role of individual differences in these effects. To accomplish these goals, brain regions in the ventral-affective and dorsal-executive neural systems, specifically sensitive to the presence of emotional distraction were defined as *a priori* regions of interest, based on our initial study using a similar WM task with distraction (Dolcos and McCarthy, 2006). That study involved three distracter conditions: emotional (Emo), neutral (Neu), and scrambled (Scr), and for the purpose of the current study the following two *t* maps were used: Emo > Scr, to identify regions of the ventral-affective system and Scr > Emo, to identify regions of the dorsal-executive system, both identified using an intensity threshold of $p < 0.005$, uncorrected (Lieberman and Cunningham, 2009). Activity within these *a priori* defined ROIs from Dolcos and McCarthy (2006) was further investigated to address the questions of the present investigation, as described below.

Related to our first main goal, to identify brain regions linking the WMI and EME effects of emotion, *t* maps contrasting the emotional and neutral distracters were computed for items that impaired WM and were later remembered: (Emo *WM-F and EM-R* > Neu *WM-F and EM-R*), for activity in the ventral-affective network and (Neu *WM-F and EM-R* > Emo *WM-F and EM-R*), for activity in the dorsal-executive network. To identify brain mechanism linking the initial effect on WM to the long-term impact on EM in conditions where participants coped with the presence of emotional distraction, we investigated activity for trials in which emotion enhanced EM without disrupting WM. For this, first, *t* maps contrasting the emotional and neutral distracters were computed for items that were associated with WM success and were later remembered: (Emo *WM-R and EM-R* > Neu *WM-R and EM-R*), for activity in regions of the ventral network, and (Neu *WM-R and EM-R* > Emo *WM-R and EM-R*), for activity in regions of the dorsal network. Then, to further check whether activity in these regions was also specifically linked to WM success, the maps identifying regions associated with WM success for items that were later remembered, as identified above, were inclusively masked with *t* maps contrasting activity for items associated with WM success vs. impairment. The latter were separately calculated for trials with emotional and neutral distracters that were subsequently remembered in the EM task: (Emo *WM-R and EM-R* > Emo *WM-F and EM-R*), for activity in ventral, and (Neu *WM-R and EM-R* > Neu *WM-F and EM-R*), for activity in dorsal regions. The main focus of the present investigation was on identifying the brain regions involved in *linking* the immediate impact of emotional distraction on WM and the subsequent EM for the distracters themselves. For this reason, the main analysis focused on trials corresponding to distracters meeting both criteria (impaired WM and were subsequently remembered: i.e.,

WM-F and EM-R). Activity for these trials was separately identified for the emotional and neutral distracters and then compared to each other. Hence, the link between WM and EM was identified at the level of the trials and the impact of emotion was calculated relative to the neutral stimuli with a similar outcome – i.e., Emo *WM-F and EM*-R > Neu *WM-F and EM-R*, for activity in the ventral system, and the reverse contrast for activity in the dorsal system. Importantly, the fact that some participants did not show an overall impairing effect of emotional distraction at the behavioral level did not affect the analyses of the fMRI data, as the trials linking the opposing effect of emotion on WM and EM could be identified in all participants regardless of the overall impact of emotional distraction on WM.

Related to the second main goal, the role of individual differences in the susceptibility to emotional distraction was investigated using two main analyses, as follows. One analysis involved comparisons of subjects showing a WMI effect (WMI subgroup) with those who did not (Non-WMI subgroup), in response to emotional relative to neutral distraction. This analysis involved a between-samples comparison, to identify differences in brain activity between these two subgroups, in the ventral and dorsal networks. For this, subject-level effects contrasting brain activity for emotional and neutral distracters were first calculated (i.e., Emo > Neu, in the ventral, and Neu > Emo, in the dorsal system), to be used as input for second level between-groups *t*-tests. Then, to make sure that regions identified by the between-groups analysis were also sensitive to the effects of emotional distraction, the resulting *t* maps were inclusively masked with statistical maps identifying a main effect of emotion in the targeted group (*in*creased vs. *de*creased activity in the ventral or dorsal systems, respectively). For example, increased activity to emotional distraction in the ventral system, in the WMI subgroup was identified by [WMI subgroup (Emo > Neu) > Non-WMI subgroup (Emo > Neu)] ∩ [WMI subgroup (Emo > Neu)]. This more stringent approach ensured that the effect captured by the between-groups comparison came from a difference going in the expected direction in the group of interest, and is not driven by the lack of effects coupled with differences going in opposite direction in the other group. The other main analysis involved identification of brain-behavior relationships by calculating co-variations between the fMRI signal and behavioral and personality measures, to further clarify the significance of effects in brain areas showing differences in activation. The focus was on measures indexing susceptibility to distraction, as reflected in the WM performance and personality scales, such as BIS, which measures a personality trait that has been linked to impaired executive performance. While the stringent masking criteria employed may have offered enough protection against Type I error, given the relatively small sample (Yarkoni, 2009), the findings regarding individual differences are provisional in nature and should be treated with caution.

Within the *a priori* defined *ventral* and *dorsal* ROIs (based on the Dolcos and McCarthy, 2006 data identified at a threshold of $p < 0.005$), activity in the areas identified by the contrasts described above was assessed with a threshold of $p < 0.05$, uncorrected. This allows direct comparison with a complementary study investigating similar issues in the perceptual domain (Shafer and Dolcos, 2012). Unless otherwise noted, an extent threshold of five contiguous voxels was used in all analyses. Finally, in-house manually traced ROIs on the normalized SPM brain template and the Automated Anatomical Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) were used to confirm localization of and to display the effects from AMY and HC.

RESULTS

BEHAVIORAL RESULTS

Overall, WM performance was equivalent across both trial types [emotion = 74.8%, neutral = 74.8%; $t(16) = 0.01$; $p = 0.989$]. Although this result was inconsistent with the expected pattern of lower WM performance in response to emotional relative to neutral distracters observed in other previous investigations using similar tasks with emotional distraction (e.g., Dolcos and McCarthy, 2006; Anticevic et al., 2010; Denkova et al., 2010), this result was not totally surprising given the expected individual variation in the response to emotional distraction (Dolcos et al., 2008). To investigate whether this null finding at the group level was related to individual differences in behavioral responses, we examined whether subsets of subjects showed different WM performance to emotional relative to neutral distracters. For this, the subjects sample was split into two subgroups, as a function of WM performance, as follows. Subjects showing the expected pattern of impaired WM performance to emotional relative to neutral distracters (WMI subgroup), and subjects not showing this pattern (Non-WMI subgroup). About 60% of the subjects ($N = 10$) showed the pattern of impaired WM performance to emotional relative to neutral distracters [WMI subgroup: emotional = 75%, neutral = 79%; $t(9) = 2.76$, $p = 0.022$], whereas the remaining ∼40% of the subjects ($N = 7$) did not show it (Non-WMI subgroup: emotional = 74.4%, neutral = 68.7%). It should be noted that the fact that some participants did not show an overall impairing effect does not affect the analyses of the fMRI data focusing on the trials associated with WM errors and successful subsequent EM. Regarding the EM performance, as expected, the majority of subjects (∼90%, $N = 15$) remembered better the emotional relative to neutral distracters [emotional = 75.5%, neutral = 69.3%; $t(16) = 3.44$, $p = 0.003$], and this effect was strongest in trials associated with the highest level of confidence [LOC3: emotional = 35.1%, neutral = 27.9%; $t(16) = 3.52$, $p = 0.003$]. Further explorations of EM performance revealed a tendency for the participants who showed impaired WM performance to emotional distraction (WMI subgroup) to have better EM for the distracters themselves (WMI subgroup: emotional EM = 78.1%, neutral EM = 72.8%; Non-WMI subgroup: emotional EM = 71.8%, neutral EM = 64.4%), although this difference was not statistically significant. A mixed-design ANOVA (WM subgroup × Distracter type) on EM performance confirmed these impressions, yielding a significant main effect of Distracter type [$F(1, 15) = 11.62$, $p = 0.004$], a marginal effect of subgroup [($F(1, 15) = 4.18$, $p = 0.059$], and no interaction effects ($p = 0.585$). Overall, these results show a differential impact of emotional distraction on WM vs. EM and suggest a link between the initial and long-term effects of distraction.

To further elucidate these differential effects of emotional distraction on WM and EM, additional analyses were performed on behavioral and personality data. These analyses revealed that

subjects showing systematic impaired WM performance in the presence of emotional distraction (WMI subgroup) also experienced the emotional distracters as more emotional. Specifically, in addition to overall greater ratings for emotional than neutral distracters observed across all subjects [emotional = 6.5; neutral = 2.5; $t(16) = 15.56$, $p < 0.001$], the WMI subgroup also perceived the negative pictures as more negative relative to the neutral pictures (WMI subgroup: emotional = 6.8, neutral = 2.5; Non-WMI subgroup: emotional = 6, neutral = 2.6). This was reflected in higher individual indices of emotional sensitivity [$t(15) = 1.77$, $p = 0.049$, one-tailed]. In addition, the WMI subgroup also had lower scores in the Self Control subscale of the BIS questionnaire [$t(15) = 1.77$, $p = 0.049$, one-tailed]. There were no other differences between the WMI vs. Non-WMI subgroups. Interestingly, correlation analyses showed that the scores for negative general affective state, as assessed by post-WM task PANAS-state, were negatively correlated* with the WM scores for trials with negative distracters ($r = -0.51$, $p = 0.043$; *based on data from 16 subjects due to missing PANAS values for one participant). In other words, participants who were affected more by the negative distraction during the WM task also reported more negative emotions following the task.

Taken together, the behavioral results identified differential effects of emotion on WM vs. EM, consistent with a link between the initial and long-term effects of distraction, and that these effects were influenced by individual differences. Results from analyses of brain imaging data conducted to investigate the neural correlates of these effects are presented below.

fMRI RESULTS

Neural mechanisms linking the differential impact of emotional distraction on WM and EM

Concomitant WMI and EME effects of emotion were associated with increased AMY-HC activity and reduced dlPFC activity. Analyses contrasting activity for the emotional and neutral distracters that disrupted face WM performance but were later remembered in the EM task (i.e., Emo *WM-F and EM-R* > Neu *WM-F and EM-R*) identified increased activity in the same AMY region linked to both WMI and EME effects (see red blob in **Figure 2**). However, the same trials were associated with opposing modulation of HC (increased) and dlPFC (decreased; as identified by the reverse contrast Neu *WM-F and EM-R* > Emo *WM-F and EM-R*) activity (see the green and blue blobs in **Figure 2** depicting HC and dlPFC, respectively; see also **Table 1**). In addition, investigation of brain-behavior relationships linked to differences in WM performance identified a negative correlation between left AMY activity to emotional vs. neutral distracters, and WM performance to emotional distracters ($r = -0.55$, $p = 0.01$; Talairach

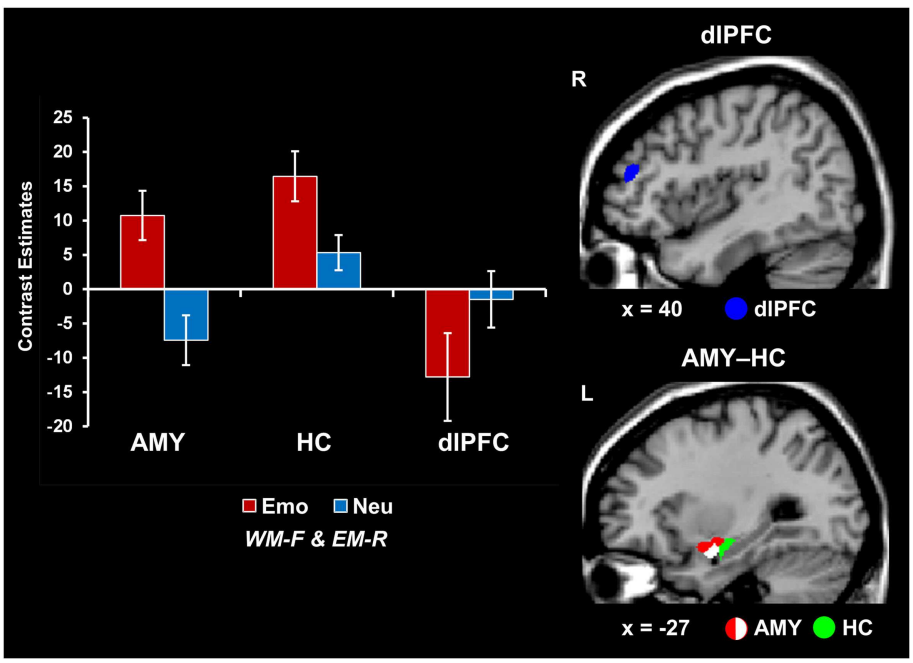

FIGURE 2 | Opposing patterns of activity in AMY and HC vs. PFC linked to WMI and EME effects of emotion. Increased activity in both AMY (red blob) and HC (green blob) and greater deactivation in the dlPFC (MFG, BA46; blue blob) were observed in response to emotional relative to neutral distracters that impaired WM performance and were later remembered (i.e., Emo *WM-F and EM-R* > Neu *WM-F and EM-R*, for activity in the ventral and Neu *WM-F and EM-R* > Emo *WM-F and EM-R* for activity in the dorsal systems). A negative correlation was also identified between left AMY activity and WM performance to emotional distracters (white blob; see Results). The bar graphs show the contrast estimates, as extracted from for peak voxels in left AMY (Talairach coordinates: $x = -27$, $y = 3$, $z = -10$), HC (Talairach coordinates: $x = -28$, $y = -12$, $z = -12$), and the right dlPFC (MFG, BA46; Talairach coordinates: $x = 43$, $y = 38$, $z = 23$). The activation maps are superimposed on high-resolution brain images displayed in sagittal view (x indicates the Talairach coordinate on the left-right axis of the brain). AMY, amygdala; HC, hippocampus; dlPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; Emo/Neu *WM-F and EM-R*, emotional/neutral distracters that impaired WM and were later remembered. Error bars represent standard errors of means.

Table 1 | Opposing effects in ventral affective and dorsal-executive neural systems linked to WMI and EME effects of emotion.

Brain regions		BA	Talairach coordinates			*T* value	Mask
			x	*y*	*z*		
Emo WM-F and EM-R > Neu WM-F and EM-R							
mPFC	L medial frontal gyrus	8	−16	32	40	2.77	4.18
	L superior frontal gyrus	8/9	−16	31	50	2.79	4.06
	R medial frontal gyrus	8	6	44	41	5.15	4.83
	R superior frontal gyrus	9	14	49	20	5.12	5.33
vlPFC	L inferior frontal gyrus	45	−49	28	10	2.52	3.77
	R inferior frontal gyrus	44/45	54	12	17	2.55	3.33
latPFC	R inferior frontal gyrus	9	51	19	21	2.97	5.52
MFC	R superior frontal gyrus	6	6	27	54	2.79	3.41
PrCG	R precentral gyrus	6	43	−1	34	3.24	3.71
TOC	L fusiform gyrus	37	−45	−52	−16	3.45	9.62
	L middle temporal gyrus	37/39	−46	−58	5	3.54	6.51
	L inferior temporal gyrus	19	−46	−57	−6	4.48	6.71
	L middle occipital gyrus	19	−46	−77	11	3.03	7.06
	R middle temporal gyrus	19	36	−59	14	3.73	3.38
	R middle occipital gyrus	18	28	−81	8	4.31	9.97
	R lingual gyrus	18	36	−65	−5	2.95	5.1
Precuneus	R precuneus	7	24	−55	46	6.8	4.03
	R precuneus	31	28	−74	16	5.55	6.71
	L precuneus	31	−27	−75	18	2.01	4.22
MTL	L amygdala		−27	3	−10	7.88	4.6
	L hippocampus		−27	−12	−8	3.24	5.27
	R amygdala		18	−5	−7	6.53	5.11
	R hippocampus		32	−8	−10	2.48	4.75
Insula	L insula		−34	−3	14	2.73	3.3
Subcortical	L hypothalamus		−8	−5	−4	3.34	4.67
	L lateral globus pallidus		−23	−8	−4	3.69	3.93
	L medial globus pallidus		−16	−5	−4	3.3	3.85
	L thalamus		−12	−17	6	2.68	4.64
	R medial globus pallidus		18	−5	−3	7.57	3.42
	R putamen		21	6	−2	3.96	3.38
	R thalamus		6	−18	14	2.33	3.09
Midbrain	L red nucleus		−1	−27	−6	5.06	5.23
	R mammillary body		7	−8	−7	4.58	4.59
Cerebellum	L declive		−45	−67	−17	3.25	12.42
Neu WM-F and EM-R > Emo WM-F and EM-R							
dlPFC	R middle frontal gyrus	46	43	38	23	2.82	3.94
MFC	R medial frontal gyrus	6	6	−18	57	2.14	3.53
PrCG	R precentral gyrus	6	51	−7	19	2.82	3.1
PCL	L paracentral lobule	6	−9	−30	59	3.39	3.67
	R paracentral lobule	6	6	−30	59	2.2	2.99
LTC	L superior temporal gyrus	22	−57	−9	6	5.38	2.98
	L superior temporal gyrus	41	−49	−36	11	5.13	4.87
	L middle temporal gyrus	21	−60	−35	0	2.46	3.08
	L middle temporal gyrus	20	−57	−38	−7	2.25	3.19
	R superior temporal gyrus	22	54	−24	3	5.39	3.35
	R superior temporal gyrus	41/42	51	−33	13	4.29	3.22
SPL	R superior parietal lobule	7	32	−73	44	2.6	3.35
TPC	L angular gyrus	39	−50	−68	33	2.13	4.26
	L inferior parietal lobule	39	−50	−62	41	2.25	5.19

(Continued)

Table 1 | Continued

Brain regions		BA	Talairach coordinates			*T* value	Mask
			x	*y*	*z*		
Cuneus	L cuneus	19	−5	−76	37	3.64	3.54
	L cuneus	18	−16	−99	2	3.28	3.61
PHC	L parahippocampal gyrus	19	−31	−46	−1	2.55	3.48
	R parahippocampal gyrus	19	32	−43	−3	2.45	4.7
Subcortical	L caudate		−16	23	17	3.56	3.44

The table identifies brain regions mediating both the WM impairing and EM enhancing effects of emotion by contrasting emotional (Emo) and neutral (Neu) items that impaired WM and were later remembered (WM-F and EM-R). Effects in the ventral affective (Emo WM-F and EM-R > Neu WM-F and EM-R) and dorsal executive (Neu WM-F and EM-R > Emo WM-F and EM-R) networks were masked by their corresponding a priori ROIs (i.e., Emo > Scr in the ventral and Scr > Emo in the dorsal networks, respectively; see Materials and Methods). mPFC, medial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; latPFC, lateral prefrontal cortex; MFC, medial frontal cortex; PrCG, precentral gyrus; TOC, temporal-occipital cortex; MTL, medial-temporal lobe; dlPFC, dorsolateral prefrontal cortex; PCL, paracentral lobule; LTC, lateral temporal cortex; SPL, superior parietal lobule; TPC, temporal-parietal cortex; PHC, parahippocampal cortex. Significance thresholds are $p < 0.05$ for the effects of emotion and $p < 0.005$ for the a priori masks.

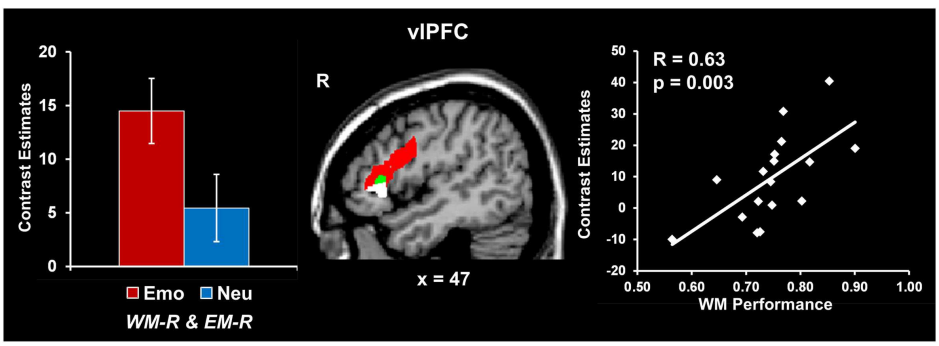

FIGURE 3 | Increased right vlPFC activity linked to coping with emotional distraction and enhanced EM. Right vlPFC showed increased activity to emotional distracters associated with WM success and later remembered relative to both neutral distracters associated with WM success (red blob) and emotional distracters associated with WM impairment (green blob). A positive correlation was also identified between activity in this right vlPFC area and WM performance for emotional distraction (white blob; see Results). In contrast, the left inferior frontal cortex showed increased activity to emotional distracters associated with WM success relative to emotional distracters associated with WM impairment, independent of whether they were later remembered or not (Talairach coordinates: $x = -46$, $y = 8$, $z = 22$; not shown). This suggests a hemispheric dissociation between brain activity involved in coping with emotional distraction (left vlPFC) and linking coping mechanisms with increased subsequent EM for the distracting information (right vlPFC). The bar graph shows contrast estimates for the peak voxel in right vlPFC for the comparison between emotional and neutral stimuli associated with WM success and later remembered (Talairach coordinates: $x = 43$, $y = 23$, $z = 14$). The scatter plot shows the co-variation between brain activity and WM performance, as extracted from the peak voxel of the green blob (Talairach coordinates: $x = 47$, $y = 24$, $z = 7$). The activation maps are superimposed on a high-resolution brain image displayed in sagittal view (x indicates the Talairach coordinate on the left-right axis of the brain). vlPFC, ventrolateral PFC; Emo/Neu *WM-R and EM-R*, emotional/neutral distracters that did not impair WM and were later remembered. Error bars represent standard errors of means.

coordinates: $x = -23, y = -4, z = -14$; see the white blob overlapping with the AMY region illustrated by the red blob in **Figure 2**). In other words, participants who showed increased AMY activity to emotional distracters were also more impaired in WM performance by the presence of emotional distraction. Overall, consistent with a bottom-up effect of emotional distraction, increased AMY activity in the presence of emotional distraction was associated with lower WM performance and increased EM.

Increased vlPFC activity was linked to coping with emotional distraction and enhanced EM performance. Analyses contrasting activity for the emotional and neutral distracters that did not impair WM performance but were later remembered (i.e., Emo *WM-R and EM-R* > Neu *WM-R and EM-R*) identified increased activity in a right vlPFC region (red blob in **Figure 3**; see also **Table 2**). Importantly, activity in this vlPFC region overlapped with areas associated with successful coping with emotional distraction, as revealed by greater activity to emotional distracters associated with WM success than to those that impaired WM (i.e., Emo *WM-R and EM-R* > Emo *WM-F and EM-R*; see green blob in **Figure 3**). Moreover, investigation of brain-behavior relationships showed a positive correlation between activity in these right vlPFC areas, in response to emotional vs. neutral distracters associated with WM success and later remembered, and WM performance for emotional distracters ($r = 0.63$, $p = 0.003$; Talairach coordinates: $x = 47$, $y = 24$, $z = 7$; see the white blob in **Figure 3**). Specifically,

Table 2 | Differential effects in the ventral and dorsal neural systems linked to successful coping with emotional distraction and enhanced EM for the distracters themselves.

Brain regions		BA	Talairach coordinates			*T* value	Mask
			x	*y*	*z*		
Emo WM-R and EM-R > Neu WM-R and EM-R							
mPFC	L superior frontal gyrus	8	−9	43	48	3.24	5.23
	L medial frontal gyrus	9	−1	44	34	3.53	7.69
	R superior Frontal Gyrus	9	14	49	20	3.33	5.33
vlPFC	L inferior frontal gyrus	47	−34	26	−5	3.32	3.29
	R inferior frontal gyrus	45	43	23	14	5.38	5.25
latPFC	R inferior frontal gyrus	9	47	7	24	2.91	5.38
	R inferior frontal gyrus	44	54	16	17	2.6	4.51
PrCG	R precentral gyrus	6	43	−4	30	4.17	3.21
TP	L superior temporal gyrus	38	−38	0	−14	4.18	3.21
TOC	L inferior temporal gyrus	37	−49	−65	−3	5.73	9.52
	L fusiform gyrus	37/19	−49	−49	−16	4.62	8.03
	R fusiform gyrus	19/37	40	−65	−8	3.11	7.59
Precuneus	R precuneus	7/19	17	−66	42	4.74	3.46
Cuneus	R cuneus	18	24	−79	19	2.99	7.79
LOC	R middle occipital gyrus	19	36	−78	15	3.5	4.97
MTL	L amygdala		−30	0	−14	3.61	5.75
	R amygdala		29	−1	−6	3.75	5.5
Subcortical	L caudate		−12	1	15	3.19	4.2
	L thalamus		−5	−32	1	5.68	3.13
	L hypothalamus		−5	−5	−3	3.27	5.5
	L lateral globus pallidus		−19	−5	−4	3.11	3.57
	R thalamus		3	−28	2	5.6	3.06
	R medial globus pallidus		18	−5	−7	2.76	6.11
	R claustrum		36	3	−6	4.84	3.29
Midbrain	L mammillary body		−1	−12	−4	3.51	3.77
	R mammillary body		7	−8	−7	2.87	4.59
Cerebellum	L culmen		−42	−48	−23	3.89	11.81
	R culmen		32	−52	−18	2.91	10.6
Neu WM-R EM-R > Emo WM-R EM-R							
rPFC	L superior frontal gyrus	10	−31	50	16	3.54	5.12
	L middle frontal gyrus	10	−34	43	4	3.65	5.54
	R superior frontal gyrus	10	32	50	13	3.25	4.51
dlPFC	L middle frontal gyrus	9	−35	26	28	2.59	3.54
	R middle frontal gyrus	9	39	33	37	4	3.37
latPFC	L middle frontal gyrus	8	−35	25	42	2.69	3.05
LFC	R middle frontal gyrus	6	32	8	52	3.93	3.06
PrCG	R precentral gyrus	6	54	−6	8	6.11	3.51
	L precentral gyrus	9	−38	14	37	2.58	4.12
PoCG	R postcentral gyrus	4	13	−38	62	2.36	3.02
PCL	R paracentral lobule	6	6	−30	59	2.22	2.99
IPL	R inferior parietal lobule	40	46	−58	39	3.06	7.62
STC	L superior temporal gyrus	22	−49	−36	7	3.51	3.32
	L middle temporal gyrus	22/21	−57	−39	7	2.89	3.16
	R superior temporal gyrus	41	58	−25	10	4.27	3.62
	R superior temporal gyrus	13	47	−18	11	3.67	3.33
	R transverse temporal gyrus	41	43	−33	13	3.02	3.9
TPC	L angular gyrus	39	−35	−72	33	3.64	3.28
	L supramarginal gyrus	40	−50	−53	34	6.56	6.09

(Continued)

Table 2 | Continued

Brain regions		BA	Talairach coordinates			*T* value	Mask
			x	*y*	*z*		
PCC	L posterior cingulate	23	−5	−30	27	2.85	4.69
	R cingulate gyrus	23	2	−34	26	2.91	3.46
Precuneus	L precuneus	39	−39	−65	37	3.1	3.32
	R precuneus	19	39	−73	34	3.61	6
Cuneus	L cuneus	17/18	−12	−99	−2	2.79	3.52
Cerebellum	L dentate		−19	−55	−27	2.88	3.04

The table identifies brain regions mediating both successful coping with emotional distraction and EM enhancing effects of emotion by contrasting emotional (Emo) and neutral (Neu) items that were associated with WM success and were later remembered (WM-R and EM-R). Effects in the ventral affective (Emo WM-R and EM-R > Neu WM-R and EM-R) and dorsal executive (Neu WM-R and EM-R > Emo WM-R and EM-R) networks were masked by their corresponding a priori ROIs (i.e., Emo > Scr in the ventral and Scr > Emo in the dorsal networks, respectively; see Materials and Methods). mPFC, medial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; latPFC, lateral prefrontal cortex; PrCG, precentral gyrus; TP, temporal pole; TOC, temporal-occipital cortex; LOC, lateral occipital cortex; MTL, medial-temporal lobe; rPFC, rostral prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; LFC, lateral frontal cortex; PoCG, postcentral gyrus; PCL, paracentral lobule; IPL, inferior parietal lobule; STC, superior temporal cortex; TPC, temporal-parietal cortex; PCC, posterior cingulate cortex. Significance thresholds are $p < 0.05$ for the effects of emotion and $p < 0.005$ for the a priori masks.

consistent with a role of this region in coping with emotional distraction, participants who showed increased vlPFC activity also had higher WM performance in the presence of emotional distraction.

The role of individual differences in the impact of emotional distraction

Participants who were more susceptible to WMI by emotional distraction showed greater amygdala increases and PFC reductions. Consistent with the behavioral results, fMRI analyses comparing brain activity between participants showing impaired WM performance compared to those who were not impaired by emotional distraction (WMI subgroup vs. Non-WMI subgroup) identified increased AMY activation and dlPFC *de*activation in the WMI subgroup (see the red and blue blobs in **Figure 4** depicting AMY and dlPFC areas showing differences in activation and, respectively, *de*activation to emotional vs. neutral distraction, between the WMI and Non-WMI subgroups). Thus, individual differences in the susceptibility to emotional distraction were associated with opposing effects in ventral (AMY) and dorsal (dlPFC) regions.

Amygdala activity increased and dlPFC activity decreased with measures of impulsivity. Exploratory analyses were also performed to investigate possible relationships between individual differences in personality measures indexing impaired executive control (i.e., impulsivity) and brain activity. These analyses also targeted ventral affective and dorsal-executive regions showing sensitivity to emotional distraction, and where differences in activity were observed between the WMI and Non-WMI subgroups. These analyses revealed opposing relationships between brain activity in response to emotional distraction and individual scores for the AI subscale of BIS, in AMY and dlPFC (**Figure 5**). Specifically, AMY activity showed a positive correlation (see white blobs in **Figure 5**), whereas dlPFC activity showed a negative correlation (see blue blob in **Figure 5**) with the AI scores. In other words, participants with higher AI scores showed increased activity to emotional distraction in basic ventral emotion processing regions (AMY) and concomitant reduced activity in dorsal-executive regions (dlPFC). Notably, the positive correlation in the left AMY overlapped with the AMY area illustrated in **Figure 4**, as showing greater response to emotional distraction in the WMI subgroup (see the white blob overlapping with the red blob in **Figure 5**). Also, the positive correlation in the right AMY illustrated in **Figure 5** was driven by the WMI subgroup (WMI subgroup: $r = 0.74$, $p = 0.008$; Non-WMI subgroup: $r = 0.07$, $p = 0.44$). Thus, individual differences in attentional impulsivity were associated with opposing patterns of co-variation with activity in ventral (AMY) and dorsal (dlPFC) regions.

DISCUSSION

The present study used a novel combined WM-EM experimental paradigm to investigate (i) the relationship between the immediate impact of emotional distraction on WM and the long-term impact on EM, and (ii) the role of individual differences in the impact of emotional distraction. The first goal yielded two main findings: (1) emotional pictures that disrupted face WM but enhanced subsequent picture EM were associated with increased AMY and HC activity coupled with reduced dlPFC activity (**Figure 2**); (2) trials in which emotion enhanced EM without disrupting WM were associated with increased ventrolateral PFC activity (**Figure 3**). The second goal yielded two additional findings: (3) participants who were more susceptible to the WMI effect of emotion showed greater AMY increases and PFC reductions (**Figure 4**); (4) AMY activity increased and dlPFC activity decreased with measures of attentional impulsivity (**Figure 5**). These findings are discussed in turn below.

THE LINK BETWEEN OPPOSING EFFECTS OF EMOTIONAL DISTRACTION ON WM AND EM

(1) The present results support the idea that the relationship between the immediate impact of emotion on WM and

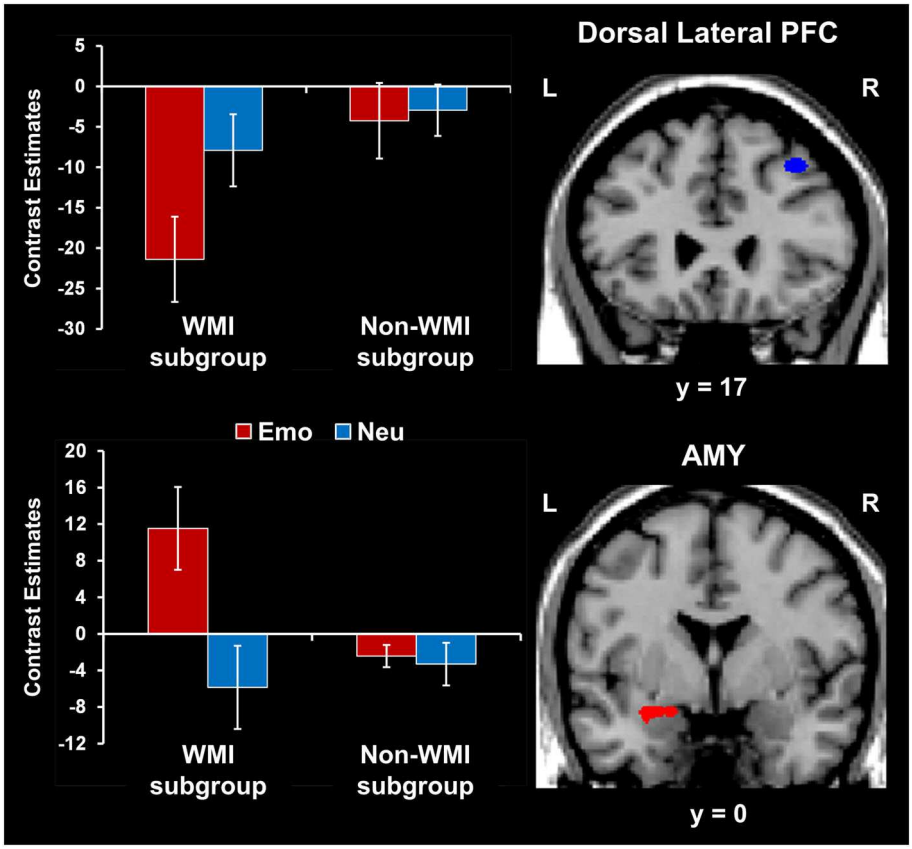

FIGURE 4 | Opposing effects of individual differences in susceptibility to emotional distraction on AMY and dorsal lateral PFC. Participants who were more susceptible to WMI by emotional distraction (WMI subgroup) showed greater AMY increases (red blob) and dorsal lateral PFC reductions (blue blob), relative to the Non-WMI subgroup. The bar graph shows contrast estimates for the peak voxels in AMY (Talairach coordinates: $x = -27$, $y = 3$, $z = -10$) and dorsal lateral PFC (Talairach coordinates: $x = 36$, $y = 17$, $z = 46$), for the two subgroups. The activation maps are superimposed on a high-resolution brain image displayed in coronal view* (y indicates the Talairach coordinate on the anterior-posterior axis of the brain). *Three voxels overlapping with the mask were identified in the dorsal lateral PFC at this location. AMY, amygdala; PFC, prefrontal cortex; Error bars represent standard errors of means.

the long-term enhancement of EM is modulated by both direct/bottom-up MTL-based and mediated/top-down PFC-based mechanisms, and that AMY has a central role in both effects. Analyses contrasting the emotional and neutral distracters that impaired WM performance and were later remembered showed that the same AMY region was linked to both of these opposing effects. However, the same trials were associated with opposing modulation of HC (increased) and dlPFC (decreased) activity. These results are consistent with previous investigations linking AMY-HC engagement to a direct route contributing to the memory-enhancing effect of emotion (Dolcos et al., 2004a,b, 2011, 2012; Kensinger and Corkin, 2004) and with studies showing that emotional distraction is linked to increased activity in ventral-affective regions (e.g., AMY) and greater *de*activation in dorsal-executive regions (e.g., dlPFC) (Dolcos and McCarthy, 2006; Dolcos et al., 2006, 2008; Anticevic et al., 2010; Chuah et al., 2010; Denkova et al., 2010).

The fact that in the present study these effects were observed within the same participants provides strong evidence that reallocation of processing resources by emotional distraction during the WM task is one of the mechanisms that contribute to better memory for the distracters themselves. Specifically, possibly as a result of activating mechanisms signaling potential danger, processing of task-irrelevant negative distraction diverts processing resources from the main WM task to processing emotional distracters, which may lead to dlPFC *de*activation (Dolcos and McCarthy, 2006), while simultaneously initiating processing that leads to enhanced EM for the distracting stimuli, via a MTL-dependent route. Alternatively, it is possible that deactivation in some of the dorsal brain areas may reflect reduced executive control to focus on the WM task, possibly due to engagement in other operations that help reduce the impact of emotional distraction; this matter should be addressed in future investigations. In addition, the negative co-variation between left AMY activity and WM performance to emotional distracters is consistent with a bottom-up effect of emotional distraction, in which increased AMY activity in the presence of emotional distraction is associated with lower WM performance and increased EM, thus

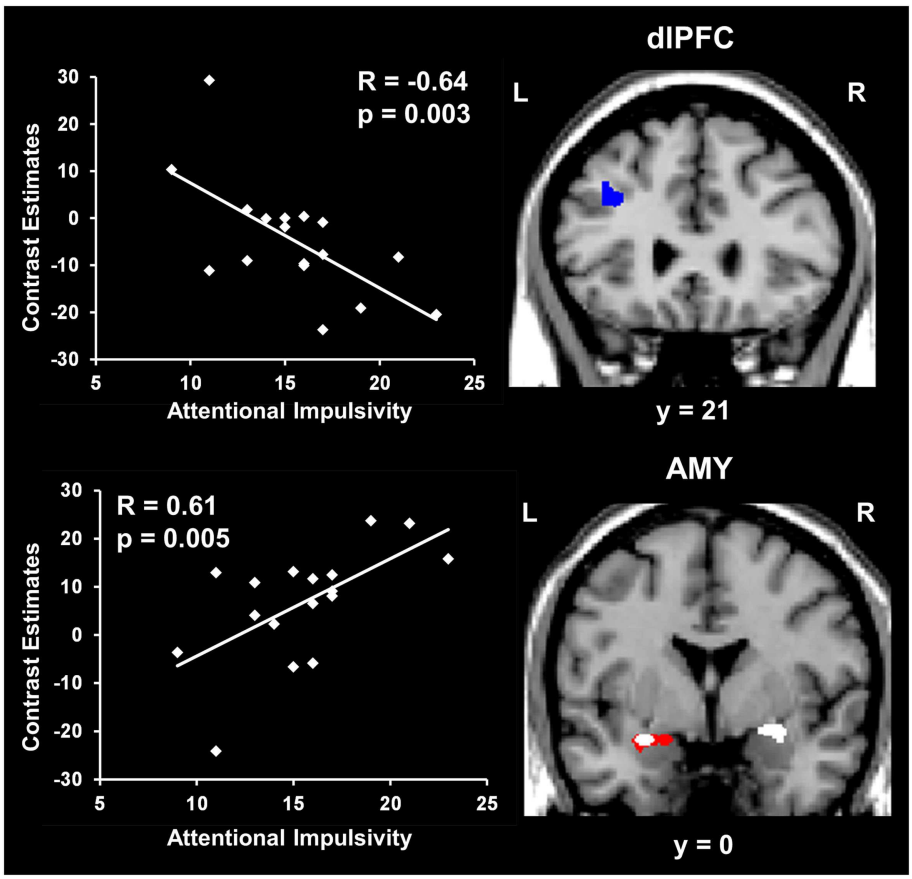

FIGURE 5 | Opposing co-variation of AMY and dlPFC activity to emotional distraction with individual differences in attentional impulsivity. Bilateral AMY activity increased (white blobs) and left dlPFC activity (BA 8/9) decreased (blue blob) with individual scores of attentional impulsivity (AI). The positive correlation identified in the left AMY (white blob) overlapped with the AMY area showing difference in activation to emotional vs. neutral distraction illustrated in **Figure 4** (red blob). The scatter plots illustrate the co-variation between brain activity for emotional vs. neutral distracters and AI scores. Contrast estimates in the scatter plots are extracted from the peak voxels in right AMY (Talairach coordinates: $x = 25$, $y = -1$, $z = -6$) and left dlPFC (Talairach coordinates: $x = -35$, $y = 21$, $z = 38$). The activation maps are superimposed on a high-resolution brain image displayed in coronal view (y indicates the Talairach coordinates on the anterior-posterior axis of the brain). AMY, amygdala; dlPFC, dorsolateral prefrontal cortex. Error bars represent standard errors of means.

pointing to a role of bottom-up/MTL-based mechanisms in these effects.

These results are consistent with findings from another investigation from our group (Shafer and Dolcos, 2012), which also identified AMY-HC activity as being common to both the immediate/impairing and the long-term/enhancing impact of emotion, but in the context of a lower-level perceptual task, and under conditions of limited processing resources available at encoding. This suggests that emotional distracters which initially impair cognitive performance, either in the context of lower/perceptual or higher/WM processing level, engage similar bottom-up/direct AMY-MTL-based mechanisms that allow them to be better remembered later. However, as discussed in the next section, unlike our previous investigation, the present study also identified top-down/indirect mechanisms contributing to the EME effect of emotion, which were linked to initial coping with emotional distraction.

(2) Turning to our second main findings, increased vlPFC activity for emotional distracters associated with stimuli that did not impair WM but were later remembered provides evidence linking the mechanisms involved in coping with emotional distraction with those involved in enhanced EM. Increased vlPFC activity and AMY-vlPFC coupling have been linked to the engagement of PFC control mechanisms in order to cope with distracting emotions, leading to a diminution of the negative impact of distracters on ongoing cognitive processes (Dolcos et al., 2006; Chuah et al., 2010; Denkova et al., 2010). Moreover, there is also evidence that deployment of coping/emotion regulation strategies modulates EM for emotional stimuli (Richards and Gross, 1999, 2000; Bonanno et al., 2004; Dillon et al., 2007), with some strategies leading to enhanced emotional memory (Dillon et al., 2007). This suggest that the initial engagement of emotion regulation strategies to cope with emotional distraction during WM in the present study also contributed to subsequent better EM for the distracters themselves, probably due to increased strategic influences on stimulus elaboration linked to a deeper level of processing (Dillon et al., 2007).

It should be noted that although overlapping areas of the right vlPFC also showed increased activity in response to emotional

relative to neutral distracters that impaired WM performance and were later remembered (**Table 1**), it also showed greater activity to emotional distracters associated with WM success than to those that impaired WM performance (**Figure 3**). Thus, together with the pattern of positive co-variation in this brain area, linking increased right vlPFC activity with better WM performance to emotional distraction, these results are consistent with the idea that enhanced recruitment of this area is associated with successful coping with emotional distraction. On the other hand, the observed increased right vlPFC activity for WM trials showing impairment in the presence of emotional distracters that were subsequently remembered was probably reflective of unsuccessful engagement mechanisms to cope with emotional distraction, that yet also contributed to enhanced memory for the distracters themselves. Overall, the present findings show that activity in specific areas of the right vlPFC reflects the deployment of control mechanisms engaged to cope with emotional distraction and reduce the WMI effect, which also has an indirect/mediated contribution to the EME effect.

Together, the findings regarding the neural correlates linking the WMI and EME effects of emotion suggest that the same bottom-up mechanisms, involving the AMY and HC, contribute to both WMI and EME effects of emotion, and that specific top-down mechanisms, involving the right vlPFC, contribute to coping with emotional distraction and to the EME effect of emotion.

THE ROLE OF INDIVIDUAL DIFFERENCES IN THE IMPACT OF EMOTIONAL DISTRACTION

(3) The present findings expand previous evidence suggesting individual variation in the response to emotional distraction (Dolcos et al., 2008) by providing insight into the factors that may influence this phenomenon and the associated neural correlates. Regarding the factors influencing differential susceptibility to emotional distraction, participants whose WM performance was impacted by emotional distraction (i.e., the WMI subgroup) also rated the negative distracters as more negative and had lower scores in a measure indexing executive control (BIS-Self Control); also, overall, subjects who had lower WM performance in the presence of emotional distraction also experienced higher negative affect following the WM task. Moreover, consistent with the idea that individual differences in the initial response to emotional distraction may also influence its long-term impact, it is possible that increased overall EM for the distracters themselves in the WMI subgroup may be linked to reallocation of resources during the initial processing of task-irrelevant information, which in turn led to a long-term EM boost for the distracting information. Regarding the neural correlates, consistent with the behavioral results, fMRI results showed that participants who were more susceptible to the WMI effect of emotion showed greater increases in ventral/bottom-up regions (AMY) and greater reductions in top-down regions (dlPFC). These findings provide novel evidence concerning the neural correlates of increased susceptibility to distracting emotions, and complement previous investigations pointing to the role of individual differences in the response to emotional distraction (Dolcos et al., 2008; Denkova et al., 2010; Iordan et al., 2013a).

(4) Providing further support to the differences in activation, correlation analyses revealed opposing patterns of co-variation of AMY and dlPFC activity with measures of trait AI – i.e., AMY activity increased and dlPFC activity decreased with AI scores. Interestingly, the group-level positive correlation with AI scores in the right AMY was driven by the subjects with increased susceptibility to emotional distraction (WMI subgroup) and overlapped with the left AMY region showing increased response in these subjects when compared to those unaffected by emotional distraction (Non-WMI subgroup). Given the evidence that AI is characterized by increased distractibility and reduced ability to focus attention (Stanford et al., 2009), and that AI has been linked to impaired executive performance (Enticott et al., 2006; Pietrzak et al., 2008; Kam et al., 2012), the present results suggest that AI may be a general executive factor that contributes to increased sensitivity to emotional distraction. This interpretation is also supported by a recent ERP study, which found an association between increased AI and inefficient functioning of the conflict detection system in a continuous performance task (Kam et al., 2012).

In sum, the present findings regarding individual differences in the susceptibility to emotional distraction point to factors that affect both the basic emotional sensitivity and general executive control. Also, these factors are linked to neural changes indexing increased sensitivity in both basic emotion processing regions (AMY), associated with bottom-up effects, and higher-level executive regions (dlPFC), associated with top-down influences.

Noteworthy, dysfunctional alterations in factors influencing emotional sensitivity and susceptibility to emotional distraction, along with changes in the associated neural correlates, could play an important role in affective disorders, such as anxiety and depression. These phenomena are linked to dysfunctional interactions between emotion and cognition, in general, which may also influence the relationship between immediate and long-term effects of emotion on memory (see Foland-Ross and Gotlib, 2012; Hayes et al., 2012; Morey and Brown, 2012 in the present research topic). Anxiety-related disorders, such as post-traumatic stress disorder (PTSD), involve pathology of both emotion and memory, which is associated with dysfunctional alterations of both bottom-up (MTL) and top-down (PFC) neural systems (Morey et al., 2009; Hayes et al., 2011). For instance, frequently reported memory-related symptoms of PTSD, such as intrusive recollections of traumatic memories (Kaspi et al., 1995; Harvey et al., 1998; McNally, 2006), have been linked to dysfunctions of the basic MTL-based mechanism (Hayes et al., 2011) identified in healthy participants as being responsible for the memory-enhancing effect of emotion (Dolcos et al., 2004b). Also, symptoms of *hypervigilance* along with an overall heightened sensitivity to both threatening and non-threatening stimuli observed in PTSD patients (Grillon and Morgan, 1999; Peri et al., 2000), have been linked to alterations of PFC function, which may explain increased non-specific distractibility to both trauma-related and unrelated stimuli in these patients (Morey et al., 2009). Given that these phenomena co-occur in clinical conditions, such as PTSD and depression, their concomitant investigation with tasks assessing both immediate and long-term effects (on WM and EM, respectively) provides a seemingly promising research venue. Such within-subjects investigations would contribute to the elucidation of the link between

enhancing and impairing effects of emotion on cognition by complementing the studies separately investigating these effects in clinical conditions (see Dolcos, 2013 in the present research topic). Overall, the present findings from healthy participants, along with evidence from clinical patients, highlight the importance of these issues and warrant further concomitant investigations of interactions between enhancing and impairing effects of emotion, in both normal and clinical conditions.

CONCLUSION

In summary, using a novel paradigm in which EM targets were initially encountered as WM distracters, the present study provided evidence for a link between the immediate and long-term impact of emotion. The present study also highlights the role of individual differences in the impact of emotional distraction. The study generated four main findings, as follows. Regarding the relationship between the immediate impact of emotional distraction on WM and the long-term impact on EM, the study yielded two findings: (1) emotional pictures that disrupted face WM but enhanced subsequent EM were associated with increased AMY and HC activity coupled with reduced dlPFC activity; (2) trials in which emotion enhanced EM without disrupting WM were associated with increased vlPFC activity. Regarding the role of individual differences in the impact of emotional distraction, the study yielded two additional findings: (3) participants who were more susceptible to the WMI effect of emotion showed greater AMY increases and PFC reductions; (4) AMY activity increased and dlPFC activity decreased with measures of attentional impulsivity. Collectively, these findings demonstrate that the immediate impact of emotional distraction on WM and the long-term impact of emotion on EM are mediated by overlapping and dissociable neural systems, involving both ventral/bottom-up and dorsal/top-down mechanisms, and that the brain regions mediating these effects are specifically sensitive to modulations by individual differences. Understanding the mechanisms mediating the impairing and enhancing effects of emotion on cognition, in general, and on memory, in particular, offers potential insights into understanding affective disorders, such as anxiety and depression, where their interaction is *dys*functional.

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Attention and awareness each influence amygdala activity for dynamic bodily expressions—a short review

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The amygdala (AMG) has long been viewed as the gateway to sensory processing of emotions and is also known to play an important role at the interface between cognition and emotion. However, the debate continues on whether AMG activation is independent of attentional demands. Recently, researchers started exploring AMG functions using dynamic stimuli rather than the traditional pictures of facial expressions. Our present goal is to review some recent studies using dynamic stimuli to investigate AMG activation and discuss the impact of different viewing conditions, including oddball detection, explicit or implicit recognition, variable cognitive task load, and non-conscious perception. In the second part, we sketch a dynamic dual route perspective of affective perception and discuss the implications for AMG activity. We sketch a dynamic dual route perspective of affective perception. We argue that this allows for multiple AMG involvement in separate networks and at different times in the processing streams. Attention has a different impact on these separate but interacting networks. Route I is engaged in early emotion processing, is partly supported by AMG activity, and is possibly independent of attention, whereas activity related to late emotion processing is influenced by attention. Route II is a cortical-based network that underlies body recognition and action representation. The end result of route I and II is reflexive and voluntary behavior, respectively. We conclude that using dynamic emotion stimuli and a dynamic dual route model of affective perception can provide new insights into the varieties of AMG activation.

Keywords: amygdala, attention, awareness, bodily expressions, emotion, dynamic stimuli

INTRODUCTION

The role of the amygdala (AMG) in processing behaviorally salient stimuli is widely documented in many animal and human studies. A variety of affective functions have been attributed to AMG activity including immediate perception of affective stimuli, learning, and conditioning as well as emotional memory (Phelps and LeDoux, 2005). The AMG is also involved in modulating cognitive functions as well as behavior and has many connections to brain areas directly involved in behavioral output (Mosher et al., 2010). As early as 1888, rhesus monkeys with a temporal cortex lesion (including the AMG) showed significant social and emotional changes. The matter was later studied systematically by Bucy and Klüver (1955) and shortly after Weiskrantz (1956) showed that bilateral ablation of the AMG was sufficient to induce the symptoms associated with the Kluver and Bucy syndrome. For a while, research focused primarily on behavioral studies in rodents (LeDoux, 1996). Human investigations of the AMG functions have been guided by and followed in the steps of the animal research findings. It is worth pointing out that the early animal studies used behavioral criteria to assess the influence of AMG on emotion processing. This may be just one of the difficulties that, combined with limited knowledge of limbic system anatomy in humans, make generalizations complicated.

Since the beginning of functional magnetic resonance imaging (fMRI) studies in humans, the AMG has also been the centerpiece of many reports in neurotypical controls (e.g., Morris et al., 1998) and various clinical groups or even populations with personality disorders and patients with focal brain damage (Morris et al., 2001; Siebert et al., 2003). Several researchers have provided extensive insights into the neuroanatomy of the AMG and the neighboring structures (Aggleton and Mishkin, 1986; Swanson and Petrovich, 1998). However, besides a general agreement on the central role of the AMG, many aspects of its functional significance for human behavior still await further clarification.

A striking finding is that the AMG exerts some of its functions of paradigmatic cognitive processes such as attention or perception either when the observer is fully aware of the nature and content of the stimulus or, alternatively, in implicit settings. This happens, for example, in settings in which visual awareness is lacking (Whalen et al., 1998; Morris et al., 1999; Liddell et al., 2005) or when the content of the stimulus is irrelevant for the task at hand (Vuilleumier et al., 2001). In the present context where these distinctions are central, we contrast studies reporting AMG activity under conditions of full awareness and normal vision of the stimulus with studies showing AMG activity under conditions in which stimulus awareness is lacking

either because of sensory or attentional manipulation or because of brain damage.

The overwhelming majority of human fMRI studies that report AMG activation have used pictures of facial expressions. As a consequence, the findings obtained with facial expressions have dominated our view of AMG functions in this past decade. But this relatively limited basis is likely to confine our understanding of the role of the human AMG. New perspectives on human emotional behavior and new technologies have now made possible to present much more realistic and rich pictures to participants in fMRI experiments (e.g., Grosbras et al., 2012). For example, stimulus duration in video clips and the presence of movement are two main features among the factors that may lead to a different picture of the relation between cognitive, task dependent, factors and affective information on AMG activation.

The theoretical vantage point from which this review proceeds has been formulated by a few authors over the last decades in both animal and human emotion research and has been discussed in different contexts, mostly related to face processing. This theoretical perspective is variedly referred to as a dual route model of affective stimulus perception (LeDoux, 1996; Vuilleumier, 2005; Tamietto and de Gelder, 2010; Garrido et al., 2012), more specifically we have referred to it as dynamic dual route model of face perception (de Gelder and Rouw, 2001; de Gelder et al., 2003). A similar approach has not yet been developed systematically as a framework for whole body expressions perception.

We believe it makes a difference for the understanding of the relation between attention, consciousness, and the AMG whether one adopts a linear or a parallel dual route model of face or body processing. In research from our own lab we have provided evidence for this dynamic dual route perspective while at the same time including in it the notion that both routes are operational in parallel (e.g., de Gelder et al., 2003). Based on our work with blindsight patients we have also stressed the notion that attention and task related factors are different from sensory unawareness and have different effects on consciousness (Tamietto and de Gelder, 2010). As we will point out below, the contrast between these routes must not be viewed as paralleling the familiar distinction between implicit versus explicit, with or without attention or non-conscious versus conscious. The importance of this model may appear more clearly when dynamic stimuli are used since dynamic images presumably trigger more or/and partly different processes in online emotion perception.

In this brief review we discuss the state of the art concerning the role of the AMG in experiments that instead of using short presentations of static stimuli have presented participants with full naturalistic videos. Using this kind of stimuli can provide us with a more detailed view of the human AMG functions. In the first part we review studies from our lab using dynamic bodily expressions to investigate AMG activation under oddball detection, with either explicit or implicit recognition demands, with variable cognitive task load, and, finally, under conditions of non-conscious perception (see **Table 1** for an overview of the discussed studies and Supplemental Online Materials for examples of the stimuli used in these studies). In the second part we spell out how controversies concerning the role of AMG in affective perception can be put in perspective when one adopts a dynamic dual route perspective on affective perception that allows for AMG involvement in separate networks and at different times in the processing streams.

The review will highlight the complex way in which emotional stimuli are processed in the brain and the interplay between emotion and cognition. Specifically, we will focus on the interaction between emotion and attention, as the latter can be considered a typical cognitive function. In fact, a central role of attention is to modulate sensory processing, for example, by increasing the firing rate in primary sensory areas or by enhancing behavioral performance. In recent years, such functions have also been reported during the processing of emotional stimuli and have been related to the activity of the AMG. Thus, converging evidence is pointing to the AMG as a central hub in the dynamic interplay between emotion and cognition and makes the study of the functional and anatomical properties of this structure a paradigmatic case for the study of emotion–cognition interaction.

DIFFERENT TASK CONDITIONS AND AMYGDALA ACTIVATION

AMYGDALA ACTIVATION UNDER ODDBALL DETECTION

Experiments using oddball detection provide valuable insight when affective processing for new classes of stimuli are investigated and they have the extra advantage of allowing a closer comparison with animal data that rarely use complex evaluative tasks. Our first study with video clips used a passive viewing paradigm requiring participants simply to detect the oddball stimuli presented upside-down (Grèzes et al., 2007). Stimuli consisted of 3 s long video clips showing a person facing the camera and opening a sliding door in an emotional or neutral manner. An important aspect of this study is that it comprised video clips as well as still images taken from the same video clips and shown for the same duration. The main finding for our present question was that viewing the action, whether static or dynamic and independently of whether the expression was fearful or neutral enhanced right AMG activity relative to scrambles. The fact that the right AMG is more activated in all conditions where a whole bodily action is contrasted with its scrambled counterpart may in part be related to the type of action used here, which always shows an other directedness. It may also be the case that even the neutral door opening action is spontaneously interpreted as having an affective significance.

Pichon et al. (2008) repeated this same design but using anger instead of fear expressions. Again, relative right AMG activation was increased regardless of explicit movement (dynamic vs. static) and emotion (anger vs. neutral). Other regions were also activated similar to observations obtained in the previous study with dynamic fearful bodily expressions (Grèzes et al., 2007), as well as a previous study using static fearful bodily expressions (de Gelder et al., 2004). In the perception of dynamic body expressions of anger, brain regions that are coupled with autonomic reactions and motor responses related to defensive behaviors, such as the ventromedial prefrontal cortex, the temporal pole, and the premotor cortex (PM) were also activated.

Another paper by Kret et al. (2011a) directly investigated the similarities and differences between the processing of dynamic

Table 1 | Overview of discussed studies using dynamic bodily expressions.

Study	Task	Stimuli	Amygdala localization	Talairach coordinates***	Results for the amygdala
Grèzes et al., 2007	Oddball detection	Person opening a door in a fearful or neutral manner and scrambles*	Whole brain analysis	Right: 27/–3/–20	Bodies > scrambles
Grèzes et al., 2009	Oddball detection	Person opening a door in a fearful or neutral manner*	Whole brain analysis	Right: –35/0/–14	–No AMG activation for fearful > neutral in ASD group –Weaker connections between the AMG and STS, IFG, and PM in the ASD group.
Kret et al., 2011a	Oddball detection	Angry, fearful, or neutral facial and bodily expressions	Functional localizer**	Right: 17/–6/–10 Left: –17/–8/20	Faces > bodies
Kret et al., 2011b	Oddball detection	Angry, fearful, or neutral facial and bodily expressions	Functional localizer**	Right: 17/–6/–10 Left: –17/–8/20	Male participants > female participants for faces > bodies contrast
Kret et al., 2011c	Oddball detection	Angry, fearful, or neutral facial and bodily expressions	Functional localizer**	Right: 21/–10/–6	Negative correlation between negative affectivity and threatening faces and bodies > neutral faces and bodies contrast
Pichon et al., 2008	Oddball detection	Person opening a door in an angry or neutral manner and scrambles*	Whole brain analysis and sphere	Body > scrambles Right: 19/–4/–8 Left: –33/–1/–17 Anger > neutral Right: 27/–3/–18	–Bodies > scrambles –Anger > neutral
Pichon et al., 2009	Emotion-naming	Person opening a door in an angry, fearful, or neutral manner	Whole brain analysis	Left: –18/–8/10	–Threatening > neutral –Positive correlation between fear recognition and fear > neutral contrast
Pichon et al., 2012	Emotion-naming and color-naming	Person opening a door in an angry, fearful, or neutral manner	Whole brain analysis	Right: 29/–7/–17 Left: –33/–5/–15	–Threatening > neutral in emotion-naming –Deactivation in the color-naming task
Pouga et al., 2010	Oddball detection	Person opening a door in a fearful or neutral manner*	Whole brain analysis	Right: 17/–8/–17 Left: –28/–3/–19	–Fear > neutral –Negative correlation between difficulty identifying emotions and fear > neutral contrast
Sinke et al., 2010	Emotion-naming and color-naming	Teasing or threatening social interaction and scrambles	Anatomically defined for individual subjects	Right AMG: 18 ± 2.4/–5 ± 3.6/–16 ± 1.7	–Deactivation in both the emotion-naming and color-naming task –Less deactivation for threatening social interactions regardless of task condition
Sinke et al., 2012	Easy or hard color-naming with focus on aggressor or passive victim	Threatening social interaction between an aggressor and passive victim	Group mask	Left AMG: –19/–7/–13	–Deactivation in both the easy and hard color-naming task –Less deactivation when focus on aggressor, especially in easy color-naming task
Van den Stock et al., 2011	Oddball detection	Person opening a door in an angry or neutral manner	Anatomically defined	Right: 19/–2/–5 Left: 22/–7/–6	–Anger > neutral only for non-conscious perception

* *Static stimuli were also shown. No difference between static and dynamic stimuli in terms of AMG activation.*

** *AMG was localized using a separate localizer run with face, body, tool, and house stimuli using a face > house contrast.*

*** *MNI coordinates were transformed to Talairach coordinates by using the Nonlinear Yale MNI to Talairach Conversion Algorithm (Lacadie et al., 2008).*

threatening facial and bodily expressions. Results showed that in this comparison right AMG activation was highest for dynamic facial expressions compared with bodily expressions. In line with the two previous studies discussed above, no difference was observed between threatening or neutral expressions. Additional analysis showed that male participants drove the difference in AMG activation between dynamic facial and bodily expressions (Kret et al., 2011b). While not statistically significant, AMG activation was highest when male participants observed female faces.

Personality factors or psychiatric disorders may also influence AMG activity. Kret et al. (2011c) looked at the role of negative affectivity in the processing of dynamic threatening facial and bodily expressions. A negative correlation between left AMG activity for threatening versus neutral faces and bodies and negative affectivity was observed (Kret et al., 2011c). In other words, people high on negative affectivity (the experience of negative emotions across time and situations) have less relative AMG activation when processing threatening facial and bodily expressions. Using the same task and dynamic stimuli as the first study from our lab (Grèzes et al., 2007), we recently showed that relative AMG activation levels do differentiate between high and low alexithymia, a personality trait associated with deficits in emotional reactivity and regulation (Pouga et al., 2010). A negative correlation was found between the level of difficulty to identify one's emotional experiences and relative right AMG activation in response to fearful stimuli. In line with this finding, adults with autism show no differential AMG activation in the perception of fearful actions (Grèzes et al., 2009). Interestingly, in the same study weaker connections between the AMG and superior temporal sulcus (STS), inferior frontal gyrus (IFG), and PM were found.

EXPLICIT VS. IMPLICIT EMOTION RECOGNITION

To further investigate AMG activation under different task conditions, Pichon et al. (2009, 2012) used the same stimuli as in previous studies (Grèzes et al., 2007; Pichon et al., 2008), namely angry, fearful, and neutral actions. Importantly, here a different task than simple oddball detection was used. The goal was to compare the pattern of brain activity in the condition of explicit recognition (naming of the represented emotion) with that observed in the alternative implicit condition where subjects had to attend to and name a colored dot. The results of this study were reported in two papers. In the first one the comparison between the neurofunctional signature of fear and that of anger under explicit task conditions was described (Pichon et al., 2009). The interesting result is that both emotion categories trigger stronger AMG activity compared with the neutral condition. We conjectured that this reflects the fact that anger as well as fear cues function as threat signals. On the other hand, we did observe an important difference at the level of AMG activity between fear and anger conditions when considering the role of the AMG in recognizing dynamic emotion actions. Recognition performance for fearful stimuli was significantly correlated with relative AMG activation for fearful expressions.

The results obtained in the comparison between emotion-naming (explicit) and color-naming (implicit) conditions allow us to enter the debate on the role of attention in AMG activation. In the literature there is a longstanding debate if implicit or pre-attentive processing of emotional stimuli triggers AMG activation. Two contradictory lines of research are described (for a review see Pessoa, 2005; Vuilleumier, 2005). Vuilleumier et al. (2001) showed that AMG activation in response to static fearful facial expressions is relatively independent of attentional demands (or less modulated by attention than other emotion-sensitive structures), whereas Pessoa et al. (2002) reported that attention to the affective stimulus is a prerequisite for AMG activation in response to static fearful and happy facial expressions. Both studies used dual-task paradigms in which they presented static emotional faces together with different unrelated stimuli and contrasted AMG activation to attended faces with that to unattended faces. Using an event-related fMRI design, the task of Vuilleumier et al. (2001) involved matching two faces similar in emotional expression (attended face) or two houses (unattended face) in a stimulus display, whereas participants in the Pessoa et al. (2002) study asked participants to judge in alternating blocks the gender of the face (attended face) or the orientation of bars (unattended face).

Using dynamic stimuli we can provide additional information in the debate on automaticity of the AMG response to threatening social information. In contrast to the observation of AMG activation to both angry and fearful social actions in the explicit recognition task (Pichon et al., 2009), no increase in AMG activation was found under implicit task demands for both angry and fearful stimuli (Pichon et al., 2012). Using a similar task, but incorporating a more social dimension, Sinke et al. (2010) used threatening or teasing social interactions between pairs of actors. Interestingly, under both task conditions deactivation in the right AMG was observed. However, deactivation was less pronounced for the threatening social interaction in both the explicit and implicit task.

These results show a complex pattern. The disengagement of the AMG (as suggested by deactivation) under implicit conditions (Sinke et al., 2010; Pichon et al., 2012) is consistent with the literature suggesting a mediating effect of attention on AMG activity to affective stimuli (e.g., Pessoa et al., 2002). To explain their effects, Pichon et al. (2012) distinguish between two subcortico-cortical networks. The first is a PM-hypothalamus-periaqueductal grey (PAG) network which functions independent of task demands and attention, while the second network, partly formed by the AMG and areas in the temporal cortex (STS, fusiform gyrus), is influenced by task demands. During a complex and challenging task multiple sources compete for attention and a successful strategy requires disregarding potentially distracting information. However, while affective information might be irrelevant to the task, it still can trigger automatic defensive processes (e.g., action preparation) mediated by the first network. Indeed, as one might expect in both the emotion- and color-naming task, participants responded slow to threatening compared with neutral actions (Pichon et al., 2012). We will come back to and extend this dynamic dual route perspective on affective perception in part II.

COGNITIVE TASK LOAD

The interaction between emotion and attention and the role of the AMG in this interaction is far from settled, as documented by the fMRI findings reported above. Moreover, the interpretation of these findings is complicated by several factors. First, fMRI measures emotion processing across a relatively long time-window. So, it is possible that initial encoding of emotions in the AMG is relatively independent from attention, but that top-down

attention modulation is involved at later stages. A critical point for future research is therefore to "isolate" AMG activity in the earliest processing stages, which are more likely to occur in an automatic, pre-attentive, rather than controlled, resource-dependent fashion (Garrido et al., 2012). Also, task-related confounds may limit the interpretation of results. For example, in the Pessoa et al. (2002) study, participants judged the gender of the faces during the attended-faces trails, whereas they judged the orientation of peripheral bars during the unattended-faces trials. Thus, not only the focus of attention, but also the cognitive load, type of judgment and task varied across conditions, whereas in the study by Vuilleumier et al. (2001) these factors remained constant.

The studies we commented upon so far all compared two different tasks with different cognitive/attentional load to assess their influence on AMG activity. Yet this does not allow an assessment of task load *per se*. Indeed, the comparison is between the effect of two very different tasks, that of explicit conscious recognition and verbal naming of the emotion versus recognition and naming of another stimulus attribute unrelated to the emotion. This is a comparison between explicit recognition of emotion and explicit recognition of a non-emotion attribute. It is important to stress that we cannot rule out that in the so-called implicit condition participants may still be fully conscious of the stimuli and recognize the emotional valence while not reporting it simply because this is not part of the task. Under such conditions there may be AMG activity observed that is related not to the explicit stimulus and task demands but triggered by the stimuli independently of the task demands. Thus the term implicit does in fact cover a host of processes that are also possibly present in the explicit condition. For that reason it is imperative to unpack the notion of implicit in a number of different dimensions. One dimensions is task load, another is visual awareness. In this section and the next one, we discuss experiments where these different dimensions were addressed separately.

The goal of the next study (Sinke et al., 2012) was specifically to assess the importance of task difficulty itself and for that purpose we adapted the attention paradigm previously used (Sinke et al., 2010; Pichon et al., 2012) to allow both the manipulation of the focus of attention and attentional load. The former was manipulated by the use of new dynamic stimuli that depicted an angry conversation between two people, with an aggressor and a passive victim, and placing the colored dots on just one person. Attentional load was manipulated by using an easy or hard color-naming task. Thus the participants processed the same dynamic stimuli while paying attention to either the aggressor or passive victim under two attentional loads (low vs. high). Behaviorally there was no difference between the focus of attention factor during the hard color-naming, while in the easy task participants perform better when the focus of attention was on the aggressor. Consistent with previous results using dynamic stimuli and implicit tasks (Sinke et al., 2010; Pichon et al., 2012), deactivation of the AMG was observed. The left AMG showed an interaction and was less deactivated when the focus of attention was on the aggressor and not on the passive victim. This effect was strongest for the easy color-naming task (Sinke et al., 2012).

Recently, Shafer and colleagues provided for the first time evidence that supported both the view of Pessoa (2005) and Vuilleumier (2005). They used a perceptual discrimination task with emotional distracters and manipulated both the emotional charge of distracting information and the task demands. Results show that a wide variety of brain regions such as the dorsal medial and ventral lateral PFC are responsive to both task demands and emotional charge of the distracting stimuli. However, while AMG activation differentiated between high and low emotional distracting stimuli no difference was found in AMG activation under different task demands (Shafer et al., 2012). Another study found deactivation of the AMG when the static emotional face was not attended (Morawetz et al., 2010). Again, no difference was found between high and low attentional demands.

PERCEPTION AND VISUAL UNAWARENESS

An important source of evidence concerning the role of the AMG in emotion processing comes from studies on patients with cortical blindness following destruction of the visual cortex. In fact, the lesion renders the patients clinically blind for the stimuli presented in the affected portion of the visual field (scotoma) and produces a pathological segregation between the major cortical route to the AMG, which is damaged, and the intact subcortical visual pathway, providing a unique experimental opportunity (Weiskrantz, 2009).

A recent behavioral/fMRI study in a patient (GY) with unilateral cortical blindness provides additional information on the effect of visual awareness on AMG activation (Van den Stock et al., 2011). While being clinically blind, GY performed above chance level in categorizing dynamic actions (same stimuli as used in Pichon et al., 2008). Furthermore, results show increased bilateral AMG activation besides superior colliculus (SC), pulvinar (Pulv), middle part of right fusiform gyrus (FG), and motor and somatosensory regions for non-consciously perceived angry actions compared with neutral actions. These results are consistent with both the literature on blindsight patients (Morris et al., 2001; Pegna et al., 2005; de Gelder and Hadjikhani, 2006) and non-conscious perception in healthy subjects (e.g., Whalen et al., 1998; Morris et al., 1999; Liddell et al., 2005).

Three findings are of relevance for the current review and the proposed dual route perspective of affective perception. First, cortical activation to non-conscious perception was restricted to the right FG, motor and somatosensory regions. Second, subcortical network activity was not found in the intact hemisphere associated with conscious perception of emotional actions. Third, cortical activation for conscious perception was observed in the prefrontal cortex (PFC), STS, precuneus and intraparietal sulcus (IPS). The results suggest that two separate neural systems underlie conscious and non-conscious perception. On the one hand, a geniculo-striate system underlies conscious perception and is mostly cortical based, while on the other hand, non-conscious perception seems based on the extrageniculo-striate and subcortical pathway including the AMG. However, several questions remain. Do these neural systems interact during the processing of emotional stimuli and what is the role of the AMG in both pathways?

THE ROLE OF THE AMYGDALA IN A DUAL ROUTE PERSPECTIVE ON AFFECTIVE PERCEPTION

THE AMYGDALA AND ATTENTION: DUAL ROUTE, DUAL INFLUENCE OF ATTENTION?

In this final part we aim to recast some of the inconsistencies concerning the role of the AMG in relation to emotion and attention within the vantage point of a dynamic dual route perspective. Ultimately, a better understanding of the respective role of the different AMG subnuclei is needed.

Traditional face processing models view perception as starting with face categorization. Once this is successfully completed, it is followed by one or more successive stages of decoding the various face attributes like identity, emotion, gender, etc. In the framework of currently known brain areas that play a role in face processing this translates as initial categorization in occipitotemporal cortex (OFA) and STS, followed by fusiform face area (FFA), then extraction of the emotional valence following connections between FFA and AMG. Alternatively, we suggested that there may be separate processing routes already in the early stages, and this view is gaining momentum from new findings (e.g., de Gelder et al., 2001, 2003; de Gelder and Rouw, 2001; Meeren et al., 2005). Besides the ventral route, there is evidence for a dorsal route whereby affective information is rapidly extracted from incompletely processed stimuli. This non-ventral route may either depend on primary visual cortex (V1) processing, as argued in the classical picture of the dorsal route, or bypass that altogether and use subcortical structures such as the SC or the visual pulvinar as entry points.

In the area of body research a very similar picture dominates and perception is also viewed as following the ventral pathway. Researchers interested in neural representations of bodies and body parts have discovered two brain areas central to neurofunctional body representation, initially the extrastriate body area (EBA) and later the fusiform body area (FBA; Urgesi et al., 2004; de Gelder et al., 2010; Downing and Peelen, 2011). They have been attributed similar functions of category-specific visual processing well-known from face perception studies, encoding the details of the body stimulus or separate parts of body shape and fine detail of that body form (Downing and Peelen, 2011).

Variants of these roles are that EBA and OFA, respectively, code the stimulus part while only at the stage of FBA and FFA the whole stimulus is encoded (for a critique of this view see de Gelder et al., 2010). Urgesi et al. (2007) argued for a distinction between local versus configural processing of bodily stimuli and the involvement of the EBA in the former, whereas the superior parietal lobe and the ventral premotor area underlie the latter. However, both areas are nodes in a ventral processing route and both are assumed to come into play before so-called higher bodily attributes are processed. Indeed, similar to the view one finds in face perception theories, it is argued about EBA and FBA also that action, identity, and emotional state represent high-level information (de Gelder et al., 2010; Downing and Peelen, 2011). In contrast, when researchers address questions of affective perception and use bodies (or faces) representing an emotion, other structures that the ones belonging to the traditional ventral object recognition route emerge. In our approach, these structures can be grouped along a dorsal processing route.

Indeed, Vuilleumier (2005) already suggested a possibility of two pathways versus two stages for emotional control of perception. In this model, the AMG either receives directly or indirectly input from the SC and Pulv and provides feedback projection to the visual areas that projects to the AMG and cortical area (two-pathways hypothesis). Alternatively, the AMG receives coarse magnocellular inputs via a first feedforward sweep not mediated by the SC and Pulv, which is followed by reentrant feedback from the AMG, and further processing in the AMG and cortical areas (two-stage hypothesis). In our dynamic dual route of affective body perception, two routes (dorsal and ventral) underlie separate processes (see **Figure 1**). Route I consists of a subcortical (SC-Pulv-AMG) and cortical pathway (SC-Pulv-AMG-OFC) that sustains rapid automatic integration of affective content in the interest of adaptive reflex-like behavior (PAG, putamen, and caudate). This route is important for body detection, early emotional processing and reflexive action (de Gelder, 2006; Pichon et al., 2012). This dorsal processing route may or may not involve V1. For the sake of clarity, we refer to these two possibilities as the cortical and the subcortical dorsal route. Following the early emotional processing the slower late emotional processing occurs along with interoceptive mechanisms (AMG, OFC, posterior cingulate, anterior insula, and somatosensory cortex). This route is well-described in literature (e.g., Dalgleish, 2004; Vuilleumier, 2005; de Gelder, 2006), and the relevant findings are consistently replicated (Rudrauf et al., 2008; Garrido et al., 2012). A recent study used diffusion tensor imaging (DTI) to investigate *in vivo* anatomical connections between AMG and subcortical visual structures in a patient with early unilateral destruction of the visual cortex and healthy controls (Tamietto, Pullens et al., 2012). This study provides some unique evidence on the subcortical part of route I. First, they showed that the SC was connected with the AMG through the Pulv in both the patient and controls. Next, unilateral destruction of the visual cortex let to qualitative and quantitative modifications along these pathways within the damaged hemisphere. Fiber tracts between the AMG-Pulv and the SC-Pulv-AMG pathway were strengthened following ipsilateral V1 lesion, connections with frontal areas were reduced and new connections were formed between subcortical visual structures in the damaged hemisphere and posterior cortical areas in the opposite hemisphere (Tamietto, Pullens et al., 2012). This study suggests that two partially distinct anatomical and functional pathways mediate non-conscious and conscious emotion processing.

Route II lies parallel to route I and plays a role in body recognition (EBA, FBA, STS), action recognition (e.g., the fronto-parietal system), and attention. It is suggested that attention by means of activity of the fronto-parietal attentional network and the basal forebrain has a bidirectional relation with this route. The end result of route II is voluntary action (fronto-motor regions), although a shortcut exists in route I to trigger more reflexive action.

The findings that feed this debate on the relationship between AMG activity and attention may be best addressed in the context of a dynamic dual route model. In fact, while AMG is part of both routes, only route II appears modulated by attention and task constraints and has a direct impact on AMG activation.

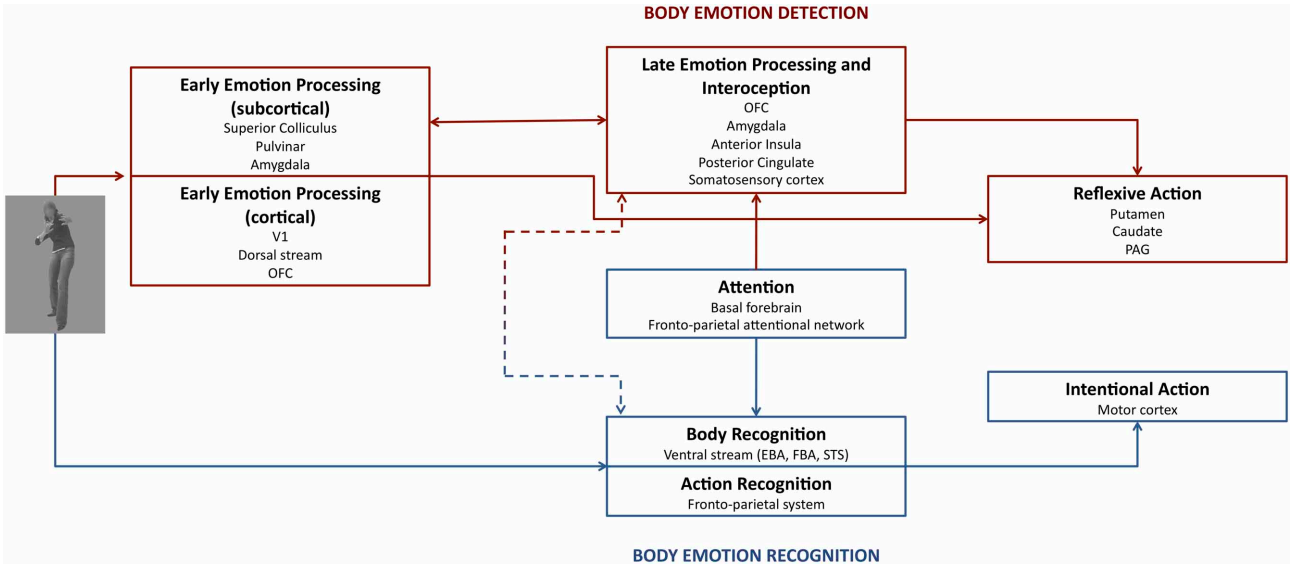

FIGURE 1 | The dual route of affective perception. Emotion bodies are processed in two parallel routes with separate functions. Route I (red) underlies body emotion detection, whereas route II (blue) is important for body emotion detection. The amygdala plays a role in both early and late emotion processing. Attention has only an influence on late emotion processing and thus on amygdala activation. See text for further details.

DUAL ROUTE: FAST PROCESSING OF EMOTIONS AND TIMING ISSUES

Current methods in human affective neuroscience appear particularly limited to provide information about time course. Speed of processing is an important aspect of dual route claims. Initial evidence is coming from studies using the high temporal resolution of MEG. For example, activity in the Pulv (10–20 ms) and Amg (20–30 ms) is found for conscious perception of fearful expressions using MEG (Luo et al., 2007). As described above, this pattern of activation is frequently observed during non-conscious emotion perception with standard fMRI methods (Tamietto and de Gelder, 2010; Van den Stock et al., 2011). Besides early activity in the Pulv and AMG, cortical activity was observed in the visual cortex (40–50 ms) and in prefrontal areas (160–210 ms) (Luo et al., 2007). Another recent MEG study tested the dual route model to AMG, which predicts two parallel subcortical and cortical routes to AMG, against a model that excluded the subcortical pathway (Garrido et al., 2012). Results showed that the dual route model better explained activity to emotionally salient stimuli, and that this subcortical route was particularly important during early stages of stimulus processing.

However, in many fMRI studies subcortical activity during conscious emotion perception is often not observed. One explanation is that cortical feedback during conscious emotion perception might reflect inhibitory modulation over the subcortical SC-Pulv-Amg pathway (Tamietto and de Gelder, 2010). This is in line with the observation that non-conscious emotional perception can co-exist and interfere with conscious perception (Tamietto and de Gelder, 2008). Furthermore, when non-conscious perception is directly contrasted with conscious perception of emotions, relatively more activity in the Pulv and SC is observed in healthy subjects (Anderson et al., 2003; Bishop et al., 2004).

But independently of these methodological limitations and initial findings it is important to avoid theoretical misconception about the timing issue. It is in evolutionary terms more important which neural pathway supports quicker behavioral output (i.e., access to visuomotor integration and action) and not which brain area starts firing first in response to visual stimulation. Thus assuming a direct linear relationship between the latency of a neural response and the latency of a behavioral response is misleading. For example, speed of spontaneous expressive actions is faster for non-conscious emotion perception (Tamietto et al., 2009).

TOWARD A BETTER UNDERSTANDING OF THE PARTS TO SEE THE WHOLE

In this review we considered the AMG as one homogenous structure, but this is certainly not the case. While an extensive discussion of the AMG subnuclei and the possible role of these structures are beyond the scope of this review, we will highlight several relevant aspects of the AMG anatomy and discuss these in terms of future research.

A widely accepted division of the human AMG is in terms of 3 main subnuclei, namely the basolateral (BLA), central-medial amygdala (CMA), and superficial amygdala (SFA; Heimer et al., 1997; Aggleton, 2000). These subnuclei have extensive afferent and efferent connections with almost all parts of the human brain and are strongly inter-connected by means of excitatory and inhibitory connections. Evidence from animal research suggests that each AMG subnuclei can be described in different terms (Davis and Whalen, 2001). The BLA and SFA complex are considered as the sensory input with the SFA specific for olfactory stimuli (Heimer et al., 1997), while the CMA is the behavioral output (for example see

Mosher et al., 2010). As discussed above we state that the AMG plays an important role in both early and late processing of affective information. This rises the question what the roles of both the CMA and BLA are in these different aspects and the time course of emotional integration and, in addition, if AMG (de)activation is specific to certain nuclei. One can hypothesize, for example, that CMA, given the connection with hypothalamic and brain stem regions (Heimer et al., 1997), would be mostly active in early reflexive affective processing and less affected by attention. The BLA is more likely to be influenced by attention, given its importance in the integration of different visual cues and the afferent connections with the thalamus, other sensory regions and orbitofrontal cortex and efferent connections to the visual stream (Davis and Whalen, 2001). A somewhat related explanation of the intriguing but contrasting finding would be that early CMA activity is down-regulated by means of inhibitory connections with the BLA due to competing sensory information and thus that the implicit processing of affective stimuli is attenuated at a later stage. Unfortunately, few neuroimaging studies have used functional or structural localization of the different AMG subnuclei and thus the question if activity in AMG subnuclei is influenced by task demands or if the two subnuclei play different roles in the dual route remains unanswered. One important indication comes from the study by Terburg et al. (2012) who had the unique opportunity to test the role of AMG subnuclei in emotion processing in subjects with Urbach-Wiethe disease (UWD), a rare genetic disorder leading to bilateral calcification of the AMG. Using behavioral evidence, eye tracking, and structural and functional MRI measurements they propose that focal bilateral BLA damage with other AMG subnuclei remaining intact leads to hyper-vigilance for both non-conscious and dynamic fearful facial expressions. This provides some clues for the current debate on AMG activity and attention and the dual route of affective perception. It suggests that the CMA is most important for reflexive action as signified by hyper-vigilance to threat cues and thus is the critical node in early emotion processing via route I, whereas BLA could underlie, as suggested by Terburg et al. (2012), down-regulation of the threat vigilance system and reflexive action by means of inhibitory projections to the CMA and could be influenced by attention. Further research should investigate whether this is indeed the case.

CONCLUSIONS

We have reviewed studies using dynamic bodily expressions and a variety of experimental setups to investigate the role of the AMG in emotion processing and the influence of attention on AMG activation. Taken together, we argue that in the dual route model of affective perception AMG activation can be observed in separate networks and at different time points. Both early and late emotion processing is partly supported by the AMG; however, only late AMG activation is influenced by attention.

With sophisticated paradigms and a wide variety of different stimuli (static or dynamic, emotional or non-emotional, facial or bodily expressions or social interactions) and the ever-expanding neuroscience toolbox one can only hope that after decades of research the question what AMG activity indicates will finally be answered.

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SUPPLEMENTARY MATERIAL

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Amygdala's involvement in facilitating associative learning-induced plasticity: a promiscuous role for the amygdala in memory acquisition

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It is widely accepted that the amygdala plays a critical role in acquisition and consolidation of fear-related memories. Some of the more widely employed behavioral paradigms that have assisted in solidifying the amygdala's role in fear-related memories are associative learning paradigms. With most associative learning tasks, a neutral conditioned stimulus (CS) is paired with a salient unconditioned stimulus (US) that elicits an unconditioned response (UR). After multiple CS-US pairings, the subject learns that the CS predicts the onset or delivery of the US, and thus elicits a learned conditioned response (CR). Most fear-related associative paradigms have suggested that an aspect of the fear association is stored in the amygdala; however, some fear-motivated associative paradigms suggest that the amygdala is not a site of storage, but rather facilitates consolidation in other brain regions. Based upon various learning theories, one of the most likely sites for storage of long-term memories is the neocortex. In support of these theories, findings from our laboratory, and others, have demonstrated that trace-conditioning, an associative paradigm where there is a separation in time between the CS and US, induces learning-specific neocortical plasticity. The following review will discuss the amygdala's involvement, either as a site of storage or facilitating storage in other brain regions such as the neocortex, in fear- and non-fear-motivated associative paradigms. In this review, we will discuss recent findings suggesting a broader role for the amygdala in increasing the saliency of behaviorally relevant information, thus facilitating acquisition for all forms of memory, both fear- and non-fear-related. This proposed promiscuous role of the amygdala in facilitating acquisition for all memories further suggests a potential role of the amygdala in general learning disabilities.

Keywords: Pavlovian conditioning, eyeblink conditioning, fear conditioning, inhibitory avoidance, cerebellum, neocortex, thalamic reticular nucleus

INTRODUCTION

It is widely accepted that the more emotionally arousing an event is (whether positive or negative), the better the event will be remembered (Cahill and McGaugh, 1995; van Stegeren et al., 1998; Cruciani et al., 2011). Such emotionally arousing events have been shown to peripherally cause many physiological changes, such as increased cortisol levels and elevated dehydroepiandrosterone (Schwartz, 2002; Dickerson and Kemeny, 2004). Investigations of the neurobiology of emotion have similarly demonstrated that emotionally arousing events modulate glucocorticoid and epinephrine levels in the brain. Many of these investigations have further suggested that the amygdala plays a key role in regulating these biochemical changes by regulating our emotional response to an event. For example, brain imaging analyses in humans have demonstrated a positive correlation between the amount of amygdala activation and degree of emotional arousal (Cahill et al., 1996; Costafreda et al., 2008). Furthermore, patients with amygdala damage exhibit impairments in their ability to recognize and express emotion (Adolphs et al., 1994, 1995). These analyses, along with rodent and non-human primate studies of amygdala function (Thompson et al., 1977; Lukaszewska et al., 1980; Swartzwelder, 1981; Rosen and Davis, 1988) have suggested that the amygdala plays a central role in mediating our emotional response to an event.

In addition to regulating the response to an emotional event, further analyses have also demonstrated that amygdala activation is directly tied to how well the emotional event is remembered. For example, memory tests in humans have found a positive correlation between the level of consolidation and the extent of amygdala activation (Cahill et al., 1996; LaBar et al., 1998). Furthermore, amygdala lesions in various species, including humans (Cahill et al., 1995), have been shown to dramatically impair a subject's ability to remember an emotional event (Werka et al., 1978; Liang et al., 1982; Jellestad and Bakke, 1985; Peinado-Manzano, 1988). Likewise, pharmacological activation of the amygdala produces a dose-dependent enhancement of memory for emotionally-motivated behavioral paradigms (Liang et al., 1986, 1990; Introini-Collison et al., 1991, 1996). These, and

other similar analyses, have strongly suggested that the amygdala plays a role in facilitating memory consolidation for emotionally arousing events.

Although most would agree with the amygdala's importance in memory consolidation, there is still debate regarding the amygdala's role as an actual site of memory storage versus simply modulating storage of memory in other brain regions. Many learning theories suggest that the most likely site for long-term memories is the neocortex (Eichenbaum et al., 1992; Squire et al., 2004). However, some findings suggest that an aspect of some memories is stored in the amygdala, especially with fear associative learning paradigms. The following review will discuss findings utilizing fear- and non-fear-motivated Pavlovian behavioral paradigms to illustrate our current understanding of how the amygdala facilitates memory acquisition and consolidation.

AMYGDALA'S ROLE IN MEMORY STORAGE

FEAR ASSOCIATIVE LEARNING

Studies utilizing fear conditioning paradigms, a type of Pavlovian conditioning, have demonstrated that the amygdala plays a role in both acquisition and consolidation of cued-fear associative learning (Kim and Jung, 2006; Johansen et al., 2011). In this review, the term *subjects* will be used when similar findings have been reported with multiple species. In cued-fear associative learning, a subject learns to associate a cue, such as a light or tone, the conditioned stimulus (CS), with an unpleasant stimulus evoking fear, such as a footshock, the unconditioned stimulus (US). To measure the strength of the tone-footshock-association, subjects are presented with the same cue in a novel environment and the fear response is recorded. Support for the amygdala playing a key role in fear associative memories stems from a myriad of studies varying in techniques, including lesioning (Blanchard and Blanchard, 1972; Kapp et al., 1979; Iwata et al., 1986; Phillips and LeDoux, 1992), electrophysiological recordings (Applegate et al., 1982; Pascoe and Kapp, 1985) and pharmaceutical manipulations (Gallagher and Kapp, 1978; Gallagher et al., 1981). The following section will focus on findings illustrating the role of the amygdala in consolidating cued-fear associations.

Amygdala as a site of storage

Analyses of amygdala function with cued-fear-conditioning have led many to suggest that the amygdala acts as a possible site of storage for these associations. In support of this theory, studies have demonstrated that the amygdala plays an essential role in retrieval of long-term fear associations (Lee et al., 1996; Maren et al., 1996; Schafe et al., 2001; Gale et al., 2004). For example, findings demonstrated that rats with lesions to the basolateral amygdala 1-day, 2-weeks, 1-month (Lee et al., 1996; Maren et al., 1996) or 16-months (Gale et al., 2004) following cued-fear-conditioning exhibit significantly less freezing behavior compared to sham controls. Additionally, inactivation of the amygdala prior to retention testing results in significantly fewer conditioned responses (CRs), compared to controls (Muller et al., 1997). Furthermore, studies disrupting protein synthesis in the amygdala, a molecular mechanism believed to be important for long-term memory consolidation (Guzowski et al., 2000; Kandel, 2001), have demonstrated impairments in fear-related memory. For example, various studies have demonstrated that disruptions in protein synthesis in the amygdala following acquisition via infusion of a protein synthesis inhibitor impair fear memory retention (Schafe and LeDoux, 2000; Duvarci et al., 2008; Kwapis et al., 2011). These studies, collectively, provide strong support for the amygdala either playing an essential role in retrieval of fear memories or that the amygdala is a site of storage for long-term fear associations.

To date, most investigations of amygdala's involvement in fear-conditioning, summarized in the discussion above, utilize a delay-conditioning paradigm; not many studies have examined the amygdala's role in a trace-fear-conditioning paradigm. In delay-conditioning, there is no separation in time between presentation of the CS and US. In contrast, there is a stimulus-free interval between the CS and US in trace-conditioning (**Figure 1**). Trace-fear-conditioning has been demonstrated to be dependent upon a number of distinct brain regions, including normal hippocampal (McEchron et al., 1998; Czerniawski et al., 2011) and medial prefrontal cortical activity (Runyan et al., 2004; Gilmartin and McEchron, 2005). However, the amygdala's role in trace-fear-conditioning is not as well understood as the hippocampus and medial prefrontal cortex. Raybuck and Lattal (2011) found that global amygdala inactivation via $GABA_A$ agonist muscimol infusion prior to trace-fear-conditioning resulted in no significant differences in freezing behavior, compared to sham and vehicle controls, suggesting that acquisition for the trace-fear-association is independent of the amygdala. In contrast, studies have found that global amygdala inactivation via infusion of the same $GABA_A$ agonist muscimol or blocking protein synthesis in the amygdala hinders acquisition for trace-fear-conditioning compared to controls (Kwapis et al., 2011; Gilmartin et al., 2012),

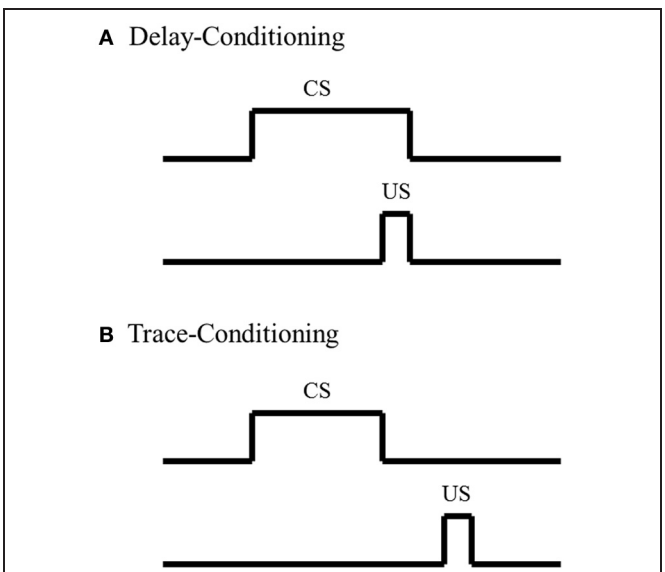

FIGURE 1 | Schematic of Pavlovian conditioning paradigms. (A) In delay-conditioning, the conditioned stimulus (CS) (e.g., tone, whisker stimulation) co-terminates with the unconditioned stimulus (US) (e.g., mild footshock, eye shock). **(B)** In trace-conditioning, there is a stimulus-free separation in time between the CS and US.

suggesting that acquisition for the trace-fear association is dependent upon amygdala involvement. Although further analyses are needed to decipher the discrepancy between these findings, one possible explanation could reside in the extent of the amygdala inactivation. Studies have shown that different amygdala nuclei play specific roles in delay-fear-conditioning (Nader et al., 2001). Such nuclei specific analyses have not been as well examined with trace-fear-conditioning and could account for the conflicting findings. Although these analyses of amygdala function in trace-fear-conditioning conflict, analyses with delay-fear associations suggest that the amygdala is critically involved and could act as a possible site of storage for trace-fear associations.

Amygdala not as a site of storage

Although most analyses of cued-fear-conditioning suggest that the amygdala is a site of storage, most learning theories suggest that the neocortex is the most likely site of storage for long-term memories (Eichenbaum et al., 1992; Squire et al., 2004). In support of this theory, studies have demonstrated that training on an object orientation task, a paradigm where non-human primates learn to direct their attention toward a specific visual stimulus, alters both neuronal sensitivity and preferred orientation in primary visual neocortex (Schoups et al., 2001; Ghose and Maunsell, 2002). Likewise, rearing rodents in an enriched environment, a learning condition where subjects are reared in an environment facilitating enhanced motor, visual, and social stimulation, induces various forms of neocortical plasticity, such as increased dendritic material (Greenough and Volkmar, 1973; Juraska et al., 1980; Juraska, 1984) and increased number of dendritic spines in primary visual neocortex (Globus et al., 1973; Diamond et al., 1975; Turner and Greenough, 1985; Kolb et al., 2003). Furthermore, findings from frequency discrimination training, where a subject learns to preferentially favor a specific tone, have been shown to alter the preferred frequency receptive field in primary auditory neocortex (Disterhoft and Stuart, 1976; Kitzes et al., 1978; Kraus and Disterhoft, 1982; Diamond and Weinberger, 1986; Edeline et al., 1993; Recanzone et al., 1993; Rutkowski and Weinberger, 2005). Finally, studies utilizing tactile discrimination, where a subject learns to dissociate two tactile stimuli, have been shown to alter somatosensory neocortical map hand representation (Jenkins et al., 1990; Recanzone et al., 1992) and alter neuronal firing rate in primary somatosensory barrel neocortex (Krupa et al., 2004) for digit and whisker stimulation, respectively. These, and similar studies, along with various learning theories, have strongly suggested that the neocortex is modulated in response to learning and is a likely location for storage of most long-term memories.

In addition to these analyses suggesting that the neocortex is a likely site of long-term memory storage, some studies have also suggested that fear associations are not stored in the amygdala, but rather stored in other brain regions, such as the neocortex. These analyses have argued that the amygdala does not act as a site of consolidation for fear, but rather facilitates our ability to express fear. For example, studies have found that inactivation of the amygdala impairs freezing behavior in rodents when presented with cat fur, a non-learned stimulus that naturally induces fear in rodents (Vazdarjanova et al., 2001). These findings suggest that amygdala lesion-induced abnormalities in cued-fear-conditioning are due to an inability to express fear rather than removal of the site responsible for fear-related memory consolidation. Further support for this theory has come from analyses utilizing inhibitory avoidance conditioning. With inhibitory avoidance conditioning, a subject learns that a dark compartment CS is associated with an unpleasant stimulus, a footshock US. However, rather than demonstrating this learned association with a fear response, the rodent demonstrates the learned association by avoiding entering the dark compartment. Note, there are many variations of this paradigm that can add other forms of learning such as an operant component; however, for the purpose of this review, we will focus on the associative aspects. Studies utilizing the inhibitory avoidance conditioning paradigm have found that post-training amygdala lesions do not impair expression of the learned fear-association (Liang et al., 1982; Parent et al., 1995). These findings suggest that the amygdala is not a site of storage for inhibitory avoidance fear associations. Furthermore, these findings suggest that the amygdala may not be a site of storage for cued-fear-conditioning. However, the molecular analyses demonstrating that post-training amygdala infusion of protein synthesis inhibitors following cued-fear-conditioning impair memory retention (Kwapis et al., 2011; Gilmartin et al., 2012) disagree with these findings, and suggest that an aspect of the cued-fear memory is stored in the amygdala. Irrespective of the specific site of storage for fear associations, these, and other studies, have collectively demonstrated that the amygdala plays an essential role in either storing fear-related memories or facilitating consolidation of fear-related memories in other brain regions.

NON-FEAR ASSOCIATIVE LEARNING: EYEBLINK CONDITIONING

The studies previously discussed, along with various others analyses examining amygdala function with fear-associative paradigms, have strongly suggested a role for the amygdala in fear associations; however, amygdala involvement in classic non-fear associative paradigms, such as eyeblink conditioning, are not as well understood. In eyeblink conditioning, a subject learns that a neutral stimulus CS, such as a tone or whisker stimulation, predicts delivery of a second stimulus US that elicits an eyeblink. After repeated CS-US pairings, the subject learns to blink when presented with the CS in anticipation of the US. In delay-eyeblink conditioning, the US co-terminates with the CS; thus there is no separation in time between the two stimuli (**Figure 1**). This form of learning is mediated by brainstem-cerebellar processing (Clark et al., 1984; Mauk and Thompson, 1987) and is not dependent upon neocortical processing (Norman et al., 1977; Oakley and Russell, 1977; Mauk and Thompson, 1987). Furthermore, various lesion and electrophysiological analyses have suggested that consolidation for delay-eyeblink associations occur in the cerebellum. For a detailed review of mechanisms for memory consolidations with delay-eyeblink-conditioning see Thompson and Steinmetz (2009). Based upon current understanding of the neuronal pathways necessary for delay-eyeblink-conditioning, the amygdala is not believed to play a prominent role in acquisition of the association (Thompson and Steinmetz, 2009). Furthermore, unlike fear associative paradigms, this form of conditioning is not predominantly believed to be fear-motivated. Although analyses of

heart rate and blood pressure, factors that increase with fear, have demonstrated increased levels within the first few CS-US pairings, these properties decrease, while the associative behavior increases with conditioning (Hein, 1969; Powell and Kazis, 1976). These studies suggest that acquisition for eyeblink conditioning is not dependent upon fear, thus further suggesting that the amygdala would not play a dominating role in task acquisition. However, studies have found that under certain conditions, the amygdala does play a role in modulating acquisition for eyeblink associations.

Delay-eyeblink conditioning

In support of a role for the amygdala in facilitating acquisition of eyeblink associations, studies examining delay-eyeblink-conditioning have found that amygdala stimulation increases the rate of acquisition for the association (Whalen and Kapp, 1991; Canli and Brown, 1996; Neufeld and Mintz, 2001). These studies strongly suggest that the amygdala can play a role in modulating memory for eyeblink conditioning, similar to fear associative learning paradigms. In support of this role, lesion studies have further suggested a more direct role for the amygdala in acquisition of eyeblink associations. Studies have found that post-training amygdala lesions do not have an effect on performance; however, pre-training amygdala lesions impair acquisition for the delay-eyeblink association (Weisz et al., 1992; Choi et al., 2001; Lee and Simons, 2004; Lindquist and Brown, 2004; Sakamoto and Endo, 2010). Furthermore, amygdala lesions have been found to reduce the rate of learning by dramatically impairing acquisition for the association during the initial days of training (Rescorla and Solomon, 1967; Choi et al., 2001; Mintz and Wang-Ninio, 2001; Lee and Simons, 2004). These findings suggest that the amygdala plays a critical role in enhancing the effectiveness of the CS early in training to assist with delivery of CRs. These, and other analyses of amygdala involvement in acquisition of the delay-eyeblink association, have offered support toward a two process model for consolidation (**Figure 2**). In this model, the initial phase of learning activates the amygdala and other emotional responses, possibly increasing the saliency of the CS. In the second (later) phase of learning, amygdala involvement decreases while motor and sensory regions solidify the association and generate well-timed CRs (Rescorla and Solomon, 1967; Choi et al., 2001; Mintz and Wang-Ninio, 2001; Lee and Simons, 2004). In support of this hypothesis, many non-specific emotional responses (e.g., increased heart rate and respiration) have been found to dissipate as appropriately timed CRs emerge (Hein, 1969; Powell and Kazis, 1976).

This theory, that the amygdala plays an initial role in learning by increasing the saliency of the behavioral events, is believed to be a general property in acquisition for other non-fear-motivated paradigms. Such a theory would suggest that the amygdala focuses one's attention on behaviorally relevant events or stimuli to facilitate acquisition and consolidation. In support of this argument, anatomical analyses of amygdala projections have found that the amygdala directly projects to the inhibitory thalamic reticular nucleus (TRN) (Zikopoulos and Barbas, 2012). The TRN receives projections from the neocortex and thalamus, but only sends inhibitory projections to the thalamus (Crick, 1984; Pinault, 2004), thus facilitating its ability to directly mediate or filter thalamocortical interactions (**Figure 3**). Further analyses have demonstrated that the TRN is activated when a subject is attending to a stimulus (Montero, 1997; McAlonan et al., 2008; Petrof and Brown, 2010). Furthermore, TRN lesions have been found to impair a rat's ability to attend to a stimulus (Weese et al., 1999). These findings, along with its anatomical connections facilitating inhibition of thalamic activation of the neocortex, have strongly suggested a role for the TRN in regulating what our brains are attending to (Crick, 1984; Pinault, 2004). Amygdala to TRN projections would allow the amygdala to directly modulate what information is conveyed to the neocortex. Such regulation would empower the amygdala to determine what our brains should attend to and thus would have tremendous implications toward more rapid acquisition of behaviorally relevant stimuli for any learning task (**Figure 3**).

Although the rodent literature has offered much support for the amygdala involvement in initial acquisition and this two process model for memory consolidation, not all studies

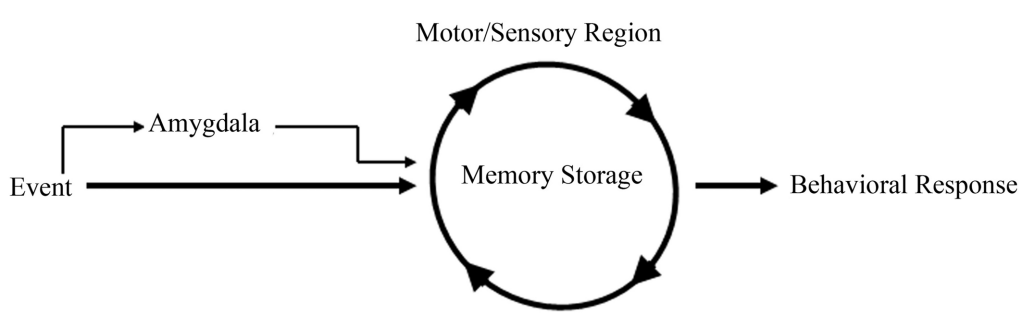

FIGURE 2 | Schematic of amygdala involvement in a two process model for memory consolidation. In phase 1 of the model, the amygdala, receiving event information, increases the saliency of the event to motor and sensory regions, thus facilitating memory consolidation and behavioral response to the event. In phase 2 of the model, motor and sensory regions, primed with amygdala activation from phase 1, begin to solidify the memory and generate appropriate behavioral responses.

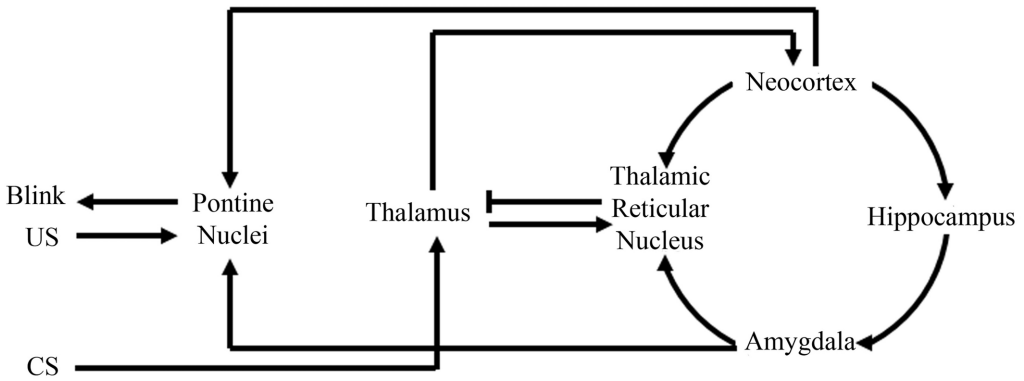

FIGURE 3 | Schematic of amygdala and thalamic reticular nucleus involvement with eyeblink conditioning. Information from the conditioned stimuli (CS) first projects to the thalamus, where it will then project to the neocortex and thalamic reticular nucleus. The thalamic reticular nucleus can then compare information from the neocortex, amygdala, and thalamus. Then, via selective inhibition of thalamic activity, the thalamic reticular nucleus can modulate what information the neocortex receives. Modulation of neocortical input would modulate neocortical activation of the pontine nuclei that directly assists in generating the appropriate conditioned response "Blink." Note in the above illustration, the amygdala can facilitate appropriate behavioral responses by not only modulating neocortical activation of the pontine nuclei via thalamic reticular nuclear stimulation, but also via direct projections to the pontine nuclei.

examining amygdala involvement have supported this theory. Some rodent studies have observed a general reduction in the rate of acquisition with amygdala lesions (Sakamoto and Endo, 2010). Furthermore, studies using rabbits have suggested that the amygdala's involvement in delay-eyeblink-conditioning is not as prominent as suggested from rodent analyses. Analysis of delay-eyeblink-conditioning in rabbits have demonstrated only mildly impaired performance with amygdala lesions (Weisz et al., 1992). In their analysis, Weisz and colleagues (1992) further demonstrated that the impairing effects of amygdala lesions in rabbits can be diminished by increasing the intensity of the auditory stimulation used for the CS. These findings suggest that the saliency of the CS could have dramatic implications toward amygdala involvement and may account for possible discrepancies with amygdala lesions across species.

Another possible explanation for some of the discrepancies between these lesion studies could reside in the size of the lesion. Anatomically, it is known that the lateral amygdala receives converging input from both the auditory CS and somatosensory US pathways (Burton and Craig, 1979; LeDoux et al., 1987, 1990; Whalen and Kapp, 1991; Weisz et al., 1992). The lateral amygdala then projects to the basolateral amygdala and finally to the central amygdala. From the central amygdala, information projects directly to the pontine nuclei that then feeds information to the cerebellum. Although these regions are interconnected, there is no reason to believe each of these nuclei, or even every cell within each nuclei, would have equal involvement in acquisition for the delay-eyeblink association. Analyses of training-induced neuronal activation in the amygdala found that about 60% of the neurons responded to the CS while about 70% responded to the US (Richardson and Thompson, 1984). Thus, partial lesions could disproportionately alter the amygdala's involvement in delay-eyeblink associations. Furthermore, when neuronal activity from specific amygdala nuclei were examined, it was determined that unlike the central amygdala, which exhibited increased activity with conditioning, the basolateral amygdala did not exhibit a learning-specific pattern of activation (Rorick-Kehn and Steinmetz, 2005). Furthermore, additional analyses determined that although the central amygdala exhibited learning-specific activation, the extent of this activation could be modulated by simply varying the intensity of the US (Rorick-Kehn and Steinmetz, 2005). These findings strongly suggest that discrepancies in amygdala lesion studies could be due to differences in training conditions and the specificity of nuclei lesioned.

Trace-eyeblink conditioning

Although there are some inconsistencies in amygdala analyses, most studies suggest that the amygdala plays a critical role in acquisition of delay-eyeblink associations; however, analyses with trace-eyeblink-conditioning have not found that the amygdala plays as prominent of a role in acquisition of the association. In trace-eyeblink-conditioning, the CS and US are temporally separated by a stimulus-free interval (**Figure 1**). This form of learning is both hippocampal- and neocortal-dependent in that pre-conditioning lesions of the hippocampus and specific regions of the neocortex impairs a subject's ability to learn the trace-eyeblink association (Solomon et al., 1986; Moyer et al., 1990; Kim et al., 1995; McGlinchey-Berroth et al., 1997; Clark and Squire, 1998; Kronforst-Collins and Disterhoft, 1998; Weiss et al., 1999; Weible et al., 2000; McLaughlin et al., 2002; Takehara et al., 2002, 2003; Han et al., 2003; Tseng et al., 2004; Galvez et al., 2007). Unlike delay-eyeblink-conditioning, where consolidation for the association is believed to reside in the cerebellum, trace-eyeblink associations are believed to also reside in the neocortex. For example, analyses of neocortical plasticity following trace-eyeblink-conditioning have demonstrated unilateral learning-specific metabolic expansion of the primary neocortical area receiving input from the CS, compared to pseudo-conditioned controls (Galvez et al., 2006, 2011). Further analyses have demonstrated that

neocortical lesions prevent acquisition for the trace-eyeblink association (Galvez et al., 2007). These, and other similar studies, have strongly suggested that the neocortex is a site of storage for trace-eyeblink associations.

With the neocortex acting as a site of storage for trace-eyeblink associations, most would speculate that the amygdala, similar to delay-eyeblink-conditioning, would play a role in facilitating consolidation. However, in trace-eyeblink-conditioning the amygdala does not appear to play as prominent of a role as observed in delay-eyeblink-conditioning. Analysis of metabolic activity in the central amygdala following eyeblink conditioning acquisition demonstrated increased activation with delay-eyeblink-conditioning; however, only a trend toward increased activation following trace-eyeblink-conditioning was observed (Plakke et al., 2009). Although this is only a single analysis, it suggests decreased involvement of the amygdala with trace-eyeblink-conditioning. However, based upon the two process model for consolidation (**Figure 2**) one would expect the amygdala to play a significant role during initial acquisition, but not once the association was learned. Furthermore, based upon the model, as the association is learned, the amygdala would decrease its involvement. This prediction of the model, along with the fact that trace-eyeblink associations require significantly more CS-US pairings, decreases the likelihood that the amygdala would still be activated following acquisition. Obviously, additional analyses of amygdala involvement in trace-eyeblink conditioning are necessary in order to make any definitive statements; however, analyses with delay-eyeblink-conditioning and the two process model for consolidation (**Figure 2**) suggest that the amygdala plays a role in facilitating initial acquisition for trace-eyeblink associations.

CONCLUSION

Over the last several decades, there has been overwhelming evidence that the amygdala plays an essential role in facilitating acquisition and consolidation of fear associations. Although there is some question regarding the specific location of long-term memory storage (whether the amygdala or another region), these analyses strongly suggest that the amygdala plays a critical role in acquisition and consolidation of fear-related memories. However, the amygdala's role is not as clearly defined when examining non-fear-related memories. Utilizing eyeblink-conditioning as a non-fear-motivated task, this review suggests that there is also substantial support for amygdala involvement in acquisition of non-fear-motivated tasks. Analyses of amygdala involvement in these non-fear-motivated tasks suggest that the amygdala acts to increase the saliency of the learned stimuli so that other brain regions can consolidate the learned response. These findings suggest a two process model for memory consolidation. In this proposed model, the amygdala facilitates determining what thalamic information is conveyed to the neocortex. In support of this model, studies have found anatomical projections from the amygdala to the TRN, a brain region critically involved in directing attentional activation of the neocortex, the most likely site of storage for long-term memories. This model would suggest that amygdala lesions would decrease the rate of consolidation by not facilitating the initial phase of learning, but these lesions would not hinder a subject's ability to eventually acquire the association. These predictions are entirely consistent with the amygdala analyses with eyeblink conditioning mentioned above. Although this model was proposed under the framework of the eyeblink paradigm, the implications of these findings would have a broader role in other non-fear-motivated tasks. Additionally, such a model would also have a role in fear-motivated tasks. However, due to the amygdala's multifaceted role in different aspects of fear-motivated tasks, it is difficult to determine if the amygdala's role in modulating thalamocortical communication decreases during task acquisition similar to that of non-fear-motivated tasks. Together, these findings suggest that the amygdala plays a promiscuous role in directing our attention toward behaviorally relevant stimuli, thus facilitating acquisition and memory consolidation for both fear- and non-fear related memories. Currently, many analyses of the amygdala's role in humans have focused on individuals suffering from fear-related disorders such as post-traumatic-stress-disorder; however, the findings presented in this review demonstrate that the amygdala may also play a critical role in non-fear-related learning, suggesting that amygdala abnormalities could also plague many other neurological disorders of learning and memory.

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Making memories matter

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This article reviews some of the neuroendocrine bases by which emotional events regulate brain mechanisms of learning and memory. In laboratory rodents, there is extensive evidence that epinephrine influences memory processing through an inverted-U relationship, at which moderate levels enhance and high levels impair memory. These effects are, in large part, mediated by increases in blood glucose levels subsequent to epinephrine release, which then provide support for the brain processes engaged by learning and memory. These brain processes include augmentation of neurotransmitter release and of energy metabolism, the latter apparently including a key role for astrocytic glycogen. In addition to up- and down-regulation of learning and memory in general, physiological concomitants of emotion and arousal can also switch the neural system that controls learning at a particular time, at once improving some attributes of learning and impairing others in a manner that results in a change in the strategy used to solve a problem.

Keywords: epinephrine, glucose, arousal, emotion, memory, learning strategy

INTRODUCTION

Hormonal responses to an emotional experience regulate memory for that experience (e.g., Gold and McGaugh, 1975; Gold, 1992; Cahill and McGaugh, 1998; Korol and Gold, 2007, 2008; de Quervain et al., 2009; Gold and Korol, 2010; Schwabe et al., 2012; Campolongo and Roozendaal, 2011; Sandi, 2011). The hormonal regulators of memory include adrenal, gonadal, and stress steroids as well as adrenal catecholamines. Of these, glucocorticoids and epinephrine respond acutely to the emotional context of an experience and appear to regulate both the strength and quality of emotional memories. Glucocorticoids have received the most attention in this respect, as noted by several recent reviews of the steroid's effects on memory (e.g., Campolongo and Roozendaal, 2011; Schwabe et al., 2010, 2012; Sandi, 2011). Of note, the effects of glucocorticoids and epinephrine on memory appear to have several points of convergence. In particular, regulation of memory by these hormones is blocked by β-adrenergic receptor antagonists injected either centrally (Quirarte et al., 1997; Clayton and Williams, 2000; Roozendaal et al., 2006; Wichmann et al., 2012) or peripherally (Gold and van Buskirk, 1978; Parfitt et al., 2012). Although generally attributed to central actions, peripheral effects of adrenergic blockade are likely to interfere with peripheral actions of epinephrine, including the subsequent breakdown of hepatic glycogen stores and liberation of glucose into the blood. Considerable evidence by us and others supports the view that peripheral endocrine events are key modulators of memory.

We discuss here evidence showing that one consequence of an emotional experience, the release of epinephrine from the adrenal gland, is a particularly important memory-enhancing process. Epinephrine effects on memory are mediated, at least in part, by subsequent increases in blood glucose levels. Glucose, in turn, can enhance memory by direct actions on the brain, and likely does so by modulating glia as well as neurons. Moreover, epinephrine enhances the durability of plasticity in a synaptic model of memory, termed long-term potentiation (LTP). These enhancing actions of epinephrine and glucose reflect acute actions that are temporally associated with the time of learning. However, under conditions of high circulating levels, e.g., after high stress or high injection dose, glucose and epinephrine can impair memory, providing a physiological substrate for the classic Yerkes-Dodson inverted-U relationship between arousal and learning and memory (Yerkes and Dodson, 1908).

In addition to providing a mechanism by which high emotion results in more robust memory for the event that initiated the emotion, neuroendocrine responses to experience can also shift the type of information or an experience's attribute to be remembered. These findings stem from studies showing that stress and arousal can alter the relative participation of multiple memory systems in a way that alters the strategy employed to solve a problem. This action is one shared by other hormones, particularly estrogens, and leads at once to better learning on some tasks and poorer learning on others. In contrast to the actions of epinephrine and glucose described above, the slower effects of estrogens and glucocorticoids, may be slower in action, setting a platform on which memories are formed (Korol and Gold, 2007; Schwabe et al., 2010).

These neuroendocrine events now known to modulate learning and memory result in conditions in which memory can be enhanced or impaired, but can also result in both enhancement and impairment at once depending on the cognitive attributes and brain regions engaged during learning. This review will describe evidence for these multiple and sometimes opposing cognitive effects of hormonal concomitants of emotion, primarily considering results obtained in laboratory rodents but also some results obtained in humans.

SUBSTRATES VS. MODULATORS

Considerable work investigates the biological components of the substrate mechanisms of memory formation. These substrate mechanisms include changes in protein and gene expression and

alterations in synaptic structure and function and are commonly considered the substrates of memory and neural plasticity (e.g., Kandel, 2001; Miyashita et al., 2008; Bekinschtein et al., 2010; Cheng et al., 2010; Roth et al., 2010; Johansen et al., 2011). These changes are initiated by a host of transient responses such as activation of transcription factors that regulate gene expression, activation of intracellular molecular signaling factors that regulate transcription factors, and alterations in calcium to regulate cell signaling factors. This list, especially if it were filled with specifics, would include serial and parallel processes that rival the central nervous system itself in complexity.

The cellular cascades constituting the substrates of neural plasticity can be initiated by the neurochemical signals that respond to an experience. While some of these cascades may be the brain's memory of an experience *per se*, others are act to modulate downstream processes within the cellular machinery. We take the view that the processes that trigger and modulate mechanisms that produce long-lasting changes in the brain in response to experiences engage and amplify or diminish key neural responses to promote or impair memory formation. In this biological scheme, neuroendocrine responses to an experience modulate the formation of memory, augmenting the long-lasting impact an experience will have on brain function, with the neuroendocrine responses themselves dissipating soon after the event, though there may also be consequences of the hormonal responses too that long outlast the hormonal signal and experience.

The scheme shown in **Figure 1** illustrates one overview of the different neurobiological consequences of an arousing vs. neutral event that may respectively be remembered well or quickly forgotten. In this scheme, an arousing event triggers the release of epinephrine with subsequent downstream actions that end with augmentation of neurochemical responses to the arousing event.

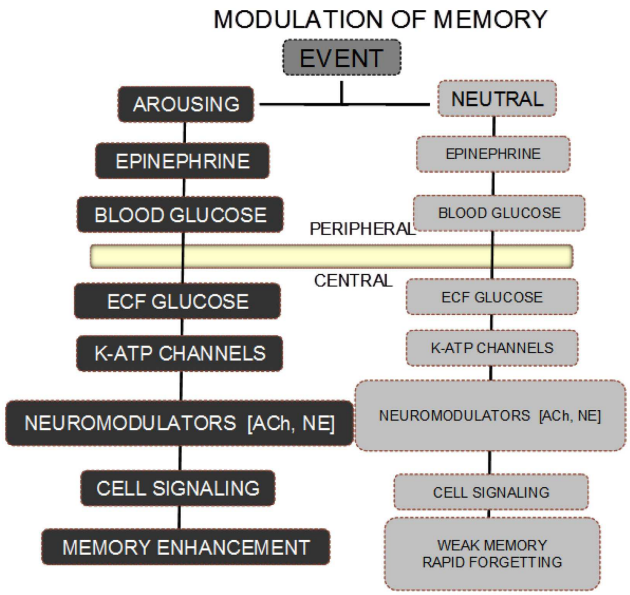

FIGURE 1 | Scheme for modulation of memory by epinephrine and glucose. A neutral event fails to initiate the release of epinephrine, resulting in absence of the biological steps downstream from an increase in circulating epinephrine levels. As a result, the memory for a neutral event is weak and rapidly forgotten. In contrast, an arousing event results in increases in epinephrine released from the adrenal medulla. The epinephrine in turn initiates glycogen breakdown to glucose in the liver, with increases in blood glucose levels. Glucose enters the brain, providing support for neurotransmitter release, activation of intracellular signals responding to receptor binding, with eventual enhancement of memory.

EMOTION AND AROUSAL – ROLE OF EPINEPHRINE

Of hormonal modulators of memory, one of the earliest (Gold and van Buskirk, 1975) and perhaps best-studied is epinephrine (cf. Gold and McGaugh, 1975; McGaugh and Roozendaal, 2002; Korol and Gold, 2007). Epinephrine is released into blood from the adrenal medulla, with the magnitude of release graded across arousal conditions. For example, placement of a rat into a novel environment results in a twofold increase in circulating epinephrine levels. Epinephrine levels increase after foot shock, in an intensity-dependent manner resulting in a four- to 10-fold increase. A more stressful experience is immersion in a tub of water, as in the swim task (often called the Morris water maze), a condition in which epinephrine levels in blood can increase as much as 20 times above baseline (cf. Gold and McCarty, 1995).

When injected near the time of training, epinephrine enhances memory for learned information in rats (Gold and van Buskirk, 1975, 1978; Sternberg et al., 1985; Williams and Clayton, 2001; McGaugh and Roozendaal, 2002) as well as in humans (Cahill and Alkire, 2003). An early demonstration of memory enhancement by epinephrine was performed using rats trained in a widely used inhibitory avoidance task. This task uses a two-compartment alley in which a well-lit start compartment is separated from a dimly lit shock compartment. Upon crossing from the lit to dark compartment, which rats typically do to escape the unfavorable bright light, the rats receive a brief foot shock. During later memory testing, rats are placed back into the light compartment and evaluated for latency to cross into (or how long they avoid crossing into) the now safe shock compartment. In the absence of experimental intervention, it is unremarkable that the latency to avoid the shock compartment is a function of shock intensity: high intensity shocks are more aversive than are low intensity shocks and result in better avoidance of the shock compartment. Importantly, high intensity shock activates neuroendocrine responses that are substantially greater than responses to low intensity shock and that produce stronger and more lasting memory for the training experience (cf., Gold and McCarty, 1995; Gold and Korol, 2010).

If the neuroendocrine response serves as a measure for the emotional intensity of the experience itself, then it should be possible to create experimentally a more intense experience by administering the hormonal consequences of that intense experience. To test this, rats received an injection of epinephrine immediately after training with a low intensity shock. When memory was assessed the next day, those rats that received a post-training injection of epinephrine avoided the shock with longer latencies to re-enter the shock compartment, i.e., the rats avoided the low intensity shock as they would a higher intensity shock. The doses of epinephrine optimal for enhancing memory, as in **Figure 2** (left), produce circulating epinephrine levels that mirror those seen in rats after a high intensity shock. Therefore, it appears that mimicking the

physiology of an emotional event can result in better memory for that event, suggesting that hormonal responses to emotion can "tag" a memory, or more precisely a time, for events that are important.

Findings like these suggest that emotions can enhance memory by engaging neuroendocrine concomitants of the experiences (to regulate memory formation. However, the relationship between hormonal activation and memory formation is non-linear, following an inverted-U dose-response function, as in **Figure 2**. The inverted-U dose-response relationship, also termed hormesis, is seen across a wide range of cellular and organismic responses to many agents. Hormesis involves beneficial effects at low levels of a factor and impairing effects at high levels of the factor (Calabrese, 2008; Mattson, 2008). Here, it is the hormonal regulation of memory that follows the inverted-U curve. However, hormesis is also evident within memory research for other treatments, surprisingly including even β-amyloid peptides generally associated with Alzheimer's Disease but which also enhance memory at low doses and impair memory at high doses (Morley and Farr, 2012; Puzzo et al., 2012).

With specific regard to memory, there are several interpretations possible for the upper end of the inverted-U where impairments occur, including ideas at different levels of analysis (cf. Gold, 2006; Calabrese, 2008; Mattson, 2008). At a cognitive level of analysis, it is possible that the impairments at the high end of the inverted-U relationship might reflect memory that is overly complete, with memory for extraneous information interfering with memory for the key information at times of retrieval. This view might be characterized as one in which learned information is embedded in too much "noise," making it difficult to extract the relevant from irrelevant information on test trials. According to this view, the inverted-U is a result of a linear increase in memory to the point of interference with specific recall. A possible biological mechanism is that high levels of epinephrine might engage additional systems- or cellular-level biological mechanisms that impair memory, perhaps including overcompensation during a homeostasis response or activation of opiate mechanisms that serve as endogenous down-regulators of memory formation; in particular, amnesia produced by high epinephrine doses can be blocked by opiate antagonists (Izquierdo, 1982; Introini-Collison and McGaugh, 1987). In contrast to the cognitive interpretation of too much memory, this biological view suggests that the inverted-U represents two separate possibly linear processes, an ascending arm by which memory formation is facilitated intersecting with a descending arm reflecting diminishing enhancement or even memory impairment.

GLUCOSE AS A MEDIATOR OF EPINEPHRINE EFFECTS ON MEMORY

Epinephrine does not cross readily from blood to brain (Axelrod et al., 1959) and therefore requires a peripheral action to mediate its effects on brain mechanisms of memory. One peripheral intermediary between epinephrine and enhancement of memory is glucose. Glucose levels increase in blood quickly in response to circulating epinephrine, largely by initiating the formation of glucose from glycogen storage in the liver. Glucose, in turn, is taken from blood into the brain via active uptake mechanisms, where glucose acts directly on several brain sites to enhance memory formation.

Like epinephrine, peripherally administered glucose enhances memory in laboratory rodents on a wide variety of tasks (for reviews: White, 1991; Gold, 2001, 2008; Korol, 2002; Messier, 2004), like epinephrine with an inverted-U dose-response curve as in **Figure 2** (right; e.g., Gold, 1986; Hall and Gold, 1986). The glucose doses that enhance memory result in blood glucose levels comparable to those seen after epinephrine doses that enhance memory. Moreover, when peripherally administered adrenergic receptor antagonists are used to block epinephrine effects on memory, the subsequent blood glucose levels, altered by blocking hepatic epinephrine receptors, again correspond to the drug effects on memory: very low and very high concentrations of blood glucose are found in conditions of poor memory while moderate levels correspond to good memory (Hall and Gold, 1986). To our knowledge, there are no explicit results that relate directly to mechanisms responsible for the falling phase of the dose-response curve.

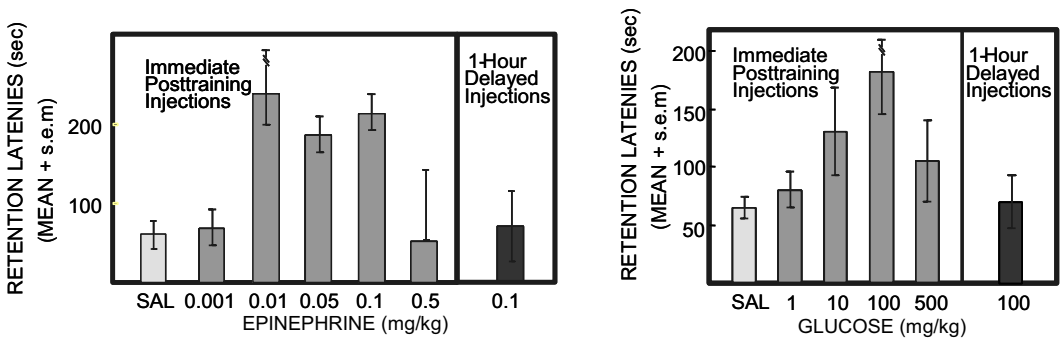

FIGURE 2 | Epinephrine and glucose enhancement of memory in rats. Rats were trained in a one-trial inhibitory avoidance task, received injections of saline, epinephrine, or glucose immediately after training, and were tested 24 h later. Note the inverted-U dose-response curves for enhancement of memory seen on the test trial. Note also that injections of epinephrine or glucose 1 h after training did not significantly enhance memory on tests 24 h later. Under other conditions, e.g., training with a higher footshock, high doses of epinephrine, and glucose impair memory (Left from Gold and van Buskirk, 1975; Right from Gold, 1986).

If glucose delivery to the brain after epinephrine release mediates the effects on memory, then microinjections of glucose into specific brain regions should also enhance memory. Enhancement of memory with central injections of glucose have been seen in many circumstances, including after glucose infusions into the hippocampus, medial septum, amygdala, and striatum (e.g., Ragozzino et al., 1995, 1998; Parent and Gold, 1997; Parent et al., 1997; McNay and Gold, 1998; McNay et al., 2000; Stefani and Gold, 2001; Canal et al., 2005; Pych et al., 2006). Some evidence suggests that peripheral and central insulin levels also influence cognitive functions (e.g., Babri et al., 2007; Moosavi et al., 2007; cf. Craft, 2007; Craft et al., 2012), opening the possibility that some effects of glucose on memory may be secondary to insulin responses. While insulin may itself modulate memory processes, findings that direct brain microinjections of glucose influence memory, in a task × brain area specific manner, suggest that circulating insulin responses are not necessary for glucose to enhance memory, though CNS insulin may be involved (e.g., Zhao et al., 2004). Moreover, the issue of whether insulin crosses from blood to brain is not fully resolved highlighting the need to identify a proxy for insulin's memory-modulating effects.

It may be surprising that glucose administration to the brain could enhance learning and memory given that it was once believed that brain extracellular glucose levels saturated uptake mechanisms in reasonably sated mammals. According to this view, additional glucose in blood or brain would be expected to have weak or no effect on neural functions. However, more recent information indicates that extracellular fluid (ECF) glucose levels in the brain are lower than previously thought. The principal source of glucose for the brain is from the blood in the cerebral vasculature (Siesjö, 1978), from where glucose crosses the blood-brain barrier via both facilitated and non-facilitated diffusion into the cerebrospinal fluid (CSF) and the ECF. Current estimates of glucose concentrations that saturation neuronal uptake of glucose are about 1.3 mM (Braun et al., 1985; Fellows et al., 1992). This value is close to the extracellular concentrations of glucose in the hippocampus of rats, ∼1.0 mM, as determined by direct measurements (Fellows et al., 1993; McNay and Gold, 1999). Also, NMR studies in humans give a very similar result for extracellular brain glucose levels (Gruetter et al., 1998). Thus, several lines of converging evidence demonstrate that basal extracellular glucose concentrations in the brains of both humans and rats are about 1 mM, and suggest that fluctuations in brain glucose levels and local use of glucose in different brain regions may be functionally important to optimal neural processing (McNay and Gold, 2002).

Considerable evidence indicates that extracellular glucose levels do in fact change during memory testing and that the changes are task- and region-specific. Extracellular concentrations of glucose in the hippocampus and striatum of rats were measured during performance of a spontaneous alternation task that assesses spatial working memory believed to tap hippocampus functions (McNay et al., 2000, 2001; Newman et al., 2011). Importantly, this task involves neither aversive nor appetitive rewards or stimuli, thus minimizing alterations in ECF glucose subsequent to changes in blood glucose that may occur with stress or food reward, for example. This task therefore provides information about glucose levels in the brain under non-emotional conditions of cognitive activity. In young adult rats, hippocampal ECF glucose concentrations decrease significantly during the behavioral testing period. Moreover, peripheral injections of glucose prior to behavioral testing enhance memory scores and block the testing-associated drop in ECF glucose in the hippocampus. Measures compared when varying task difficulty (3- vs. 4-arm mazes) showed that the decreases in ECF glucose levels varied with cognitive demands and not simply with locomotor activity. In addition, ECF glucose levels did not drop in the dorsal striatum, a brain area not implicated in processing memory in the spontaneous alternation task. The conclusion is that the neural activity required during memory testing consumes glucose in specific brain regions and that increases in circulating glucose levels fill the depletion resulting from this activity. In the spontaneous alternation task, the depletion is readily evident because the task is relatively free of stress and emotion. Under conditions of high emotion, epinephrine release into blood would initiate endogenous increases in blood glucose levels, thereby up-regulating memory, accomplishing endogenously what is produced experimentally in the example of the spontaneous alternation task.

Much is known about downstream cellular mechanisms that may contribute to glucose effects on memory. In particular, there is evidence that glucose effects on memory interact with several neurotransmitter systems to modulate memory. Evidence from many laboratories indicates that systemic glucose injections can reverse memory impairments produced by drugs that target several neurotransmitters, including glutamate, opiate, GABA, NE, and ACh (e.g., Gold, 1991; Stone et al., 1991; Walker and Gold, 1992; Ragozzino and Gold, 1995; Parent and Gold, 1997; Kopf et al., 1998, 2001; Pavone et al., 1998; Messier et al., 1999). The evidence is strongest for a role of ACh in contributing to the effects of glucose on memory, with many reports showing that glucose augments cholinergic functions (e.g., Messier et al., 1990, 1999; Durkin et al., 1992; Kopf and Baratti, 1994, 1995; Froelich et al., 1995; Micheau et al., 1995; Ragozzino et al., 1996, 1998; Kopf et al., 1998, 2001; Parkes and White, 2000). Of these, the most direct evidence comes from experiments showing that glucose augments acetylcholine release in the context of memory processing (e.g., Ragozzino et al., 1996, 1998; Messier et al., 1999). Acetylcholine, like some other neurotransmitters, has neuronal modulatory actions that amplify glutamate excitatory and GABA inhibitory mechanisms at neurophysiological and molecular levels of analysis (cf. Katz, 1999). It is this amplification of the impact of cell–cell communication during the time after an experience that may be one mechanism of the neurobiological basis for enhancement of memory by glucose.

In addition to interactions with neurotransmitter function, glucose may enhance memory through its action as an important substrate for energy production in the brain. However, glucose delivery to neurons is not always adequate to support optimal neural processing during conditions of high brain activation or low energy states. Astrocytic glial cells act as another energy source for neurons by providing lactate as an alternate energy substrate, thereby augmenting the energy derived from glucose uptake into neurons. Unlike neurons, astrocytes readily store glycogen that can be rapidly metabolized upon activation of glial neurotransmitter receptors to provide energy substrates such as lactate to neurons

(Brown et al., 2004; Magistretti, 2006; Pellerin et al., 2007). Lactate, in turn, is taken into neurons and used as a substrate for energy metabolism. According to this view, basal levels of ECF glucose can fulfill neuronal energy requirements under low-need conditions. But when the need is greater, for example during more intense cognitive functions, astrocytic glycogenolysis is activated to provide lactate, which is transported to neurons to provide a rapid boost from glial energy reserves (Chuquet et al., 2010; Newman et al., 2011; Suzuki et al., 2011).

Within this framework, glucose can act by two routes – uptake into neurons to modulate memory or uptake into astrocytes to produce glycogen stores. The astrocytic glycogen would then be available to provide additional substrates following activation of glycogenolysis by cell–cell communication via glial receptors. Thus, astrocytes may be able to supplement glucose with lactate as a source of energy provisions to regulate processing at a cellular level and more broadly to modulate memory.

A key role for glycogenolysis and lactate provision in regulating memory processing in the hippocampus was recently demonstrated through a series of experiments using *in vivo* assessment of extracellular lactate and glucose (Newman et al., 2011). Sensitive bioprobes were used to monitor, in 1 s measures, changes in extracellular levels of glucose and lactate in the hippocampus while rats were tested for working memory on a spontaneous alternation task (**Figure 3**). As seen using microdialysis methods, glucose levels decreased during testing. Of particular interest, however, is that lactate levels increased, mirroring over time the glucose responses. Close examination of the time courses of the reciprocal changes in glucose and lactate reveals that lactate apparently increases before the glucose drop. If the timing is confirmed, the likely scenario is that astrocytes are the target of neuro/glio/transmitters that initiate the breakdown of glycogen to produce and shuttle lactate to neurons. Of importance here, astrocytes have an abundance of receptors for many neurotransmitters, with several involved in initiating glycogenolysis. One of these is norepinephrine, which is released in brain in response to epinephrine, providing a very good bridge between emotions that promote memory processing, release of epinephrine peripherally, and norepinephrine centrally, and "on-demand" provision of energy substrates to facilitate the actions of neurons engaged in memory processing. Further evidence that the breakdown of glycogen to lactate is important for memory is that application of a drug to the hippocampus that blocks the breakdown of glycogen also impaired memory. The impairment was reversed by the addition by direct intrahippocampal injection of glucose or lactate, showing that neurons could use either glucose or lactate to support memory functions, presumably using either to provide adequate metabolic substrates for neuronal mechanisms important for memory processes.

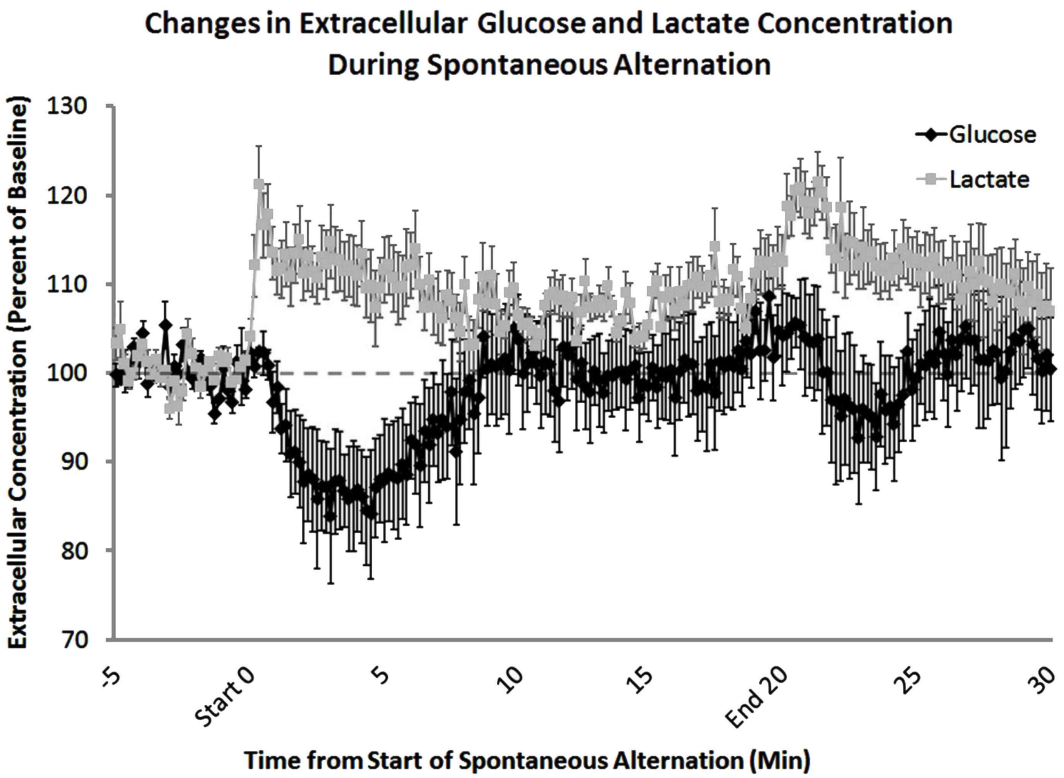

FIGURE 3 | Extracellular lactate and glucose levels in the hippocampus, measured before, during, and after behavioral testing. Using lactate- and glucose-specific biosensors, extracellular concentrations of both lactate and glucose were measured during spontaneous alternation testing. Lactate concentrations increased significantly at the beginning of behavioral testing. In contrast, glucose concentrations decreased after 5 min on the task. The increase in extracellular glucose seen 5–10 min after the start of memory testing corresponds to an increase in blood glucose levels. After the rat was removed from the maze there was a significant increase in lactate compared to baseline levels most likely due to handling (From Newman et al., 2011).

AGE-RELATED MEMORY LOSS: ACCOMPANIED BY LOSS OF GLUCOSE RESPONSES TO TRAINING

Rats and mice exhibit age-related impairments in learning and memory on many tasks. Often, the impairments can be characterized in terms of rapid forgetting, in which aged rats and mice have comparable learning and memory on tests soon after training, but poor memory at later times after training (Winocur, 1988; Barnes, 1991; Foster, 1999; Gold, 2001; Korol, 2002). There are many such examples of accelerated forgetting in aged rodents, with specific time courses that differ by task. Memory for inhibitory avoidance training, which remains stable for weeks after training in young rats, is intact soon after training and then deteriorates over the next several days (Gold et al., 1982). Rapid forgetting is also evident in the swim task, in which learning within a day appears to be forgotten overnight by aged but not young rats (Gage et al., 1984; Rapp et al., 1987; Mabry et al., 1995a). Similarly, young and aged rats have comparable memory scores on a reward reduction task when tested 1 day after training, but aged and not young rats exhibit forgetting when tested 7 days after training (Salinas and Gold, 2005). Other examples include more rapid forgetting in aged than young rats and mice on visual discriminated avoidance (Gold et al., 1982), spatial (Barnes and McNaughton, 1985), spatial reversal (Zornetzer et al., 1982), spontaneous alternation (Stone et al., 1992), and odor-reward association (Roman et al., 1996).

We have conducted a wide range of experiments to determine whether the modulators of memory, generated endogenously by training in young rats, were intact in aged rats and, if not, whether interventions might be effective at enhancing memory. The findings indicate that blood glucose responses to training or stress are severely attenuated in aged rats. For example, when aged rats are immersed in water as in the swim task, they exhibit only a minimal increase in blood glucose levels compared to that seen in young rats (Mabry et al., 1995a). Similarly, blood glucose levels increase in young adult rats as foot shock intensity, as in inhibitory avoidance training, is increased. However, aged rats do not (Mabry et al., 1995b). Interestingly, old rats do show an epinephrine response, which may actually be exaggerated compared to the response in younger counterparts. Thus, a key element important for providing the physiological consequence of emotion, i.e., epinephrine-induced release of glucose from the liver, is lost in the aged rats.

Revealing the importance of the absent glucose response to training, systemic injections of glucose enhance memory in aged rodents tested for inhibitory avoidance (Morris et al., 2010), reward reduction (Salinas and Gold, 2005), object recognition (Winocur and Gagnon, 1998), and spontaneous alternation (Stone et al., 1992; McNay and Gold, 2001), reversing age-related memory deficits on each of these tasks. In addition to results obtained with systemic administration of glucose, recent evidence shows that direct injections of glucose into the hippocampus restore memory in aged rats to the scores seen in young adult rats (Morris and Gold, 2012), supporting the theory that glucose acts directly in the brain to mediate its effects on memory. Studies using orally administered glucose in healthy young, aged, and cognitively impaired humans have shown complementary results, with glucose again having an inverted-U dose-response curve and enhancing memory on a range of tasks (cf. Korol, 2002; Messier, 2004; Gold, 2005). Some of the largest effects of glucose on memory in humans have been seen in healthy elderly people and in people with Alzheimer's Disease, particularly for tasks that reveal memory impairments, with enhancement of memory for a narrative prose passage of 30–40% in healthy individuals and as much as 100% in Alzheimer's patients (Manning et al., 1990, 1993; cf.: Gold, 2001; Korol, 2002).

Relating the findings in rats to mechanisms by which glucose enhances memory, release of acetylcholine, along with other neurotransmitters, is diminished in aged rats. Glucose enhancement of memory is accompanied by an increase in training-related release of acetylcholine in aged rats (Morris et al., 2010). Moreover, cellular responses to training subsequent to receptor activation on neurons are also diminished. One of these is activation of a transcription factor, CREB, after training. When enhancing memory, glucose also augments CREB activation (Morris and Gold, 2012).

The enhancement of memory by glucose in aged rodents, as well as in humans, is remarkably robust and returns memory formation and maintenance fully to levels seen in young adults. One implication of these findings is the aged brain *can* store and remember new memories as well as a younger brain but it does not do so because the modulatory systems that provide the biological bases of the significance of an experience are impaired. In this respect, the brain mechanisms of memory are not themselves impaired but have diminished levels of function because of poor peripheral responses to arousal. Thus, rapid age-related forgetting in old rats may reflect a primary physiological deficit of diminished ability to generate increases in blood glucose levels, i.e., an inability to engage the physiological sequelae through which emotions promote memory processing. In a sense, even seemingly salient events are non-emotional for aged rats and are not remembered well.

EMOTIONS ALTER THE BALANCE BETWEEN BRAIN MEMORY SYSTEMS

Thus far, this review has focused on a physiological system that conveys significance of an experience to the brain, augmenting memory processes when doing so. However, when considering interactions across brain memory systems, the full story is far more complex than this. As discussed below, there is evidence for competition between memory systems for control of what is learned and used to guide behavior. Enhancement of one memory system can interfere with the function of another, resulting in a condition that simultaneously improves some types of memory and impairs other types of memory. This section will discuss how these results may apply to emotions and memory.

Findings first obtained with lesion experiments and later supported by other methods support the view that there are multiple memory systems in the mammalian brain (cf. Kim and Baxter, 2001; White and McDonald, 2002; Poldrack and Packard, 2003; Gold, 2004; Korol, 2004; Mizumori et al., 2004; Kesner, 2009), each with specialized roles in the formation of specific types of memory and used for different types of learning strategies. The evidence for this in rats includes triple dissociations for different classes of learning and memory, in which damage to one of three memory systems impairs memory for only one of three different tasks (e.g., Packard et al., 1989; Kesner et al., 1993; McDonald and White, 1993; Matthews et al., 1999). In particular, damage to the

hippocampus impairs spatial (cognitive, place, win-stay) learning but does not alter egocentric (habit, response, win-shift) learning. Conversely, damage to the striatum impairs response but not place learning. In the context of multiple memory systems, damage to the amygdala impairs learning of highly emotional events, whether appetitive or aversive. Of note, the amygdala also participates more broadly in memory by modulating memories for experiences particularly sensitive to damage of other brain regions (McGaugh et al., 1996).

However, it is incomplete to say that learning in these tasks is based on a single memory system. Often lesions in one system enhance the learning of tasks associated with another system (Packard et al., 1989; McDonald and White, 1993; Matthews et al., 1999; Ferbinteanu and McDonald, 2001; Stone et al., 2005). These findings support the interpretation that activity in one neural system can interfere with behavioral output based on processing in another neural system. Moreover, pharmacological and hormonal manipulations of each memory system can alter the balance between memory systems, shifting the strategy a rat uses to solve a task (e.g., Packard and McGaugh, 1996; Packard, 1999; Conrad et al., 2001, 2004; Korol and Kolo, 2002; McIntyre et al., 2002, 2003a,b; Korol et al., 2004; McElroy and Korol, 2005; Zurkovsky et al., 2006, 2007).

A clear example of how the shift across systems can be modulated by hormones comes from studies of reproductive hormones. Across a range of experiments, estrogens have been shown to produce opposing effects on cognition, shifting the strategy used to solve a task. Bringing coherence to this field are demonstrations that estradiol treatments indeed did both, with tasks sorting according to the canonical neural system associated with the specific task to be learned. For example, under conditions of high levels of estrogens, rats show enhanced learning and memory of hippocampus-sensitive tasks, such as allocentric place learning, but impaired ability to learn striatum-sensitive tasks including those requiring stimulus-response or cued strategies (Korol and Kolo, 2002; Daniel and Lee, 2004; Korol et al., 2004; Davis et al., 2005; Zurkovsky et al., 2006, 2007, 2011).It is important to note that response learning is actually improved under low hormone states suggesting that estrogens shift the effective cognitive strategy and that in some contexts low hormonal states support better learning and memory.

Extensive evidence demonstrates that stress influences learning and memory, impairing or enhancing learning and memory under different conditions including estrogen status or whether tested in males or females (Conrad et al., 1996, 1999; Bowman et al., 2001; McEwen, 2001; Shors, 2001, 2006; Beck and Luine, 2002, 2010; Wright and Conrad, 2005; Diamond et al., 2007). Exposure to stressful stimuli that enhance trace eye blink conditioning in males, a task believed to depend on an intact hippocampus, disrupts learning, and memory in female rats. Replacement of estrogens to ovariectomized rats converts enhancements in learning by stress to impairments, suggesting that circulating ovarian hormones predisposes female rats to stress-related impairments for hippocampus-sensitive tasks. Whether or not the same sex or hormone by stress interactions would be seen for striatum-sensitive tasks is not currently known.

Of particular interest here is evidence that the balance between memory systems is modulated by stress and anxiety (Packard and Cahill, 2001; Packard, 2009). For example, stress near the time of training can shift rats toward the use of response solutions and away from the use of place solutions to solve learning tasks (Kim and Baxter, 2001; Sadowski et al., 2009), showing that stress, like estrogen status, can enhance, or impair learning depending on the task and the neural system tapped by that task. Specifically, stressors shift the preferred strategy expressed by rats from place (hippocampal) to response (striatal) solutions, with rats showing impaired learning for tasks that can be solved by a place strategy and enhanced learning for tasks that can be solved by response learning (Kim et al., 2001; Sadowski et al., 2009, **Figure 4**). Stress also leads to an increased use of stimulus-response/habit learning strategy vs. spatial learning strategy in humans (Schwabe et al., 2007, 2008; Dias-Ferreira et al., 2009).

While the findings seem clear that stress induces changes in the balance across multiple memory systems, a specific neuroendocrine basis for these effects is less clear. Recent evidence shows that corticosteroids, like stress, promote a switch between memory systems in mice (Schwabe et al., 2012). The evidence linking epinephrine and glucose to altered participation of multiple memory systems is at present indirect. Release of acetylcholine in the striatum and hippocampus may contribute to the switch between memory systems (Gold, 2003); acetylcholine release in these systems is augmented by glucose administration during training (Ragozzino et al., 1996). Extracellular lactate levels increase in a task by brain area-dependent manner, suggesting that astrocytic glycogen breakdown to lactate may also contribute to the functions of multiple memory systems as might release of other signaling molecules such as neurotrophic factors (Scavuzzo et al., 2011; Korol et al., 2012). Explicit tests of the relationships between

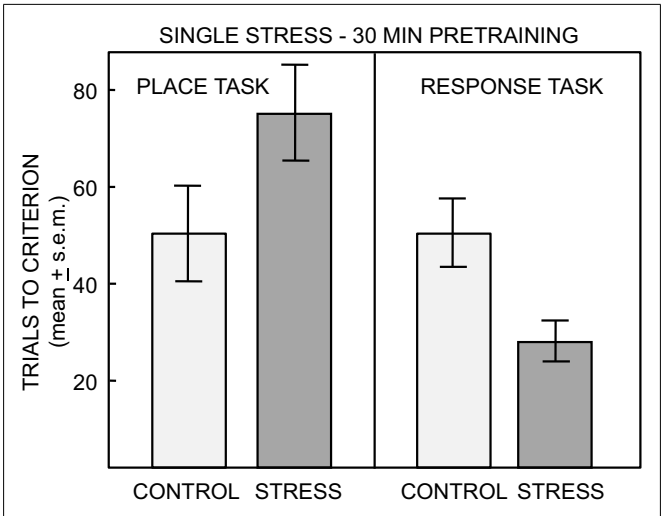

FIGURE 4 | Number of trials to reach criterion on the place and response task after no treatment or single restraint stress ending 30 min prior to training. ANOVAS revealed a significant interaction of task by treatment. Pre-training single stress impaired learning on the place task and significantly enhanced learning on the response task (From Sadowski et al., 2009).

these measures and stress effects on multiple memory systems remain to be performed.

CONCLUSION

Research on modulation of memory has revealed two important ways in which emotion, not distinguished here from arousal, can influence memory. The first is that physiological concomitants of emotion modulate memory. At a physiological level, emotional level, and memory are related in an inverted-U manner. Moderate arousal enhances memory and very high arousal impairs memory. In this way, emotions can be either good or bad factors for memory processing. The bases for these relationships appear to be found through a biology that cross many systems, in particular the adrenal gland, liver, blood, and brain. It is worth noting that there is now extensive research on humans confirming the main effects of glucose on memory (Gold, 2001; Messier, 2004; Smith et al., 2011), although differences across species are very likely to emerge with further research.

The up- and down-regulation of memory processing by physiological responses to emotion also has another dimension in shifting the strategy used to solve a problem. Evidence in rats suggests that high emotion shifts rats away from place learning strategies and toward response learning strategies. In terms of associated neural systems, the shift appears to be from hippocampus to striatum control over learning strategy.

The intersection of these modes of emotional effects on memory makes the relationships complicated but certainly tractable. Far more attention is needed to identify the conditions and mechanisms through which the convergence of the neuroendocrine responses to emotion with enhancement and impairment of memory is expressed.

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Age-related similarities and differences in brain activity underlying reversal learning

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The ability to update associative memory is an important aspect of episodic memory and a critical skill for social adaptation. Previous research with younger adults suggests that emotional arousal alters brain mechanisms underlying memory updating; however, it is unclear whether this applies to older adults. Given that the ability to update associative information declines with age, it is important to understand how emotion modulates the brain processes underlying memory updating in older adults. The current study investigated this question using reversal learning tasks, where younger and older participants (age ranges 19–35 and 61–78, respectively) learn a stimulus–outcome association and then update their response when contingencies change. We found that younger and older adults showed similar patterns of activation in the frontopolar OFC and the amygdala during emotional reversal learning. In contrast, when reversal learning did not involve emotion, older adults showed greater parietal cortex activity than did younger adults. Thus, younger and older adults show more similarities in brain activity during memory updating involving emotional stimuli than during memory updating not involving emotional stimuli.

Keywords: aging, emotion, memory updating, functional MRI, reversal learning, associative memory

In everyday life, we often encounter the same objects, people, or events in different contexts, which allows us to learn something new about old information. For example, you may place your car keys at different places throughout the day, requiring you to update your memory of where they are at any given point (i.e., updating key-location associations). Also, you may see your officemate everyday but notice that he is in a bad mood on a particular day based on the changes in his facial expression (i.e., updating person-expression associations). In this paper, we use the term "updating" to refer to new learning of old information that you have previously encountered, as illustrated in the examples above. The ability to update associative information is an important aspect of memory as well as a critical skill for social adaptation, as it allows one to flexibly update information and respond appropriately to a given situation. In younger adults, updating emotionally arousing information has been shown to be more difficult than updating neutral information (Mather and Knight, 2008; Novak and Mather, 2009), and to activate frontopolar/orbitofrontal (OFC) regions more than updating neutral information in working memory (Nashiro et al., 2012b) as well as in long-term memory (Sakaki et al., 2011). However, it has not been clear whether older adults show similar differences across emotional and neutral updating tasks. Given the fact that the ability to update associative information declines with age (Mell et al., 2005; Weiler et al., 2008), it is important to understand whether and how the effects of emotional arousal on memory updating changes with age. As a first step, the current study focused on examining brain mechanisms underlying updating with the presence and absence of emotion in older adults compared with younger adults.

In contrast with its role in new learning, the amygdala may work against updating emotional memories. Much previous work indicates that amygdala activity during initial learning of emotional material is associated with enhanced long-term memory for that information (e.g., Cahill et al., 1996; Hamann et al., 1999; Dolcos et al., 2004; LaBar and Cabeza, 2006; Murty et al., 2010; Kensinger et al., 2011). Similarly, animal studies in long-term memory indicate that the amygdala enhances memory consolidation for emotional events (McGaugh, 2000). However, the same processes that allow the amygdala to help maintain the original representations of emotional memories could make it more difficult to update those representations.

Recent research suggests that frontopolar/OFC regions play a critical role in updating emotional memory by countering amygdala activity. One recent study using a long-term memory paradigm (Sakaki et al., 2011) found that the frontopolar OFC regions showed greater activity while learning new associations for old emotional items than for new emotional items. In addition, they found that the frontal pole had negative correlations with the amygdala when people learned new associations to old emotional items.

Reversal learning tasks are often used to study short-term memory updating (e.g., Kringelbach and Rolls, 2003; Ghahremani et al., 2010). Similar to the findings in long-term memory (Sakaki et al., 2011), our recent study on reversal learning (Nashiro et al., 2012b) revealed that the frontopolar OFC

regions showed greater activity while people were engaged in emotional than neutral memory updating. We also found greater negative correlations between the OFC and the amygdala when updating negative associations than when updating neutral associations. These results suggest that the frontopolar OFC helps update old emotional memories by suppressing the amygdala's protection of old representations in both long-term and short-term memory.

Animal experiments using reversal-learning tasks requiring updating stimulus-reward contingencies based on feedback provide further evidence for the opposing roles of the amygdala and OFC. One study (Stalnaker et al., 2007) used a reversal learning task of odor-solution associations and demonstrated that reversal learning was impaired in the OFC-lesioned group but was not affected in the amygdala-lesioned group. Strikingly, damage to both OFC and amygdala did not impair reversal learning compared to a control group without any lesions. The results suggest that the amygdala protects old emotional representations making it hard to update them, whereas the OFC opposes this amygdala effect. Extinction tasks involving long-term memory also require updating of associations and amygdala lesions have been shown to facilitate the extinction of emotional instrumental responses in macaque monkeys, whereas OFC lesions impair extinction (Izquierdo and Murray, 2005).

Since the studies described previously were all conducted with younger humans or on animals, it remains unclear whether these brain mechanisms would also apply to older adults. In general, evidence suggests that the amygdala remains relatively intact in older adults (for review see Nashiro et al., 2012a); however, previous findings regarding age-related changes in the frontopolar OFC are more ambiguous. In terms of age-related structural changes, previous research found age-related volume declines in lateral and orbital frontal gray matter (Tisserand et al., 2002) and in the frontal pole gray matter (Salat et al., 2001; John et al., 2009). In contrast, another study (Salat et al., 2001) found that OFC volume accounted for a larger proportion of prefrontal volume for older adults than for younger adults, suggesting the OFC declines less with age than other prefrontal regions. A study with a particularly large sample of participants ($N = 883$) is consistent with this lack of OFC decline, as negative correlations between age and cortical thickness were seen in lateral and superior prefrontal regions, but not in the medial OFC (Fjell et al., 2009). A functional MRI study (Lamar et al., 2004) examined age differences in OFC function by employing delayed match and non-match to sample tasks previously shown to elicit OFC involvement. They found that younger compared with older adults showed greater activity in the lateral OFC (BA 47), suggesting that age-related alteration in lateral OFC recruitment contributes to older adults' poor performance on the tasks. However, since this study used neutral stimuli, it is unclear whether the same task involving emotional stimuli would also result in age differences in lateral OFC activity. Although not emphasized in their report, the same study also indicated that there were no age-related differences in frontopolar (BA 10) activity during non-match in contrast to match to sample tasks, consistent with the possibility that the frontal pole functions similarly between younger and older adults.

Despite the fact that it remains unclear how age might affect the structure and function of the frontopolar OFC regions and the interactions between these regions and the amygdala, previous behavioral studies suggested that younger and older adults showed similar enhancing and impairing effects of emotional arousal on associative memory and memory updating (Kensinger, 2008; Nashiro and Mather, 2011; Nashiro et al., 2013). Thus, the current study examined whether the brain mechanisms underlying emotional memory updating are also similar between the two age groups.

METHODS

PARTICIPANTS

Nineteen undergraduates ($M_{age} = 25.38$, age range = 19–35, 11 males, 8 females, $M_{education} = 15.3$) and 22 older adults ($M_{age} = 68.00$, age range = 61–78, 11 males, 11 females, $M_{education} = 16.4$) participated in the study. The results from the younger participants are described in Nashiro et al. (2012b). Participants provided written informed consent approved by the University of Southern California (USC) Institutional Review Board and were paid for their participation. Prospective participants were screened and excluded for any medical, neurological, or psychiatric illness. Two younger and two older adults were excluded from all analyses due to very poor task performance (their number of errors or number of no responses was greater than 3 standard deviations above the mean). One older adult was excluded due to indications of a previous stroke, which was unknown to the participant prior to the study.

MATERIALS

The face stimuli were color images obtained from the FACES database developed at the Max Planck Institute for Human Development (Ebner et al., 2010), which included young, middle-aged, and older adults' female and male faces.

Thirty individuals' faces, which had neutral, happy, angry, and eyeglasses versions, were used in the main experiment. These faces were grouped into 15 pairs of two faces from the same age group (i.e., five pairs of younger faces, five pairs of middle-aged faces, and five pairs of older faces), and the gender of each pair was always the same (i.e., male–male, female–female pairs). One out of five pairs in each age category was randomly selected and assigned to each participant, resulting in three pairs from different age groups being used for each participant. Which of the three pairs were used for which of the three conditions was randomly determined for each participant. Gender of face pairs were counterbalanced across participants, such that half of the participants saw two female pairs and one male pair while the other half saw one female pair and two male pairs. Which face in a pair appeared on the left vs. right side of the screen was randomized on each trial.

BEHAVIORAL PROCEDURES

We used a reversal learning task, which is designed to test the ability to update associative information in working memory. The details of the procedure were described in our recent publication (Nashiro et al., 2012b) and will be briefly summarized below.

The main experiment consisted of positive, negative, and neutral blocks, the order of which was randomized across the participants. At the beginning of each block, a prompt appeared; "Who is happy?" "Who is angry?" or "Who wears glasses?" in the positive, negative, or neutral conditions respectively (**Figure 1**). Each trial lasted for 6 s, which consisted of (1) selection, (2) feedback, and (3) fixation periods. (1) Selection period: two neutral faces were presented with a white background. Participants were asked to select one face with the target characteristics (happy, angry, or eyeglasses) by pressing a key corresponding to the left or right side of the screen. (2) Feedback period: immediately after their response, feedback was presented for 1 s on a gray background. If the response was correct, the selected face changed (into a happy face, angry face, or face with eyeglasses), while the other face remained neutral. If the response was incorrect, both of the faces remained neutral. When the participant did not respond within 4 s, the warning "please respond faster" was displayed in the center of the screen instead of feedback faces. (3) Fixation period: the trial ended with a fixation cross for the remainder of the 6 s.

After 3–6 consecutive correct responses, which face was correct was reversed. We used a randomized variable acquisition criterion of 3–6 trials correct before each reversal in order to keep the participants engaged in the task as well as making which trials involved a reversal unknown to the participants until they received feedback. They were asked to keep track of the correct face and change their answers as soon as noticed the switch.

TRIAL MODELING

Each trial was categorized as one of three trial types: reversal, acquisition, and other. "Reversal" described individual trials where the participant selected the previously correct person, but because this answer was no longer correct, the feedback was a neutral face expression of the selected person. Reversal trials were defined so that they were always followed by a response shift in the next trial; thus, trials where the participant selected the previously correct person, but did not change their response in a subsequent trial were not included. This categorization allowed us to capture brain activity when the participant made a final error immediately before switching their response. It should be noted that there were no differences in terms of the perceptual properties or the stimulus emotionality across positive, negative, and neutral conditions during the reversal trials since participants viewed two neutral faces during reversal in all conditions. "Acquisition" included trials in which the participant's correct choices of a particular person led to a change in the face (i.e., happy face, angry face, or face appearing with eyeglasses). The first trial of each condition was modeled as "other" (regardless of whether the subject made a correct or incorrect choice), as these trials required subjects to guess and do not reflect learning (or failure of learning) of previous associations. The rest of the trials, which did not fall into the categories of reversal or acquisition trials, were also aggregated as "other." For example, "other" includes trials where the participant chose incorrect faces before reaching the criterion

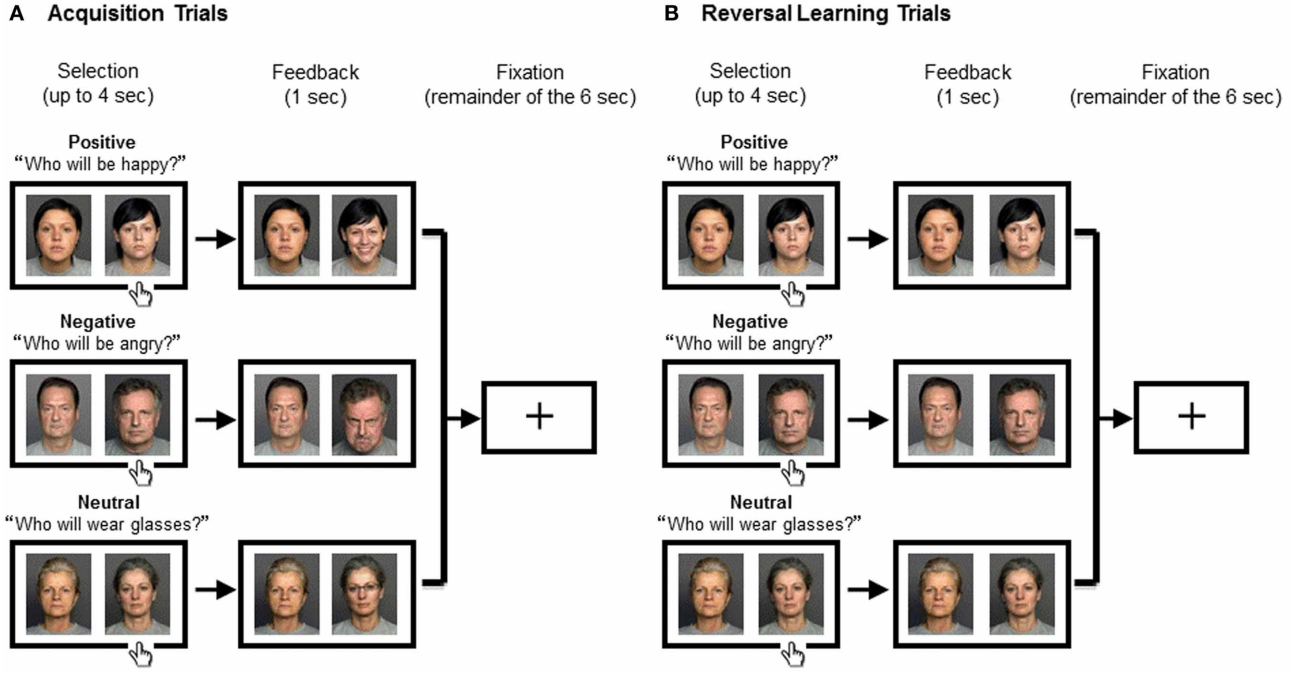

FIGURE 1 | Experimental Procedure. The positive (top), negative (middle), or neutral blocks (bottom) were assigned to the participant in a random order. The two people were randomly assigned to the right or the left of the screen. The trial began with a presentation of two people displaying neutral expressions during which the participant had to select one person by pressing a key. Feedback was presented for 1 s, which was followed by a fixation cross for the remainder of the 6 s. **(A)** In Acquisition Trials where the response was correct, the selected face changed (into a happy face, angry face, or face with eyeglasses, respectively), while the other face remained neutral. **(B)** In Reversal Learning Trials where the response was incorrect, both of the faces remained neutral. Across conditions, the task for the subject was to keep track of the correct person because it switched mid-game. The correct person changed after several (between three and six) consecutive correct trials; the number of trials before the change was unknown to the subject.

(3–6 consecutive correct responses) or trials where the participant failed to respond within 4 s.

FUNCTIONAL MRI DATA ACQUISITION AND PREPROCESSING

Imaging was conducted with a 3 T Siemens MAGNETOM Trio scanner with a 12-channel matrix head coil at the University of Southern California Dana and David Dornsife Neuroimaging Center. The imaging parameters were repetition time (TR) = 2000 ms, echo time (TE) = 25 ms, slice thickness = 3 mm, inter-slice gap = 0 mm, flip angle (FA) = 90°, final voxel dimension = 3 × 3 × 3 mm, and field of view (FOV) = 192 × 192 mm. Data preprocessing were performed using FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl), which included motion correction with MCFLIRT, spatial smoothing with a Gaussian kernel of full-width half-maximum 5 mm, high-pass temporal filtering equivalent to 100 s, and skull stripping of structural images with BET. MELODIC ICA (Beckmann and Smith, 2004) was used to remove noise components. Registration was performed with FLIRT; each functional image was registered to both the participant's high-resolution brain-extracted structural image and the standard Montreal Neurological Institute (MNI) 2-mm brain.

fMRI DATA ANALYSES

Whole-brain analysis

For each reversal trial for each participant, stimulus-dependent changes in BOLD signal were modeled with regressors for feedback and fixation periods. We expected that on reversal trials, participants should try to update associations between face and outcomes not only during the brief feedback period but also during the subsequent fixation. Thus, signal from the feedback and fixation periods were averaged for each valence condition to capture more reliable BOLD signal for reversal learning. The selection period (the initial presentation of two neutral faces) was modeled as the baseline level of activity and therefore was not included as a regressor. Motion regressors were also included. "Acquisition" and "other" trials were also modeled. The regressors were convolved with a double-gamma hemodynamic response function and temporal filtering was applied as well. Temporal derivatives of each of the regressors were also included.

Whole-brain analyses were conducted using FSL FEAT v. 5.98 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Z (Gaussianised T/F) statistic images were thresholded at the whole-brain level using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001) unless otherwise noted. Locations reported by FSL were converted into Talairach coordinates by the MNI-to-Talairach transformation algorithm (Lancaster et al., 2007). These coordinates were used to determine the nearest gray matter using the Talairach Daemon version 2.4.2 (Lancaster et al., 2000).

Regions-of-interest (ROI) analyses

Previous research suggests that the lateral OFC, in particular, plays an important role in reversal learning (Hampshire and Owen, 2006; O'Doherty et al., 2001). Therefore, we performed ROI analyses to examine whether this OFC sub-region shows different activities in reversal learning across the conditions. The left and right lateral OFC were structurally defined using UCLA's Laboratory of Neuro Imaging LPBA40 atlas (Shattuck et al., 2008), set at a 0.5 probabilistic threshold.

Given past findings that the amygdala plays a role in reversal learning (Izquierdo and Murray, 2005; Stalnaker et al., 2007) and our interest in how emotional reversal learning differs from non-emotional reversal learning, we performed ROI analyses for the left and right amygdala. The amygdala was segmented from each participant's high resolution structural scan using FreeSurfer (surfer.nmr.mgh.harvard.edu) and FSL FAST (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). For each hemisphere for each participant, we examined the results from each segmenting software and selected the one judged as more accurate for further manual correction. Next, manual correction of this selected ROI was carried out and erroneous voxels in non-amygdala regions (e.g., hippocampus, white matter) were removed. For both ROI analyses, FSL Featquery was used to extract percent signal change values.

Functional connectivity analyses

The structurally defined amygdala (defined as described above) served as a seed region. To examine functional connectivity, we applied a beta series correlation analysis, which has been found to be an effective measure for functional connectivity (Rissman et al., 2004; Gazzaley et al., 2005). We combined feedback and fixation periods for each reversal trial for each participant. Stimulus-dependent changes in BOLD signal were then modeled with regressors for the "feedback and fixation" period for each reversal trial, while the selection period served as baseline. This allowed us to obtain trial-to trial parameter estimates of reversal-specific activity. First, a new GLM design file was constructed where each reversal trial was coded as a unique covariate, resulting in up to 39 independent variables (the maximum number of reversal trials achieved by participants across all three conditions). To reduce the confounding effects of the global signal change, the mean signal level over all brain voxels was calculated for each time point and was used as a covariate. The model also involved additional nuisance regressors for acquisition and "other" trials. Second, the least squares solution of the GLM yielded a beta value for each reversal trial for each individual participant. These beta values were then sorted by conditions. Third, mean activity (i.e., mean parameter estimates) was extracted for each individual reversal trial from a seed region. Fourth, for each condition, we computed correlations between the seed's beta series and the beta series of all other voxels in the brain, thus generating condition-specific seed correlation maps. Correlation magnitudes were converted into z-scores using the Fisher's r-to-z transformation. Condition-dependent changes in functional connectivity were assessed using random-effects analyses, which were thresholded at the whole-brain level using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$.

RESULTS

BEHAVIORAL RESULTS

We found no significant main effects of group or condition, and no interactions between group and condition in any measure, as reported below (also see **Table 1**).

Table 1 | Behavioral results showing no significant differences between group and conditions.

Condition	Reversal error		Other error		Acquisition trials		Reaction time (ms)	
	Younger	Older	Younger	Older	Younger	Older	Younger	Older
Positive	10.41 (0.49)	10.63 (0.46)	4.00 (0.68)	4.11 (0.64)	5.18 (0.25)	4.96 (0.23)	740	760
Negative	10.82 (0.44)	10.68 (0.42)	3.24 (0.67)	3.84 (0.63)	4.93 (0.14)	4.72 (0.13)	700	740
Neutral	10.94 (0.50)	10.21 (0.47)	3.47 (0.92)	5.16 (0.87)	4.90 (0.23)	5.12 (0.22)	720	830

The table shows the means of the total number of reversal errors (A), the total number of other errors (B), the average number of trials before reaching the acquisition criteria (C), and the average reaction time immediately after reversal trials (D). There were no significant differences between groups and among conditions, and no significant interactions in any measure.

The errors made in the first trial of each condition were excluded, as those were guessing errors and were not due to failure of learning previous associations. The rest of the errors were divided into two types: reversal and other. The total number of reversal errors was calculated for each condition. A 2 (group: younger, older) × 3 (conditions: positive, negative, neutral) mixed analysis of variance (ANOVA) revealed no significant findings. There were no significant differences between groups, $F_{(1,\ 34)} = 0.14$, $p = 0.71$, and conditions, $F_{(2,\ 68)} = 0.39$, $p = 0.68$. No significant interaction between group and condition was found, $F_{(2,\ 68)} = 1.50$, $p = 0.23$. Similarly, there were no significant findings in the total number of other errors between groups, $F_{(1,\ 34)} = 0.74$, $p = 0.40$, and between conditions, $F_{(2,\ 68)} = 1.71$, $p = 0.19$. No significant interaction between group and condition was found, $F_{(2,\ 68)} = 1.79$, $p = 0.17$. The average number of trials before reaching the acquisition criteria (3–6 consecutive correct responses) was calculated for each condition. There were no significant differences between groups, $F_{(1,\ 34)} = 0.09$, $p = 0.77$, and between conditions, $F_{(2,\ 68)} = 1.45$, $p = 0.24$, and there was no significant interaction between group and condition, $F_{(2,68)} = 1.36$, $p = 0.26$. Lastly, to examine how quickly participants responded to the correct face after making reversal errors, the average reaction time for trials immediately after reversal trials was calculated for each condition. There were no significant differences between groups, $F_{(1,\ 34)} = 2.24$, $p = 0.14$, and between conditions, $F_{(2,\ 68)} = 2.89$, $p = 0.06$, and no significant interaction between group and condition, $F_{(2,\ 68)} = 2.01$, $p = 0.14$.

fMRI RESULTS

First, we contrasted brain activity during reversal and acquisition in order to examine the brain regions that are more important for reversal learning than acquisition. For the rest of the analyses, we contrasted brain activity during reversal learning in different conditions. In these contrasts across conditions, there were no differences in the perceptual properties or the visual stimulus emotionality, as all reversal trials involved seeing neutral faces.

COMMON ACTIVATION BETWEEN YOUNGER AND OLDER ADULTS

Brain regions showing greater activity during reversal than acquisition in both groups

Reversal-acquisition contrasts were first performed at the single-subject level for all conditions. These were then entered into a second-level random-effects analysis to determine the brain areas that showed significantly greater activity in reversal than acquisition trials across subjects. Collapsed across groups and conditions, reversal compared with acquisition trials produced increased activity in inferior frontal gyrus/OFC (BA 47), frontal pole (BA 10), inferior frontal gyrus (BA 9), anterior cingulate cortex (BA 24 and 32), and insula (BA 13). Furthermore, putamen, caudate, thalamus, posterior cingulate cortex (BA 23 and 30), precentral gyrus (BA 6), superior temporal gyrus (BA 22), and inferior parietal lobule (BA 40) showed increased activity in reversal than acquisition trials. Thus, consistent with previous research (e.g., Kringelbach and Rolls, 2003; Rolls and Grabenhorst, 2008; Ghahremani et al., 2010; Tsuchida et al., 2010), the OFC and the frontal pole showed greater activity during reversal than acquisition trials, indicating these regions were involved in reversal learning. In a second level analysis, we also examined group differences using independent *t*-tests; but found no differences in either younger-older or older-younger contrasts, suggesting that the two groups produced similar activity during reversal compared with acquisition trials.

Brain regions showing different activity during emotional vs. neutral reversal learning in both groups

Next, we examined whether reversal learning in the positive and negative emotion conditions produced different patterns of brain activity than reversal learning in the neutral condition across younger and older adults. Thus, the analyses below collapsed across groups. The whole-brain analysis revealed greater activity in the negative than neutral conditions in inferior frontal gyrus/OFC (BA 47, **Figure 2A**), frontal pole (BA 10), superior frontal gyrus (BA 9), and anterior cingulate (ACC; BA 32). Other regions showing significant differences in the negative-neutral contrast are reported in **Table 2**. There were no significant findings in other contrasts (negative-positive, positive-negative, positive-neutral, neutral-positive, neutral-negative). However, when we used a lower threshold (a voxel-threshold of $z = 2.3$), the positive-neutral contrast yielded similar results to the ones in the negative-neutral contrast. Compared with the neutral condition, the positive condition produced greater activity in inferior frontal gyrus/OFC (BA 47; **Figure 2B**), frontal pole (BA 10), and ACC (BA 32). Although these results based on use of a lower threshold should be interpreted with caution, they provide useful information about the similarities between the positive and negative conditions in contrast with the neutral condition. Next, the positive and negative conditions (together called the emotion condition) were combined and contrasted against the neutral condition. The emotion condition yielded greater activity in areas including inferior frontal gyrus/OFC (BA 47), frontal

Table 2 | Brain activity showing significant differences between conditions during reversal learning in younger and older adults.

Area	H	*BA*	MNI			Talairach			*Z*-max
			x	*y*	*z*	*x*	*y*	*z*	
NEGATIVE > NEUTRAL									
Putamen	L		−26	−2	6	−25	−4	9	3.71
Putamen	L		−32	−2	4	−31	−4	7	3.41
Inferior frontal gyrus	L	47	−52	20	−14	−49	18	−7	3.34
Middle occipital gyrus	L	18	−22	−94	14	−22	−90	8	3.45
Fusiform gyrus	L	37	−48	−54	−2	−46	−52	−3	3.45
Middle occipital gyrus	L	19	−26	−92	16	−25	−89	10	3.35
Cuneus	L	17	−8	−84	12	−9	−81	7	3.2
Posterior cingulate	L	31	−6	−38	32	−7	−40	29	3.2
Culmen	L		−4	−72	−2	−5	−69	−4	3.16
Anterior cingulate	L	32	−2	44	−20	−3	41	−10	3.37
Superior frontal gyrus/frontal pole	R	9/10	4	70	18	3	62	26	3.29
Anterior cingulate	L	32	−2	44	−10	−3	40	−1	3.29
Inferior frontal gyrus	R	47	56	22	−8	51	19	0	3.25
Inferior frontal gyrus	R	47	52	22	−14	47	20	−6	3.23
Claustrum	R		38	16	−8	34	14	−1	3.03
Superior temporal gyrus	R	42	66	−30	16	60	−31	17	3.19
Superior temporal gyrus	R	42	58	−34	12	52	−35	13	3.07
Middle temporal gyrus	R	21	66	−22	−6	60	−22	−2	3.02
Thalamus	L		−6	−24	−4	−7	−24	−2	3.53
Thalamus	L		−6	−24	0	−7	−24	2	3.4
Thalamus	L		−8	−22	4	−9	−23	6	3.29
Positive > Neutral	No significant results								
Negative > Positive	No significant results								
Positive > Negative	No significant results								
Neutral > Negative	No significant results								
Neutral > Positive	No significant results								
EMOTION > NEUTRAL									
Fusiform gyrus	L	37	−48	−54	−2	−46	−52	−3	3.37
Fusiform gyrus	L	37	−58	−56	6	−55	−54	4	3.24
Middle temporal gyrus	L	21	−68	−20	−10	−64	−19	−8	3.15
Lingual gyrus	L		−6	−84	8	−7	−81	4	3.33
Cuneus	R	18	6	−78	14	4	−76	10	3.06
Culmen	L		−4	−72	−2	−5	−69	−4	3.02
Inferior frontal gyrus	L	47	−36	32	−4	−34	29	3	3.31
Inferior frontal gyrus	L	47	−52	20	−14	−49	18	−7	3.28
Inferior frontal gyrus	L	47	−44	28	−12	−42	26	−5	3.22
Anterior cingulate	L	32	−2	44	−20	−3	41	−10	3.57
Anterior cingulate	L	32	−2	46	−12	−3	42	−3	3.4
Frontal pole	R	10	2	66	−12	1	61	−1	3.19
Neutral > Emotion	No significant results								

pole (BA 10), and ACC (BA 32) than did the neutral condition, whereas the reverse contrast showed no significant findings (**Table 2**; **Figures 2C,D**).

ROI analysis for the OFC

A 2 (group: younger, older) × 3 (condition: positive, negative, neutral) mixed analysis of variance (ANOVA) was performed on the percent signal change from the left and right lateral OFC. There was a significant effect of condition in the left lateral OFC, $F_{(2,\ 68)} = 11.08$, $MSE = 0.03$, $p < 0.001$, $\eta_{p2} = 0.25$, whereas there was no significant effect of group ($p = 0.19$) and no significant interaction between group and condition ($p = 0.30$). *Post-hoc t*-tests suggest that the left lateral OFC showed significantly greater activity in the negative than the neutral conditions, $t_{(35)} = 4.46$, $p < 0.001$, and in the positive than the neutral conditions, $t_{(35)} = 3.16$, $p = 0.003$, whereas there was no significant difference between the negative and the positive conditions ($p = 0.18$; see **Figure 3A**). These results suggest that the left lateral

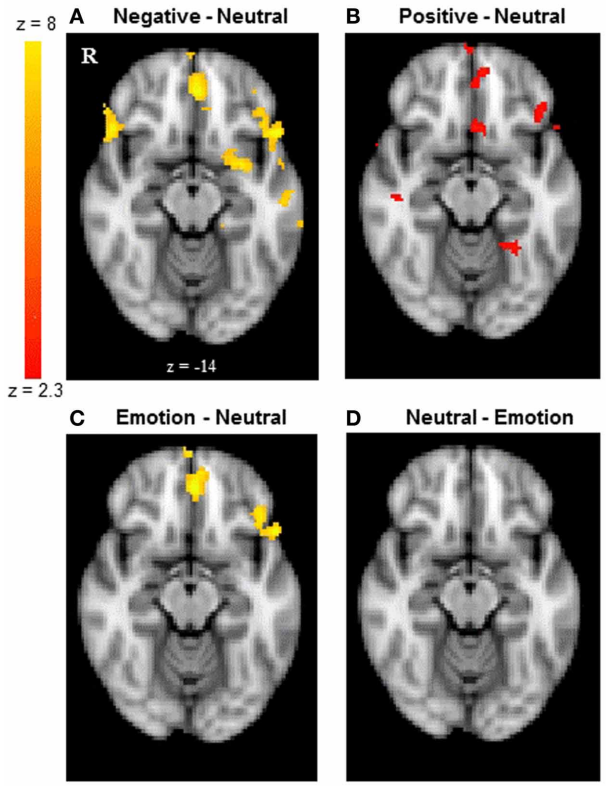

FIGURE 2 | The frontal pole and OFC showed similar activity between younger and older adults. The results shown here are collapsed across groups. **(A)** The frontal pole and OFC showed greater activity when participants reversed negative associations than neutral associations. **(B)** The positive-neutral contrast also showed a similar pattern of frontopolar OFC activity when a lower threshold (a voxel-threshold of $z = 2.3$) was used. Although the low-threshold map should be interpreted with caution, it provides useful information about the similarities between the positive and negative conditions in contrast with the neutral condition. **(C)** When positive and negative conditions were combined, the emotion condition showed greater activity in the frontal pole and OFC than did the neutral condition, **(D)** whereas the reverse contrast showed no significant findings. The images were thresholded at the whole-brain level using clusters determined by $z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$, except for panel **(B)**.

OFC is more involved in emotional reversal learning than in neutral reversal learning in both younger and older adults. For the right OFC, there was a significant effect of group ($M_{younger} = -0.002$; $M_{older} = 0.10$), $F_{(1, 34)} = 4.38$, $MSE = 0.07$, $p = 0.04$, $\eta_{p2} = 0.11$, but no other findings. Across conditions, older adults recruited the right lateral OFC more than did younger adults, but no significant effects of condition were found.

ROI analysis for the amygdala

We conducted 2 (group: younger, older) × 3 (conditions: conditions: positive, negative, neutral) mixed ANOVAs on the percent signal change from the left and right amygdala. There was a significant effect of condition in the left amygdala, $F_{(2, 68)} = 3.48$, $MSE = 0.15$, $p = 0.04$, $\eta_{p2} = 0.09$. A *post-hoc* *t*-test indicated that the left amygdala showed significantly greater activity in the negative than the neutral conditions, $t_{(35)} = 2.71$, $p = 0.01$ (**Figure 3B**). The right amygdala showed a similar pattern, although the result was only marginally significant, $F_{(2, 68)} = 2.94$, $MSE = 0.15$, $p = 0.06$, $\eta_{p2} = 0.08$. The right amygdala also showed significantly greater activity in the negative than the neutral conditions, $t_{(35)} = 2.19$, $p = 0.04$. No age group differences were found in any of these analyses.

Functional connectivity analysis with the amygdala as a seed region

A whole-brain connectivity analysis with the left amygdala as a seed region was conducted for each condition. The negative condition produced a significant inverse correlation between the left amygdala and the right middle frontal gyrus/frontal pole (BA 9, 10) whereas such negative correlations were not observed in the positive and neutral conditions (**Table 3**). The same analysis with the right amygdala as a seed region did not show negative correlations with the frontopolar regions in any of the conditions. No age differences were found in any of these analyses.

AGE-RELATED DIFFERENCES IN BRAIN ACTIVITY DURING REVERSAL LEARNING

Although no age-related differences were observed in the frontopolar OFC and the amygdala, the whole-brain analyses for the negative-neutral and neutral-negative contrasts revealed age differences in the inferior parietal lobule (BA 40), superior temporal gyrus (BA 39, 42), precuneus (BA 7), precentral gyrus (BA 6), and postcentral gyrus (BA 3). Similarly, significant age differences were found for the emotion-neutral and neutral-emotion contrasts in inferior parietal lobule (BA 40) and superior temporal gyrus (BA 39, 42). To better identify the nature of these age-by-emotion interactions, we directly compared younger and older adults separately for each of the three emotion conditions. The positive and negative conditions did not produce significant age differences in any of the brain regions. In contrast, in the neutral condition, older adults showed greater activity in the inferior parietal lobule (BA 40), superior temporal gyrus (BA 41, 42), precentral gyrus (BA 4, 6), and superior occipital gyrus (BA 19) than did younger adults (see **Figure 4**).

DISCUSSION

This study aimed to examine whether brain mechanisms underlying emotional memory updating would be similar between younger and older adults. Our results demonstrated that across age groups, emotional reversal learning produced greater activity in the OFC and the frontal pole than did neutral reversal learning. Importantly, frontopolar/OFC activity did not significantly differ between younger and older adults during emotional reversal learning. Consistent with previous research suggesting that the amygdala remains relatively intact with age, both groups showed significantly greater activity in the amygdala during negative than neutral reversal learning. Furthermore, both groups showed negative correlations between the amygdala and the middle frontal gyrus/frontal pole (BA 9/10) during negative reversal learning. Past research revealed that the frontal pole has negative correlations with the amygdala when updating old emotional memories (Finger et al., 2008; Sakaki et al., 2011). Our findings are

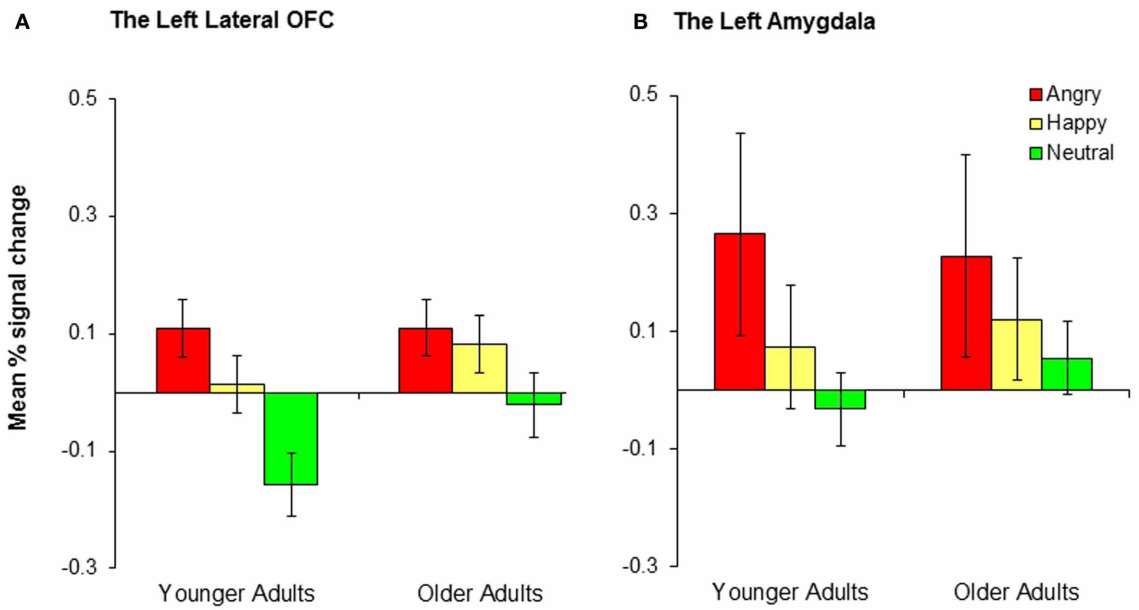

FIGURE 3 | Younger and older adults showed similar patterns of activity in (A) the left lateral OFC and (B) the left amygdala across conditions. Collapsed across groups, participants showed significantly greater activity in the negative than neutral conditions and the positive than neutral conditions, although the differences in the positive-neutral contrast for the left amygdala did not achieve significance.

Table 3 | Brain regions showing negative connectivity with the left amygdala across groups.

Area	H	*BA*	MNI			Talairach			*Z*-max
			x	*y*	*z*	*x*	*y*	*z*	
NEGATIVE									
Inferior parietal lobule	R	40	48	−48	44	44	−49	40	3.97
Inferior parietal lobule	R	40	48	−50	52	44	−52	47	3.87
Inferior parietal lobule	R	40	40	−44	38	37	−45	35	3.86
Middle frontal gyrus	R	9	42	18	38	39	13	39	5.16
Middle frontal gyrus	R	9	44	24	36	41	19	37	4.68
Frontal pole	R	10	32	60	20	29	54	25	4.56
Precuneus	R	7	8	−72	50	6	−72	44	4.61
Precuneus	R	7	6	−56	64	4	−58	57	4.12
Precuneus	R	7	−18	−78	50	−19	−78	43	3.46
POSITIVE									
Precuneus	R	7	18	−78	52	16	−78	45	3.92
Precuneus	R	31	6	−74	28	4	−73	24	3.76
Precuneus	R	7	14	−78	52	12	−78	45	3.74
NEUTRAL									
Precuneus	R	7	−4	−80	50	−5	−80	43	4.18
Cuneus	R	19	2	−82	44	0	−81	38	4.08
Cuneus	R	18	2	−76	36	0	−75	31	3.84

consistent with those previous results and suggest that the frontopolar OFC helps update old associations by down-regulating the amygdala's protection of old representations (Schoenbaum et al., 2007; Stalnaker et al., 2007). It is interesting that similar negative correlations have been seen across studies using different types of associations to be updated, including both item-context associations (as in Sakaki et al., 2011) and within-item feature associations (as in the current study). This suggests that, despite differences in whether the hippocampus, perirhinal cortex, or parahippocampal cortex is most critical for the specific type of binding involved (Diana et al., 2010; Staresina et al., 2011), the amygdala's involvement in updating associations to emotional

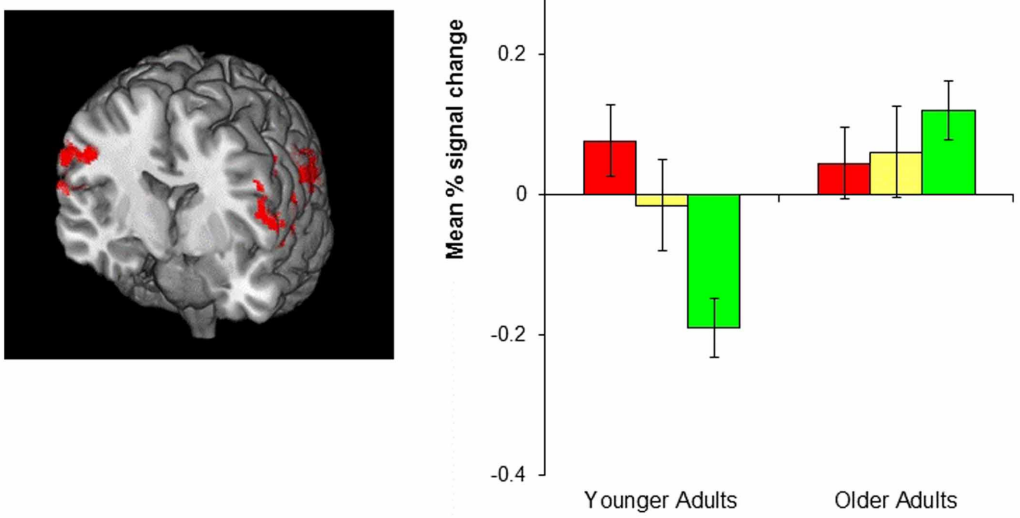

FIGURE 4 | The left image shows age-related differences in the parietal cortex in the neutral condition. Older adults showed greater parietal cortex activity than did younger adults. The image was threshholded at the whole-brain level using clusters determined by $z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$. The bar graph on the right shows the mean % signal change in the bilateral parietal cortex, revealing that younger adults showed greater parietal cortex activity in the negative and positive than in the neutral conditions ($p = 0.001$, $p = 0.034$, respectively) whereas older adults showed no difference across conditions.

memories is modulated by frontopolar OFC. Importantly, our results suggest that this mechanism applies to both younger and older adults. The similarity of the relationship between the frontopolar OFC and amygdala among younger and older adults is consistent with evidence that these regions are relatively well-maintained in aging (Salat et al., 2001; Fjell et al., 2009; Nashiro et al., 2012a).

In contrast with emotional reversal learning, neutral reversal learning produced age-related differences in the parietal cortex, such that older adults showed greater parietal cortex activity than did younger adults. This age difference seems to be due to the fact that younger adults recruited this region only for emotional reversal learning, but not for neutral reversal, whereas older adults showed similar parietal cortex activation across all types of reversal learning (see the bar graph in **Figure 4**). This was indicated by significantly greater parietal cortex activity in both the negative and positive conditions than the neutral condition in younger adults, while there was no difference between conditions in older adults. Previous research suggests that the ventral parietal cortex, which showed the most age differences during neutral reversal, reflects bottom-up attention processes elicited by the retrieval cues or by behaviorally relevant stimuli, especially when they are unexpected (Corbetta and Shulman, 2002; Cabeza et al., 2008, 2011). Thus, one possibility is that younger adults paid greater attention to the cues that signaled emotional reversals than the cues indicating neutral reversals, perhaps due to the fact that reversing emotional associations was harder than reversing neutral associations. This is in line with previous evidence suggesting that emotional information is more difficult to update than neutral information (Mather and Knight, 2008; Novak and Mather, 2009). Older adults, on the other hand, might have found emotional and neutral reversals equally difficult resulting in similar level of attention to both types of cues. However, it remains unclear why older adults did not show greater parietal cortex activity in the emotion than the neutral conditions, an issue that needs to be addressed in future studies.

It is unclear why we did not observe negative correlations between the amygdala and the frontopolar regions in the positive condition, unlike those seen in the negative condition. One possible explanation is that positive reversal learning did not evoke as strong an emotional response as did negative reversal learning; therefore, reversals of positive associations required less frontal involvement to modulate old representations in the amygdala than did reversals of negative associations. In fact, our ROI results suggest that bilateral amygdala showed less activity during positive than negative reversal learning in both groups (albeit non-significantly so); this might suggest that positive reversal learning requires fewer resources to down-regulate the amygdala than does negative reversal learning.

In summary, the current study provides new information about age-related similarities and differences in the brain mechanisms of memory updating. Our results suggest that younger and older adults activate similar brain regions during emotional (in contrast with neutral) reversal learning. This is consistent with previous findings suggesting that the effects of emotional arousal on memory remain similar between younger and older adults.

In addition, we found age group differences in parietal cortex activity only during neutral memory updating. Future studies should investigate the nature of this age difference. This line of research is particularly important for older adults who experience daily challenges in memory updating, as it may help us distinguish when and how emotion benefits or impairs new learning as well as develop strategies to reduce age-related declines in this cognitive domain.

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High reward makes items easier to remember, but harder to bind to a new temporal context

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Learning through reward is central to adaptive behavior. Indeed, items are remembered better if they are experienced while participants expect a reward, and people can deliberately prioritize memory for high- over low-valued items. Do memory advantages for high-valued items only emerge after deliberate prioritization in encoding? Or, do reward-based memory enhancements also apply to unrewarded memory tests and to implicit memory? First, we tested for a high-value memory advantage in unrewarded implicit- and explicit-tests (Experiment 1). Participants first learned high or low-reward values of 36 words, followed by unrewarded lexical decision and free-recall tests. High-value words were judged faster in lexical decision, and more often recalled in free recall. These two memory advantages for high-value words were negatively correlated suggesting at least two mechanisms by which reward value can influence later item-memorability. The ease with which the values were originally acquired explained the negative correlation: people who learned values earlier showed reward effects in implicit memory whereas people who learned values later showed reward effects in explicit memory. We then asked whether a high-value advantage would persist if trained items were linked to a new context (Experiments 2a and 2b). Following the same value training as in Experiment 1, participants learned lists composed of previously trained words mixed with new words, each followed by free recall. Thus, participants had to retrieve words only from the most recent list, irrespective of their values. High- and low-value words were recalled equally, but low-value words were recalled earlier than high-value words and high-value words were more often intruded (proactive interference). Thus, the high-value advantage holds for implicit- and explicit-memory, but comes with a side effect: High-value items are more difficult to relearn in a new context. Similar to emotional arousal, reward value can both enhance and impair memory.

Keywords: reward, value, context, free recall, lexical decision, implicit memory, explicit memory

1. INTRODUCTION

When faced with items of differing reward values, an individual has the possibility of prioritizing their efforts to learn as much as possible about the higher-valued items, likely at the expense of knowledge about the lower-value items. If people took advantage of this, they could maximize their accumulation of reward. In seeking reward, it may not only be beneficial to remember the values of items, but also related information such as the precise context in which the item was found, which we refer to as the reward-maximization hypothesis. Alternatively, reward value may be emotionally arousing; thus, effects of reward value on memory may resemble those found with emotional arousal. Emotionally arousing items are generally remembered better, but memory for related contextual information is often impaired (Easterbrook, 1959; Burke et al., 1992; Christianson, 1992; Mather and Sutherland, 2011; Madan et al., 2012). Such impairment may be caused by diverting attention toward the arousing stimulus itself, and away from its context. If reward value functions like emotional arousal, then higher reward value should result in enhanced performance on some tests of memory (e.g., memory for the experienced items alone), but not others (e.g., judging whether an item was presented in a specific context), which we refer to here as the value-interference hypothesis. Whether higher reward value universally results in better item-memory across different types of memory tests (explicit and implicit), and whether reward value results in better memory for context is unknown. Finding a benefit for high-value items in rewarded memory tests tells us that participants are capable of prioritizing high-value items, but leaves open the question of whether participants favor high-value items when the procedure does not dictate that they should do so. Thus, our first objective was to test whether a memory advantage for words that were previously trained to have a high (versus a low) reward value persists in later *unrewarded* implicit- and explicit-memory tests (Experiment 1), to test for the generality of reward-value enhancements. Our second objective was to test whether an item-memory advantage for high-value words generalizes if the trained words have to be studied and memorized in a new context (Experiments 2a and 2b).

Rewarded memory tests in numerous studies have shown that people are able to prioritize learning of high-value over low-value items, both words and images (Harley, 1965; Tarpy and Glucksberg, 1966; Weiner, 1966; Weiner and Walker, 1966; Loftus and Wickens, 1970; Bjork and Woodward, 1973; Eysenck and Eysenck, 1982; Castel et al., 2002, 2007, 2009; Adcock et al., 2006; Gruber and Otten, 2010; Kuhl et al., 2010; Shohamy and Adcock, 2010; Soderstrom and McCabe, 2011; Wolosin et al., 2012; Watkins and Bloom, unpublished manuscript). For example Castel et al. (2002), showed participants words along with numerical reward values ranging from 1 to 12. Participants were instructed to remember the words with the highest values as best as possible, to maximize the total value of their recalled words. High-value words were recalled more than low-value words. This suggests people were able to flexibly adjust the allocation of cognitive resources during learning to favor items with higher value over those with lower value, and thus maximize earned reward. Assuming a limited resource model, the authors also suggested that if a particular item is allocated more resources, it will be remembered better, but at the expense of the other studied items.

Prioritization effects are not limited to recall; Adcock et al. (2006) demonstrated an enhancement of memory due to reward value using a different explicit memory test: recognition. They presented participants with a high- or low-value reward cue ("$5.00" or "$0.10") followed by a scene image. Participants were asked to remember the scenes (presented during reward anticipation) and were told that they would earn the respective reward amount if they successfully recognized the images in a memory task the following day. In the recognition test, participants earned the respective reward for recognition hits, and were penalized for false alarms. Hit rates were higher for high- than low-value items. Again, this result demonstrates people's ability to explicitly prioritize items associated with a higher-value reward over those with a lower-value reward, both during encoding and retrieval.

Such enhancements of memory due to reward value have been found with tests of explicit memory. However, reward value could influence implicit memory in equally powerful ways. That is, reward value might modulate behavior even when the participant is not deliberately trying to retrieve item-values. This would extend the prioritization findings beyond a deliberate encoding/retrieval strategy, and would suggest that in addition, participants may have a cognitive bias toward high-value items. Although it has never been tested directly, some findings are consistent with the hypothesis that higher reward values lead to better implicit memory: Rewards that are presented subliminally can influence behavior (reviewed in Custers and Aarts, 2010). For example, participants respond more quickly (∼20 ms) in simple monetary incentive tasks when the trial is preceded by a high-value reward cue, than if it is preceded by a low-value reward cue (e.g., the participant is presented with the reward cue, and told to press a button once a target appears; Abler et al., 2005; Sescousse et al., 2010; Staudinger et al., 2011). Furthermore Pessiglione et al. (2007), presented participants with coin images of either 1-pound or 1-pence and asked them to squeeze a handgrip to earn the corresponding monetary reward. Coin images were presented either subliminally (for 17 or 50 ms) or supraliminally (100 ms). Participants squeezed the grip harder on the higher-value trials, even when the coin image was not consciously perceived. Hence, consciously and unconsciously processed reward cues can have analogous effects. Subliminally presented higher-value rewards also recruited more attention than lower-value rewards (pupil dilation: Bijleveld et al., 2009) and increased accuracy in arithmetic (Bijleveld et al., 2010). Though none of these studies have directly shown that reward value can enhance implicit memory, they provide at least indirect support for the hypothesis that high-value items could enhance implicit memory.

We also wanted to clearly separate the value-learning phase, which should be rewarded by necessity, from the later memory phase, which should be unrewarded. Our reasoning was as follows: to interpret the prioritization effects, one must consider that participants were instructed to prioritize. The positive prioritization results, therefore, tell us that participants are capable of prioritization. We ask here whether participants have a bias toward better memory for higher-value stimuli in an unrewarded memory test, even when there is no immediate need to favor the encoding of high-value stimuli. By clearly separating the value-learning phase from the memory study phase (Experiments 2a and 2b) and test phase (all experiments here), we can test whether people possess a learning bias universally favoring high over low-reward value items or reward value might interfere with new learning.

Raymond and O'Brien (2009) conducted an experiment along these lines, testing for the non-deliberate effects of reward value on memory (see also Wittmann et al., 2005, 2011), but it is difficult to determine whether their results were driven by implicit- or explicit-memory retrieval. In their value-learning task, stimulus values were learned with repeated experience, and the effects of the learned values on memory were later tested with an unrewarded, modified attentional blink (AB) task. Participants were first presented with pairs of faces and asked to choose one. Faces within-pair differed in their probability of reward (0.20 or 0.80; reward value across pairs was positive, negative, or neutral). Unlike a conventional AB task, Raymond and O'Brien (2009) asked participants not simply to respond when they saw the target image, but instead to indicate whether the target image was an old face from the prior value-learning task, or a new face (i.e., old/new recognition). If a target image were to overcome the AB, it may also be better retrieved in explicit recognition-memory. Higher-value faces were indeed more often recognized as old than lower-value faces, even though, critically, performance in this task was unrewarded. Raymond and O'Brien (2009) concluded that more attentional resources are recruited for stimuli that previously acquired a higher value. Their results also demonstrate a prioritization from a value-learning task where target items are encoded incidentally. However, we suggest that the following interpretations are possible: (a) High-value faces were primed more during value-learning, leading to enhanced implicit memory for higher-value faces during the AB task. Greater priming for the higher-value faces may have led to increases in subjective experiences of familiarity in the recognition-memory test in the AB task. (b) Old/new recognition is a test of explicit memory. Participants may have recognized the high-value faces in the AB task due to episodic recollection (i.e., explicit memory). (c) Recognition in the AB task may have resulted from a combination of implicit- and explicit-memory. Thus, while Raymond and O'Brien's results provide evidence of a

reward-based enhancement of recognition-memory, it is unclear whether this was an enhancement of implicit- or explicit-memory or a mixture both.

In the current study, we first asked if previously learned reward values also enhance item accessibility in an implicit test of memory: lexical decision (Experiment 1). Participants were first presented with words in a two-alternative choice value-learning task, in which they learned, by trial-and-error with feedback, that half of the words led to a high-value reward and half of the words led to a low-value reward (also used by Madan and Spetch, 2012). This value-learning task is similar to previous reward-learning procedures used by Estes and others (e.g., Pubols, 1960; Estes, 1962, 1966, 1972; Humphreys et al., 1968; Allen and Estes, 1972; Medin, 1972a,b) as well several more recent reward-learning studies (e.g., Johnsrude et al., 1999, 2000; Frank et al., 2004, 2006; Bayley et al., 2005; Pessiglione et al., 2006; Valentin and O'Doherty, 2009; Voon et al., 2010; Gradin et al., 2011). Participants were then presented with an unrewarded lexical decision task, in which words from the value-learning task were shown again. Finally, in an unrewarded test, participants were asked to freely recall all the words from the session (value-learning phase and lexical decision). We predicted that explicit memory (free recall) would be enhanced by reward value. We further predicted that implicit memory would be enhanced due to reward value, as measured in the lexical decision task, if reward value enhances memory retrieval even when participants do not deliberately prioritize the retrieval of high-value items over low-value items. If memory is enhanced in both memory tests, we will then ask whether the two effects could have the same underlying cause or not. This will be done by correlating the high-value advantage in lexical decision with the high-value advantage in free recall across participants. If the correlation is large and positive, this would suggest that memory, both implicit and explicit, can be enhanced by reward value through a singular mechanism that globally enhances memory performance. However, implicit- and explicit-memory functions are supported by separable memory systems, both in behavior (e.g., May et al., 2005; Gopie et al., 2011) and in the brain (e.g., Rugg et al., 1998; Schott et al., 2005, 2006). If we instead find that performance in the two memory tasks is uncorrelated or even produce a negative correlation, this would suggest that enhancements of memory due to value are driven by separable reward-based modulations of different kinds of memory.

In a second pair of experiments, we asked if the enhancement of explicit memory due to reward value would persist if items with previously learned reward values were re-studied in a new context. Participants in Experiments 2a and 2b were first given the same value-learning task as in Experiment 1. Following this, participants were asked to study several lists composed of previously learned high- and low-value words, as well as new items, in an unrewarded free-recall task. In this free-recall task, participants had to disregard their memory for items from the value-learning task and instead, confine their memory retrieval to only the most recently studied list (a specific, temporally defined context). Experiments 2a and 2b were identical except that a faster presentation rate was used in Experiment 2b to test whether the results of Experiment 2a could be due to time-consuming processes applied during study, such as deliberate encoding of reward value. Because the list length was short (nine words per list), we expected that total probability of recall might not be a sensitive enough measure; we therefore additionally examined output order and intrusion rates to test whether high- or low-value items were remembered better.

According to the reward-maximization hypothesis, participants devote more resources to learning higher-value items than lower-value items. This should generalize to learning in a new context (determining whether an item was presented within a specific context), which leads to the prediction that free recall will be enhanced for high-value words in Experiments 2a and 2b. According to the value-interference hypothesis, cognitive resources may be diverted to high-value items, and this is at the expense of attention to other related information, including the list context. Thus, the value-interference hypothesis leads to the prediction that free recall will be worse for high-value items, and that high-value items will be intruded more than low-value items (due to failures of list discrimination).

2. EXPERIMENT 1

2.1. METHODS

2.1.1. Participants

A total of 99 introductory psychology students at the University of Alberta participated for partial fulfillment of course credit. Five participants were excluded due to machine error. All participants had learned English before the age of six and were comfortable typing. Participants gave written informed consent prior to the study, which was approved by a University of Alberta Research Ethics Board.

2.1.2. Materials

Words were selected from the MRC Psycholinguistic database (Wilson, 1988). Imageability and word frequency were all held at mid-levels and all words had six to seven letters and exactly two syllables. We additionally used the Affective Norms for English Words (ANEW; Bradley and Lang, 1999) to exclude words with moderately arousing, positive, or negative emotional connotations[1] (e.g., "assault," "hatred," and "heaven") which could interfere with learning reward values (e.g., participants may find it difficult to learn that "hatred" is a high-value word, or that "heaven" is a low-value word). Two words were removed manually as they were deemed by the authors to be emotional in nature, but were not included in ANEW (e.g., "terror," "regret"). A total of 21 words were excluded this way, and the final word pool consisted of 160 words (**Table 1** reports word pool properties).

For the lexical decision phase, 160 pronounceable non-words were generated with the LINGUA non-word generator (Westbury et al., 2007), using a pre-compiled word frequency dictionary (Shaoul and Westbury, 2006). To match the length of the non-words to the words, we generated 87 six-letter and 73 seven-letter non-words.

[1]Our criteria regarding the ANEW were to exclude words with an arousal rating greater than 5.5 scored on a scale from 1 (not arousing) to 9 (highly arousing), and a valence rating (also on a scale from 1 to 9) of either (a) less than 4 (negative), or (b) greater than 7 (positive). Note that we chose to keep two words that did meet the exclusion criteria: "dancer" and "rescue."

Table 1 | Word pool statistics, as obtained from the MRC Psycholinguistic database (Wilson, 1988).

	Concreteness	Imageability	Word frequency	Word length	Number of syllables
Mean	439	467	22	6.46	2
SD	99	80	12	0.50	0
Min	243	248	7	6	2
Max	580	578	52	7	2

2.1.3. Procedure

Prior to the experiment, participants were informed that the experiment was a "word choice task," and that they would receive a payment proportional to the total points earned in the value-learning task of the experiment, in addition to their partial course credit.

The experiment consisted of a sequence of four tasks: value-learning, lexical decision, free recall, and a value-judgment task. Participants were not provided with details of the subsequent task until the current task was completed.

2.1.3.1. Value learning. Participants were shown two words on the computer screen simultaneously. Words were selected at random from our word pool of 160 words. Participants were to choose one of the two words in each choice set by pressing the "Z" or "/" key of a computer keyboard to choose the word presented on the left or right side of the computer screen, respectively.

For each participant, 36 words were randomly selected from the word pool, and each word was randomly assigned to one of two reward values: 1 or 10 points (low- or high-value, respectively). Trial choices were pseudorandomly generated, with each word used one time per choice set, but each set always consisted of one high- and one low-value word. This constraint was not revealed to the participant. After each choice, the participant saw the reward in the center of the screen for 2000 ms; if they chose a high-value word, an image of a pile of coins was presented; if they chose a low-value word, an image of a penny was presented. The participant's current point balance was continually presented at the bottom of the screen throughout the duration of the value-learning task. There was no time limit on the choices and participants were given a 1000-ms delay before the next choice.

Training consisted of 18 choice sets per block for 13 blocks. At the end of the session, participants were paid $1.00 for every 500 points earned during the value-learning task, rounded up to the nearest 25-cent amount. Participants earned between $3.25 and $5.00 in this task.

2.1.3.2. Lexical decision. An additional 18 words, selected at random from the same pool as the trained words, were included as new words. Participants were asked to judge the lexical status of 108 items: 36 trained words, 18 new words, and 54 non-words. Each item was presented for up to 10,000 ms, and the participant pressed either "Z" on the computer keyboard to indicate that the item was a proper English word, or "/" to indicate that the item was a not a word. A fixation cross ("+") was presented for 1000 ms to separate each decision prompt.

The 108 items were preceded by eight practice items (four words/four non-words) to attenuate a possible recency effect over the last words from the preceding value-learning task.

2.1.3.3. Free recall. In a final free-recall task, participants were given 5 min. to recall all of the words they could remember from the study, in any order. Participants were asked to type out their responses, terminated with the ENTER key. After each response, a blank screen was presented for 500 ms. Repeated recalls of the same words were ignored.

2.1.3.4. Value judgment. To measure participants' explicit memory of the reward values for each item, we included a value-judgment task following free recall. At the end of the experiment, participants were presented with each of the words previously shown in the value-learning task, one at a time, and asked to judge how many points each word had been worth in the initial value-learning task. Participants were told to press the "Z" key if they thought the word was worth 1 point, or "/" for 10 points.

2.1.4. Data analysis

Effects were considered significant based on an alpha level of 0.05. For response time analyses, only correct responses were analyzed. Response time analyses were conducted on the within-subject median response time for each condition.

For lexical decision, only responses made between 200 ms and the individual participant's mean plus 3 SD were included in the analysis (0.61% trials excluded).

2.2. RESULTS AND DISCUSSION

Accuracy in the value-learning task was measured as the proportion of trials on which the participant chose the high-value word. This measure began at chance, as the participant could not know which was the high-value word. In the last block of the value-learning task, accuracy was significantly greater than chance and near ceiling [$M \pm 0.95$ CI $= 0.94 \pm 0.02$ correct; $t(93) = 37.34$, $p < 0.001$] (**Figure 1A**).

Lexical decision was significantly more accurate for the previously rewarded old words than for the untrained, new words [$t(93) = 6.94$, $p < 0.001$; old words: 0.99 ± 0.03 correct; new words: 0.95 ± 0.14 correct]. Participants also identified the old words significantly faster than the new words [$t(93) = 12.77$, $p < 0.001$, $M(\text{new}) = 708 \pm 12$ ms; $M(\text{old}) = 591 \pm 8$ ms]. There was no difference between accuracy for high- and low-value words [$t(93) = 0.00$, $p > 0.1$; high value: 0.99 ± 0.04 correct; low-value: 0.99 ± 0.04 correct]. Importantly, high-value words were identified significantly faster than low-value words [$t(93) = 2.42$, $p < 0.05$; $M(\text{high}) = 584 \pm 9$ ms; $M(\text{low}) = 599 \pm 8$ ms] (**Figure 2A**). Thus, trained words were primed, and high-value words were primed more than low-value words, a novel finding that suggests that reward value can influence implicit memory.

Probability of free recall (**Figure 2B**) was greater for high-value words than low-value words [$t(93) = 4.40$, $p < 0.001$; $M(\text{high}) = 0.50 \pm 0.04$; $M(\text{low}) = 0.40 \pm 0.03$]. "New" words (from the lexical decision task) were also recalled, but far less often than the previously rewarded words [$t(93) = 23.80$, $p < 0.001$;

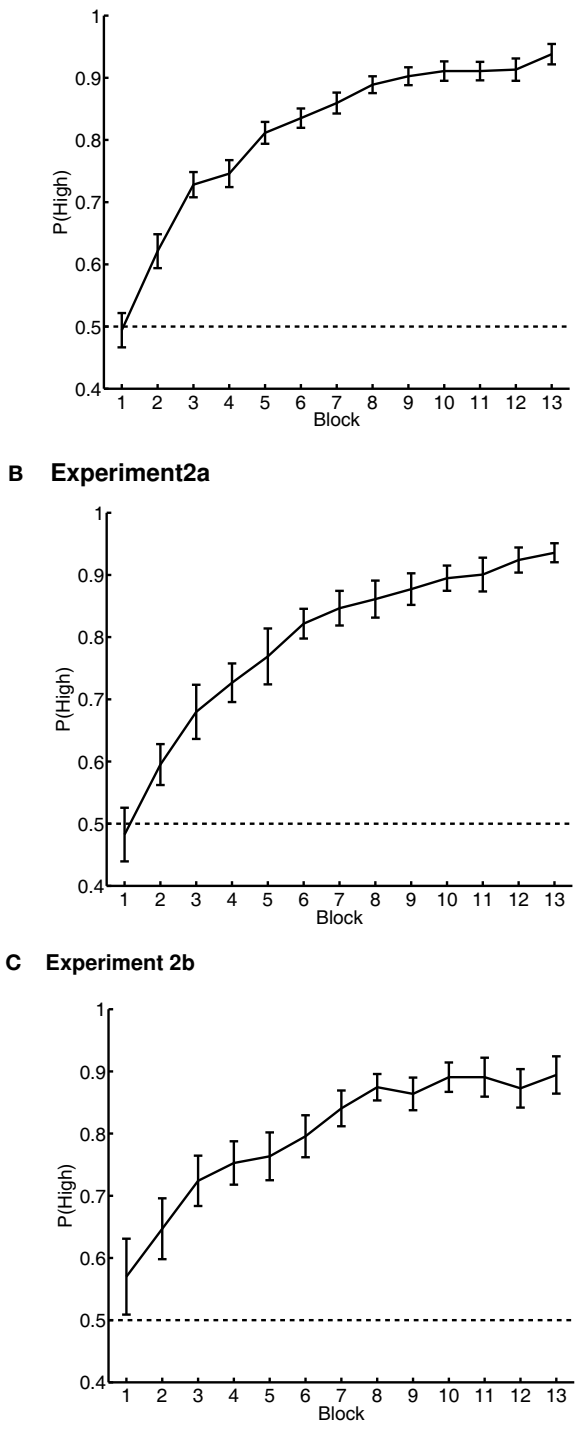

FIGURE 1 | Value-learning task results in Experiments 1 (A), 2a (B), and 2b (C). Performance is shown as the probability of choosing the high-value word over the low-value word in each of the learning blocks 1 to 13. Chance probability of choosing the high-value word is indicated by the dashed line. Error bars are 95% confidence intervals around the mean, corrected for inter-individual differences (Loftus and Masson, 1994).

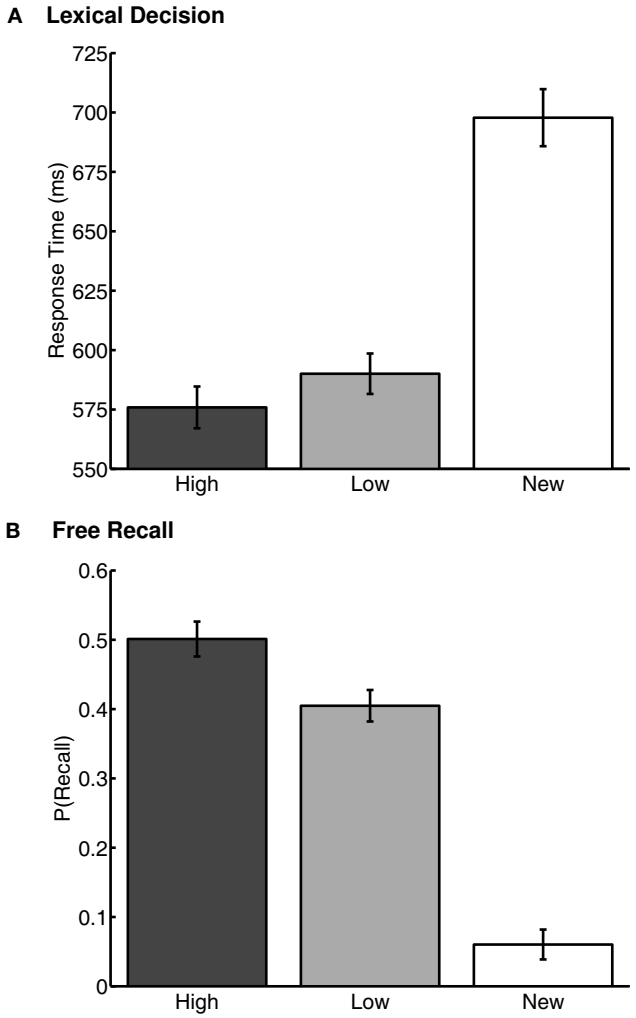

FIGURE 2 | Performance in the memory tasks in Experiment 1. (A) Response times from the lexical decision task. **(B)** Proportion of total words recalled from the free recall task. "High" and "Low" represent the high- and low-value words, respectively. "New" represents words first used in the lexical decision task, that were not present in the value-learning task. Error bars are 95% confidence intervals, corrected for inter-individual differences (Loftus and Masson, 1994).

$M(\text{new}) = 0.06 \pm 0.01$; $M(\text{old}) = 0.45 \pm 0.03$]. Thus, value also influenced explicit memory retrieval, replicating prior findings.

We next asked if the memory effects of value depended on the level of performance during value training. However, the asymptotic accuracy in the value-learning task (averaged over the last four trials) did not correlate significantly with the value effects on both memory tests [both p's > 0.1].

In the value-judgment task, participants rated the value of the previously rewarded words much better than chance [$M = 0.87 \pm 0.03$ correct; $t(93) = 25.65$, $p < 0.001$]. The accuracy of judgments was similar for high-value words [$M(\text{high}) = 0.88 \pm 0.03$ correct] and low-value words [$M(\text{low}) = 0.87 \pm 0.03$ correct; $t(93) = 1.16$, $p > 0.1$]. That is, participants had substantial, though

not perfect, explicit memory for the value of both high and low-value words. In the value-learning task, because all responses were a choice between a high- and a low-value item, those responses cannot be used to determine whether high and low values were learned to the same level. In the value-judgment task, items were judged individually; thus, the near-equivalence of value judgments of high- and low-value items suggests that participants learned the values of high- and low-value words equally well. This rules out the possibility that participants simply remembered the high-value words better because they performed the value-learning task better for high- than low-value items. It could further be argued that the value judgments for both types of items could have been based on memory for high-value items alone: A participant then would decide to judge a high-value item as "high" based on their memory for that item's value, but to judge all items for which they had no such memory as a "low" item. That is, value judgments would be made on a single value dimension. If only the strength of memory for high-value items was used to make judgments along this dimension, high-value words could be correctly classified as high (those with sufficient high-value item-memory strength), low-value words could be correctly classified as low (those with insufficient high-value memory strength), and high-value words could be incorrectly classified as low (those with insufficient high-value memory strength). However, low-value words could not be incorrectly classified as high-value words this way. As reported, we did observe such errors in 13.2% of the low-value words. Note also that the probability of judging a low item as high was quite close to the probability of judging a high item as low (12.5%). Thus, regardless whether participants are basing their choices on a singular value dimension, they are doing so with the same accuracy for low as for high items. This suggests that the quality of memory (i.e., variance in memory strength for both word types along a value dimension) is equivalent for both types of words.

One plausible explanation of our results is that, instead of value, our effects on memory are due to choice behavior: the more often a participant chose an item during value-learning, the more they remembered that item in the later memory tests (see Weber and Johnson, 2006). Since choice frequency and value are highly confounded (i.e., the task *requires* choosing high over low-value items), a combined correlation spanning all items would not be possible either. As an alternative, we calculated choice frequency as the mean number of times a participant chose a high-value item, across all 13 blocks of the value-learning task, minus the mean number of times they chose a low-value item: DiffCF = *mean*[*choice frequency* (*H*)] − *mean*[*choice frequency* (*L*)]. DiffCF thus measures a participant's bias toward choosing high- over low-value words. DiffCF is, of course, expected to be highly correlated with accuracy, since participants are indeed asked to choose high items and to avoid low items. Confirming this, the correlation between participants' accuracy in the value-training task and the DiffCF measures was highly significant [$\rho(93) = 0.48$, $p < 0.001$]. To rule out that choice frequency significantly co-varied with our effects of value on implicit- and explicit-memory, we then correlated DiffCF with: (a) the effect of value on lexical decision performance (the normalized difference in response times due to reward value: DiffLD = $[RT(low) - RT(high)]/0.5[RT(low) + RT(high)]$; (b) the effect of value on free-recall performance, DiffFR = proportion of recalled high-value words, divided by the total number of words recalled. DiffCF correlated with neither the effect of reward value on implicit memory, nor the effect of reward value on explicit memory [lexical decision: $\rho(93) = 0.075$, $p > 0.1$; free recall: $\rho(93) = 0.074$, $p > 0.1$]. Thus, the bias to choose high over low-value words in the value-learning task did not account for the effects of reward value on implicit- or explicit-memory. This is consistent with Madan and Spetch (2012), who also ruled out choice frequency as a possible determining factor of subsequent memory with a similar training procedure.

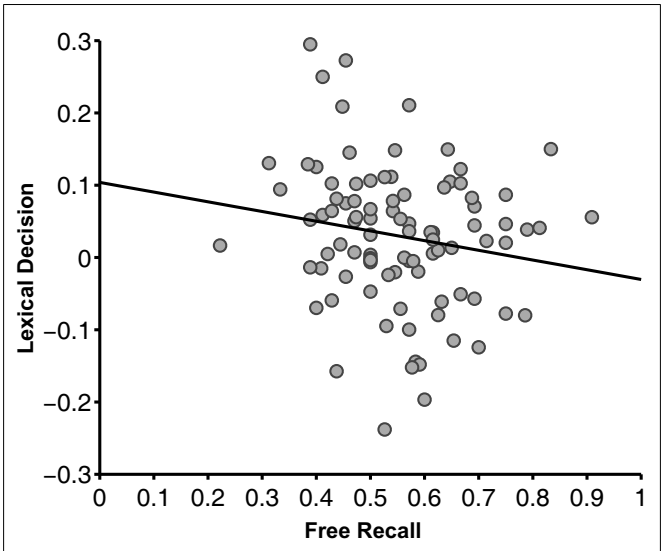

FIGURE 3 | Correlation between lexical decision and free recall tasks in Experiment 1 [$\rho(93) = -0.20$, $p < 0.05$]. The lexical decision measure was the facilitation of high-value words compared to low-value words (difference in response time) divided by the participants' average response time. The free recall measure was the proportion of recalled words that were high value, divided by the total number of words recalled from the value-learning task. Each dot represents an individual participant.

Next, we asked whether the effects of reward value on our two memory tests were related, explaining common variance across participants, or unrelated, explaining different subject variability. Participants who demonstrated greater value-based facilitation in lexical decision had *less* value-based facilitation in free recall [$\rho(93) = -0.20$, $p < 0.05$] (**Figure 3**). The fact that a positive correlation was not observed suggests that there are at least two partly dissociable mechanisms by which value can influence memory.

Because lexical decision always preceded final free recall, we were concerned that the negative correlation between the two value-based facilitation effects on memory could be due to the influence of lexical decision on free recall. If a word had a long response time in lexical decision, perhaps that would correspond to increased encoding of the word; a poor lexical decision response might then turn into an increased probability of free recall. We tested for this kind of effect with within-subjects analyses. We compared lexical decision response times for words that were or were not free recalled, separately for high- and low-value words. Lexical decision response times were not significantly different

between later recalled and later not recalled words [high value: $t(93) = 1.13$, $p > 0.1$, Cohen's $d = 0.07$; low-value: $t(93) = 0.60$, $p > 0.1$, $d = 0.04$]. Thus, the effect of an item's value on explicit memory is not explainable by its effect on implicit memory, or vice versa, and this rules out explanations due to the fixed task order, i.e., the possibility that the negative correlation between value-based facilitation effects was merely due to further encoding during lexical decision. Instead, we found no relationship between lexical decision time for an item and its later recall probability, in line with our previous interpretation of the between-subjects correlations: the enhancements in the two tasks were driven by different mechanisms.

We had not expected the negative correlation between the effects of value on implicit- and explicit-memory. In an attempt to derive an explanation *post hoc*, we took a closer look at our data. Perhaps the observed negative correlation between implicit- and explicit-memory had been driven by differences in participants' learning strategies in the value-learning task (even though, as reported above, the asymptotic accuracy in the value-learning task did not correlate significantly with the value effects on the two memory tests). We speculated that participants who learned values earlier may be the ones who showed greater effects of value on implicit memory, because they would have had a larger number of trials on which they knew the correct values. In contrast, participant who took longer to learn presumably found the value-learning task more challenging early on; for these participants, value may have been used more as a deliberate retrieval cue in later explicit memory. For this purpose, we measured how long it took for participants to reach an 80% accuracy criterion in the value-training task (i.e., trials-to-criterion, TTC: choosing the high-value item on 80% of all trials within a block). We then correlated TTC with reward effects on the lexical decision task (DiffLD) and with reward effects on free recall (DiffFR). Note that 6 participants never reached the 80% accuracy criterion; for these participants, the TTC was set to 14, i.e., one greater than the actual number of trial blocks presented in the value-learning task. This correction to the TTC measure served to denote that these participants required more learning trials to reach 80% accuracy. In line with our reasoning, we found that participants who reached the learning criterion *earlier* exhibited stronger implicit memory effects due to reward value (i.e., greater priming in the lexical decision task, DiffLD) [$\rho(93) = -0.22, p < 0.05$]. This may provide evidence that participants who had learned items values earlier (fewer trials-to-criterion) had more trials on which to accumulate value learning, which then enhanced implicit memory for high-value items. Complementing this result, we found that participants who took *longer* to reach the learning criterion exhibited stronger explicit memory effects due to reward value (i.e., greater difference in recall probabilities in the free-recall task, DiffFR) [$\rho(93) = 0.24$, $p < 0.05$]. This is consistent with the idea that participants for whom value learning was initially more challenging may have used value more as an explicit memory cue in free recall. Further, when controlling for trials-to-criterion in a partial correlation analysis, the negative correlation between the effects of value on lexical decision and free recall was no longer negative, and far from significant [$\rho_p(93) = 0.040$, $p > 0.1$]. Although our specific interpretation is *post hoc* and should be considered with caution, the results of this analysis at least suggest that the way people learned the values initially mediated the mutually exclusive effects of value on implicit- and explicit-memory.

2.3. SUMMARY

Experiment 1 revealed that high-value words were subsequently remembered better than low-value words in *both* implicit- and explicit-unrewarded memory tests. The effect of value on memory in these two memory tasks was slightly negatively correlated, suggesting the presence of at least two mechanisms mediating the memory enhancement by reward value, rather a global enhancement of memory due reward value. Different initial value-learning strategies may have contributed to this negative correlation.

The enhancement of implicit memory by value (i.e., an accessibility bias for high-value items), is a finding without direct previous evidence. Although the influence of reward value on response time in our lexical decision task was relatively small (∼15 ms), this is consistent with studies that presented a reward cue in monetary incentive tasks and found that reward value facilitated response time by ∼20 ms (Abler et al., 2005; Sescousse et al., 2010; Staudinger et al., 2011). Furthermore, nearly all prior studies demonstrating the reward-based enhancement of memory used procedures that led to the deliberate prioritization of encoding due to reward value. Here we used a procedure where participants incrementally learned values and found the enhancement of both implicit- and explicit-memory due to reward value. Because the memory tests were unrewarded, and no prioritization instructions were given, this suggests that not only can participants prioritize when asked to, but they exhibit a bias to learn high-value words better than low-value words. Such a bias may serve them well in naturalistic situations, in which items usually retain their value.

3. EXPERIMENTS 2A AND 2B

We next asked whether the high-value item advantage observed following training in Experiment 1 would extend to a new learning situation involving the reward-value-trained items. Having established that the value-learning procedure in Experiment 1 can enhance explicit memory due to reward value, we used the same procedure to test for effects of reward value on new learning involving value-trained words in a different context. Following training as in Experiment 1 and a distractor task, we had participants learn word lists consisting of trained words and untrained words. In a study/test procedure, participants viewed each new list, followed by delayed free recall.

As in Experiment 1, our dependent measure in the free-recall task was the proportion of words recalled of each word type (high value, low value, or new). However, proportion of recalls is a rather coarse measure of memory, as it collapses across all responses given by a participant on a list. Apart from being a test of item retrievability, free recall is also a test of associations between items and a specific list context. In other words, words output earlier in free recall represent the items that are easier to retrieve and also have the strongest associations with the current target-list context (e.g., Bjork and Whitten, 1974; Crowder, 1976; Raaijmakers and Shiffrin, 1981; Howard and Kahana, 1999; Brown et al., 2007). Likewise, late

in the recall sequence, responses are more likely guesses. Thus, in addition to recall accuracy, we tested if any word type (high value, low value, and new) was recalled significantly earlier or later than any other word type.

We considered two hypotheses: our reward-maximization hypothesis led to the prediction that participants will recall more high-value than low-value words, due to prioritized study of the words that had the high values previously, similar to previous studies finding an enhancement of memory due to reward value when rewards are earned for successful memory performance (e.g., Castel et al., 2002; Adcock et al., 2006). This hypothesis is also suggested by investigations of the effects of emotional arousal on memory, such as Hadley and MacKay's (2006) priority-binding hypothesis which proposes an enhancement of contextual binding due to arousal (also see Siddiqui and Unsworth, 2011). Alternatively, our value-interference hypothesis led to the opposite prediction: Words with a previously acquired high reward value will be harder to learn and remember in a new context than words with a low-reward value if higher values direct attention toward the high-value items themselves, but away from other pertinent information. This hypothesis also suggests that for the high-value words, participants will find it difficult to constrain their memory retrieval processes to just the list context of the most recently studied list and will instead erroneously recall more high-value words than low-value words. This hypothesis is based on studies finding an impairment of new associative memories between cues that had previously been predictive of emotionally arousing information (Mather and Knight, 2008; Novak and Mather, 2009; Sakaki et al., 2011; Nashiro et al., 2012). For example, Mather and Knight (2008), found that participants had more difficulty learning new associations between sounds/faces and nearby presented digits (and other contextual information), if the sounds/faces had initially been paired with negative images, an effect that did not occur when they had been paired initially with neutral images. This suggests, emotional arousal may have interfered with participants' ability to learn subsequent associations. Furthermore, Novak and Mather (2009) had participants learn screen locations for neutral and negative images. When locations for individual pictures remained the same over several study–test cycles, participants made more location memory errors for emotional than neutral images in later cycles. Thus, an initial incorrect association between an emotional picture and a location may have led to more interference with learning the correct association than an initial incorrect association for a neutral picture. Moreover, when the locations for individual pictures were switched after three cycles, participants were worse at updating their memory with the new locations for negative images as opposed to neutral images. Together, these findings imply that emotional items are more affected by proactive interference from previous experience with the items, which may present as impaired learning of new associations with such items.

We conducted two variants of this experiment; Experiment 2b had a faster list presentation rate, to further test whether possible effects of previous reward value on new list learning are driven by a time-consuming strategy applied during study (i.e., value-based prioritization of encoding or retrieval).

3.1. METHODS

3.1.1. Participants

A total of 72 introductory psychology students at the University of Alberta participated for partial fulfillment of course credit. All participants had normal or corrected-to-normal vision, learned English before the age of six, and were comfortable typing. Participants gave written informed consent prior to the study, which was approved by a University of Alberta Research Ethics Board. Participants never participated in more than one of Experiment 1, 2a, and 2b. Experiment 2a had 40 participants; Experiment 2b had 32 participants.

3.1.2. Materials

The same materials as used in the training phase of Experiment 1 were used in both Experiments 2a and 2b.

Six maze puzzles were generated for the distractor task using an online maze generator (http://www.hereandabove.com/maze/mazeorig.form.html). Mazes were made using the generator's default settings.

3.1.3. Procedure

The experiment consisted of three tasks performed in a fixed sequence: value-learning, maze distractor, and study/test free recall of six nine-word lists. Participants were not provided with details of the subsequent task until the current task was completed.

3.1.3.1. Value learning. The procedure was the same as in Experiment 1.

3.1.3.2. Maze distractor. To reduce the very high level of proactive interference from the value-training phase on the free-recall phase, we included a non-verbal distractor task following value training. Participants were given 5 min. to complete pencil-and-paper mazes. When participants finished one maze, they were provided with another maze. This procedure was repeated until the 5 min. had elapsed, at which point the maze was removed and the participant advanced to the study/test free-recall task. On average, participants completed 2–3 mazes within the 5 min.

3.1.3.3. Study/test free recall. Participants were told to study each list of words and that their memory for the list would be tested, but that they would not earn any reward in this phase. Participants first studied one practice list of 9 words from the word pool that were excluded from analyses, and 6 experimental lists of 9 words each: 3 high-value words from the value-learning task, 3 low-value words from the value-learning task, and 3 new words (random order of presentation in each list).

Each word was presented for 1800 or 800 ms (Experiment 2a and 2b, respectively), after which the screen was cleared for 200 ms. After being presented with all 9 words, participants were given a distractor task that consisted of four equations in the form of A + B + C = ___, where A, B, and C were randomly selected digits between 2 and 8. Each equation remained in the center of the screen for 5000 ms. The participant was asked to type the correct answer during this fixed interval, after which the screen was cleared for 200 ms.

After the distractor, participants were given 1 min. to recall as many of the words from the list that they could (i.e., free recall).

Participants were asked to type out their responses. After each response, a blank screen was presented for 500 ms. Participants were allowed to pause prior to the presentation of the next list. This procedure (list encoding, math distractor, and list free recall) was repeated for all 6 lists.

3.1.4. Data analysis

Effects were considered significant based on an alpha level of 0.05. ANOVAs are reported with Greenhouse–Geisser correction for non-sphericity where appropriate and *post hoc* pairwise comparisons are Bonferroni-corrected.

Because the value-learning task consisted of 13 trials, which means participants had 13 presentations of each stimulus, we expected there to be a large amount of proactive interference. As participants could not advance to the next list until the full minute expired, we expected later responses to include a high level of guesses. However, we were also concerned that some participants may not have understood that they were to confine their responses to the very last list presented. Therefore, to identify such non-compliant participants, we screened out participants who had extremely low accuracy *early* in the output sequences.

We calculated the average proportion of correct recalls within the first four responses to ensure that participants included in the analysis attempted to recall items from the most recent list (i.e., that they followed instructions). We found that most participants responded with three correct recalls in their first four responses [Experiment 2a: $M = 3.46$; Experiment 2b: $M = 3.32$]. However, five participants produced an average of one or fewer correct recalls in their first four responses [Experiment 2a: two participants; Experiment 2b: three participants] and were excluded from further analyses. Excluding these participants, the number of correct recalls in the first four responses did not substantially change the mean correct recalls within the first four recalls of the entire samples [Experiment 2a: $M = 3.50$; Experiment 2b: $M = 3.35$]. Similarly, total number of correct recalls did not change much [Experiment 2a, total sample: $M = 9.45$; Experiment 2a, excluding 2 participants: $M = 9.35$; Experiment 2b, total sample: $M = 9.91$; Experiment 2b, excluding 3 participants: $M = 9.39$]. Thus, exclusion of these five participants did not substantially change the observed recall patterns. For the remaining participants, analyses were carried out after removing extra-experimental intrusions and within-list repetitions.

3.2. RESULTS AND DISCUSSION

3.2.1. Value learning

The value-training data resembled the data in Experiment 1 (**Figures 1B,C**). Performance again began near chance, and improved across blocks; in the last block (block 13), accuracy was significantly greater than chance [Experiment 2a: $t(37) = 31.16$, $p < 0.001$, $M = 0.94 \pm 0.03$ correct; Experiment 2b: $t(30) = 12.83$, $p < 0.001$, $M = 0.89 \pm 0.06$ correct].

3.2.2. Study/test free recall

3.2.2.1. Proportion of words recalled. In each of Experiments 2a and 2b, we conducted repeated-measures ANOVAs on Word Type (high value, low value, and new) on the proportion of words recalled. Proportion recalled was defined as the average number of correct words recalled of each word type across lists, divided by 3 (the number of words of each type in each list). The main effects of Word Type were not significant in either experiment [Experiment 2a: $F(2,67) = 1.08$, $p > 0.1$, $\eta_p^2 = .03$, $M(\text{high}) = 0.56 \pm 0.04$, $M(\text{low}) = 0.57 \pm 0.04$, $M(\text{new}) = 0.53 \pm 0.05$; Experiment 2b: $F(2,52) = 2.74$, $p > 0.1$, $\eta_p^2 = .08$, $M(\text{high}) = 0.52 \pm 0.05$, $M(\text{low}) = 0.51 \pm 0.06$, $M(\text{new}) = 0.44 \pm 0.06$] (**Figure 4**). The lack of a difference in recall rates of high-value and low-value words suggests that, by this measure, effects of previously learned value on memory had been neutralized.

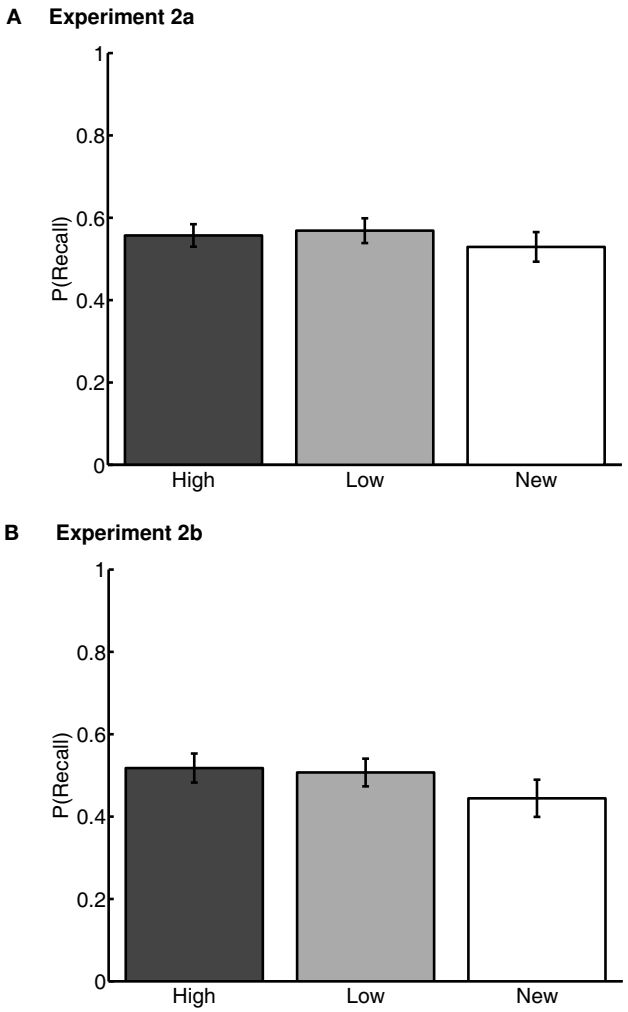

FIGURE 4 | Correct recall rates for Experiments 2a (A) and 2b (B). "High" and "Low" represent high- and low-value words, respectively, from the value-learning task. "New" represents words that were not present in the value-learning task, but only in study-test free recall. Error bars are 95% confidence intervals, corrected for inter-individual differences (Loftus and Masson, 1994).

3.2.2.2. Output order. To analyze output order for each Word Type (high value, low value, and new) directly, we borrowed the logic of the Wilcoxon–Mann–Whitney rank-sum test on the output positions of each word type to derive a measure of differences in median output position for each Word Type (as suggested by Hubert and Levin, 1978). For each list, for each pairwise Word Type

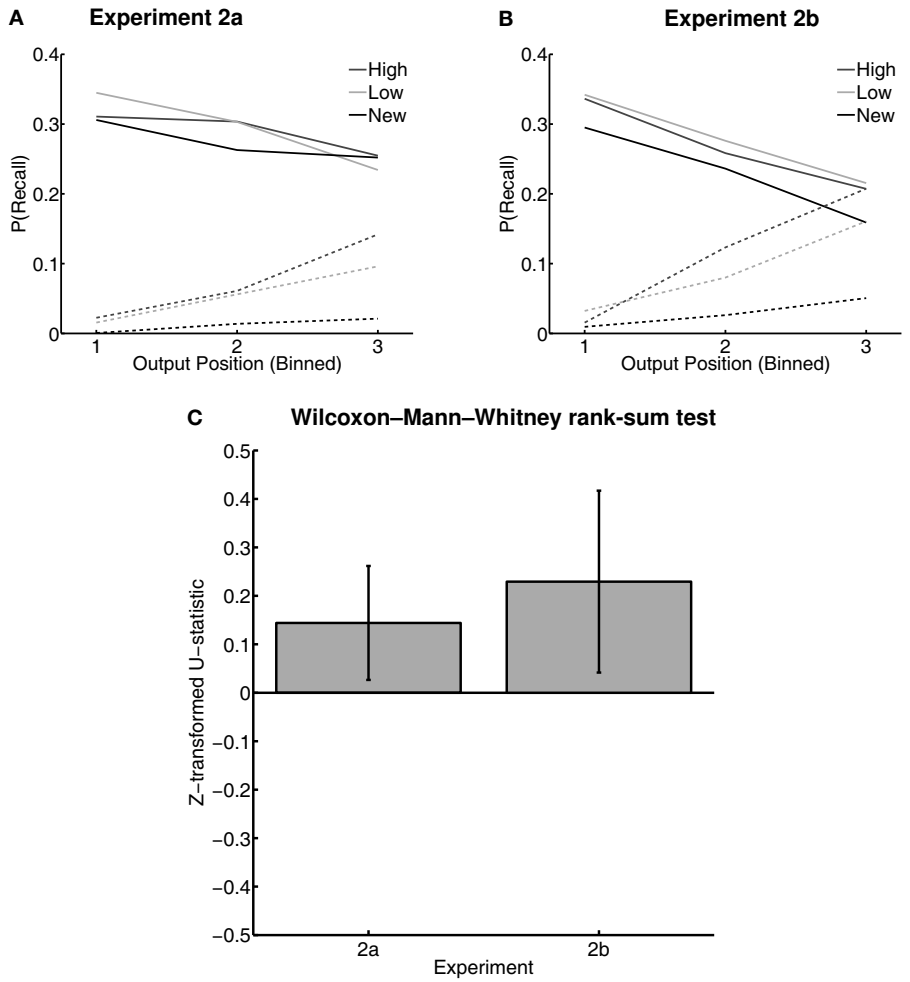

FIGURE 5 | Output positions in the free recall task of Experiments 2a and 2b. Probability of recall of each word type for vincentized output position bins in the free recall task of Experiments 2a **(A)** and 2b **(B)**. "High" and "Low" represent high- and low-value words, respectively, from the value-learning task. "New" represents words first that were not present in the value-learning task. Solid lines and markers represent correct responses; dashed lines with hollow markers represent intrusion responses. Error bars were omitted for visual clarity. **(C)** Plots of the *Z*-transformed *U*-statistics comparing median output positions for high- versus low-value words in both Experiments 2a and 2b. Larger values represent later output positions. Error bars are 95% confidence intervals.

comparison, the U-statistic was Z-transformed and then averaged across lists to obtain a measure for each participant. Because these values were already Z-scores, they were then compared with a t-test against zero for each comparison between Word Types. Participants with no recalls of a given Word Type in two or more lists were excluded from this analyses as they did not contribute additional information to this analysis (leaving $N = 35$ and 29 in Experiments 2a and 2b, respectively). In both experiments, low-value words had significantly earlier median output positions than high-value words [Experiment 2a: $mean(Z_U) = 0.14$, $t(34) = 2.40$, $p < 0.05$, $d = 0.46$; Experiment 2b: $mean(Z_U) = 0.23$, $t(28) = 2.35$, $p < 0.05$, $d = 0.42$] (**Figure 5**), suggesting that low-value words were easier to recall. High- and low-value words did not differ significantly in median output position relative to new words [all p's > 0.1].

3.2.2.3. Intrusions. In Experiment 1, we found that high-value items were more retrievable in a final free-recall test. Therefore, participants might be more likely to guess high- than low-value words in free recall of the 9-word lists in Experiments 2a and 2b. If list discrimination were enhanced for high-value words, following from the reward-maximization hypothesis, participants should make fewer intrusions of high-value words than low-value words. However, if participants had a more difficult time determining whether high-value items belonged to the current list, following from the value-interference hypothesis, then we should instead find more intrusion responses for high-value words than for low-value words. As words were not re-used from one list to the next, intrusions were defined as words that were not on the target (most recently studied) list. Intrusions could come from the training or else from prior free-recall study lists.

Repeated-measures ANOVAs were conducted on intrusion rates. The measure was the proportion of all responses (excluding extra-experimental intrusions and repetitions) on a given list that were intrusions of each word type, averaged across lists.

Participants with fewer than three intrusions in total were excluded from only this analysis as they provided an insufficient number of data points (leaving $N = 24$ and 22 included participants in Experiments 2a and 2b, respectively). The main effect of Word Type was significant in both experiments [Experiment 2a: $F(2,3,4) = 22.11$, $p < 0.001$, $\eta_p^2 = .51$, $M(\text{high}) = 0.11 \pm 0.03$, $M(\text{low}) = 0.070 \pm 0.024$, $M(\text{new}) = 0.018 \pm 0.010$; Experiment 2b: $F(2,3,4) = 23.14$, $p < 0.001$, $\eta_p^2 = .50$, $M(\text{high}) = 0.13 \pm 0.04$, $M(\text{low}) = 0.081 \pm 0.017$, $M(\text{new}) = 0.029 \pm 0.018$] (**Figures 6A,B**). High-value words were more likely to intrude than both low-value words [Experiment 2a: $t(23) = 2.55$, $p < 0.05$; Experiment 2b: $t(21) = 3.12$, $p < 0.01$] and new words [Experiment 2a: $t(23) = 6.73$, $p < 0.001$; Experiment 2b: $(21) = 6.00$, $p < 0.001$]. Low-value words were also intruded more than new words [Experiment 2a: $t(23) = 4.64$, $p < 0.001$; Experiment 2b: $t(21) = 4.84$, $p < 0.001$]. This result also supports the value-interference hypothesis, which suggested that high-value words are harder to place uniquely within the target list (i.e., contextual binding). Moreover, the small advantage of high-value words over low-value words following training in Experiment 1 (ratio of ∼5:4) evolved into a much larger ratio (∼3:2) in the intrusion rates of Experiments 2a and 2b. If guessing were purely based on better retrievability caused by high value and measured by final free recall in Experiment 1, we would have expected the same ratio for intrusion rates, as the words would inherit the same distribution from the final free-recall data. The fact that the ratio is exaggerated for intrusions here suggests that this measure is influenced by more than just item retrievability; we suggest that high-value words were not only sampled more often as candidate responses, but were also screened less well, and thus, were more likely to be recalled in error.

3.3. SUMMARY

In both Experiment 2a and 2b, previously trained words were correctly recalled at equal rates, regardless of reward value; thus, the advantages we saw for high-value words in Experiment 1 did not carry forward to a situation in which participants had to relearn subsets of trained words and link them to a specific, new list context. Moreover, high-value words were output *later* in the recall sequence than low-value items, and were more likely to be retrieved erroneously (reflecting proactive interference). This suggests that they were more weakly linked to the current-list context, and were more difficult to accurately screen based on recent-list membership. This pattern of findings held both for a slower presentation rate (2 s/word in Experiment 2a) and for a faster presentation rate (1 s/word in Experiment 2b), and the magnitudes of the output-order and intrusion-rate effects were similar between experiments (**Figures 5** and **6**). This suggests that the effects of value unlikely result from a deliberate, effortful, and time-consuming process during study (e.g., participants deliberately diverting attention toward the low-value words). It is more plausible that the difference between performance on high- and low-value words was due to persisting effects of reward value on memory from the value-learning task. This would make current-list membership more confusable for high-value items and screening candidate responses more difficult for high- than for low-value items.

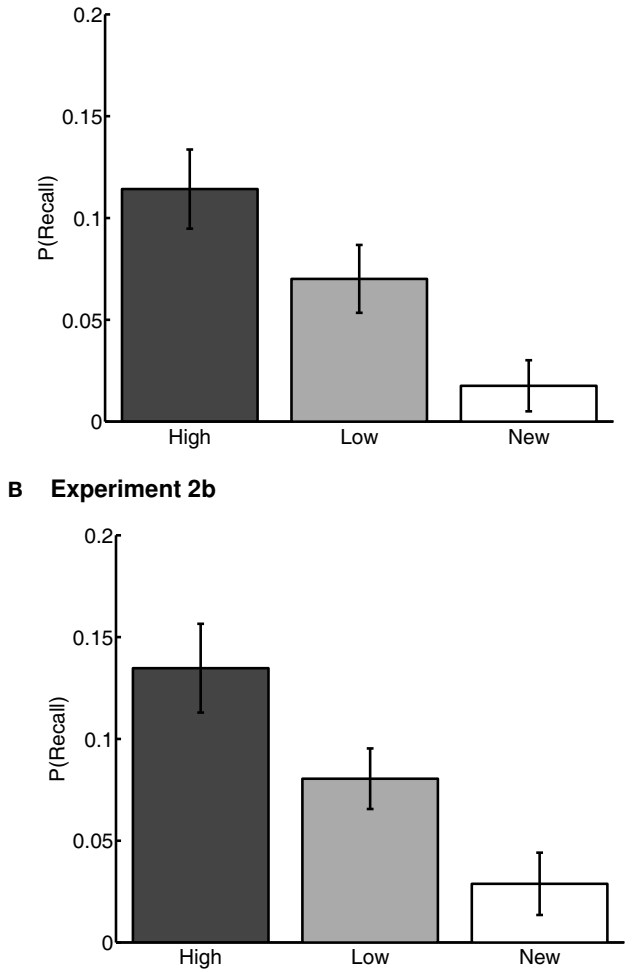

FIGURE 6 | Intrusion rates during free recall in Experiments 2a (A) and 2b (B). "High" and "Low" represent high- and low-value words, respectively, from the value-learning task. "New" represents words first that were not present in the value-learning task. Error bars are 95% confidence intervals, corrected for inter-individual differences (Loftus and Masson, 1994).

4. GENERAL DISCUSSION

In two studies, we investigated the influence of previously trained reward value on unrewarded tests of memory. In Experiment 1, implicit memory (facilitated access in lexical decision) was enhanced by reward value, in addition to enhanced explicit memory due to reward value (probability of recall in final free recall). These two memory enhancements were negatively correlated across participants, suggesting the presence of at least two mechanisms whereby reward value can influence memory. In Experiments 2a and 2b, we found that previously learned reward values can cause problems for contextual binding, when trained items needed to be tied to a new, specific context (namely, belonging to the most recent list). Low-value items were produced earlier in recall than high-value items, and high-value items intruded more often, suggesting that they were not effectively screened as

belonging to the wrong list. The interactions between reward value and memory are thus multifaceted, with implicit- and explicit-memory being enhanced due to reward value through different mechanisms (Experiment 1), and reward value leading to impaired memory for contextual information (Experiments 2a and 2b).

4.1. INFLUENCE OF REWARD VALUE ON IMPLICIT- AND EXPLICIT-MEMORY

In Experiment 1, we observed an enhancement of both explicit *and* implicit memory due to reward value. Since value enhanced both our memory measures, one may have expected that value-learning globally enhanced all kinds of learning of high-value items. For instance, enhanced memory could have been driven by value solely through the recruitment of additional attentional resources during the value-learning task: If participants paid more attention to the high-value items than the low-value items during this first phase, high-value items may then be more primed in lexical decision and more retrievable in free recall. Both enhancements would then have originated from a single, global, value-learning mechanism resulting in a high, positive correlation between the two measures. However, implicit- and explicit-memory are supported by distinct neural pathways (e.g., Rugg et al., 1998; Schott et al., 2005, 2006). Thus, it is also plausible that value may *separately* enhance implicit- and explicit-memory, and such enhancements would be uncorrelated or negatively correlated (also see May et al., 2005; Gopie et al., 2011). Our results favored the latter hypothesis: implicit- and explicit-reward-based enhancements were negatively correlated across participants. In other words, participants who demonstrated greater reward value facilitation in lexical decision had *less* reward facilitation in free recall. Prior research also supports the notion of different value-based learning strategies leading to differential engagement of between implicit- and explicit-memory (Wimmer and Shohamy, 2011, see also Bayley et al., 2005). This apparent trade-off between memory systems due to learning strategy is also supported by research on the effects of stress on memory, where deliberative (i.e., goal-directed) and procedural (i.e., habit-based) learning strategies can similarly be learned through two distinct memory systems (Schwabe and Wolf, 2011; Schwabe et al., 2011a,b,c).

One possible source of this negative correlation may be behavior during the value-learning task, as suggested by the correlation analyses involving the trials-to-criterion measure. Trials-to-criterion explained the negative correlation between the effects of reward value on implicit- and explicit-memory. We suggest that the effects of value on implicit memory benefited from participants having more experience with the knowledge of the values of items. That is, the earlier someone learned to prefer the high- over the low-rewarding item during the training task, the more exposures to correct pairings of their own choice and high rewards they would have had. Such increased exposure and procedural practice of correct response-high reward pairings could then have selectively promoted the formation of an implicit memory bias. In contrast, free recall is a self-cued memory task; thus, value would be expected to influence free recall insofar as a participant includes value as part of their retrieval cue. Participants who initially found the value-learning task more challenging may have been oriented more toward value during the free-recall test, thus producing a positive relationship between trials-to-criterion and the effect of value free recall, opposite to what was observed with the effect of value on lexical decision. This indirect evidence of two distinct value-learning mechanisms may be related to similar dissociations in probabilistic value-learning strategies reported by others (Humphreys et al., 1968; Allen and Estes, 1972; Estes, 1972; Medin, 1972a).

Although lexical decision and free recall test implicit- and explicit-memory, respectively, the two tests also differ in several other ways, so alternative interpretations of the cause of the dissociation must be considered. First, the dependent measure in lexical decision was response time, a measure of access speed; in free recall, the dependent measure was probability of recall, a measure that is sensitive to sampling probability and recovery processes, as well as memory cueing processes (e.g., Raaijmakers and Shiffrin, 1981). Our dissociation could therefore reflect differential influences of reward value on access speed versus sampling, recovery or cueing processes. Second, participants are presented with a copy-cue to judge in lexical decision, but in free recall, participants must apply their own retrieval cues to generate responses. Our dissociation could thus reflect distinct influences of reward value on judgment processes versus item-retrieval processes (cf. Humphreys et al., 1989). Regardless of which of these accounts is correct, our findings extend the boundary conditions of reward-value enhancement of memory effects, and suggest that the effect of reward value on memory is non-unitary.

4.2. INFLUENCE OF PREVIOUSLY LEARNED REWARD VALUES ON CONTEXTUAL BINDING

In Experiments 2a and 2b, what started as an advantage for high-value words (evident in Experiment 1) became a disadvantage when participants had to overcome proactive interference from the value-training phase and learn new sets of words that included both trained and untrained words. High- and low-value words were recalled at equivalent rates overall, but low-value words were produced earlier in output. High-value words were intruded more (and even more than expected based on the final free-recall rates of Experiment 1). These findings suggest less effective contextual binding for high- than for low-value words. This contradicts our reward-maximization hypothesis, and suggests that there are limits to the degree to which participants are biased to modulate their learning to maximize cumulative reward; one such limit is in relearning high-valued items in new, specific contexts.

If the additional resources devoted to high-value items included processing items within their context (i.e., the most recent list), then one would also expect participants to be able to rule out words that were recalled from previous contexts (i.e., the value-learning task or previous lists in the free-recall task), which is inconsistent with the elevated intrusion rate for high-value words in Experiments 2a and 2b. Thus, our findings are more consistent with our value-interference hypothesis, which posits that reward value impairs contextual binding. These results are also in line with findings obtained with manipulations of emotional arousal, where memory for the arousing items is enhanced, but the learning of new associations involving such items is impaired (Mather and Knight, 2008; Novak and Mather, 2009; Sakaki et al., 2011; Nashiro et al., 2012).

Although positive, as well as negative emotional items can be remembered better than emotionally neutral items (e.g., Dewhurst and Parry, 2000; Siddiqui and Unsworth, 2011), it would be reasonable to argue that the influence of reward value on memory may be more similar to the influence of positive – not negative – emotion on memory. While many studies have found that emotion can enhance memory for items and often impairs memory for associations, the majority of these findings used negatively valenced emotional stimuli (Fredrickson, 1998). Whereas negative emotions lead to attentional narrowing (e.g., the weapon focus effect; Loftus et al., 1987), positive emotion can to lead to a broadening of attention (Fredrickson, 1998). When participants are asked to learn associations containing emotionally positive, negative, or neutral items, participants are often better able to learn pairs with positive items than pairs with negative items (Zimmerman and Kelley, 2010; Okada et al., 2011; Pierce and Kensinger, 2011), suggesting that positive emotion can enhance participants' ability to form associations between items. (Note that sometimes an association-memory impairment has been observed even with positive stimuli, e.g., Mather and Knight, 2008.) If this interpretation is correct, and reward value functions similar to positive emotionality, then one would expect reward value-based facilitation of free recall in Experiments 2a and 2b, inconsistent with our results. We recently showed previously reported arousal-based enhancements in association-memory could instead be attributed to enhanced memory for the target items, and that this item-memory effect can mask an underlying impairment of association-memory (Madan et al., 2012). Thus, it is similarly possible that prior findings regarding the effects of positive emotion on associative learning may be composed of conflicting effects. Finally, false memories can be viewed as failures of contextual discrimination. Emotion, both induced in the participant, and emotionality of items, can increase rates of false memories. This has been found for both negative and positive emotions (Storbeck and Clore, 2005; Corson and Verrier, 2007; Dehon et al., 2010), and appears similar to the list-discrimination problems we found for high-value items here.

4.3. IMPLICATIONS FOR PREVIOUS FINDINGS OF REWARD-VALUE ENHANCEMENTS OF MEMORY

Reconsidering Raymond and O'Brien (2009) we detailed in the Introduction, our results suggest that their findings may have resulted from a summation of two distinct enhancement effects, one acting on implicit and the other acting on explicit memory. Regarding studies that have found that participants can prioritize their memory processes based on specific item-values presented alongside stimuli (Harley, 1965; Tarpy and Glucksberg, 1966; Weiner and Walker, 1966; Bjork and Woodward, 1973; Eysenck and Eysenck, 1982; Castel et al., 2002; Adcock et al., 2006; Gruber and Otten, 2010; Kuhl et al., 2010; Soderstrom and McCabe, 2011; Watkins and Bloom, unpublished manuscript), advantages in recall and recognition for high-value items resemble the enhancement effect we found in the final free-recall measure of Experiment 1. However, in all these studies, values were presented with items, but participants were never asked to link those items to a new context. Our findings in study/test free recall in Experiments 2a and 2b raise the possibility that if participants have to learn new lists composed of previously prioritized items, their memory might be compromised by the kind of value-based interference effect found here. In particular, given that the intrusion pattern was the largest effect we observed in Experiments 2a and 2b, we would predict that items previously linked to higher values would be intruded more – that is, participants would continue to produce them as responses even when inappropriate. In turn, since prioritization procedures directly ask participants to favor high-value items, whereas our procedure did not, it is quite possible that the list-discrimination procedure we found for high-value words could be overcome again if participants were asked to prioritize high-value words in later list learning.

5. CONCLUSION

Reward value can enhance memory for higher-valued items by increasing access speed and probability of retrieval. These dual enhancement effects of value on implicit- and explicit-memory measures may, in turn, be the results of dual value-learning styles. These enhancement effects come with a side effect of a poorer ability for participants to bind high-value items uniquely to a specific context, suggesting that items with high reward value can have a deleterious effect on subsequent memory tasks.

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The theory behind the age-related positivity effect

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The "positivity effect" refers to an age-related trend that favors positive over negative stimuli in cognitive processing. Relative to their younger counterparts, older people attend to and remember more positive than negative information. Since the effect was initially identified and the conceptual basis articulated (Mather and Carstensen, 2005) scores of independent replications and related findings have appeared in the literature. Over the same period, a number of investigations have failed to observe age differences in the cognitive processing of emotional material. When findings are considered in theoretical context, a reliable pattern of evidence emerges that helps to refine conceptual tenets. In this article we articulate the operational definition and theoretical foundations of the positivity effect and review the empirical evidence based on studies of visual attention, memory, decision making, and neural activation. We conclude with a discussion of future research directions with emphasis on the conditions where a focus on positive information may benefit and/or impair cognitive performance in older people.

Keywords: positivity effect, aging, emotion regulation, motivation, attention, memory

THE THEORY BEHIND THE AGE-RELATED POSITIVITY EFFECT

The positivity effect refers to a relative preference in older adults (compared to younger adults) for positive over negative material in cognitive processing. Since the first explicit reference to the positivity effect in 2004 (Kennedy et al., 2004) more than 100 peer-reviewed articles have addressed the concept[1]. This flurry of scholarship has provided overwhelming support for the basic concept but also has added to our understanding of the subtleties and limitations of the theory while enriching our understanding of the role of emotion in cognitive processing in both younger and older people. Below we articulate the operational definition of the positivity effect and ground it in the theoretical framework of socioemotional selectivity theory (SST; Carstensen, 2006). We then consider the empirical literature, arguing that the pattern of findings that has emerged in recent years better supports a top-down, motivational explanation for positivity than accounts that attribute positivity to cognitive or neurological decline. Finally, we propose potential future research directions and discuss ways in which the positivity effect may exert beneficial and detrimental influences on cognitive processing.

THE OPERATIONAL DEFINITION AND THEORETICAL FOUNDATION OF THE POSITIVITY EFFECT

Our research group coined the term "positivity effect" to describe mounting evidence that older adults show a relative preference for positive over negative information in attention and memory (Charles et al., 2003; Mather and Carstensen, 2003; Mikels et al., 2005). "Effect" was chosen over "bias" when the term was coined because age differences are as frequently driven by a preference for negative material in the young as they are driven by a preference for positive material in the old. The positivity effect concerns the relative difference between older and younger people in attention to and memory for *positive* as opposed to *negative* material[2].

The positivity effect was initially identified by investigating postulates of SST, a life-span theory of motivation (Carstensen, 1993, 2006; Carstensen et al., 1999). According to SST, a core constellation of goals operates throughout adulthood, including basic goals associated with attachment and control as well as goals associated with instrumental needs and emotional gratification. The key postulate of SST is that the relative importance of goals within this constellation changes as a function of future time horizons. Because chronological age is inversely associated with actual and perceived time left in life, systematic age differences emerge in preferred goals. Importantly, according to SST, age differences in goal hierarchies reflect perceived future time more than time since birth (viz., chronological age). When the future is perceived as long and nebulous, as it typically is in youth, future-oriented goals related to gathering information and expanding horizons are prioritized over emotional gratification. When time horizons are constrained present-oriented goals related to emotional satisfaction and meaning are prioritized over goals associated with long-term rewards. In addition to emphasizing changes in goals with age, the theory predicts that when younger people perceive time constraints or older people perceive the future as relatively long, age differences are reduced or eliminated. A number of empirical investigations

[1]Publication counts based on results of searching "positivity effect" in the PsychInfo database aging topic area.

[2]This is not to be confused with preferential memory and attention for emotional relative to neutral stimuli, which is relatively stable across age groups (see, for example, Murphy and Isaacowitz, 2008). Unfortunately, readers often mistake the headline conclusion from Murphy & Isaacowitz to mean that evidence for the positivity effect is qualified when in fact nearly three-quarters of the studies submitted to their meta-analysis lacked age comparisons of any kind and about half of the studies failed to include positive/negative contrasts. Only 15% of the studies Murphy & Isaacowitz included in their meta-analysis allowed for age and valence comparisons.

have supported this claim (e.g., Fredrickson and Carstensen, 1990; Fung et al., 1999; Fung and Carstensen, 2004). When life's fragility is made salient by events like September 11th or the SARS epidemic in Hong Kong, for example, age differences in socioemotional goals disappear (Fung and Carstensen, 2006). Similarly, under experimental conditions that extend time horizons, older peoples' goals closely resemble younger peoples' goals (Fung et al., 1999). Thus, the influence of time horizons on goals has been well-established. The theoretical perspective of SST argues that age-related changes in goals are adaptive, reflecting the reality that changing time horizons and ultimately mortality impose. SST incorporates an evolutionary component that presumes considerable advantages to life course changes in goals. Focusing on individual strivings early in life and focusing on emotional goals later in life, which typically benefit kin, improves reproductive success (see Carstensen and Löckenhoff, 2003). The presence of grandparents increases the survival odds of grandchild offspring in humans and some other mammals, for example (Hawkes, 2003).

Socioemotional selectivity theory maintains that perceived time horizons play an important role in signaling these shifts in motivation. When futures are long and nebulous, acquiring knowledge and exploring help prepare individuals for an array of uncertain challenges looming ahead. As time horizons grow shorter, future-oriented goals related to preparation for the long-term grow less important and present-oriented goals related to emotional meaning, emotion regulation, and well-being gain in priority. Accordingly, many observed age-related changes in emotion, cognition, and behavior are presumed to be top-down and fluid (varying as a function of motivation) rather than bottom-up and fixed (varying as a function of biological aging or experience).

Early in the last decade, our research team began to test hypotheses about the ways in which motivational changes postulated by SST may influence cognitive processing. These efforts expanded upon a large and rich literature in psychology documenting the powerful influence that goals exert on cognitive processing. From classic studies by Neisser and colleagues on inattentional blindness (e.g., Neisser, 1979) to more recent studies on the subconscious priming of explicit goals (e.g., Chartrand and Bargh, 1996; Moskowitz, 2002), the literature has revealed powerful top-down effects of goals on information processing. We reasoned that because chronically activated goals appear to change systematically with age, such changes may consequently direct attention and memory toward or away from emotional material in systematic ways.

When our research team began to examine questions about potential effects of motivation on cognitive processing, previous findings suggested that whereas younger people appear to privilege negative information in cognitive processing (Baumeister et al., 2001; Rozin and Royzman, 2001), older people commonly privilege positive information. Indeed, several early studies found a classic crossover interaction between age and valence (e.g., Mather et al., 2004; Mikels et al., 2005). Of course, a positive processing preference can result from heightened processing of positive *and/or* reduced processing of negative information. Even when older adults show greater attention to negative than positive but attend significantly less to negative than younger adults, the pattern would qualify conceptually as a positivity effect.

Accumulating evidence indicates that the positivity effect emerges reliably from all combinations of heightened processing of positive and reduced processing of negative information. In some studies, age differences are driven by younger peoples' greater attention to and/or memory for negative material (e.g., study 2 in Charles et al., 2003; study 2 in Ready et al., 2007; Shamaskin et al., 2010). In other studies differences reflect relatively deeper processing of positive material by older people (e.g., Isaacowitz et al., 2006b; study 3 in Mather and Knight, 2005). Several investigations find that while both older people and younger people attend to negative stimuli more than positive, older people do so significantly less than younger people (e.g., Comblain et al., 2004; Kensinger et al., 2007).

The positivity effect has been documented across a variety of experimental paradigms and a wide range of stimuli, also supporting the robustness of the effect. Studies of visual attention using dot-probe and eye-tracking paradigms show that, compared to younger adults, older adults direct their gaze toward happy and away from angry or sad faces (Mather and Carstensen, 2003; Isaacowitz et al., 2006a,b). The positivity effect also emerges in studies of working memory (Mikels et al., 2005), short-term memory (Charles et al., 2003), autobiographical memory (Kennedy et al., 2004; Schlagman et al., 2006), and even false memories (Fernandes et al., 2008). Compared to younger adults, older adults appear to privilege positive over negative stimuli across a wide range of experimental materials including emotionally valenced images (Charles et al., 2003; Spaniol et al., 2008), word lists (Piguet et al., 2008), emotional faces (Mather and Carstensen, 2003; Leigland et al., 2004), and health-related messages (Shamaskin et al., 2010). Such findings suggest that the effect is not limited narrowly to a certain type of stimuli. The positivity effect is also evident in decision making. Compared to younger people, older people pay greater attention to positive as compared to negative attributes when choosing among doctors and hospitals (Löckenhoff and Carstensen, 2007, 2008), cars (Mather et al., 2005), and consumer products (Kim et al., 2008). Compared to younger adults, older adults also remember their choices in a manner that is positively skewed – either via disproportionately recalling positive attributes and/or via attributing positive attributes to chosen options and negative attributes to rejected options (Mather and Johnson, 2000; Mather et al., 2005; Löckenhoff and Carstensen, 2007, 2008).

Although the majority of empirical findings have been interpreted through the lens of SST, viable alternative explanations for the empirical phenomenon have been offered. Most notably, Labouvie-Vief et al. (2010) have argued that positive material is preferred by older people because negative information, by comparison, is more cognitively demanding. Along similar lines, the aging-brain model proposed by Cacioppo et al. (2011) suggests that the positivity effect in memory[3] arises from age-related neural degeneration in the amygdala leading to dampened emotional responses to negative stimuli. In addition to these theoretical alternatives, several investigators have failed to observe age-related positivity effects. The literature is now sufficiently large and the

[3]It should be noted that the aging-brain model (Cacioppo et al., 2011) focuses solely on the downstream consequences of presumed amygdala dysfunction for memory and does not address the positivity effect in attention.

methodologies sufficiently diverse that conceptual alternatives and empirical findings – especially those that have failed to observe positivity – can be examined in ways that clarify the nature and source of these intriguing age differences.

The motivational perspective of SST provides clear and testable predictions about the conditions under which the positivity effect should appear and when it should not. As noted above, positivity theoretically reflects controlled cognition, is driven by chronically activated goals, and is adaptive for well-being. Thus, the effect should be most evident when individuals have sufficient cognitive resources to direct attention, when processing occurs under the scope of conscious (as opposed to automatic) control, when individuals are allowed to pursue chronically activated goals without external interference, and when regulating emotions contributes to well-being. Conversely, the effect should not appear when cognitive resources are limited, when information processing is automatic, when contexts impose situation-specific goals that conflict with chronically activated goals, and when prioritizing emotion regulation has significant risks. To assess the empirical support for these predictions we review the extensive research literature on the positivity effect.

In reviewing the empirical literature we focus on three key conceptual issues: First, we present evidence suggesting that the positivity effect represents controlled processing not cognitive decline. Second, we critically examine experimental procedures and conditions under which the positivity effect is and is not observed, illustrating that the effect is malleable rather than unreliable. Finally, we consider whether effect is adaptive or maladaptive for older adults' everyday functioning.

CONTROLLED PROCESSING OR COGNITIVE DECLINE?

According to the motivational perspective offered by SST, the positivity effect stems from age-related shifts in goal priorities that increase the salience of emotionally gratifying information in attention and memory. Because cognitive resources are required to direct information processing toward goal-relevant stimuli and away from less relevant stimuli (Mather, 2006), the positivity effect will be most evident in individuals with relatively good cognitive control. This postulate clearly distinguishes SST from explanations rooted in cognitive decline. Reasoning from the latter positions, if positive material were preferred because negative material is difficult to process, individuals low in cognitive control would show the strongest preference for positive material. Mather and Knight (2005) conducted two studies to examine the role of cognitive control in positivity. In the first study, older and younger participants were asked to view a series of emotionally evocative and neutral pictures. After a 20-min delay, participants were administered an incidental recall test. Compared to younger participants, older participants recalled a greater proportion of positive images and a lesser proportion of negative images. In subsequent analyses, the researchers examined individual differences as a function of cognitive control and found that the positivity effect was most evident in participants with high levels of cognitive control. In a subsequent study, older and younger participants were asked to view the same images from the first study while they monitored and detected changes in a sequence of sounds. In this dual-task paradigm, older adults recalled a greater proportion of negative images and fewer positive images relative to younger adults. In other words, when cognitive resources were experimentally diverted, the preference for positive over negative information was reversed. Using the same divided-attention task, Knight et al. (2007) found similar effects in visual attention. When attention was divided (viz., participants performed a tone-detection task while viewing experimental materials), older adults spent more time than younger adults viewing negative than positive pictures and faces. In contrast, when asked to simply to view the images, older adults attended more to positive versus negative stimuli. Younger adults showed the opposite pattern. These findings indicate that positivity effects depend on the availability of cognitive resources. Positivity is evident when resources are relatively abundant and undivided, but absent when resources are relatively meager or divided.

The critical role of cognitive resources in the positivity effect is further highlighted by research comparing the emotional memory of healthy younger and older adults with older adults suffering from Alzheimer's disease (AD; Fleming et al., 2003). When all three groups were asked to recall lists of positive, negative, and neutral words, AD patients remembered a greater proportion of negative versus positive words compared to both control groups[4]. In combination with findings from Mather and Knight (2005) the observed patterns essentially rule out cognitive decline as a root cause of positivity. Not only do people who are low in cognitive reserves show the least positivity, they sometimes favor negative information.

Explanations for the positivity effect based on motivation versus degradation are distinguished not only by their emphasis on cognitive resources, but also by predictions regarding the automaticity and temporal signature of positivity. Cognitive decline and neural degradation-based accounts are premised on assumptions that positivity arises from automatic processes associated with affect optimizing (Wurm, 2011) or amygdala dysfunction (Cacioppo et al., 2011), respectively. By contrast a motivational account attributes positivity to more controlled shifts in attentional resources. Thus, the time course of attentional preferences is important. Automatic accounts would predict immediate evidence of positivity whereas SST predicts a somewhat delayed onset. Existing findings support the latter perspective. The time course of attentional preferences for pairs of faces (in which one is emotional and the other is neutral) indicates a delayed onset of positivity consistent with a deliberate re-allocation of resources (Isaacowitz et al., 2009a). In the latter study, which used eye-tracking to discern a precise timeline of gaze patterns, older adults' preferential attention toward positive stimuli emerged relatively late after stimulus presentation (500 ms). Attentional diversion from negative faces was slower still (3 s). Whereas an automatic account of the positivity effect would be associated with rapid onset of selective attention, findings suggest that older adults' early attention – i.e., within 500 ms of stimulus onset – is actually skewed *away* from positive faces, and that their fixation biases toward positive and away from

[4]Findings in this area are mixed. See Hot et al. (2012), in the current special issue for a review.

negative faces increases over time. Complementary evidence for the delayed onset of positivity was reported by Williams et al. (2006). They used an event-related potential (ERP) paradigm to track the temporal pattern of neural responses while people viewed emotional faces. As in the study by Isaacowitz et al. (2009a), Williams et al. did not observe a positivity effect in the rapid processing of emotionally salient stimuli. On the contrary, age was associated with reduced activation in the medial prefrontal cortex within 150 ms of viewing happy faces. Yet activation increased later (180–450 ms after onset) in processing of fearful faces. This pattern suggests that only responses to fearful faces are down-regulated.

The lack of positivity for relatively automatic processing is also evident in memory for arousing versus non-arousing words (Kensinger, 2008). Kensinger presented lists of words varying systematically in both valence and arousal and subsequently tested incidental memory. Although a positivity effect was observed in memory for non-arousing emotionally valenced words, older and younger adults showed equivalent recall for arousing positive and negative words, which appear to be processed in a more automatic manner than non-arousing words (for a discussion, see Kensinger, 2004). Together, findings from these studies suggest that positivity is absent early in processing and emerges during more controlled stages of information processing.

Recent evidence based on neuroimaging also supports motivational accounts and speaks against neural degradation. Indeed, activation patterns in prefrontal regions associated with emotion regulation parallel the behavioral findings discussed above: Older versus younger adults recruit medial prefrontal regions (e.g., anterior cingulate) implicated in the regulation of emotion to a greater extent when processing negative versus positive images (Williams et al., 2006; Leclerc and Kensinger, 2011), suggesting that they actively down-regulate affective responses to negative but not positive stimuli. In a recent study by Ebner et al. (2012), older adults showed greater activation than younger adults in subregions of the dorsomedial prefrontal cortex (e.g., anterior cingulate and medial frontal gyrus) while processing angry versus happy faces.

Whereas prefrontal regions are recruited more for negative versus positive stimuli with age, activation in subcortical neural regions associated with emotional processing (e.g., amygdala) follows the opposite age-by-valence interaction (for a review, see Samanez-Larkin and Carstensen, 2011). In a seminal study by Mather et al. (2004), older adults showed greater amygdala activation while attending to and rating positive versus negative images, whereas amygdala activation in younger adults was equivalent across image valence. Recently Leclerc and Kensinger (2011) replicated the effect: younger adults showed greater amygdala activation in response to negative versus positive images. St. Jacques et al. (2010) posited that the distinct patterns of neural activation observed in prefrontal and subcortical regions are complementary. They proposed that increased motivation to regulate emotion leads older adults to actively engage the mPFC differently than younger adults, which in turn yields diverging amygdala activation patterns. Consistent with this interpretation, they found evidence of greater functional connectivity between the anterior cingulate cortex and right amygdala for older versus younger adults during the viewing and rating of emotionally salient images. In addition to attention and memory, positivity effects have been observed in neural regions involved in anticipatory reward. Whereas older and younger adults show similar levels of activation when anticipating rewards, only younger adults showed increased activation (caudate and insula) when anticipating losses (Samanez-Larkin et al., 2007).

Age differences in neural recruitment while processing positive versus negative information have also been observed at the level of whole-brain activity as indicated by late positive potential (LPP) brain waves (Kisley et al., 2007). The LPP waveform, which peaks several hundred milliseconds after stimulus onset (e.g., between 400 and 900 ms in the Kisley et al., 2007 study) tracks the relevance of stimuli (Schupp et al., 2000) and the allocation of attentional resources (Hajcak et al., 2006). Kisley et al. (2007) measured LPP within an adult sample while participants viewed and categorized a series of emotionally evocative images. Results indicated a systematic age-by-valence interaction in LPP amplitude consistent with the positivity effect: Whereas LPP amplitude did not differ by age in response to viewing positive images, the LPP amplitude evoked by negative images was inversely associated with age, indicating that older adults devote fewer neurocognitive resources to processing negative but not positive stimuli.

Reasoning from Cacioppo et al.'s (2011) aging-brain model, the positivity effect would emerge from dampened emotional responses to negative (but not positive) stimuli caused by selective neural degeneration in the amygdala. However, research findings reviewed above suggest that age differences appear in both negative *and* positive reactivity, and across subcortical *and* prefrontal regions. Given common brain regions for processing negative and positive stimuli, one would expect dampened reactivity to negative and positive stimuli. Moreover, the age-by-valence interactions in PFC activation suggest selective control of negative and positive. Specifically, older adults devote more neurocognitive resources to processing positive stimuli and down-regulating emotional responses to negative information. Thus, taken together, patterns of prefrontal and subcortical neural activity provide additional support for top-down processing.

MALLEABLE OR UNRELIABLE?

Several studies have not observed age differences in positivity, raising questions about the reliability and robustness of the effect (e.g., Kensinger et al., 2002; Grühn et al., 2005; Budson et al., 2006; Gallo et al., 2009). On close examination, however, the experimental designs in studies that fail to observe positivity also impose goals on participants that likely supplant chronically activated goals. Positivity is reduced when experimental instructions impose goals that interfere with chronically activated goals. That is, when experiments require participants to process stimuli in a particular way, e.g. by providing instructions about encoding stimulus valence (Kensinger et al., 2002) or asking participants to accurately remember all information (Grühn et al., 2005), positivity is not evident. In the latter study participants were asked to read lists containing positive, negative, and neutral words under the explicit instruction to "recall as many words as possible" for a subsequent memory test (Grühn et al., 2005, p. 582). Under these circumstances, both younger and older adults remembered more negative than positive words. An age-by-valence interaction was not observed.

On the other hand, positivity appears reliably when experiments do not impose constraints on processing; for example when participants are asked to simply "view" experimental materials, rather than explicitly process or commit them to memory. In such studies, positivity is observed in attention (e.g., Mather and Carstensen, 2003; Isaacowitz et al., 2006b) and memory (e.g., Charles et al., 2003; Kwon et al., 2009). We maintain that such approaches maximize the likelihood that chronically activated goals will influence cognitive processing. Our research group conducted two studies to explicitly test these contentions. The first study, by Löckenhoff and Carstensen (2007), found that when asked to simply review features of health care plans and physicians in order to choose among them, older adults disproportionately reviewed positive features of the alternatives. Positivity in review was eliminated, however, when experimental instructions explicitly primed informational goals (i.e., "please focus on specific facts and details"). Similar effects of goal manipulations on positivity were observed in autobiographical memory for emotional, mental, and physical well-being (Kennedy et al., 2004). In the latter study, the oldest (versus youngest) participants showed positive memory biases when their recall was prompted by open-ended instructions. However, when recall was prompted by instructions to focus on emotion or accuracy both age groups showed positive and negative memory biases, respectively[5].

Although more research is needed, we expect that instructions that tell participants how to process information are likely to mask age differences in goals. These varied illustrations of the context sensitivity or malleability of the positivity effect support the theoretical contention that top-down processing is involved in positivity. Such findings also speak strongly against cognitive decline and neural degradation as the basis for positivity, because such explanations would not be sensitive to contextual cues.

ADAPTIVE OR MALADAPTIVE?

A key tenet of SST is that observed age differences in motivation reflect *adaptive* shifts in goals as people face changing time horizons. Generally speaking, maximizing information seeking and exploration is adaptive when time horizons are long whereas maximizing emotional well-being is adaptive when time horizons are relatively short. Of course, in the vast majority of studies on the positivity effect, there is no downside to attending to or remembering positive versus negative information in a biased manner. Fixating more on a happy versus angry face or remembering a photo of a smiling baby while forgetting one of a corpse has no detrimental consequences in the laboratory. But everyday life does present situations in which selective attention and memory are likely maladaptive. The question that arises is whether prioritization of positive information is set aside when stakes are high. Do older adults also show positive default processing tendencies when making high-stakes medical or financial decisions? That is, will positivity be observed when reviewing information about critical health care decisions (e.g., whether to treat cancer via surgery versus radiation therapy) and whether to invest retirement savings in a new company? Preliminary evidence suggests that the answer may be no. In a recent study by our research group (English, 2012), healthy and unhealthy older adults made a series of health-related (e.g., among physicians) and non-health-related decisions (e.g., among cars). Findings revealed significantly less positivity in health-related information review among participants in poor health relative to healthy participants. When making non-health-related decisions health status was unrelated to information review patterns. These findings indicate that older adults do indeed engage with negative material in contexts where avoiding it may have detrimental effects on well-being.

Older adults' adaptive engagement with negative material also extends to situations involving threat. Prior research has found that younger people identify threatening (i.e., angry) faces faster than other emotions (for a review, see Vuilleumier, 2002), a pattern that has been interpreted as an adaptive and automatic response to threat (Öhman et al., 2001). Mather and Knight (2006) asked whether positivity in cognitive processing would preclude older people from displaying a similarly adaptive pattern. They administered a visual search task in which younger and older individuals were presented with an array of schematic faces containing eight neutral distractor faces and one target face depicting a happy, sad, or angry expression. Though theoretical accounts of positivity based on decline or degradation would predict age-related impairments in the speed of detecting angry versus happy faces, results indicated that older participants were faster to identify angry faces than happy or sad faces (younger adults showed a similar pattern). Thus, older adults prioritized the processing of negative over positive information when it held survival value (i.e., for angry but not sad faces).

Although evidence suggests that positivity is suppressed in situations where attending to negative information is adaptive, is positivity amplified when prioritizing emotional well-being is especially beneficial? There is some evidence that a positivity effect in gaze preferences is exacerbated in contexts that demand the regulation of emotion. Isaacowitz et al. (2008) observed minimal age differences in attentional preferences when individuals were induced into feeling neutral or positive moods[6]. However, when induced into negative moods, a robust positivity effect emerged. Younger adults oriented strongly toward negative faces whereas older adults oriented strongly toward positive faces. Thus, there is some intriguing evidence that older adults may actively deploy positivity to improve mood.

DOES THE POSITIVITY EFFECT ENHANCE OR IMPAIR COGNITIVE PROCESSING?

One reasonable hypothesis, based on the literature reviewed above, is that older peoples' preferential attention to and memory for positive versus negative information gives rise to suboptimal outcomes for decision making and deliberative problem solving.

[5]Prior to providing retrospective reports, participants assigned to the accuracy-focused condition were told to "answer the questions as accurately as you can," whereas participants in the emotion-focused condition were instructed to "focus on how you are feeling while answering the questions." Participants in the control (i.e., open-ended) condition were simply asked to "answer the questions as you think you answered them back then."

[6]In the neutral and positive affect conditions the only significant age difference was that younger adults attended more to positive faces compared to older adults.

In this section we discuss empirical evidence that supports or contradicts such predictions.

As noted above, older adults disproportionately seek, attend to, and remember positive more than negative information when making decisions (Mather et al., 2005; Löckenhoff and Carstensen, 2007, 2008; Kim et al., 2008). But does this cause them to make poor choices? Extant research on risky and riskless decision making suggests that the answer, to date, is no. Mikels and Reed (2009) found that older adults were no more likely than younger adults to make suboptimal decisions (i.e., selecting an option with a lower expected value) when considering risky choices framed in terms of losses as opposed to gains. Another study using a sample of adults spanning the adult age range failed to observe age-by-valence interactions in risky choices; all age groups made objectively better decisions on gain versus loss trials (Weller et al., 2011). The positivity effect also does not appear to impair risk*less* decisions. Using multi-choice, multi-attribute decision tasks involving both positive and negative cues (i.e., choices among grocery stores and apartments), Hess et al. (2012) observed equivalent decision quality among younger and older adults. Evidence also suggests that the positivity effect does not impair – and may even benefit – subjective choice quality. For example, when older adults were asked to make lists of pros and cons to guide decisions among actual consumer products (i.e., a pen, mug, flashlight, and whiteboard) they reported more satisfaction than younger adults with their choices (e.g., Kim et al., 2008). By contrast, satisfaction did not differ across age groups when participants did not make pro-con lists prior to choosing. Taken together, the evidence thus far suggests that older adults' preferential processing of positive versus negative information does not impair their decision making ability, and in some cases may lead to improved decision outcomes.

Given that effective interpersonal problem solving necessitates processing and acting upon negative and positive information, one might expect that older adults' avoidance of negative information would be detrimental. Moreover, prior research points to an association between advanced age and the disproportionate use of avoidant versus instrumental strategies (e.g., Blanchard-Fields et al., 2007). Here too, however, evidence suggests that problem solving abilities improve with age. Despite older adults' general preference for avoidant strategies, it appears that they apply a greater range of problem solving strategies more flexibly across situations compared to younger adults (for a review, see Blanchard-Fields, 2007).

By no means is the evidence on this point conclusive. Indeed, preferential processing of any category of stimuli is likely to involve some downside. However, in the domains of decision making and problem solving, findings to date fail to raise red flags.

FUTURE DIRECTIONS

Although researchers have made a great deal of progress understanding the positivity effect, many questions remain. Evidence that positivity in cognitive processing is causally related to emotional well-being in older adults is scant, for example (for a discussion, see Isaacowitz and Blanchard-Fields, 2012). SST maintains that behavioral and cognitive selection operate in the service of emotion-related goals. Selective exposure is arguably the most effective way to regulate emotional states and there is considerable evidence that older people are more selective than younger people in their choice of social partners and environments (for a review, see Charles and Carstensen, 2010). Despite abundant evidence that older people are both relatively more selective (Charles and Carstensen, 2010) and experience a relatively positive balance of emotions in daily life (Carstensen et al., 2011), a causal link between selective exposure and emotional well-being has not been established.

Isaacowitz and Blanchard-Fields (2012) proposed the intriguing idea that positivity may also operate in the active regulation of negative mood states. To our knowledge, the mood-benefiting effects of positivity in online regulation have been demonstrated in only one study. Interestingly, findings suggested that executive control was a key moderator. Only older adults who had high levels of executive control and showed positive gaze preferences avoided negative mood changes (Isaacowitz et al., 2009b). This finding fits well with research conducted by Mather and others linking stronger evidence of positivity to greater cognitive control (e.g., Mather and Knight, 2005), and contributes to arguments that that top-down processing is required for deployment of goal-directed efforts.

Because laboratory experiments generally rely on weak emotional elicitors, such as synthetic face stimuli and word lists, which are unlikely to alter emotion states regardless of processing tendencies, strong tests of hypotheses about online regulation have yet to appear in the literature. Future research should examine the link between positivity in emotional processing and outcomes using stimuli that elicit stronger and more long-lasting effects on emotional experience.

Our research group has begun to test hypotheses about ways in which positivity may heighten older peoples' susceptibility to problems encountered in everyday life, such as financial fraud. It is well-established that older people are the most frequent targets of financial scams and, for a variety of reasons, may be particularly susceptible, although great susceptibility has not been established (Shadel, 2012). Preferences that favor positive and ignore negative information could contribute to such susceptibility, either because potential warning signs are ignored or because messages about too-good-to-be-true prospects are especially salient. On the other hand, research reviewed above suggests that older people may discard positivity in high-stakes situations. Because of its dire consequences for older people, examining the role of positivity in fraud victimization is a worthwhile aim for future research.

Decision quality remains an important and understudied issue, and there are many reasons to expect that decision quality may suffer with age (see Peters et al., 2011, for an excellent review). Although, as noted above, recent findings offer no support for claims that positivity *per se* impairs older adults' decision outcomes, the downstream effects of positivity in attention and memory on choice quality remain largely unexplored. To our knowledge no study has examined objective choice quality for actual (as opposed to hypothetical) decisions across age groups and as a function of information valence[7]. Given that millions

[7]Although participants in the Kim et al. (2008) study made decisions about actual as opposed to hypothetical options, objective decision quality could not be examined because the options were roughly equivalent in value and utility.

of older adults are tasked with making important health-related decisions each year (e.g., Medicare Part D), it is imperative to understand whether motivations to seek positive and avoid negative information undermine the quality of these decisions. A related question for future research to consider is whether positive features of options drive choices more than negative features among older adults.

Both fraud victimization and decision making represent domains in which future research is needed to elucidate the precise conditions under which older adults' relative bias toward the positive may be adaptive versus maladaptive. Such insights will have valuable applications to public policy: If, for example, older adults' increased attention and memory for positive information improves their decision making for positively framed attributes, then physicians, hospitals, and policy makers might consider reframing decisions accordingly, so as to optimize choice quality.

The contributions of meaningfulness and time perspective to positivity have yet to be explored. SST maintains that age differences in the salience of emotionally meaningful goals are driven by constraints on future time. A considerable number of empirical studies in the realm of social choice support this contention (for a review, see Charles and Carstensen, 2010). To date, however, no studies have linked time horizons and meaningfulness to *positivity in cognitive processing*. SST predicts that relative to younger adults, older adults will devote more resources to processing highly meaningful information even if it engenders negative emotions. Although strong tests of this prediction have not been carried out, there is some suggestion that this may be the case. Fung et al. (2008) examined attentional preferences among Chinese residents of Hong Kong, a culture in which positive information is considered to be less meaningful than in Western cultures. Using the same eye-tracking paradigm as Isaacowitz et al. (2006b), Fung et al. found no evidence of positivity in the East Asian sample. In fact, older adults in their study demonstrated a greater preference for negative faces than did younger adults. Aside from illustrating that positivity may be culturally specific, these findings suggest the possibility that the positivity effect as it is typically observed does not depend on the valence of positive information *per se*, but rather the meaning attached to positive information. Because the study did not explicitly manipulate the meaningfulness of positive or negative stimuli, the lack of an observed positivity effect could reflect any number of cultural differences between Eastern and Western samples, of course, such as dialectical thinking or the degree to which mixed emotions are experienced. On the other hand, the positivity effect *has* been observed and replicated in picture memory among Korean samples (Kwon et al., 2009; Ko et al., 2011), adding further nuance to conclusions about cross-cultural relevance. To bring needed clarity to this area, future research would benefit from testing the positivity effect in contexts where emotional valence and meaningfulness can be better separated. In addition, because time horizons are the presumed theoretical drivers of age differences in goals that underlie the positivity effect, research on the role of perceived time in positivity is needed.

CONCLUDING THOUGHTS

As we have reviewed above, the motivational explanation for the positivity effect finds considerable support in the empirical literature. Research findings from dozens of studies are consistent with theoretically derived postulates that positivity reflects controlled cognition and chronically activated goals, is influenced by situational or contextual factors, and is largely adaptive for everyday functioning and well-being. Recent research has helped to illuminate conditions where the positivity effect is most and least likely to appear: Positivity appears when cognitive resources are available, when experimental tasks or stimuli do not activate automatic processing, and when information processing is unconstrained by external factors such as task instructions. In contrast, positivity is not observed when cognitive resources are significantly reduced (due to cognitive decline or experimental manipulations), when experimental tasks or stimuli elicit automatic processing or when situational demands supplant chronically activated goals. It appears increasingly that positivity may be reduced when the stakes are high. Taken together, the phenomenon appears to reflect a default cognitive processing approach in later life that favors information relevant to emotion-regulatory goals. Older people place high value on goals related to well-being and, all things being equal, cognitive processing operates under the influence of such goals.

In less than a decade, the positivity effect has become a well-replicated empirical observation. As more evidence accumulates and the guiding theory becomes more nuanced and detailed, it will be possible to test its various aspects with greater precision.

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The role of affect in attentional functioning for younger and older adults

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Although previous research has shown that positive affect (PA) and negative affect (NA) modulate attentional functioning in distinct ways, few studies have considered whether the links between affect and attentional functioning may vary as a function of age. Using the Attention Network Test (Fan et al., 2002), we tested whether participants' current state of PA and NA influenced distinct attentional functions (i.e., alerting, orienting, and executive attention) and how the relationships between affective states and attentional functioning differ in younger (18–25 years) and older (60–85 years) age groups. While there were age differences in alerting efficiency, these age differences were mediated by PA, indicating that the higher state PA found in older adults may contribute to age differences in alerting. Furthermore, age group moderated the relationship between PA and orienting as well as NA and orienting. That is, higher levels of PA and lower levels of NA were associated with enhanced orienting efficiency in older adults. Neither PA nor NA had any influence on executive attention. The current results suggest that PA and NA may influence attentional functioning in distinct ways, but that these patterns may depend on age groups.

Keywords: affect, age differences, attentional networks, individual differences, attention

INTRODUCTION

According to Larsen (2000), *affect* is the evaluative "feeling tone associated with mood and emotion" that is "felt as good or bad, as pleasant or unpleasant, as a felt tendency to approach or avoid" (p. 130). Affective states can be categorized into positive affect (PA) and negative affect (NA), and can influence on attentional processing (e.g., Fredrickson, 2004; Bless and Fiedler, 2006; Forgas, 2008). Advancing age is associated with emotional well-being, characterized by more positive emotional experience (decreased NA and increased or continuing PA) than found among younger adults (e.g., Mroczek and Kolarz, 1998; Charles et al., 2001). This age-related emotional experience led researchers to investigate the link between emotional aging and selective attention to affective content (e.g., Carstensen and Mikels, 2005). Few studies, however, have examined how age-related differences in affective experience influence multiple aspects of attention, such as alerting, orienting, and executive attention (e.g., Posner and Petersen, 1990). This is a critical goal of the current study because emotional factors may differentially influence theses aspects of attention (e.g., Moriya and Tanno, 2009; Jiang et al., 2011), and as suggested by age-related differences in affective experience, this may vary by age (Phillips et al., 2002b).

Attention is not a unitary function, but it encompasses multiple functions (e.g., Posner and Petersen, 1990; Fan et al., 2005; Posner and Rothbart, 2007). Posner and Petersen (1990) have distinguished three anatomically distinct attentional networks that serve different attentional functions: alerting, orienting, and executive attention. *Alerting* is defined as the ability to achieve and maintain an alert state, and facilitates response readiness for an incoming stimulus. *Orienting* refers to the ability to select and shift attention toward the location of an incoming stimulus. *Executive attention* involves the ability to resolve conflicts among various competing responses, thus the capacity to select relevant information and ignore irrelevant information. The Attention Network Test (ANT), a combination of Posner's (1980) spatial cuing task and Eriksen and Eriksen's (1974) flanker task, was developed to simultaneously assess the efficiency of each of the three attentional networks (Fan et al., 2002). In the ANT, the alerting effect is assessed by comparing RTs for targets preceded by alerting (warning) cues informing the temporal onset of the target with those not preceded by any cue. The orienting effect is assessed by comparing RTs for spatially cued targets with RTs for neutrally cued targets, and the orienting response is elicited via a peripherally presented cue without moving the eyes; therefore, *covert* orienting is measured in the ANT (Fernandez-Duque and Posner, 2001). Executive attention is assessed by comparing RTs for targets flanked by congruent distractors with those flanked by incongruent distractors (i.e., the conflicting effect). Behavioral studies using the ANT showed that estimates of efficiency in alerting, orienting, and conflict resolution were uncorrelated (e.g., Fan et al., 2002; Waszak et al., 2010). Moreover, neuroimaging studies further demonstrated mappings between these effects and three separate anatomical systems associated with each network (despite shared common activation sites among the networks; Fan et al.,

2003, 2005; Posner and Rothbart, 2007, for a review). For example, the alerting network has been related to activation of the right frontal cortex and parietal region, while orienting network has been associated with posterior brain areas, including the superior parietal lobe, temporal parietal junction, and the frontal ocular fields. Executive attention is associated with the anterior areas of the frontal cortex (see Posner and Rothbart, 2007, for a review).

Operating a motor vehicle is one example of a daily task for many adults which requires effective functioning of the three attentional networks. For example, someone with good alerting may be better able to maintain a vigilant state while driving, being aware of *when* important information such as road signs, obstructions, and other vehicles appear. People who have high orienting functioning may be more sensitive to detect the direction from *where* that outside information is coming. The ability to effectively orient attention could potentially make the difference between avoiding and hitting objects that come into the path of the moving vehicle. Good executive attention is essential for negotiating complex traffic situations. Making the correct judgments and determining what environmental information is relevant in helping to make those judgments and what is not, is critical for safe driving. Because of age-related declines in sensory and motor systems (Seidler et al., 2010), good attentional functioning while driving may be even more critical for older individuals. Indeed one study found poorer performance on an executive functioning measure among those older adults who had been in an auto accident as compared to those who had not (Daigneault et al., 2002).

Aging has been associated with differential effects on the three attentional networks. There is evidence that healthy aging is associated with decreased alerting efficiency (Jennings et al., 2007; Isaacowitz et al., 2008; Gamboz et al., 2010). Age-related changes in the noradrenergic system, which make it difficult for older adults to maintain a vigilant state, have been attributed to age-related declines in alerting functioning (Jennings et al., 2007). On the other hand, no reliable age differences in orienting or executive attention networks were reported (e.g., Festa-Martino et al., 2004; Jennings et al., 2007; Gamboz et al., 2010), although a decline in neural functioning of these networks was reported (Lorenzo-Lopez et al., 2002; West and Moore, 2005). One study by Mahoney et al. (2010), which included a wide range of older adults, found that increasing age is associated with decreased executive attention efficiency. The findings on age differences in executive attention may support the recent argument by Verhaeghen (2011) that age-related deficits in executive control are overstated, as executive control related to resistance to interference (often measured by Flanker and Stroop tasks) shows a lack of age-related declines.

It has been well-demonstrated that individuals with mood disorders such as anxiety and depression show attentional bias toward negative information as these individual have difficulty disengaging attention from such stimuli (e.g., Koster et al., 2005; Mogg et al., 2008). Similarly, PA has been associated with attentional bias toward reward-related stimuli (Tamir and Robinson, 2007). In addition to attentional biases to emotional information modulated by PA or NA, affect also influences multiple aspects of attention that involve non-emotional information.

According to the Broaden-and-Build Theory (Fredrickson, 1998, 2001, 2004; Isen, 1999), PA expands or broadens attentional scope, leading to more creative and flexible thinking (Ashby et al., 1999). The down side of this broadening effect is that PA has been linked to impaired executive attention, as PA increases inhibition costs (Biss et al., 2009). PA has been associated with a larger flanker interference (Rowe et al., 2007) or a larger Stroop interference (Phillips et al., 2002a), impaired planning (Phillips et al., 2002b) and greater priming for distraction (Biss et al., 2009; Biss and Hasher, 2011). There is also evidence that PA enhances the rapid covert orienting of attention (Compton et al., 2004), but this PA modulation was found in individuals with low PA. Compton et al. (2004) interpreted their findings as showing "a corresponding lack of flexibility in attentional processing associated with low PA" (p. 741), which may increase more attentional bias toward a cued location. In contrast to the link between PA and attention, NA has been linked to the narrowing scope of attention (Fredrickson and Branigan, 2005), focusing more on details of a stimulus or the environment (Forgas, 1999). For example, Vermeulen (2010) has shown that NA increased inhibitory responses to task-irrelevant stimuli, while PA decreased the inhibition of distractors.

Relatively few studies have examined the link between affective states and different functions of attention, using the ANT (e.g., Moriya and Tanno, 2009; Pacheco-Unguetti et al., 2010; Jiang et al., 2011; Lyche et al., 2011). Across these studies, NA was associated with enhanced alerting (Pacheco-Unguetti et al., 2010; Jiang et al., 2011; Lyche et al., 2011; cf., Moriya and Tanno, 2009). This pattern is consistent with the idea suggesting that NA modulates the activation of noradrengeric systems, which maintain vigilant attention (Sullivan et al., 1999; Jiang et al., 2011). The studies yielded mixed results regarding the relationship between NA and orienting. Pacheco-Unguetti et al. (2010) showed that NA (particularly an anxious state) was related to enhanced alerting and orienting, while Moriya and Tanno (2009) found NA (state and trait anxiety, and depression) associated with decreased orienting efficiency (Moriya and Tanno, 2009). On the other hand, some studies found no association between NA and orienting (Finucane et al., 2010; Jiang et al., 2011; Lyche et al., 2011). These mixed findings may be attributable to method variance in the diverse ways affect is assessed; in these studies, individual differences in affect is assessed by self-reported questionnaires, or by experimentally induced mood procedures.

Investigations into the link between PA and attentional networks are limited (Finucane et al., 2010; Jiang et al., 2011). The few existing studies reported no association between PA and any of the three networks, although one might expect that PA may be associated with orienting (Compton et al., 2004) and executive attention (e.g., Phillips et al., 2002a; Rowe et al., 2007; Biss and Hasher, 2011). Nevertheless, the association between PA and attentional networks has not been significantly explored yet; therefore, it seems to be important to further examine the effect of PA on the functions of attentional networks.

Findings that state affect influences attention raises questions about the attentional functions of individuals who tend to experience certain affective states more frequently than others. A large body of literature indicates that older adults report experiencing more PA and less NA than their younger counterparts

(e.g., Mroczek and Kolarz, 1998; Charles et al., 2001; Carstensen et al., 2011). According to socioemotional selectivity theory (SST; Carstensen and Turk-Charles, 1994; Carstensen et al., 1999), such positive emotional experiences are attributable to limited future time perspective that leads older adults (and others facing similar time horizons) to prioritize goals related to emotion regulation over other goals. Such motivational shifts, occurring with age, have been attributed what has been labeled the *positivity effect* when processing emotional information displayed by older adults. The positivity effect is a pattern of preferential processing of positive information over negative information (e.g., Carstensen and Mikels, 2005). A number of studies using eye-tracking to measure gaze patterns occurring during the processing of emotional stimuli, have demonstrated that older adults, compared to their younger counterparts, showed looking preferences toward positive and away from negative stimuli (when the positive or negative stimulus was paired with neutral stimuli; Isaacowitz et al., 2006; Isaacowitz and Noh, 2011, for a review). Indeed, older adults' positive gaze patterns have been directly linked to their attempt to regulate emotion. Older adults commonly display mood-incongruent gaze patterns such that, in a negative mood state, they displayed more positive gaze preferences than those in a positive or neutral mood state. In the same task, younger adults showed more mood-congruent gaze patterns, such that their gaze preferences reflected their mood states (i.e., a more positive gaze pattern when in good moods, a more negative gaze pattern when in bad moods; Isaacowitz et al., 2008). Parallel to these behavioral findings, at the neural level, amygdalar engagement was equivalent among both younger and older adults (the amygdalar is the key structure responsible for processing of emotional information; Forgas, 2008); however, older adults have shown enhanced recruitment of dorsolaterral prefrontal regions (DLPFC) during encoding of negative stimuli (St Jacques et al., 2010). DLPFC is known as the key structure responsible for cognitive control of emotion (for reviews see Vuilleumier and Huang, 2009; Dolcos et al., 2011). Therefore, greater frequency of activation of the DLPFC may explain the increased motivation found among older adults to regulate emotion generated by negative stimuli (St Jacques et al., 2010; Dolcos et al., 2011).

Despite the growing knowledge linking the DLPFC, amygdalar activation, and emotion regulation, it remains unclear whether there are age differences in multiple aspects of attention as function of PA and NA when processing non-emotional information. A study by Phillips et al. (2002b) examined whether there were age differences in the effects of induced positive and negative mood on executive attention (i.e., planning). They found that older adults in both positive and negative mood states showed greater impairment in a planning task than younger adults. The authors interpreted this results as evidence that experiencing emotionally salient events before tasks may have more adverse effects on executive attention in older adults. There is also indirect evidence that older adults with good alerting and executive attention efficiency were more likely to rely on attentional strategies (i.e., attending to positive information) in order to regulate their emotions (Isaacowitz et al., 2009; Noh et al., 2011). It therefore seems reasonable to expect that there may be age differences in how affect influences the fundamental processes by which attention operates.

The current study aimed at investigating age differences in the relationship of state PA and NA to attentional networks using the ANT. While state PA and NA and trait PA and NA are related (Watson and Clark, 1984), focusing on state PA and NA allowed us to determine how potentially modifiable state affect can impact the functioning of the attentional networks. Moreover, given age-related changes in affective states (e.g., Mroczek and Kolarz, 1998), examining the link between state affect, and attentional networks across age groups may increase variability of state PA and NA, and thus could help resolve past mixed findings on this link. We hypothesized that PA and NA may exert differential effects on attentional networks and the pattern would vary by age groups (Phillips et al., 2002b). For alerting, we predicted that NA would be associated with enhanced alerting efficiency (e.g., Pacheco-Unguetti et al., 2010; Jiang et al., 2011). For orienting, PA would be associated with diminished orienting efficiency (Compton et al., 2004). NA may also be associated with orienting efficiency; however, previous findings on this subject are somewhat conflicting. In light of these mixed results, the current researchers feel it is important to further examine the link between NA and orienting in the current study. For executive attention, PA would be associated with decreased executive attention efficiency (Phillips et al., 2002a; Rowe et al., 2007). Although studies using the ANT found a lack of evidence for linking PA and executive attention, investigations were limited; therefore, it seems to be reasonable to expect such an association given previously reported findings (e.g., Phillips et al., 2002a; Rowe et al., 2007). With regard to age differences, we made three predictions. First, despite age-related declines in alerting efficiency (Jennings et al., 2007), we anticipated that older adults in a higher NA state would be more alert than those with in a lower NA state, as older adults with higher NA are motivated to regulate their emotion, which increases vigilance. Second, in light of findings that link older adults' selective attention toward positive information to their mood states (Isaacowitz et al., 2008, 2009; Noh et al., 2011), we hypothesized that older adults' orienting efficiency would be more likely to be influenced by their affective states than younger adults. In particular, NA would generate more efficient orienting, even for non-emotional processing. Although the ANT measures covert orienting while previous eye-tracking studies (showing age-related positive gaze preferences as a function of mood states) measured *overt* orienting attention (Isaacowitz et al., 2008, 2009; Noh et al., 2011), it has been suggested that both types of attentional orienting share the same neruroanotomical substrates (Fernandez-Duque and Posner, 2001). Third, older adults in both PA and NA states would show diminished executive attention as demonstrated by Phillips et al. (2002b).

MATERIALS AND METHODS

PARTICIPANTS

Seventy-six younger adults (44 female; aged 18–25 years) and 69 older adults (53 female; aged 60–85 years) participated in the current study. Younger participants were recruited from an introductory psychology course and flyers posted on campus. Older adults were recruited from a lifelong learning program. Participants received either course credit or monetary stipend. The data for the current study come from a larger study that looked age differences in gaze preferences (Isaacowitz et al., 2008). An additional one

younger and two older adults were tested, but their data were removed for high error rates (mean accuracy rate >80%). **Table 1** shows the participants' demographic characteristics, visual acuity, and cognitive functioning.

MEASURES

Affect

The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was used to assess the participant's current emotional experiences (or states). The PANAS is a 20-item, self-rated measure comprised of two independent dimensions of PA and NA. It consists of 20 adjectives reflecting of positive (10 items, e.g., "interested," "alert," "excited," and "enthusiastic") and negative (10 items, e.g., "guilty," "upset," "distressed," and "irritable") affect. Respondents are asked to rate the extent to which they have felt this way in the indicated time frame (*today* for the current study) on five-point Likert-type scales. The scale points are: 1 – "very slightly or not at all," 2 – "a little," 3 – "moderately," 4 – "quite a bit," and 5 – "extremely." The PANAS is the most widely used scale to measure current affective states (Crawford and Henry, 2004). Watson et al. (1988) reported alpha coefficients for various time-frames ranging from 0.86 to 0.90 for the PA scale and 0.84 to 0.87 for the NA scale. Test-retest reliability for an 8-week period ranged from 0.47 to 0.68 for PA and from 0.39 to 0.71 for NA. Crawford and Henry (2004), in a study involving a large sample drawn from the general adult population (18–91 years), obtained similar reliability scores of both scales to those found in Watson et al. (1988) and demonstrated the construct validity of the PANAS scales. The reliabilities for the PANAS found in the current study were high in both our younger and older samples (younger adults: $\alpha_{PA} = 0.92$ and $\alpha_{NA} = 0.82$; older adults: $\alpha_{PA} = 0.83$ and $\alpha_{NA} = 0.93$).

Table 1 | Means and standard deviations of participants' demographic information and results from perceptual and cognitive tests.

Variable	Younger		Older	
	M	SD	*M*	SD
EDUCATION (%)				
4-Year college degree or more	15.79		91.30	
Some college	25.00		1.45	
Completed high school only	51.32		7.25	
Some high school or less	7.89		0.00	
HEALTH				
Self-rating of health	3.96	0.77	3.72	0.91
VISION MEASURES				
Rosenbaum near vision*	23.36	3.86	30.43	5.54
Pelli-Robson contrast*	1.53	0.13	1.40	0.13
COGNITIVE MEASURES				
MMSE*	29.68	0.57	28.97	1.01
Digit symbol substitution*	72.11	0.09	53.54	11.16
Shipley vocabulary test*	14.20	9.81	16.56	2.39
AFFECT MEASURES				
PANAS positive affect*	29.07	8.78	34.09	5.74
PANAS negative affect*	16.27	5.31	13.83	5.97
ATTENTION NETWORK TASK				
ANT alerting effect (RT in ms)*	42.32	26.72	23.64	38.15
ANT orienting effect (RT in ms)	41.88	22.31	46.07	33.06
ANT conflict effect (RT in ms)	134.29	55.14	148.23	93.47
ANT mean accuracy (percentage correct)	98.00	5.81	97.04	4.37

*The tests used were as follows: self-reported current health, ranging from 1 (poor) to 5 (excellent); Rosenbaum pocket vision screener for near vision (Rosenbaum, 1984); Pelli-Robson contrast sensitivity chart (Pelli et al., 1988); mini-mental state examination (MMSE; Folstein et al., 1975); digit symbol substitution, a subtest of the Wechsler adult intelligence scale – revised (Wechsler, 1981); Shipley vocabulary test (Zachary, 1986); positive and negative affect schedule (PANAS; Watson et al., 1988); attention network task (ANT; Fan et al., 2002). All participants had a MMSE score of 27 or higher. RT, response time. *Significant age differences at $p < 0.05$.*

Attention

Figure 1 illustrates the sequence of the ANT. In the ANT, a fixation cross of variable duration (400–1600 ms) was presented at the beginning of each trial. This was followed by one of four cue conditions: no cue, center cue, double cue, and spatial cue. The cue (i.e., an image of an asterisk) was presented for 100 ms. On no cue trials, no cue appeared, but a fixation cross was presented; on center cue trials the cue occurred at the location of the fixation cross; on double cue trials the cues appeared above and below the fixation cross; and on spatial cue trials the cue appeared in the same location as the upcoming target, thus it always predicted the target location. After the cue disappeared, another fixation period of 400 ms was provided and a target-flanker display appeared above or below the fixation cross until the participant gave a response, but for no longer than 1700 ms. The target stimulus (i.e., central arrow pointing left or right) was surrounded by flankers on each side and there were three flanker types: congruent (arrows pointing the same direction as the target, central arrow), incongruent (arrows pointing the opposite direction of the target arrow), and neutral (dashes). After the response was given, the last fixation period was presented (3500 ms minus the first fixation period minus target RT). The total duration for each trial was 4000 ms. The JAVA version of the ANT (downloaded from Fan J's website) was used in the current study.

PROCEDURE

Participants were tested individually. After providing informed consent, participants completed a demographic questionnaire and measures of visual acuity, cognition, and affect, followed by the ANT. In the ANT, participants were instructed to press a key indicating the direction of a centrally presented target arrow (pointing either left or right) that appeared above or below a fixation cross, shown in the center of the screen. The ANT began with 24 practice trials (with feedback following errors), followed by three experimental blocks (96 trials/block without feedback) separated by a short break. Participants were instructed to maintain their fixation at the fixation cross all the time, to identify the direction of the target arrow, and that quick and accurate responses would be important.

RESULTS

PRELIMINARY ANALYSES

Table 1 depicts mean group differences in the PANAS and the ANT assessed using one-way analysis of variances (ANOVAs) between

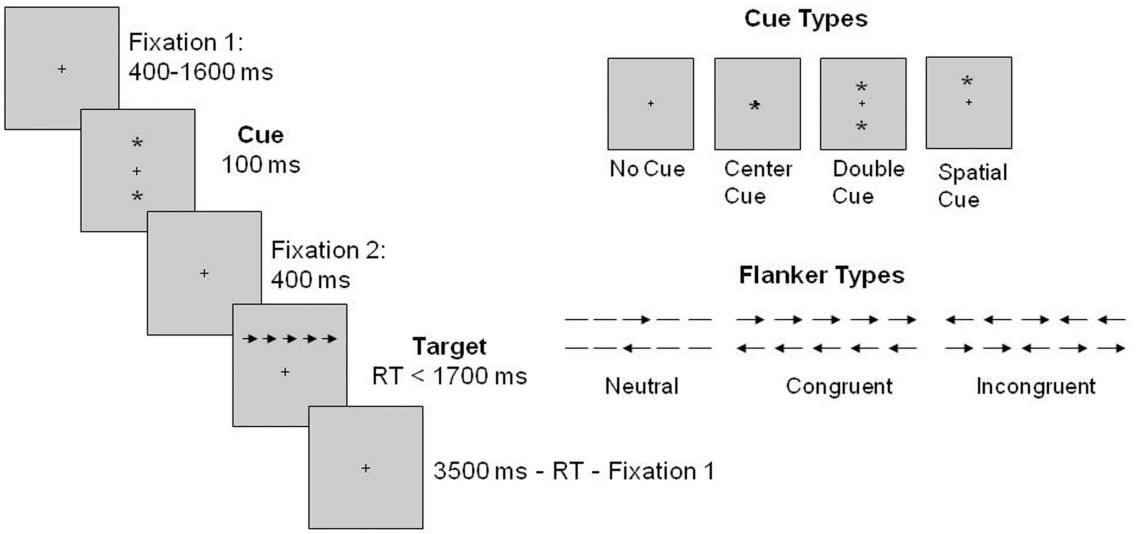

FIGURE 1 | Sequence of events for each trial of the ANT based on Fan et al. (2002).

younger and older groups. For age differences in the PANAS, the older group scored significantly higher on the PA scale compared to the younger group, $F(1, 143) = 16.25$, $p < 0.001$, but scored lower on the NA scale, $F(1, 143) = 6.81$, $p < 0.05$. Thus, consistent with numerous previous findings (e.g., Mroczek and Kolarz, 1998), older adults, on average, reported experiencing more positive states and less negative states than their younger counterparts.

Regarding the ANT performance, the JAVA-ANT provides precalculated scores for each network. The efficiency of each attentional network is calculated using subtractions to determine the influence of alerting cues, orienting cues, and flankers on RTs. The alerting effect is calculated as $RT_{\text{no cue}} - RT_{\text{double cue}}$. The orienting effect is calculated as $RT_{\text{center cue}} - RT_{\text{double cue}}$. The conflict effect (i.e., executive attention) is defined as $RT_{\text{incongruent}} - RT_{\text{congruent}}$. Higher scores on the alerting and orienting effects are indicative of faster cue-related performance [i.e., faster RTs due to warning (alerting) and spatial (orienting) cues]. Higher scores on the conflict effect are indicative of slower RTs due to incongruent flankers (i.e., the costs associated with conflict resolution).

One sample t-tests were used to examine whether calculated network scores were different from zero and the results indicated that all the network scores were significantly different from zero (all $ps < 0.001$) for both younger and older adults. Thus, each network score for both age groups provides a usable index of efficiency of each network. Next, age differences in the ANT performance were tested and the results revealed a significantly reduced alerting effect in the older compared to the younger group, $F(1, 143) = 11.83$, $p < 0.01$ (see **Table 1**), and equivalent orienting and conflict effects in both groups, $F < 1$, and $F(1, 143) = 1.22$, $p = 0.27$, respectively. In order to control for the possibility that age-related declines in speed of processing (Salthouse, 1991) influenced the age difference in the alerting effect, the alerting effect as a function age was re-tested while controlling for age differences in speed. The scores on the Digit Symbol Substitution test (Wechsler, 1981), which indeed revealed age-related slowing in processing speed (see **Table 1**), were used as a covariate. The age differences in the alerting effect remained significant after adjusting for age differences in speed. As shown in **Table 1**, there were no age differences in the mean ANT accuracy, indicating accuracy was equally high for both younger and older adults, $F(1, 143) = 1.23$, $p = 0.27$.

Table 2 | Correlations between the study's main variables in the two age groups.

	PA	NA	Alerting	Orienting	Conflict
PA	1	−0.13	−0.13	0.29*	0.10
NA	−0.10	1	−0.02	−0.23†	0.07
Alerting	−0.24*	0.08	1	0.07	−0.17
Orienting	0.02	0.23*	−0.17	1	0.04
Conflict	−0.10	−0.12	0.08	−0.03	1

Correlations below the diagonal are from the younger age group. Correlations above the diagonal are from the older age group. $^{\dagger}p < 0.07$, $^{*}p < 0.05$.

Next, **Table 2** presents the correlations between the study's main variables (attention network scores, PA, and NA) in the two age groups. Within the ANT, there were no significant correlations among alerting, orienting, and executive attention for both age groups (e.g., Fan et al., 2002). In the younger group, PA was inversely associated with alerting efficiency, whereas NA was positively associated with orienting efficiency. In the older group, neither PA nor NA was associated with alerting efficiency; however, PA was positively related with orienting efficiency, whereas NA tended to be inversely associated with orienting efficiency. Neither PA nor NA was associated with conflict resolution efficiency (i.e., executive attention) for both age groups.

THE MODERATING ROLE OF AGE

To test whether the effects of PA and NA on attentional networks were moderated by age, we performed moderated regressions

analyses. With each attentional network as a dependent variable, two hierarchical multiple regression analyses were conducted separately for PA and NA. Thus, a total of six regression models were conducted. In the first step of the regression analyses, we included gender (0 = male) and speed of processing as control variables, because age groups had a higher percentage of women, and older adults, on average, were slower in their processing speed than younger adults. In the second step, we tested the main effects of age (0 = younger adults) and PA or NA for significance. Finally, we entered the interaction terms between age group and PA or NA in the last step of the analyses. All continuous predictor variables, except for gender and age, were standardized prior to performance of analyses.

The results of the main effects and interaction effects are reported in **Table 3**. Across all regression models, gender failed to account for the efficiency of attentional networks, and speed only accounted for alerting efficiency in that slower speed of processing predicted reduced alerting efficiency. For the alerting model with PA, age did not significantly predict alerting efficiency; however, higher levels of PA were associated with lower alerting efficiency. Despite this association, the age by PA interaction was not significant. For the alerting model with NA, the main effect of age was significant as older adults exhibited lower alerting efficiency than younger adults. Neither the main effect of NA nor the age by NA interaction was significant. Thus, the alerting models indicated that age did not moderate the effects of PA and NA on alerting efficiency.

For the orienting model with PA, neither age nor PA predicted orienting efficiency; however, there was a significant age by PA interaction. In addition, for the orienting model with NA, none of the main effects were significant; though, the age by NA interaction effect was significant. To illustrate the obtained interaction effects, we plotted in **Figure 2** the association between PA and NA (1 SD above and below the sample mean) and orienting efficiency separately for younger and older adults employing commonly used regression techniques (Aiken and West, 1991). The obtained pattern of results in **Figure 2A** indicated that the largest orienting effect was found among older adults with higher levels of PA. A calculation of the simple slopes further supported this interpretation: experiencing higher levels of PA significantly associated with greater orienting efficiency among older adults ($\beta = 13.29$, $p < 0.05$), but not among younger adults ($\beta = 1.02$, $p = 0.73$). Conversely, the obtained pattern of results in **Figure 2B** showed that larger orienting effects were found among older adults with lower levels of NA and younger adults with higher levels of NA. A calculation of the simple slopes, however, indicated that the slope for older adults was significant ($\beta = -7.25$, $p < 0.05$), but not for younger adults ($\beta = 5.39$, $p = 0.12$). Thus, experiencing lower levels of NA was significantly associated with greater orienting efficiency among older adults. Finally, for the conflict models, neither PA nor NA predicted conflict resolution. Moreover, age did not exert a significant interaction with PA or NA on conflict resolution.

Table 3 | Hierarchical regression analyses predicting attentional networks from age group, PA, NA, and the age group by PA/NA interactions.

	ΔR^2	β		ΔR^2	β
ALERTING					
Step 1	0.04				
Gender		−6.54			
Speed		5.74*			
Δ*F*-value		$F(2, 142) = 2.86^{\dagger}$			
Step 2	0.07			0.04	
Age		−13.13	Age		−18.05*
PA		−6.65*	NA		0.99
Δ*F*-value		$F(2, 140) = 5.73$*	Δ*F*-value		$F(2, 140) = 3.08$
Step 3	0.00			0.00	
Age PA		−0.65	Age × NA		−3.13
Δ*F*-value		$F(1, 139) < 1$	Δ*F*-value		$F(1, 139) < 1$
ORIENTING					
Step 1	0.01				
Gender		3.01			
Speed		−2.09			
Δ*F*-value		$F(2, 142) < 1$			
Step 2	0.02			0.00	
Age		−2.06	Age		1.02
PA		$4.56^{\dagger}$	NA		−1.36
Δ*F*-value		$F(2, 140) = 1.68$	Δ*F*-value		$F(2, 140) < 1$
Step 3	0.04		Step 3	0.05	
Age × PA		12.26*	Age × NA		−12.64**
Δ*F*-value		$F(1, 139) = 5.14$*	Δ*F*-value		$F(1, 139) = 7.15$**
CONFLICT					
Step 1	0.01				
Gender		2.74			
Speed		−7.96			
Δ*F*-value		$F(2, 142) < 1$			
Step 2	0.00		Step 2	0.01	
Age		4.88	Age		5.52
PA		<1	NA		<1
Δ*F*-value		$F(2, 140) < 1$	Δ*F*-value		$F(2, 140) < 1$
Step 3	0.01		Step 3	0.01	
Age × PA		17.57	Age × NA		14.29
Δ*F*-value		$F(1, 139) = 1.36$	Δ*F*-value		$F(1, 139) = 1.19$

*Gender was coded as 0 (male) and 1 (female). Age coded as 0 (younger adults) and 1 (older adults). PA, positive affect; NA, negative affect. $^{\dagger}p < 0.07$, *$p < 0.05$, and **$p < 0.01$.*

THE MEDIATING ROLE OF STATE AFFECT

To determine whether age differences in PA and NA accounted for age differences in alerting, we performed a mediation analysis, using age and alerting as independent and dependent variables and affect variables as mediators. While recent work has suggested important problems with meditational analyses using cross-sectional aging data when the mediator is supposed to represent a developmental process (see Lindenberger et al., 2011), we considered PA and NA as potential *states* that could mediate the relationships of interest, not as developmental outcomes themselves. Thus, meditational analyses may still be appropriate in this context.

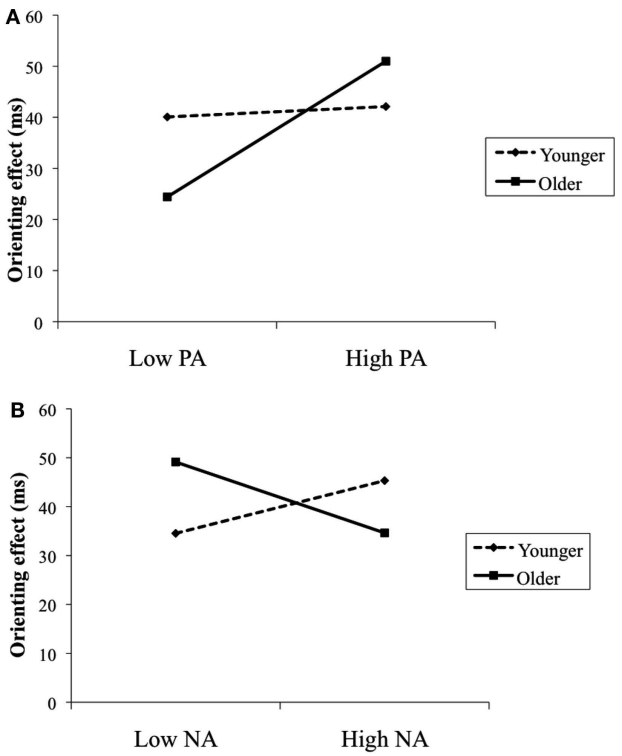

FIGURE 2 | Age as a moderator of the relationship between PA and orienting effect (A) and the relationship between NA and orienting effect (B). Results were controlled for gender and speed.

The analysis of mediation effects used a multiple mediation model with both PA and NA entered simultaneously using Preacher and Hayes' (2008) method for testing mediation. By testing for mediation effects through both PA and NA, we were able to compare the size of each effect as well as its significance as a mediation effect. Following Preacher and Hayes' (2008) method, we used a bootstrapping procedure to compute SEs and 95% confidence intervals around the indirect effect (i.e., the effect of age on alerting through PA and NA). This method uses 5,000 bootstrapped samples to estimate the bias-corrected and accelerated confidence intervals. Indirect effects were considered as significant when the confidence interval did not include zero. The SPSS macros that Preacher and Hayes provided were utilized for this procedure. In this analysis, age (0 = younger adults) was the independent variable, alerting was the dependent variable, and PA and NA were mediators. Preacher and Hayes (2008) recommended use of bootstrap SEs and confidence intervals over the Sobel test because the latter involves the assumption of the normality of the estimates of the indirect effect, which is normal only in large samples. However, for convenience, we also report the traditional mediation significance test by the Sobel test. In addition, unstandardized regression/path coefficients were reported in the current model because standardized coefficients for a dichotomous variable (i.e., *age*) had no meaningful interpretation (Preacher and Hayes, 2008). Significance tests of the mediation effect can be found in **Table 4**.

Table 4 | Magnitude and confidence intervals of the multiple mediation test of the relationship BETWEEN age and alerting through PA and NA.

	Bootstrap results for mediation effects			
	Mediation effect	SE	95% confidence interval	
			Lower	Upper
MEDIATORS				
Total mediated effect	**−5.46**	3.36	−13.89	−0.30
PA	**−5.29**	2.78	−12.85	−1.30
NA	−0.17	1.66	−5.15	2.27
CONTRAST				
NA-PA	**−5.11**	3.12	−12.79	−0.15

Boldface type highlights a significant effect as determined by the 95% bias-corrected and accelerated confidence interval based on 5,000 bootstrap samples.

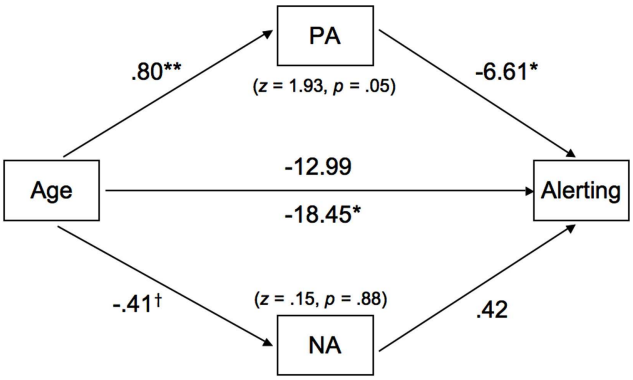

FIGURE 3 | The mediated roles of positive affect (PA) and negative affect (NA) on the age-alerting association. Path coefficients are unstandardized beta weights while controlling for gender and speed. The *z*-values (and associated *p*-values) refer to Sobel test results, assessing the significance of the role of each moderator. Two direct effects of age on alerting are included. The coefficient below the path is representative of a model that did not include any mediators; the coefficient above the path is with PA and NA as mediators. Results were controlled for gender and speed of processing. $^{\dagger}p < 0.07$, $^{*}p < 0.05$, and $^{**}p < 0.01$.

The total mediation effect of PA and NA was significant; however, this effect was driven by PA, as the mediation effect of NA did not attain significance. Although the result of the Sobel test was only marginally significant (see **Figure 3**), the fact that zero fell outside the confidence interval (−12.89 to −1.30; see **Table 4**) indicated a significant mediation effect (Preacher and Hayes, 2008). As can be seen in **Figure 3**, older adults were more likely to report a higher state of PA ($b = 0.80$, $p < 0.01$), which had a negative prediction effect for differences in alerting efficiency ($b = -6.61$, $p < 0.05$). At the same time, age was a significant predictor of alerting without the mediators in the model ($b = -18.45$, $p < 0.05$), but the direct effect became non-significant in the presence of the mediators, suggesting that PA largely mediated the age differences in alerting.

DISCUSSION

The current study investigated age differences in the links between affect and attentional functioning. From preliminarily analyses on mean differences, we found that older adults in the current study reported experiencing more PA and less NA than did younger adults. Thus, the finding is consistent with previous studies of age-related decreases in experience of NA (e.g., Mroczek and Kolarz, 1998; Carstensen et al., 2011), which suggest that as people get older, they report more positive and less negative affective states. With regard to age differences in the efficiency of attentional networks, older adults were found to show decreased alerting efficiency compared with younger adults (even when adjusting for speed of processing), but there was no evidence of age differences in the efficiency of orienting and executive attention. These results are consistent with previous findings (Festa-Martino et al., 2004; Fernandez-Duque and Black, 2006; Jennings et al., 2007; Gamboz et al., 2010). Noradrenergic transmission has been linked to alerting (Fernandez-Duque and Posner, 2001; Fan et al., 2009), as well as associated with NA (Sullivan et al., 1999), suggesting that age-related declines in the noradrenergic activation system (Jennings et al., 2007) might explain the main effect of age on both alerting and NA.

Results from the correlation analysis showed no association among the three network scores for both younger and older age groups, indicating the functional independence of alerting, orienting, and executive attention (e.g., Fan et al., 2002; Moriya and Tanno, 2009). Younger and older adults showed somewhat different patterns of correlations between affect and attentional networks, which were further examined by the moderation and mediation analyses.

AGE DIFFERENCES IN THE ASSOCIATION BETWEEN AFFECT AND ALERTING

Higher PA was associated with diminished alerting, but age group did not moderate the relationship between PA and alerting. This finding is inconsistent with our hypothesis and divergent from previous work linking NA and alerting (e.g., Pacheco-Unguetti et al., 2010; Jiang et al., 2011; Lyche et al., 2011). It is perplexing why PA, not NA, was related with alerting functioning in the current study. If PA broadens attention and thinking (Fredrickson, 1998, 2001), which is hypothesized to induce loosened control of attention (Biss and Hasher, 2011), PA could also modulate the alerting network in similar ways. It has been shown that the processes involved in alerting and executive attention share a common brain region in the frontal-parietal lobe, though the two processes are dissociable at the behavioral level (Fan et al., 2007). The executive attention system was associated with dopaminergic transmission (Fan et al., 2009), which was associated with PA (Ashby et al., 2002). Together, the findings provide indirect evidence that PA may also be related to alerting. However, given no evidence for the link between PA and executive attention in the current study, it seems to be unlikely that high PA is also linked to impaired alerting. The reduced alerting effect can also be interpreted as the facilitated ability to prepare and sustain alertness in the *absence* of a warning cue. Therefore, it may be more plausible, however speculative, that diminished alerting associated with PA indicates higher vigilance and, therefore, an increased ability to maintain alertness in the *absence* of a warning cue.

The results from the mediation analysis further indicate that the majority of the age-related variance in the alerting effect was associated with PA. PA fully mediated age differences in alerting. The present finding may, in part, align with the earlier finding of Phillips et al. (2002b) that older adults in both positive and negative mood states showed worse performance on a task of executive attention than younger adults. It is interesting that we observed this pattern in alerting performance. The present finding, in conjunction with Phillips et al.'s (2002b), may suggest that increased PA is more likely to influence attentional functioning for older adults than for younger adults.

Although we predicted that older adults with higher NA would be more alert that those with lower NA, as they might be more motivated to regulate emotion, we found no supporting evidence for this link. Thus, SST does not seem to be a fitting explanation for this pattern. There may be several tentative explanations for the association between PA and alerting in older adults. One possibility is that, as we speculated above, if the effect of PA on alerting reflects better ability to prepare and sustain alertness in the absence of warning cues, the present result may suggest that high PA could enhance alertness in the absence of warning cues for older adults. Another possibility is that, as we speculated above, if the effect of PA on alerting reflects greater vigilance in the *absence* of warning cues, the present result may suggest that high PA could enhance alertness when warning cues are *not* present. An underlying mechanism for this greater alertness may be related to dopaminergic and norepinephrinergic pathways from the amygdala (LeDoux, 2007 for review of afferent amygdala input) which could be affected by levels of PA. We should caution that this interpretation is speculative and PA actually may be related to worse alerting. In addition, more work is needed in order to determine how the relationship between age and PA influences the neural functioning that is implicated in alerting.

The lack of NA effect on alerting can be explained, in part, by the fact that the NA state measured in the current study may not be strong enough to generate findings similar to those measured in previous studies. For example, previous studies either selected individuals with extreme NA states, such as depression (Lyche et al., 2011), or experimentally manipulated negative mood (Pacheco-Unguetti et al., 2010; Jiang et al., 2011). The current study, on the other hand, assessed naturally occurring individual differences in NA in healthy participants. The arousal levels involved in these varying NA states may differ (Jefferies et al., 2008), though the possibility of this phenomenon does require further investigation. In the current study, the average level of NA reported by the participants was quite low (as indicated in **Table 1**). This might have resulted in the relatively lower level of arousal of NA found as compared to previous studies. Future studies should address how different ranges of NA states, as well as levels of arousal, may be related to the function of alerting, and how these factors interact with one another to influence the function of alerting, as well as age differences in the NA-alerting link.

AGE DIFFERENCES IN THE ASSOCIATION BETWEEN AFFECT AND ORIENTING

Age group did moderate the relationship between PA and orienting as well as NA and orienting. That is, older adults experiencing higher PA and lower NA exhibited better orienting followed by

spatial cues than those experiencing lower PA and higher NA. On the other hand, orienting efficiency among younger adults was not significantly influenced by the levels of PA and NA, although the results of the correlations indicate that NA was positively associated with orienting for younger adults (Pacheco-Unguetti et al., 2010). Thus, supporting our hypothesis, affect states were more likely to influence orienting for older adults. Though our hypothesis was supported, we particularly expected that higher NA would produce more efficient orienting in older adults as previous studies demonstrated pronounced gaze preferences toward positive stimuli in a negative mood state among older adults (e.g., Isaacowitz et al., 2008); however, the pattern in the data showed that older adults experiencing more positive and less negative affective states oriented attention to the cued location much more quickly. This finding conflicts with Compton et al.'s (2004) reports that individuals with low PA showed greater spatial cueing effects than individuals with high PA. As Compton et al. (2004) argued, if greater spatial cueing effects associated with low PA are due to decreased cognitive flexibility associated with low PA, the present finding with older adults may also reflect decreased cognitive flexibility associated with high PA and low NA among older adults. However, as high PA has been closely linked to increased cognitive flexibility (Ashby et al., 1999), this may not be the case. It is noteworthy that there are some methodological differences between Compton et al. (2004) and the current study. Compton et al. (2004) only included younger participants and their orienting task included both valid and invalid cue trials, while the ANT task used in the current study only included valid cue trials. Therefore, the present finding indicates that older adults with high PA and low NA benefited more from valid cues in orienting attention, but cannot address the impact of invalid cues. Future studies should further test whether older adults with high PA or low NA also have difficulty disengaging attention from invalidly cued locations. This may help elucidate whether or not the orienting effect associated with high PA and low NA in older adults reflects decreased cognitive flexibility.

The orienting network is governed by two neural mechanisms: the dorsal frontospatial network (DAN) and ventral frontoparietal network (VAN; Corbetta and Shulman, 2002). DAN is involved in top-down control of directing attention to the location-directing cue and making eye-movements to sensory stimuli, while VAN is involved in disengagement of attention when invalid cue is presented so attention has to be shifted away from its current focus toward the opposite visual field (Corbetta and Shulman, 2002). Because invalid cue trials were not included in the ANT in the current study, the present orienting effect may be related to DAN. However, it is proposed that DAN and VAN interact in a way that DAN provides a signal to VAN in order to maintain a certain attentional balance between the two systems when focusing attention (Corbetta et al., 2008). The present results, therefore, may indicate this orienting system remains balanced in younger adults and is somehow disrupted in older adults by high PA and low NA states. Further, both networks rely on cholinergic transmission (Fan et al., 2009). A deficit in cholinergic transmission in Alzheimer's disease produces enhanced benefit from valid cues (Parasuraman et al., 1992). Therefore, the present orienting effects could also reflect cholinergic transmission associated with high PA and low NA, which may affect activity in DAN during engagement of attention to valid cues. This possible link needs more investigation.

Alternatively, our finding may indicate that older adults with high levels of PA states may seek out more PA in an effort to perpetuate an "upward spiral" of positive emotion (Fredrickson and Joiner, 2002). These individuals may find more positive information in the world around them, and may maintain greater happiness because of what they find, which could lead them to rely on environmental cues to orient their attention. This possibility might be supported by a recent study by Waldinger et al. (2011). They showed that older adults high in life satisfaction displayed increased connectivity of within an amygdala-mediated network in response to positive information, as compared to negative information. In line with Waldinger et al. (2011), our findings may suggest that older adults reporting high levels of PA states may be more sensitive to environmental cues to orient attention. However, it remains important to test whether individual differences in affective states in older adults are related to orienting attention, and more specifically to emotionally valenced information.

AGE DIFFERENCES IN THE ASSOCIATION BETWEEN AFFECT AND EXECUTIVE ATTENTION

There is no evidence from the present results that PA had any effect on executive attention. Thus, the present finding is not in line with the Broaden-and-Build Theory of positive emotions (Fredrickson, 1998). Martin and Kerns (2011) suggest that PA is related to some aspects of executive attention, such as working memory and planning, but it may have little impact on prepotent response inhibition, which is related to flanker interference. However, Rowe et al. (2007) found supporting evidence for the Broaden-and-Build Theory using the flanker task. The discrepancy between the result of this study and that of Rowe et al. (2007) may lie in a difference in the flanker task, as Rowe et al. (2007) manipulated the distance between the flankers and target, while the current study had no such manipulation. Consistent with the present finding, previous studies using the ANT also reported a lack of association between PA and flanker interference (Jiang et al., 2011; Lyche et al., 2011; Martin and Kerns, 2011; cf., Rowe et al., 2007). Thus, future research should, therefore, not only consider different executive functions, but also take into account variations of the flanker task.

Inconsistent with our hypothesis and Phillips et al.'s (2002b) results, we found no evidence for diminished executive attention among older adults in either PA or NA states. The discrepancy between our finding and those of Phillips et al. (2002b) may lie in the task used to assess executive attention and the way affect was measured. Such methodological differences may cause different results. Therefore, future research should be conducted to examine whether the influence of affect on executive attention is dependent upon how executive attention and affect (or mood) are assessed.

LIMITATIONS AND CONCLUSION

The current study has several important limitations that are important to note. Most importantly, the data in the current study come from self-reported measures of affect and from non-clinical participants. Thus, the data may reflect restricted ranges of affect that may not be sensitive to detect possible affect-attention relationships. In addition, because the context of

emotion regulation was not directly manipulated in the current study, how age-related changes in affective experiences and shifts in emotional goals interact to influence attentional functioning remains in question. This limitation could be attributed to the fact that we found no evidence for our hypotheses regarding the attentional performance of older adults with high NA. Future research will need to make explicit the connections between age differences in affect-attention links as a function of emotional goals. Further, this study is cross-sectional and does not include middle-aged participants, which precludes a direct examination of age-related changes in affect and attentional networks and how these changes influence one another. Finally, although the current study provides initial behavioral evidence regarding age differences in the effects of PA and NA on attentional networks, future brain-imaging studies will shed further light on the interactive processing of affect and attentional networks at a neural level.

These limitations notwithstanding, the results presented here show that attention is indeed a multifaceted construct and each facet can be affected differently by PA and NA. Additionally, individual difference factors such as age should continue to be taken into account when researchers study the affect-attention relationship. Extending the previous studies showing age differences in attentional orienting to emotional information, the present results indicate that age differences in alerting and orienting can be modulated by state PA or/and NA when the task is non-emotional. Experiencing high positive and low negative affective states may be adaptive in later years of life. The present results that such positive affective profile is more likely to influence attention for older adults than younger adults suggest that this relationship may occur in order to compensate for age-related changes in internal resources. This relationship needs further investigation.

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Electrophysiological evidence for adult age-related sparing and decrements in emotion perception and attention

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The present study examined adult age differences in processing emotional faces using a psychological refractory period paradigm. We used both behavioral and event-related potential (P1 component) measures. Task 1 was tone discrimination (fuzzy vs. pure tones) and Task 2 was emotional facial discrimination ("happy" vs. "angry" faces). The stimulus onset asynchrony (SOA) between the two tasks was 100, 300, and 900 ms. Earlier research observed larger age deficits in emotional facial discrimination for negative (angry) than for positive (happy) faces (Baena et al., 2010). Thus, we predicted that older adults would show decreased attentional efficiency in carrying out dual-task processing on the P1 (a component linked to amygdalar modulation of visual perception; Rotshtein et al., 2010). Both younger and older groups showed significantly higher P1 amplitudes at 100- and 300-ms SOAs than at the 900-ms SOA, and this suggests that both age groups could process Task 2 faces without central attention. Also, younger adults showed significantly higher P1 activations for angry than for happy faces, but older adults showed no difference. These results are consistent with the idea that younger adults exhibited amygdalar modulation of visual perception, but that older adults did not.

Keywords: aging, emotion perception, automaticity, ERPs, psychological refractory period

ELECTROPHYSIOLOGICAL EVIDENCE FOR ADULT AGE-RELATED SPARING AND DECREMENTS IN EMOTION PERCEPTION AND ATTENTION

Some studies with younger adults have shown that early emotion perception of angry faces does not require attentional resources, suggesting that some emotion perception is automatic (e.g., Shaw et al., 2011). However, there is evidence suggesting that for some older adults, emotional processing of negative stimuli (Leigland et al., 2004; Baena et al., 2010) and positive stimuli (Allen et al., 2011) is compromised (relative to younger adults). We hypothesize that this is the result of age-related changes in the ventral affective system (see Dolcos et al., 2011). The ventral affective system is hypothesized to be a reflexive system involving early emotional evaluation in threat perception (including the visual cortex, fusiform gyrus, amygdala, and ventromedial prefrontal cortex [VMPFC]), whereas the dorsal attentional stream is thought to involve later "cognitive" executive functions (the frontoparietal attentional system) (Dolcos et al., 2011; see also, Corbetta et al., 2008). Evidence consistent with a ventral affective system deficit is that older adults show deficits in: discriminating emotional faces—especially negatively valenced emotional faces (Baena et al., 2010), emotional decision making (Denburg et al., 2005), and emotionally linked episodic memory (Allen et al., 2005, 2011). These are known symptoms of individuals with VMPFC damage (Bechara et al., 2000; Denburg et al., 2005) and/or amygdalar deficits (Leigland et al., 2004).

The goal of the present study is therefore to examine potential age differences in emotional processing. Similar to Shaw et al. (2011), we used Psychological Refractory Period (PRP) paradigm and measured the event-related potential (ERP) elicited by emotion stimuli. However, while Shaw et al. examined spatial attention automaticity using the N2pc ERP component, we examined attentional automaticity across age (younger and older adults) using the P1 ERP component. The P1 component (measured at the O1 and O2 electrode sites) is a visual perceptual response known to be modulated by the amygdalar function with emotional faces (Rotshtein et al., 2010). The P1 component is a particularly sensitive measure of emotional processing because Rotshtein et al. isolated the P1 ERP effect on epilepsy patients. They compared healthy controls, individuals with medial temporal lobe epilepsy (MTLE) surgery that spared the amygdala (MTLE-control), and individuals with MTLE surgery that resulted in amygdalar damage (MTLE-amygdala). The MTLE-amygdala patients (with damage to the amygdala) showed no appreciable P1 effects to emotional faces, but the MTLE-control and healthy participants did show large P1 effects to emotional stimuli (e.g., fearful vs. neutral faces). It is important that the larger P1 effect for fearful faces than for neutral faces in the two control groups was not the result of general perceptual activation because inverted faces showed no increased positivity for the fearful faces for the P1 component. Also, Holmes et al. (2008, 2009b) used the P1 component to study emotional facial discrimination in individuals with low and high trait anxiety. Consequently, there is evidence that the P1 ERP is a measure of perceptual processing and is generated by extrastriate visual cortex and fusiform gyrus (Di Russo et al., 2002; Amaral, 2003; Phelps and LeDoux, 2005). Critical to the present study is the finding that the amygdala appears to modulate perceptual processing

when a visual stimulus has an emotional valence (Holmes et al., 2008, 2009a,b; Rotshtein et al., 2010). An additional question to be addressed in the present study is whether increased adult age modulates exogenous attention involving emotional stimuli [what Dolcos et al. (2011) termed the ventral affective system] in a reflexive manner. Our present working hypothesis is that if older adults exhibit a deficit in ventral affective processing, then they should show a reduced P1 emotional valance effect relative to younger adults. We also predict that this age difference should be particularly salient when central attentional resources are engaged by another non-emotional task (in the present study, Task 1).

PSYCHOLOGICAL REFRACTORY PERIOD PARADIGM

We aimed to determine if emotional faces (Task 2) can still be processed even when central attentional resources are engaged by the processing of another task (Task 1) and how the processing is modulated by age. We used the PRP paradigm (Telford, 1931; Welford, 1952; Pashler, 1984), which is a widely used method for the examination of dual-task processing. In this paradigm participants are required to perform two tasks (Task 1 and Task 2) for which the stimuli are separated by a variable time interval, which is known as the stimulus onset asynchrony (SOA). The common finding is that Task 2 performance tends to decline as SOA decreases—and this phenomenon is known as the PRP effect (Telford, 1931; Pashler, 1984).

Pashler (1984) proposed the central bottleneck model to account for the PRP effect (see also Welford, 1952). The model postulates that central processing stages, such as response selection, for Task 1 and Task 2 do not operate in parallel and are instead processed serially. However, peripheral processing stages, such as perceptual encoding, can occur in parallel with all the other stages. The variable of SOA is theorized to measure the duration of the central attentional bottleneck (see **Figure 1**). This is because the basic assumption of this model is that Task 1 response selection must be completed before Task 2 response selection can begin. At long SOAs, there is enough time to complete Task 1 response selection before Task 2 response selection begins, so there is no bottleneck. However, at short SOAs, Task 2 is presented before Task 1 response selection is complete, and this results in a delay before Task 2 response selection can begin. On the other hand, Task 1 performance typically is unaffected by SOA because response selection for this task is completed before that of Task 2, so there is no delay (Pashler, 1984; Lien and Proctor, 2002; Ruthruff et al., 2009).

The locus-of-slack logic is a common method used to determine which operations are subject to this central bottleneck (Schweickert, 1978). According to this logic, if the manipulated

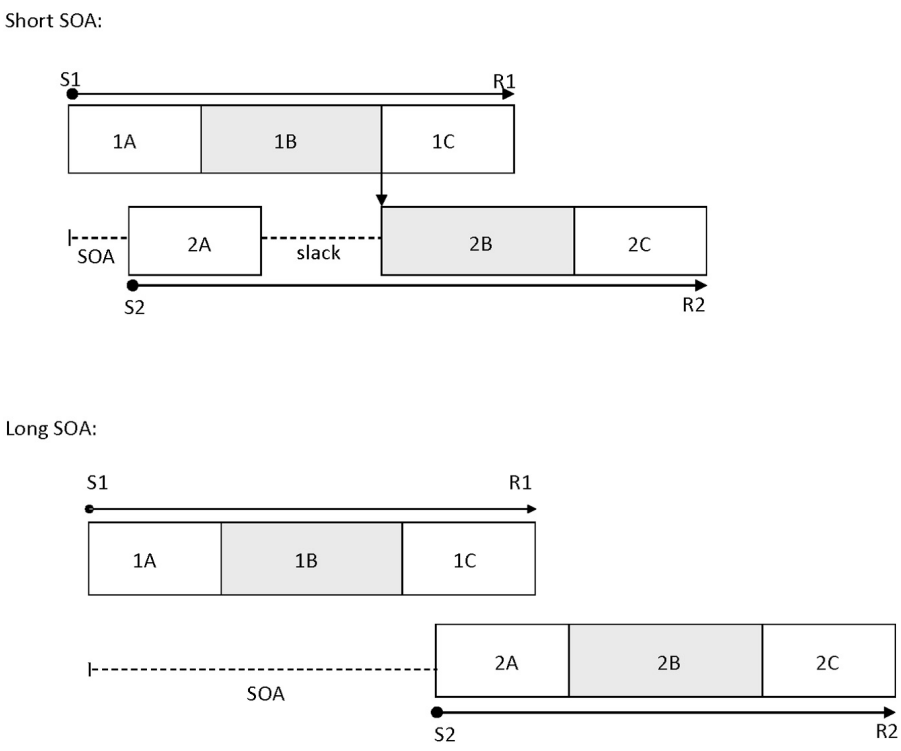

FIGURE 1 | The temporal relations between processing stages of Task 1 and Task 2 at a short SOA (top panel) and a long SOA (bottom panel) in the psychological refractory period paradigm, as suggested by the central bottleneck model. This model assumes that perceptual and response initiation/execution stages of Task 2 can operate in parallel with any stage of Task 1, but that central stages of Task 2 cannot start until central stages of Task 1 have been completed. 1A, 1B, and 1C are the perceptual, central, and response initiation/execution stages of Task 1, respectively. 2A, 2B, and 2C are the corresponding stages for Task 2. S1: stimulus for Task 1; S2: stimulus for Task 2; R1: response for Task 1; R2: response for Task 2; SOA: stimulus onset asynchrony.

Task 2 variable affects the stages prior to the bottleneck, then the effects of the Task 2 variable should be much smaller at short SOAs than at long SOAs, reflecting in an underadditive interaction between its effect and SOA (i.e., the slack effect). However, if the manipulated Task 2 variable affects the stages during or after the bottleneck, then the effects of the Task 2 variable will be additive with the SOA effect. A number of processes are indicated to be subject to the bottleneck, including response selection (Lien et al., 2002), word identification (Lien et al., 2008), memory encoding (Jolicoeur, 1998), mental rotation (Ruthruff et al., 1995), memory retrieval (Carrier and Pashler, 1995), and difficult perceptual judgments such as box-width judgment (Johnston and McCann, 2006). Due to the relatively wide variety of processes which are influenced by the bottleneck, the overall general resource attributed to all of them is commonly referred to as central attention (Johnston et al., 1995). However, some highly skilled tasks like word frequency effects in visual word recognition have been shown to exhibit slack effects (Allen et al., 2002; Lien et al., 2006).

Another (perhaps more direct) method of measuring parallel processing in the PRP paradigm was to use the ERP measure, which was applied by Shaw et al. (2011). Shaw et al. used a dual-task paradigm in which Task 1 involved two-choice tone discrimination (pure vs. fuzzy tones). For Task 2, one happy face and one angry face were presented adjacent to each other. This study had some similarities to the study of Tomasik et al. (2009) that used a behavioral version of this PRP paradigm and failed to observe slack effects for difficulty effects in emotional facial discrimination. That is, Tomasik et al. found additivity between emotional facial discrimination difficulty effects and SOA, suggesting that emotion perception was not automatic. However, the Shaw et al. study did not directly test for emotional discrimination and difficulty effects. Instead, their participants were asked to decide the gender (Experiment 1) or spatial location (Experiment 2) of a given facial emotion (emotion type was a between-subjects variable and facial emotion was easy to determine in Shaw et al.). The rationale for the Shaw et al. study was that behavioral measures of performance such as reaction time (RT) and accuracy might not be sensitive to early processing, but that electrophysiological-based ERP measures might be more sensitive to this early type of processing.

Shaw et al. (2011) used SOAs between Task 1 and Task 2 of 50, 200, and 1000 ms. They reasoned that if the shift of spatial attention to the targeted facial emotion (as indexed by the N2pc effect in ERPs) could occur without central attention resources, then N2pc effects linked to this face should not appreciably differ across SOA. That is, N2pc effects should be approximately constant across SOA. Alternatively, if this shift in spatial attention demands central attentional resources, then the N2pc effect should be delayed or attenuated at short SOAs (in an analogous manner to latencies from Task 2 being prolonged by 200–400 ms in the PRP effect). In contrast to this prediction, Shaw et al. observed statistically equivalent N2pc amplitudes at all three SOAs, with the effect elicited by angry faces being more pronounced than the effect elicited by happy faces, suggesting that emotion perception can be processed automatically (i.e., without central attention) for younger adults. Even though there was not an Emotion Type × SOA interaction in Shaw et al.'s study (suggesting a similar pattern for N2pc effects across SOA for both angry and happy faces), the N2pc amplitudes across all three SOAs were greater for angry faces than for happy faces—suggesting the attentional bias toward angry faces (also see Holmes et al., 2009a; but see Brosch et al., 2011). Different from Shaw et al. (2011), we examined directly emotion perception by asking participants to determine whether a single human face was "happy" or "angry". Also, we used the P1 component (Rotshtein et al., 2010) instead of the N2pc (Luck and Hillyard, 1994) component used by Shaw et al. to assess emotional perception during dual-task processing because the P1 component is thought to measure amygdalar modulation of visual perceptual responses to human faces that differ in emotional valance (Holmes et al., 2008, 2009a,b; Rotshtein et al., 2010) (in our case, the emotional valence effect). However, the same logic holds for the P1 component as the N2pc component—except that we were interested in whether participants can begin Task 2 response selection of a single emotional face before completing Task 1 (pure vs. fuzzy tone) response selection. Based upon Shaw et al. (who observed a much stronger N2pc effect for angry faces than for happy faces—see their Figures 2 and 3) we predict an attentional bias for angry faces, at least for younger adults.

EMOTIONAL PROCESSING IN THE BRAIN

Adaptive behavior tends to rely on fast recognition of cues from the environment to establish threat or safety, and one such cue is facial expression (Fitzgerald et al., 2006). Research has suggested that humans are particularly efficient at processing human emotional expressions (Vuilleumier, 2000, 2002; Frischen et al., 2008). Vuilleumier et al. (2001) and Anderson et al. (2003) both observed amygdalar responses to facial expressions that seemed to be independent of attentional modulation using fMRI methods. Also, as noted above, Shaw et al. (2011) found very early N2pc activation using ERP methods for emotional faces that almost certainly was a reflexive effect, and this suggests that these early emotional effects were modulated by the amygdala. Overall, then, these results provide strong evidence that the processing of facial emotional processing can have early effects on attention. However, in the following section we will develop a more thorough model that can account for apparent early reflexive, affective processes, and later cognitive processing involved in selective attention.

As noted earlier, there is accumulating evidence for an early, reflexive ventral affective system that is modulated by affective valences and a later, controlled-process dorsal attentional stream that is cognitive in nature (Corbetta et al., 2008; Dolcos et al., 2011). The ventral affective system includes the amygdala and VMPFC and is likely a "survival" system (Allen et al., 2008). This system is likely what is referred to as exogenous attention for emotional stimuli. This system monitors incoming sensory information for potential threat and can "disengage" existing cognitive attention toward an incoming perceptual threat if such a threat is encountered (and the same process could occur if incoming information with a positive emotional valence suggested available safety). For example, if an individual steps

out onto a crosswalk (directed by cognitive attention) and then automatically jumps back onto the sidewalk because exogenous attention has detected a rapidly approaching car that has run a red light, this would be an example of the ventral affective system (exogenous attention) "grabbing" attention away from endogenous cognitive attention. The dorsal attentional stream involves "endogenous" attention and is thought to be mediated by the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the frontoparietal attentional pathway (Corbetta et al., 2008; Dolcos et al., 2011).

The PRP paradigm allowed us to "peek into the black box" of attentional dynamics between these two systems. The most parsimonious interpretation of Shaw et al. (2011) results in which short SOAs resulted in the same amplitude N2pc effect as longer SOAs is that the ventral affective system was able to process Task 2 negative emotions in parallel with Task 1 response selection. In the present study, we predict that the same pattern of results in P1 effects will occur for younger adults, but that older adults will show attenuated P1 emotional valence effects due to a deficit in the ventral affective system. The rationale for this hypothesis will be further developed in the next section.

AN EMOTION PERCEPTION DEFICIT MODEL OF AGING

There have been many aging studies that examined behavioral and neuropsychological assessment tasks associated with ventral affective system function (Lamar and Resnick, 2004; Allen et al., 2005, 2011; Denburg et al., 2005; Baena et al., 2010). Also, Lamar et al. (2004) found fMRI evidence of an orbitofrontal cortex deficit for older adults (using a delayed match and nonmatch to sample paradigm), Fjell et al. (2009) found a drop in longitudinal MRI volume in healthy aging for the amygdala, and especially critical to the present study, St. Jacques et al. (2010) found impaired functional connectivity with the amygdala and visual cortical areas in older adults (relative to younger adults). Thus, past research has suggested multiple possibilities as to why older adults have less efficient emotional processing than younger adults. Some research has suggested that older adults may exhibit neural degeneration of the amygdala relative to younger adults (Leigland et al., 2004; Fjell et al., 2009) and that this results in different areas of the brain, such as the VMPFC, compensating for this loss. However, studies have also reported age-related decline in tasks associated with VMPFC function (Allen et al., 2005, 2011; Denburg et al., 2005; Baena et al., 2010; although see MacPherson et al., 2002). Indeed, Timpe et al. (2011) found that older adults with emotional decision-making deficits showed a reduction in white-matter intactness in the frontal cortex (relative to older adults without emotional decision-making deficits) as measured by diffusion tensor imaging. Thus, there are age-related deficits for either amygdalar processing or VMPFC processing, or both based on results from imaging and behavioral studies (e.g., Lamar et al., 2004; Allen et al., 2005, 2011; Denburg et al., 2005; Fjell et al., 2009; Baena et al., 2010; St. Jacques et al., 2010; Timpe et al., 2011). We hypothesize that these imaging and behavioral results are consistent with an *emotion perception deficit model* of aging. Specifically, it is proposed that older adults exhibit either structural of functional deficits that make it more difficult for the amygdala to modulate visual perception.

SOCIOEMOTIONAL SELECTIVITY THEORY

Carstensen et al. (1999) have proposed that older adults become more sensitive to positively valenced emotional stimuli because of social contexts and motivation. This model is termed Socioemotional Selectivity Theory (SST). These researchers postulated that this positive bias is due to the fact that seniors have less remaining life expectancy, so they tend to identify negative experiences as having less useful information, and, therefore, attribute more emphasis on positive affect (known as the "late positivity effect"). Some researchers have suggested that older adults become more efficient at behavioral regulation of physiological responses to emotional stimuli than do younger adults (Carstensen and Mikels, 2005; Mather and Carstensen, 2005). For example, Mather et al. (2004) reported that older adults had reduced fMRI amygdalar activation for negative pictures relative to younger adults (but not so for positive pictures). Also, LeClerc and Kensinger (2008) found greater fMRI activation in the VMPFC for positive emotional stimuli for older adults but for negative emotional stimuli for younger adults. The reason that SST is pertinent to the present study is because it predicts that older adults' positivity bias is the result of a later-life positivity bias accomplished through emotional regulation—rather than due to a neural deficit occurring earlier in the ventral affective system. The present study provides a mechanism to test the emotion perception deficit hypothesis of Allen et al. (2005) and the SST of Carstensen et al. (1999). This is because the two models make different predictions with regard to how P1 ERP amplitude will vary across younger and older adults using a PRP paradigm. The emotion perception deficit model predicts, in at least some older adults, that the ventral affective system declines and that these changes impair emotion perception and emotional decision making. Thus, this model predicts age differences in P1 amplitude for emotional facial discrimination. Specifically, younger adults should show larger P1 effects for angry faces than for happy faces (based on Holmes et al., 2008), but that older adults should show no emotional valence effects. In other words, it is predicted that younger adults will show emotional modulation of the P1 perceptual component, but that older adults will show just a perceptual response not modulated by emotional valence. Alternatively, the SST predicts that older adults experience a developmental change resulting in better emotional regulation so that negative emotions are inhibited allowing positive emotions to be more pronounced. Consequently, the SST predicts an attenuated effect for older adults for negative emotional faces but a stronger emotional response by older adults to positive emotional faces (e.g., Mather et al., 2004; LeClerc and Kensinger, 2008). Also, older adults should show higher P1 amplitudes for happy faces than for angry faces, whereas younger adults should show the opposite effect (LeClerc and Kensinger, 2008).

THE PRESENT STUDY

The P1 ERP component is the peak associated with an early visual perceptual response that can be modulated by emotional valence. Our basic model is illustrated in **Figure 2**. This model (based upon Allen et al., 2005, 2011; Holmes et al., 2008, 2009a,b; Baena et al., 2010; Rotshtein et al., 2010; Dolcos et al., 2011) includes a "posterior portion" as well as an "anterior portion." The posterior

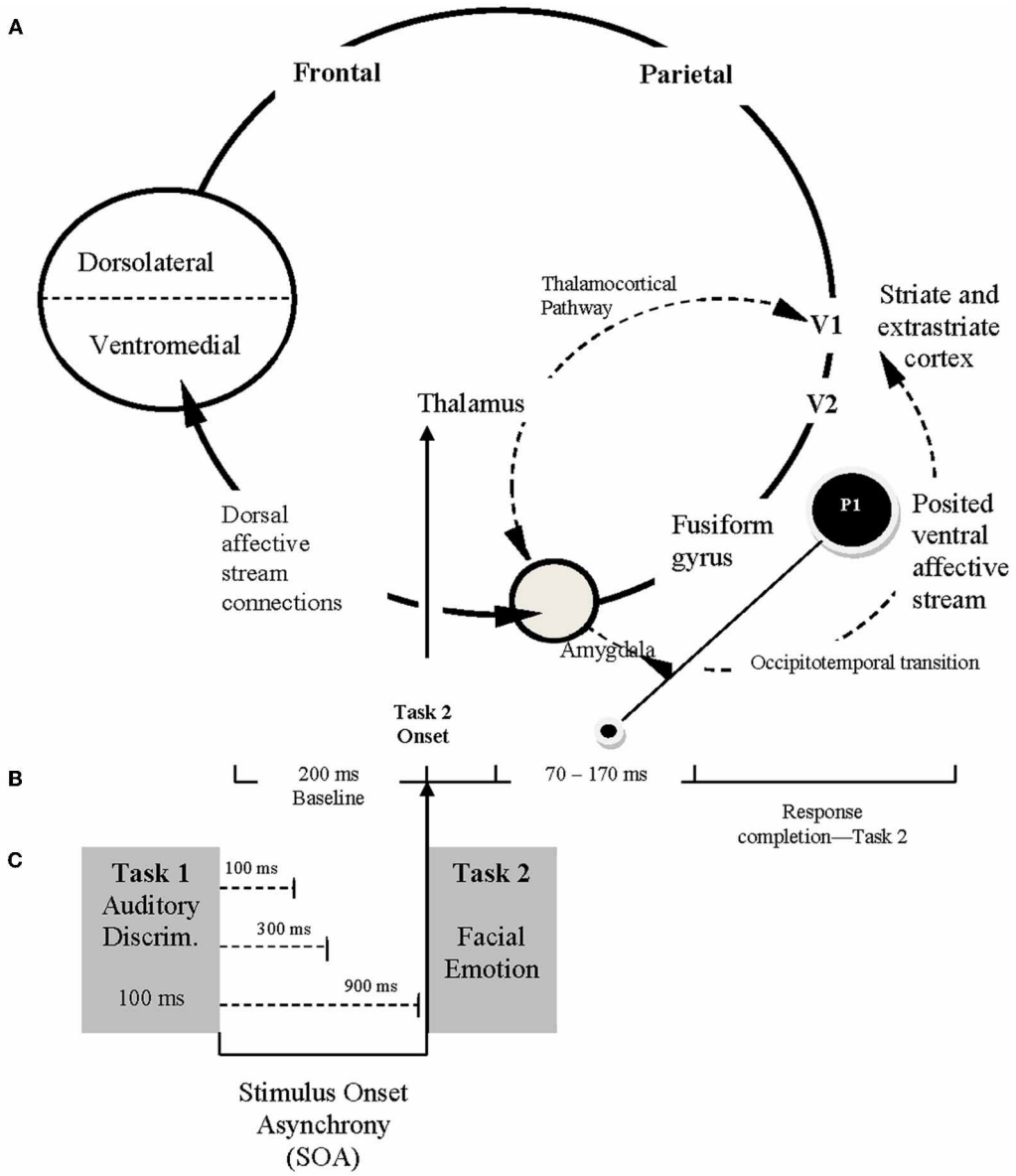

FIGURE 2 | Conceptual framework for ERP study. (A) The posited neural framework involved in processing facial emotion. The ventral affective stream (posterior system) involves reciprocal and neuromodulatory influences between the amygdala and extrastriate-fusiform gyrus network (occipitotemporal transition). The dorsal affective stream (anterior system), includes the amygdala and higher order interactions with prefrontal cortical regions (less emphasized in the current study). **(B)** Schematic illustration of the time course for ERP recordings, reflecting the 200 ms baseline captured prior to Task 2 presentation and the 70–170 ms period immediately after Task 2 presentation during which P1 is recorded (O1–O2 electrodes). **(C)** The sequence of Task 1 and Task 2 presentation, emphasizing the relationship among Task 2 onset (following a specific stimulus onset asynchrony [SOA]), the temporal framework for ERP recordings, and the capture of P1 from occipital O1 and O2 electrodes.

portion of the model includes the primary (V1) and secondary (V2) visual cortices, the fusiform gyrus (areas known to be closely associated with face perception), and the amygdala (the brain location most often associated with emotional arousal/activation, see **Figure 2A**). Conceptually, the anterior portion of the model includes the amygdala (the emotional "accelerator"), VMPFC (socioemotional control), and the dorsolateral prefrontal cortex (cognitive control). The present study is designed to examine the posterior portion of the model while largely attenuating (because of the 70–170 ms recording window of the P1) what is believed to be top-down feedback associated with the ventromedial and dorsolateral prefrontal cortex areas (i.e., the frontal portion) from biasing a more direct examination of amygdalar modulation of early visual perception (by using just an early ERP component).

The present ERP study with its emphasis on temporal precision can be used to replicate and extend the findings of fMRI study reported St. Jacques et al. (2010). Specifically, the present P1

ERP paradigm (refer to **Figure 2B**) allows a more temporally precise measure (the hemodynamic response in fMRI takes 2000 ms per stimulus to occur; Buckner, 1998) of their fMRI-based observation of an age deficit in functional connectivity between the amygdala and the bi-lateral visual cortex (our recording sites of O1 and O2 are located bi-laterally over the visual cortices). Our method also allows a distinction to be made between a perceptual deficit and what is posited to be an amygdalar modulation deficit. Evidence consistent with a perceptual deficit would be a main effect for age, and evidence consistent with an amygdalar modulation of visual perception would be an interaction involving age and emotion type (e.g., the logic used by Holmes et al., 2008, 2009a,b and Rotshtein et al., 2010). Note that we are assuming that early amygdalar activation is greater for negatively valanced emotional faces than positively valenced emotional faces, and this seems to be consistent with Holmes et al. (2008, 2009a,b)—who emphasized the importance of negatively valenced faces.

PREDICTIONS

There are two categories of predictions in the present study, conceptually embellished in **Figure 2**. First, if emotion perception can occur automatically (without central attention), then either RT or accuracy for Task 2 (facial emotion discrimination task) should show progressively smaller task difficulty effects as SOA decreases (an SOA × Difficulty interaction, refer to **Figures 1** and **2C**), or the P1 effect should remain constant across SOA (or the shortest SOA should show at least as high of P1 amplitude as the longest) (Shaw et al., 2011). If increased adult age moderates attentional effects, then the aforementioned effects should interact with age.

The second category of predictions concerns whether SST (e.g., Carstensen et al., 1999) or the emotion perception deficit model (Allen et al., 2005; Denburg et al., 2005) better fit the present behavioral and/or electrophysiological (P1) results. As noted above, SST predicts better performance for older adults on happy faces than on angry faces, but the reverse for younger adults (Mather et al., 2004; LeClerc and Kensinger, 2008). On the other hand, the emotion perception deficit model predicts that older adults are especially likely to show a performance deficit for angry faces (relative to younger adults), but similar performance to younger adults on happy faces (Baena et al., 2010). That is, younger adults should show a larger P1 effect for angry faces than for happy faces, but older adults should show similar P1 effects for both angry and happy faces.

METHOD

PARTICIPANTS

There were 14 younger adults (10 female) and 14 older adults (7 female) who participated in this study. Data from one older adult were excluded due to low accuracy (<80%). Thus, a total of 14 younger and 13 older adults were included in the final data analyses. Younger adults were undergraduates at Oregon State University who participated in exchange for extra course credit. Their mean age was 19 years (range: 18–23 years). Older adults were individuals who resided in nearby communities. They were paid $20 for their participation. Their mean age was 70 years (range: 61–85 years). All participants reported having normal or corrected-to-normal visual acuity. None reported having any cognitive, neurophysiological dysfunction.

APPARATUS AND STIMULI

Stimuli were presented on an IBM-compatible microcomputer connected to a 19-in. ViewSonic monitor and were viewed from a distance of about 55 cm. The Task-1 stimulus was a pure tone or white noise (22 kHz, 8 bits, and 100 ms duration) and was presented via speakers on both sides of the computer monitor. The Task-2 stimuli contained one picture in the center of the screen, which subtended a visual angel of 6.23° (width) × 8.79° (height). There were 40 pictures with different actors (four categories: 10 male/angry, 10 male/happy, 10 female/angry, and 10 female/happy) taken from Tottenham et al. (2009). Within each category, the emotion expression was easy to determine for half of the faces (the easy condition) and was difficult to determine for the other half of the faces (the difficult condition; see Tomasik et al., 2009, for details). Each face was presented 30 times (excluding practice trials) per participant. For both tasks, manual responses were collected using a response box containing five buttons labeled 1–5 from left to right.

DESIGN AND PROCEDURE

Each trial started with the presentation of the fixation display for 800 ms. The Task-1 auditory stimulus then sounded for 100 ms. After one of three SOAs (100, 300, or 900 ms) randomized within blocks, the Task-2 picture appeared in the center until the participant responded.

For Task 1, participants were asked to press the button labeled "1" with their left-middle finger for a pure tone and press the button labeled "2" with their left-index finger for a white noise (similar to a hissing sound). For Task 2, participants were instructed to respond to the emotion expression of the face. They were asked to press the button labeled "4" with their right-index finger for angry faces and press the button labeled "5" with their right-middle finger for happy faces. They were asked to respond to Task 1 and Task 2 quickly and accurately. Also, they were asked to respond to Task 1 before Task 2. Immediately after a response was recorded, the next trial began with the 800-ms fixation display.

Participants performed one practice block of 24 trials, followed by 15 experimental blocks of 80 trials each (a total of 1200 experimental trials). After each block, participants received a summary of their mean RT and accuracy for that block and were encouraged to take a break.

EEG RECORDING AND ANALYSES

The EEG activity was recorded using Q-cap AgCl electrodes from F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2, T7, T8, P7, P8, PO7, and PO8. These sites and the right mastoid were recorded in relation to a reference electrode at the left mastoid. The ERP waveforms were then re-referenced offline to the average of the left and right mastoids (see Luck, 2005). The horizontal electrooculogram (HEOG) was recorded bipolarly from electrodes at the outer canthi of both eyes, and the vertical electrooculogram (VEOG) was recorded from electrodes above and below the midpoint of the left eye. Electrode impedance was kept below 5 kΩ. EEG, HEOG, and VEOG were amplified using Synamps2 (Neuroscan) with a gain

of 2,000 and a bandpass of 0.1–50 Hz. The amplified signals were digitized at 500 Hz.

Trials with possible ocular artifacts were identified in two steps (see also Lien et al., 2008). First, trials with ocular artifacts were rejected automatically using a threshold of ± 75 μV for a 1400 ms epoch beginning 200 ms before Task-2 stimulus onset to 1200 ms after Task-2 stimulus onset. Next, each of these candidate artifact trials was inspected manually. Rejection of trials with ocular artifacts in the EEG data led to the elimination of 5% of trials, but no more than 19% for any individual participant.

To quantify the overall magnitude of the P1 effect, we focused on the time window 70–170 ms after Task-2 stimulus onset. Specifically, the P1 effect was measured as the mean amplitude during this time window for electrode sites O1 and O2, relative to the mean amplitude during a 200-ms baseline period prior to Task-2 stimulus onset.

RESULTS

In addition to trials with ocular artifacts, we excluded trials from the final analyses of behavioral data (RT and proportion of errors; PE) and EEG data if RT for Task 1 (RT1) or Task 2 (RT2) was less than 100 ms or greater than 3000 ms (0.7% of trials for younger adults and 0.5% of trials for older adults). Trials were also excluded from RT and EEG analyses if either response was incorrect. Analysis of variance (ANOVA) was used for all statistical analyses (see below for details), with an alpha level of 0.05 to ascertain statistical significance. The *p*-values were adjusted using the Greenhouse-Geisser epsilon correction for nonsphericity, where appropriate.

BEHAVIORAL DATA ANALYSES

Data were analyzed as a function of age group (younger vs. older adults), Task 2 difficulty (easy: an extreme version of an emotional face vs. difficult: a morphed face that was in between a given emotional expression and neutral), Task 2 emotion (angry vs. happy), and SOA (100, 300, or 900 ms). Age group was a between-subject variable, whereas others were within-subject variables. **Tables 1** and **2** show mean RT and PE for Task 1 and Task 2, respectively.

For Task 1, RT1 decreased as SOA increased, $F_{(2,\ 50)} = 8.46$, $p < 0.001$, $\eta_p^2 = 0.25$ (see **Figure 3**). This decrease was more pronounced for older adults than younger adults, $F_{(2,\ 50)} = 6.48$, $p < 0.01$, $\eta_p^2 = 0.21$. Mean RT1 was 9 ms slower when Task 2 was an angry face (668 ms) than when it was a happy face (659 ms), $F_{(1,\ 25)} = 4.47$, $p < 0.05$, $\eta_p^2 = 0.15$. The three-way interaction between age, Task 2 emotion, and SOA was significant, $F_{(2,\ 50)} = 3.80$, $p < 0.05$, $\eta_p^2 = 0.13$. Older adults exhibited longer RT1 at short SOAs when Task 2 was an angry face than a happy face (difference in RT1 = 25, 18, and −10 ms at the 100, 300, and 900 ms SOAs, respectively), whereas no consistent pattern was observed for younger adults (difference in RT1 = 3, −8, and 11 ms at the 100, 300, and 900 ms SOAs, respectively).

Task 1 PE (PE1) decreased as SOA increased, $F_{(2,\ 50)} = 24.10$, $p < 0.0001$, $\eta_p^2 = 0.49$. In contrast to RT, this decrease was more pronounced for younger adults than older adults, $F_{(2,\ 50)} = 9.04$, $p < 0.001$, $\eta_p^2 = 0.27$. No other effects were significant.

For Task 2, the overall RT2 was longer for older adults (RT2 = 1019 ms) than younger adults (RT2 = 814 ms), $F_{(1,\ 25)} = 15.08$, $p < 0.001$, $\eta_p^2 = 0.38$. A large PRP effect of 439 ms on RT2 was observed, $F_{(2,\ 50)} = 451.73$, $p < 0.0001$, $\eta_p^2 = 0.95$. The PRP effect was larger for older adults (503 ms) than younger adults (379 ms), $F_{(2,\ 50)} = 9.73$, $p < 0.001$, $\eta_p^2 = 0.28$. RT2 was 47 ms longer in the difficult condition (940 ms) than in the easy condition (893 ms), $F_{(1,\ 25)} = 100.46$, $p < 0.0001$, $\eta_p^2 = 0.80$ (see **Figure 3**). The difficulty effect was larger for older adults

Table 1 | Mean response time (RT in ms) and proportion of errors (PE) for Task 1 as a function of age group (younger vs. older), Task-2 difficulty (easy vs. difficult), Task 2 emotion (angry vs. happy), and stimulus onset asynchrony (100, 300, and 900 ms).

	Stimulus onset asynchrony					
	100 ms		300 ms		900 ms	
	RT	PE	RT	PE	RT	PE
YOUNGER						
Easy						
Angry	655(37)	0.072(0.016)	624(30)	0.038(0.011)	643(44)	0.028(0.009)
Happy	655(39)	0.053(0.012)	639(33)	0.030(0.009)	638(44)	0.027(0.008)
Difficult						
Angry	652(40)	0.059(0.014)	629(34)	0.039(0.012)	652(44)	0.025(0.010)
Happy	647(35)	0.053(0.013)	631(41)	0.039(0.011)	636(41)	0.026(0.008)
OLDER						
Easy						
Angry	770(47)	0.024(0.008)	702(54)	0.019(0.005)	622(33)	0.018(0.008)
Happy	736(40)	0.031(0.007)	694(46)	0.021(0.005)	639(42)	0.016(0.004)
Difficult						
Angry	746(44)	0.026(0.007)	708(45)	0.018(0.007)	621(34)	0.018(0.008)
Happy	731(45)	0.019(0.006)	679(44)	0.018(0.006)	623(36)	0.017(0.005)

Note: The standard error of the mean is shown in parentheses.

Table 2 | Mean response time (RT in ms) and proportion of errors (PE) for Task 2 as a function of age group (younger vs. older), Task-2 difficulty (easy vs. difficult), Task 2 emotion (angry vs. happy), and stimulus onset asynchrony (100, 300, and 900 ms).

	Stimulus onset asynchrony					
	100 ms		300 ms		900 ms	
	RT	PE	RT	PE	RT	PE
YOUNGER						
Easy						
Angry	966(47)	0.063(0.020)	771(36)	0.061(0.027)	588(23)	0.050(0.015)
Happy	1016(53)	0.110(0.016)	828(47)	0.099(0.023)	623(27)	0.092(0.023)
Difficult						
Angry	1004(51)	0.079(0.022)	790(42)	0.076(0.020)	632(28)	0.070(0.017)
Happy	1039(50)	0.149(0.028)	843(53)	0.121(0.037)	665(34)	0.124(0.026)
OLDER						
Easy						
Angry	1249(46)	0.023(0.005)	998(49)	0.032(0.006)	731(22)	0.029(0.005)
Happy	1223(34)	0.058(0.016)	1006(47)	0.039(0.010)	28(28)	0.039(0.010)
Difficult						
Angry	1295(38)	0.096(0.025)	1082(44)	0.092(0.025)	818(21)	0.115(0.032)
Happy	1285(44)	0.057(0.016)	1051(46)	0.056(0.011)	775(32)	0.037(0.012)

Note: The standard error of the mean is shown in parentheses.

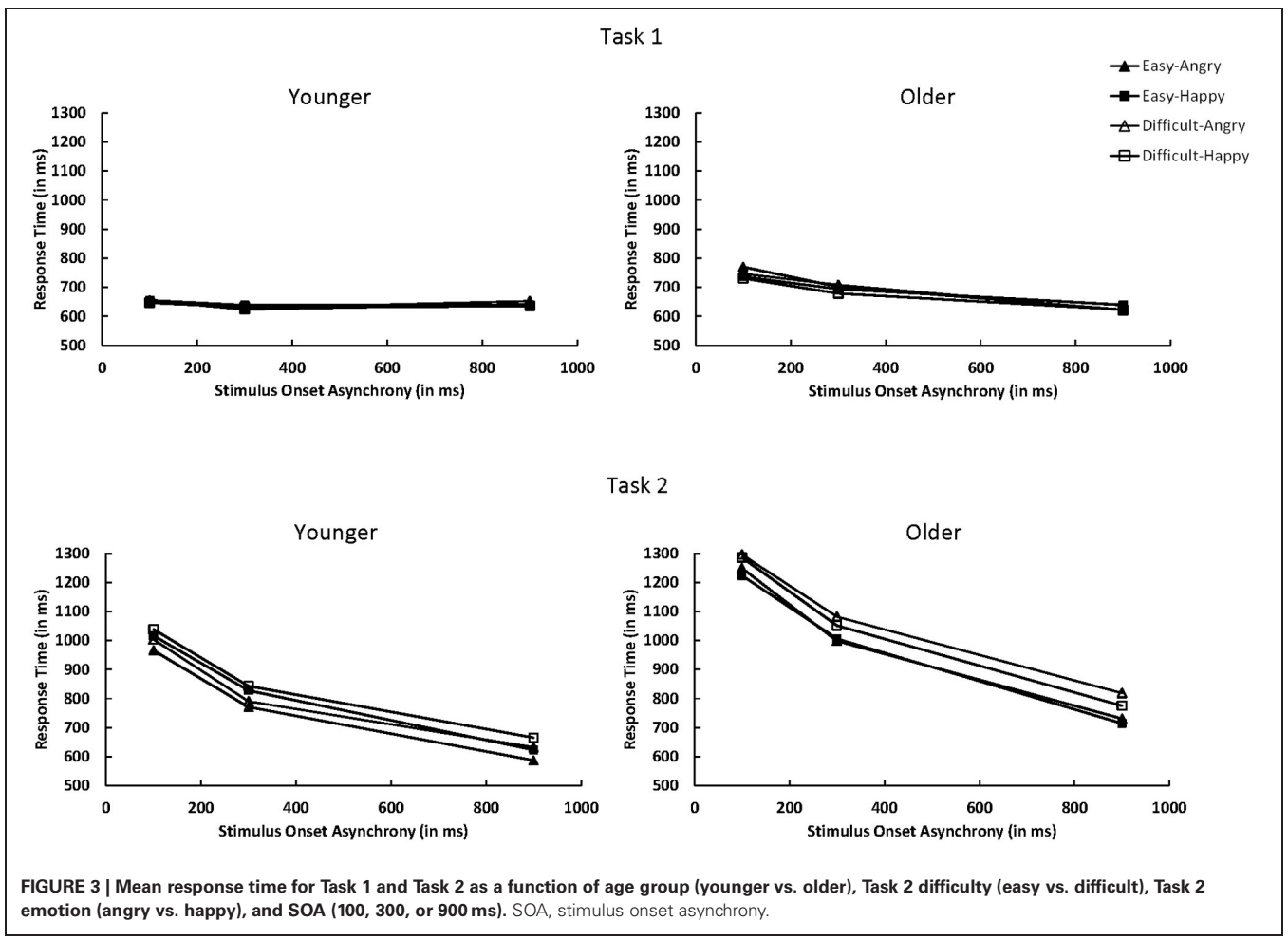

FIGURE 3 | Mean response time for Task 1 and Task 2 as a function of age group (younger vs. older), Task 2 difficulty (easy vs. difficult), Task 2 emotion (angry vs. happy), and SOA (100, 300, or 900 ms). SOA, stimulus onset asynchrony.

(64 ms) than younger adults (30 ms), $F_{(1, 25)} = 13.13$, $p < 0.01$, $\eta_p^2 = 0.34$. Older adults had longer RT2 for angry faces than happy faces (1029 ms vs. 1009 ms), whereas younger adults had longer RT2 for happy faces than angry faces (836 ms vs. 792 ms), $F_{(1, 25)} = 13.00$, $p < 0.01$, $\eta_p^2 = 0.34$.

As in Tomasik et al. (2009) study, the interaction of Task 2 difficulty and SOA on RT2 was not significant, $F_{(2, 50)} = 2.22$, $p = 0.1195$, $\eta_p^2 = 0.08$; the difficulty effect was 42, 41, and 59 ms at 100, 300, and 900 ms SOAs, respectively. However, there was a trend toward underadditivity because the difficulty effect was reduced by 17 ms. The additivity between Task 2 difficulty and SOA was similar for younger and older adults, $F < 1.0$. For younger adults, the difficulty effect was 30, 17, and 44 ms at the 100, 300, and 900 ms SOAs, respectively. For older adults, the effect was 54, 65, and 74 ms at the 100, 300, and 900 ms SOAs, respectively.

Task 2 PE (PE2) was 0.032 higher for the difficult condition than for the easy condition, $F_{(1, 25)} = 28.10$, $p < 0.0001$, $\eta_p^2 = 0.53$. As in RT2, older adults had higher PE2 for angry faces (0.065) than happy faces (0.048), whereas younger adults showed an opposite pattern (0.116 for happy faces and 0.067 for angry faces), $F_{(1, 25)} = 6.35$, $p < 0.05$, $\eta_p^2 = 0.20$. The three-way interaction between age group, Task 2 difficulty, and Task 2 emotion was significant, $F_{(1, 25)} = 6.07$, $p < 0.05$, $\eta_p^2 = 0.10$. For older adults, higher PE2 for angry faces than happy faces was evident in the Task 2 difficult condition (0.101 vs. 0.050, respectively) but not in the easy condition (0.028 vs. 0.045). For younger adults, higher PE2 for happy faces than angry faces was evident in both the easy condition (0.100 vs. 0.058) and the difficult condition (0.131 vs. 0.075). No other effects were significant.

ERP ANALYSES

The P1 data analyses focused on the time window of 70–170 ms after Task-2 stimulus onset (Rotshtein et al., 2010, used 100–150 ms, but we slightly extended this to 70–170 ms, see **Figure 2B**). The P1 data were analyzed as a function of age group (younger vs. older adults), Task 2 difficulty (easy vs. difficult), Task 2 emotion (angry vs. happy), hemifield (left [O1 electrode] vs. right [O2 electrode]), and SOA (100, 300, or 900 ms). **Figure 4** shows these P1 effects averaged across the electrodes O1 and O2. For each participant, there were a total of 1200 experimental trials. With the variables of SOA (3 levels), Task 2 Difficult (2 levels), and Task 2 Emotion (2 levels), there were a total of 100 observed trials for each SOA before trials that fell outside our RT cutoff or showed ocular artifacts were rejected.

The overall P1 effect was larger at the 300 ms SOA (5.357 μV) than at the 100 ms SOA (3.240 μV) or the 900 ms SOA (0.812 μV), $F_{(2, 50)} = 54.15$, $p < 0.0001$, $\eta_p^2 = 0.68$. This interpretation of the main effect was confirmed by post-hoc pairwise tests—300 ms vs. 100 ms, $F_{(1, 25)} = 27.25$, $p < 0.0001$; 300 ms vs. 900 ms, $F_{(1, 25)} = 89.65$, $p < 0.0001$; 100 ms vs. 900 ms, $F_{(1, 25)} = 32.61$, $p < 0.0001$. The interaction between Task 2 difficulty and Task 2 emotion was significant, $F_{(1, 25)} = 4.48$, $p < 0.05$, $\eta_p^2 = 0.15$; Angry faces elicited a larger P1 effect than happy faces in the easy condition (3.218 μV vs. 2.909 μV, respectively) but a similar P1 in the difficult condition (3.160 μV vs. 3.203 μV, respectively). This pattern was further qualified by a Group × Difficulty × Emotion interaction, $F_{(1, 25)} = 6.65$, $p < 0.05$, $\eta_p^2 = 0.21$ (younger adults: easy: angry = 3.67 μV, happy = 3.08 μV, difficult: angry = 3.45 μV, happy = 3.64 μV; older adults: easy: angry = 2.77 μV, happy = 2.74 μV, difficult: angry = 2.87 μV, happy = 2.77 μV).

To interpret this three-way interaction, we ran separate simple effects analyses by Task 2 difficulty. For easy trials, the Group × Emotion interaction was significant, $F_{(1, 25)} = 4.67$, $p < 0.05$, so younger adults did show a larger emotion effect than older adults. For difficult trials, though, the Group × Emotion interaction was not significant, $F_{(1, 25)} = 2.10$, $p = 0.16$. To clarify the Group × Emotion simple effect for easy trials, we ran separate analyses across age group. For younger adults, there was a simple effect of emotion, $F_{(1, 13)} = 5.13$, $p < 0.05$ (angry = 3.67 μV, happy = 3.08 μV), but the simple effect for emotion was not significant for older adults ($p = 0.77$) (angry = 2.77 μV, happy = 2.74 μV). This means that younger adults showed significantly higher amplitude P1 components for angry faces than for happy faces, but that there was no difference in emotional valance for older adults.

There was also a Difficulty × Hemifield interaction, $F_{(1, 25)} = 10.16$, $p < 0.01$, $\eta_p^2 = 0.29$. This interaction occurred because for the left hemifield (the electrode O1), difficult trials showed higher amplitudes (3.355 μV) than easy trials (3.092 μV), but for the right hemifield (the electrode O2), easy (3.284 μV) and difficult (3.308 μV) trials showed similar amplitudes. No other effects reached statistical significance. Finally, because our prediction was that older adults should be especially likely to show lower amplitudes at the 100 ms SOA than at longer SOAs, and we did observe a Group × SOA interaction that approached significance, $F_{(1, 25)} = 2.37$, $p = 0.11$, we analyzed the data separately by SOA. We observed simple effect of age that approached significance at the 100 ms SOA, $F_{(1, 25)} = 3.47$, $p = 0.07$ (younger = 4.20 μV, older = 2.82 μV), but not at the 300 ms SOA ($p = 0.41$) (younger = 5.88 μV, older = 4.84 μV) or the 900 ms SOA ($p = 0.55$) (younger = 0.67 μV, older = 1.07 μV).

DISCUSSION

The present study provided both ERP evidence for age-related sparing of attentional capacity (i.e., automatic processing) and for an age-related deficit in the processing of angry faces on trials with more pronounced emotional expressions (i.e., "easy" trials—in contrast to trials with faces with less pronounced emotional expressions, or "difficult" trials—these stimuli were closer to neutral). That is, younger adults showed significantly higher P1 amplitude for angry, easy trials than for happy easy trials, but older adults showed almost identical P1 amplitudes for both angry and happy easy trials. These ERPs results, then, replicate the results of St. Jacques et al. (2010) who used fMRI methods and observed a functional connection deficit for older adults (in the circuit connecting the top–down feedback loop from the amygdala to the early visual processing areas (primary and secondary cortices). On the other hand, we observed typical behavioral effects for a PRP task. We will first discuss the behavioral results and then the ERP data.

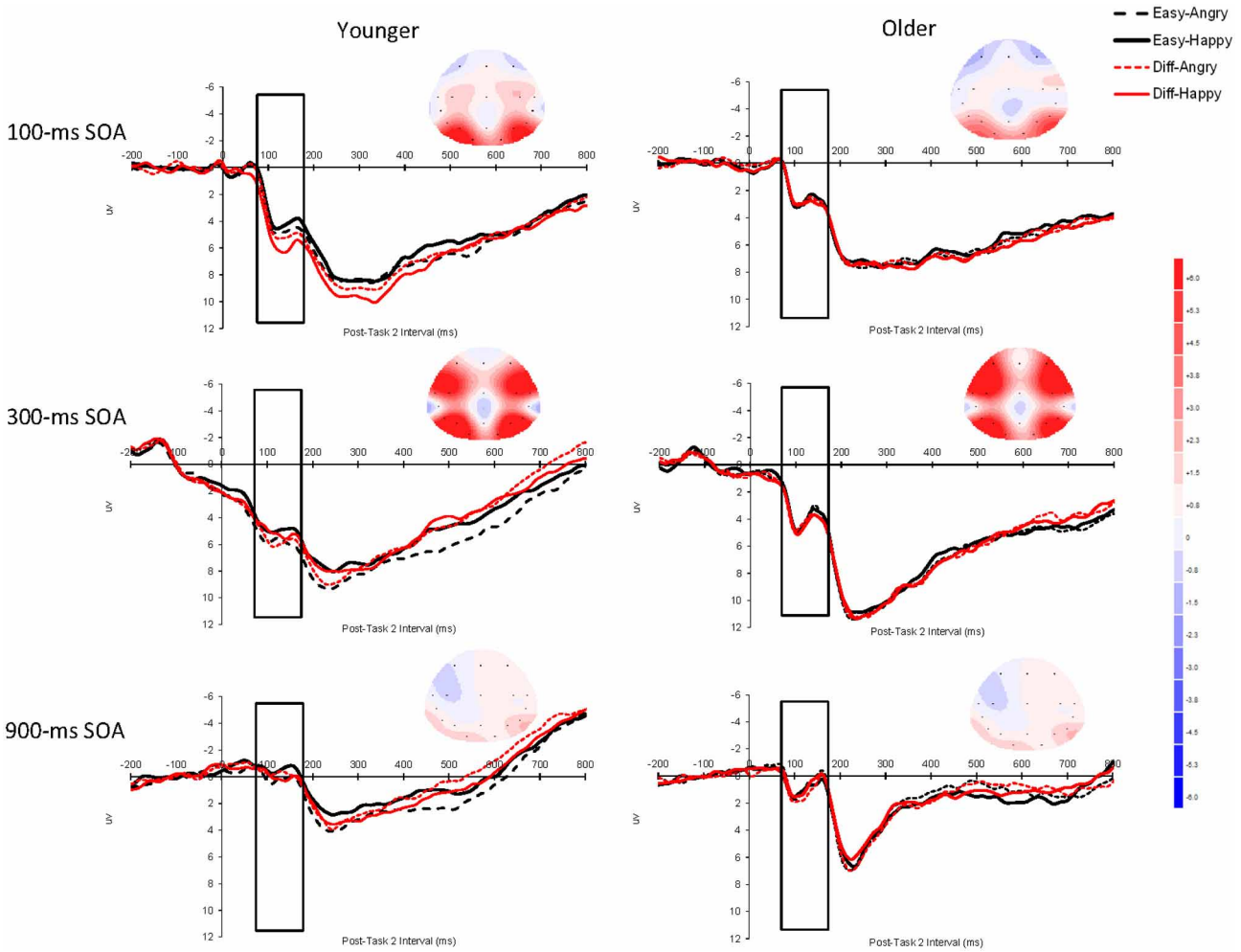

FIGURE 4 | Grand average event-related brain potentials (ERPs) for P1 elicited by Task 2 as a function of Task 2 difficulty (easy vs. difficult), Task 2 emotion (angry vs. happy), and SOA (100, 300, or 900 ms) for younger adults and older adults averaged across the electrodes O1 and O2. The unfilled rectangular boxes indicate the time window used to assess P1 (70–170 ms after Task-2 stimulus onset). The scalp topography of the ERPs was obtained during the time window 70–170 ms after Task 2 stimulus onset for each SOA. The baseline period was the 200 ms prior to Task-2 stimulus onset. Negative is plotted upward and time zero represents Task-2 stimulus onset. SOA: stimulus onset asynchrony.

BEHAVIORAL FINDINGS

For Task 2, both age groups showed PRP effects for RT2, although older adults showed larger PRP effects than did younger adults. PRP effects are thought to measure the delay in access to Task 2 response selection while individuals are completing processing on Task 1 response selection at short SOAs (Pashler, 1984). Thus, the larger PRP effect for older adults than younger adults reflects the central bottleneck to be larger for older adults than for younger adults, which is quite common (e.g., Allen et al., 2002, 2009; Lien et al., 2006). Another finding from the RT2 data was that older adults were faster in responding to happy than to angry faces, but younger adults were faster in responding to angry than to happy faces. This is a slight departure from earlier studies on single-task, facial emotional discrimination such as Baena et al. (2010) who observed that both age groups showed faster responses to happy faces than to angry faces, but that the effect was more exaggerated for older adults. Finally for Task 2, we observed additivity for RT2 between SOA and task difficulty, with a trend toward underadditivity—a result that replicated Tomasik et al. (2009). This is tempered behavioral evidence that processing stage before response selection for Task 2 emotions cannot be processed in parallel with response selection for Task 1 tones (because of the trend toward underadditivity). However, the trend toward underadditivity for RT along with similar P1 amplitudes at short and long SOAs do suggest that information for Task 1 and Task 2 can be processing simultaneously. Also, behavioral indices of performance may be controlled by later dorsal attentional stream processes, and it may not be possible to eliminate the structural bottleneck when both tasks must be processed with the dorsal attentional stream.

For RT1, there was a backward correspondence effect (Lien and Proctor, 2000). That is, RT1 was affected by Task 2 emotion type (RT1 was slower if Task 2 involved an angry face compared to a happy face). Backward correspondence effects are considered to

be evidence of parallel processing (Lien and Proctor, 2000). The slight increase in RT1 as SOA decreased was offset by the reverse effect for Task 1 errors. Thus, there appeared to be no appreciable effect for SOA on Task 1.

ERP FINDINGS

As noted in the Introduction, Shaw et al. (2011) found that the N2pc effect (a measure of spatial attention) was not modulated by SOA (and all amplitudes were significantly higher than zero). Also, these investigators found a stronger effect for angry faces than for happy faces (although this was a between-subjects effect). This was interpreted by Shaw et al. of evidence of automatic emotional processing. In the present study, we used the P1 component because of evidence of its association to amygdalar activation in epilepsy patients (Rotshtein et al., 2010). The PRP logic for whether central attention is required for Task 2 emotion perception, though, is the same for both Shaw et al. (N2pc) and the present study (P1). The present Task 2 still involved faces with different emotions and we used three different SOAs between Task 1 and Task 2, except the present study tested both younger and older adults (the Shaw et al. study presented two adjacent faces and asked participants to make a gender discrimination of a given emotion type, or the location discrimination of a given emotion type rather than directly making an emotional discrimination). In the present study, the amplitude for the 100 ms SOA was significantly higher than the amplitude from the 900 ms SOA. This finding suggests that participants were apparently able to process emotional faces at the 100 ms SOA. This leaves two unresolved issues, though. First, why was the amplitude for the 300 ms SOA higher than the amplitude for the 100 ms SOA? One possibility is that automaticity is graded (Pessoa et al., 2002). That is, perhaps at the 100 ms SOA individuals have enough amygdalar activation to carry out facial discrimination, but that at the 300 ms SOA there is an even stronger level of amygdalar activation. However, this graded interpretation is complicated by the fact that the P1 effect was significantly larger at the 100 ms SOA than the 900 ms SOA. Finally, and probably most perplexing, why was the P1 effect so small at the 900 ms SOA? An understanding of this drop in the P1 effect at 900 ms SOA relative to 100 ms and 300 ms SOAs will take additional empirical work to interpret, although we did observe clear evidence of Task 2 P1 effects at a short SOA (100 ms) that are consistent with the idea that individuals can process Task 2 stimuli simultaneously with the processing of Task 1 information for certain tasks (also see Shaw et al., 2011).

Another important issue to consider is why the behavioral data showed just a trend toward underadditivity (evidence for automatic emotion perception), but the ERP data showed stronger evidence consistent with emotion perception without central attention. As noted in Shaw et al. (2011), ERP components may be more sensitive than behavioral measures because they are a more direct measure of early emotional processing. We believe that this finding provides additional evidence of the efficacy of using ERPs to study attention and perception. These results are similar to those observed by Shafer et al. (2012). These investigators also observed evidence of both automatic emotional processing and non-automatic emotional processing in the same study (using fMRI methods).

It is important to note that the present P1 data cannot be easily accounted for by anything other than an emotional effect because emotion type interacted with age group and task difficulty. One might be concerned with the possibility that something like an early perceptual effect for Task 2 or even Task 1 modulation was driving the P1 effect. However, early perceptual effects for Task 2 were constant across different stimuli—the only thing that varied was emotion type. Also, Task 1 was a non-emotional task (pure vs. fuzzy tones). Thus, it is unclear how Task 1 could have modulated emotion type effects in Task 2.

THEORIES OF AGING AND EMOTION PERCEPTION

As noted earlier, there are different theories of aging and emotion regulation. Clearly the most widely studied theory is the SST of Carstensen et al. (1999). This model proposes that older adults change their emotional regulation system to emphasize positive emotions and inhibit negative emotions. The present behavioral data seem to be partially consistent with this idea. Namely, younger adults processed angry faces faster than happy faces, but older adults showed the reverse effect. This is essentially the same pattern of results observed by Mather et al. (2004) and LeClerc and Kensinger (2008) using an fMRI paradigm. Thus, one possibility is that younger adults are maximally sensitive to the threat perception aspects of negatively valenced emotional stimuli (e.g., Allen et al., 2008), but that older adults are better able to block out negatively valenced stimuli (this would likely reflect an example of greater VMPFC executive control on the part of older adults). However, the electrophysiological ERP data from the present study showed a much more complicated picture of the processing dynamics of emotional facial discrimination. In particular, older adults showed no difference in P1 amplitude for happy and angry faces, but younger adults observed the more typical pattern of significantly larger P1 amplitude for angry faces than for happy faces on easy trials (e.g., see Holmes et al., 2008, 2009a,b). If older adults were better at emotional regulation such that positive emotional content was able to pass through the system more efficiently than negative emotional content, then one would predict higher-amplitude P1 effects for happy than for angry faces. One possibility is that the emotional regulation observed by Mather et al. (2004) and LeClerc and Kensinger (2008) occurs after the time period measured by the present P1 ERP component. Indeed, this view is consistent with Mather and Carstensen (2005) who claim an emotional regulation locus rather than an emotional arousal/activation locus of older adults' late positivity effect.

Another finding was that older adults, in general, showed a trend toward lower P1 amplitudes—especially at the 100 ms SOA ($p < 0.07$). These results seem to be more consistent with a more general drop in perceptual object activation in older adults (both in angry and happy faces). However, it is important to note that this trend toward a sensory deficit on the part of older adults cannot explain the emotional valance age difference observed for more pronounced emotional expressions (i.e., the Age Group × Difficulty × Emotion Type interaction).

ARE THERE AGE DIFFERENCES IN AMYGDALAR PROCESSING?

The present observation of emotional valence modulation of the P1 perceptual ERP effect for younger adults but not for older adults is consistent with the notion that younger adults exhibit amygdalar modulation of the visual cortices, but that older adults do not (see Rotshtein et al., 2010). This evidence is consistent with the fMRI functional connectivity results of St. Jacques et al. (2010) in which older adults appeared to exhibit a functional connectivity deficit in this circuit between the amygdala and the visual cortices. It is also consistent with the amygdalar volumetric loss for older adults that Fjell et al. (2009) observed using longitudinal methods. However, this view is not necessarily consistent with the meta-analysis results of Nashiro et al. (2012). Nachiro et al. reviewed the fMRI literature and failed to find evidence of an appreciable amygdalar decline with increased adult age. As illustrated in **Figure 2**, though, the amygdala is part of multiple systems involved in emotional processing. It can directly act on incoming stimulus information (the posterior portion of our model illustrated in **Figure 2**—emotional arousal/activation) as well as receiving top–down feedback from the prefrontal mechanism (the anterior portion of the model typically referred to as emotional regulation). Because the hemodynamic response used in fMRI takes 2 s to develop per stimulus (Buckner, 1998), fMRI research is likely measuring the amygdalar activation involving the top-down modulation by prefrontal mechanisms (the anterior portion of **Figure 2**) instead of the arousal of the amygdala by the visual cortices, and interactive modulation of the visual cortices by the amygdala that occurs in less than 200 ms (Cornwell et al., 2008; also see the anterior portion of **Figure 2**). Thus, it will take additional research on this topic to clarify the precise time course of potential age differences in amygdalar function. However, there is now DTI tractography evidence that the neural circuit connecting the amygdala with the fusiform gyrus and the visual cortices is the inferior longitudinal fasciculous (ILF) (Catani et al., 2003). Thus, this functional connectivity age difference observed by St. Jacques et al. (2010) and the differential modulation of emotional valence on visual perception across age observed on the P1 data in the present study could be a white-matter integrity deficit in the ILF neural pathway more than a deficit in amygdalar function, *per se*.

GRADED CAPACITY SHARING AND RECRUITMENT

Another possible explanation of the present results is that Task 1 and Task 2 share processing resources (a graded capacity-sharing model). This sort of model would predict that the brain would recruit additional resources at shorter SOAs (when central attention would need to process both Task 1 and Task 2) relative to the longest SOA (900 ms—when Task 1 response selection would be completed before Task 2 was presented). Older adults tend to show more neural recruitment (as measured by PET scanning) than younger adults on some tasks (Grady et al., 1995, 1996; Cabeza et al., 1997; Madden et al., 1999), and this has been taken as evidence that older adults attempt to compensate for less efficient processing by recruiting more neurons. A recruitment model would seem to predict higher amplitudes at the 100 ms SOA than the 300 ms or 900 ms SOAs, and that older adults should show higher amplitudes than younger adults. While this interpretation is theoretically intriguing (because of the aging research on neural recruitment), the present P1 amplitudes for the 300 ms SOA were significantly higher than for the 100 ms SOA. Also, older adults did not exhibit higher P1 amplitudes than younger adults. However, without this disconfirming evidence, one might have claimed that perhaps the P1 component was really showing the attentional capacity allocated to Task 2 rather than to an emotional response (but see Holmes et al., 2008, 2009a,b). Overall, though, it does not appear that the present results are consistent with the attentional capacity (rather than emotional activation) interpretation.

GENERAL SENSORY VISUAL DEFICITS

One potential interpretation of the present results is that older adults simply experienced a general sensory deficit. Indeed, Lindenberger and Baltes (1994) and Baltes and Lindenberger (1997) proposed a "common cause" model of aging in which a general/common sensory deficit mediated all age differences in cognition. However, other studies have provided both cross-sectional (e.g., Allen et al., 2001) and longitudinal (e.g., Anstey et al., 2001) evidence that there is unique age-related variance that cannot be accounted for by a common factor. Even though a precise test of this issue requires mediational analyses rather than the moderation analyzes afforded by ANOVA, the present Age Group × Difficulty × Emotion Type interaction does not appear to be consistent with a common-cause interpretation. First, a general sensory decrement in the visual cortices would have no mechanism to respond to emotional valance (the Nim Stim faces are equated on perceptual difficulty). This would seemingly require that the amygdala modulate visual cortex activation levels differentially across emotion type (e.g., Holmes et al., 2008, 2009a,b; Rotshtein et al., 2010). In particular, the finding that younger adults responded differentially to angry and happy less-distorted faces, but that older adults showed similar activation levels for both emotion types suggests that amygdalar modulation of the visual cortex occurred in the present study.

LIMITATIONS AND FUTURE RESEARCH

The main limitation of the present research is a lack of generalization and replication. For example, does one observe this age deficit for negatively valenced stimuli that are faces, or would it generalize to other familiar perceptual objects (e.g., snakes vs. a mother holding her baby compared to angry vs. happy faces)? Future research that extends the P1 effect to other types of stimuli is needed. The work of Holmes et al. (2008, 2009a,b) does suggest that a similar pattern of results is obtained when one compares non-anxious and anxious participants (instead of younger and older adults), but it will still be important to replicate and extend the present age effects.

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Impact of negative emotion on the neural correlates of long-term recognition in younger and older adults

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Some studies have suggested that the memory advantage for negative emotional information over neutral information ("negativity effect") is reduced in aging. Besides the fact that most findings are based on immediate retrieval, the neural underpinnings of long-term emotional memory in aging have so far not been investigated. To address these issues, we assessed recognition of neutral and negative scenes after 1- and 3-week retention intervals in younger and older adults using functional magnetic resonance imaging. We further used an event-related design in order to disentangle successful, false, and true recognition. This study revealed four key findings: (1) increased retention interval induced an increased rate of false recognitions for negative scenes, canceling out the negativity effect (present for hit rates only) on discrimination in both younger and older adults; (2) in younger, but not older, adults, reduced activity of the medial temporal lobe was observed over time for neutral scenes, but not for negative scenes, where stable or increased activity was seen; (3) engagement of amygdala (AMG) was observed in older adults after a 3-week delay during successful recognition of negative scenes (hits vs. misses) in comparison with neutral scenes, which may indicate engagement of automatic processes, but engagement of ventrolateral prefrontal cortex was unrelated to AMG activity and performance; and (4) after 3 weeks, but not after 1 week, true recognition of negative scenes was characterized by more activity in left hippocampus and lateral occipito-temporal regions (hits vs. false alarms). As these regions are known to be related to consolidation mechanisms, the observed pattern may indicate the presence of delayed consolidation of true memories. Nonetheless, older adults' low performance in discrimination of negative scenes could reflect the fact that overall, after long delays of retention, they rely more on general information rather than on perceptual detail in making recognition judgments.

Keywords: aging, amygdala, emotion, episodic memory, hippocampus, long-term memory, prefrontal cortex, recognition

INTRODUCTION

Emotion is closely linked to memory because of its importance for survival (e.g., remembering that a previously experienced situation was life-threatening). Hence, negative emotions may enhance memory retrieval and be resistant to forgetting (Weymar et al., 2011). Numerous studies have demonstrated better recognition of negative compared to neutral information in young adults (Kensinger, 2007). This effect may partly reflect reduced forgetting via enhanced consolidation mechanisms (LaBar and Phelps, 1998; Sharot and Phelps, 2004; Sharot and Yonelinas, 2008; Pierce and Kensinger, 2011). This "negativity effect" has been linked to engagement of the amygdala (AMG) in association with the hippocampus (HC) during processing of emotional information, notably at encoding (see Murty et al., 2010; Sabatinelli et al., 2011, for meta-analyses, and Dolcos et al., 2012 for a recent review). Fewer studies have investigated the neural underpinnings of emotional retrieval, especially after long retention intervals. Yet, these studies showed specific or more AMG activity during retrieval of emotional compared to neutral information, for retention intervals between 5 min and 1 year (Dolan et al., 2000; Dolcos et al., 2005; Kensinger and Schacter, 2005, 2007; Keightley et al., 2011).

Socioemotional selectivity theory postulates increased emotion regulation with advancing adult age. This assertion is based on the perception of remaining lifetime driving motivations and goals (e.g., Carstensen et al., 1999). Some research reveals a "positivity effect," where positive events are enhanced and therefore better remembered, along with a reduced "negativity effect," where negative events are more likely to be forgotten in older adults (Charles et al., 2003; Mather and Carstensen, 2005; Mather, 2008, 2012; Spaniol et al., 2008; Reed and Carstensen, 2012). However, while findings regarding the positivity effect converge toward a preservation of this effect in aging, results concerning the negativity effect are mixed, as several studies show a memory advantage of negative over neutral information also in older adults (Kensinger et al., 2002; Denburg et al., 2003; Otani et al., 2007; Murty et al., 2009; Gavazzeni et al., 2012). To our knowledge, only Waring and Kensinger (2009) have tested the effect of retention interval on

emotional memory in aging. Despite a general age-related decrease in recognition accuracy, both younger and older adults demonstrated similar memory enhancement for positive and negative scenes. Moreover, this effect was most pronounced for the longest retention interval (1 day vs. a few minutes), suggesting preserved consolidation mechanisms for emotional informating in aging, at least over 1 day of retention.

Relatively little is known about how the brain processes emotional information in old age (see also Ebner et al., 2012; Pollock et al., 2012). In the following, we review findings from four studies. In all of them, older participants showed a negativity effect, inconsistent with the Socioemotional selectivity theory. Both St Jacques et al. (2009b) and Kensinger and Schacter (2008) showed that AMG was engaged in both younger and older adults during successful encoding of negative pictures. In St Jacques et al., a hemispheric age-related difference was observed: there was greater activity in left AMG in the younger group, and greater activity in right AMG in the older group. By contrast, Fischer et al. (2010) reported age-related differences in brain activity during successful encoding of fearful faces: more AMG and HC activity was found in the younger group, and more activity in the right prefrontal cortex (PFC) was observed in the older group. Murty et al. (2009) scanned younger and older adults during emotional retrieval. Similar to Fischer et al. (2010), the young exhibited more AMG activity, whereas the old showed more PFC activity. Overall, the emerging pattern from these studies is an age-related reduction of AMG activity coupled with increased PFC activity during encoding and retrieval of emotional information. Some authors have interpreted this shift in patterns of activity as compensatory (Murty et al., 2009), and others have argued that it reflects increased regulation of emotional processes with age-related differences in AMG-PFC functional connectivity (for review, see St Jacques et al., 2009a). However, these interpretations are based on encoding data mostly, while Murty et al.'s encoding-retrieval study was a blocked design, showing therefore sustained rather than transient brain activity, the latter allowing to investigate *successful* retrieval. Moreover, in the aforementioned studies, the retrieval session took place from 2 to 45 min after the encoding session, precluding conclusions about neural substrates of long-term emotional memory in aging. Hence, in the present study we sought to uncover transient neural activity during emotional long-term retrieval in aging.

Fischer et al. (2010) noted an important feature of aging effects on recognition memory, namely the tendency to produce more false recognitions of negative emotional items among older adults. Emotionality may result in more false alarms (FA), because of greater semantic cohesiveness of emotional items (e.g., emotional items tend to belong to semantic categories in which instances share more features than for neutral items; Maratos et al., 2000; Marchewka et al., 2008). In this case, individuals may base their recognition decision on general characteristics, or in other words on familiarity processes. Conversely, others have argued that emotionality may reduce false memories, because emotion increases item distinctiveness (Kensinger and Corkin, 2004; for review, see Kensinger, 2012). In this case, recognition would be based on recollection mechanisms (e.g., recognition of specific features of the items). Thus, findings are mixed and the studies in question used short retention intervals. In a study of younger adults, Howe et al. (2010) found a significant increase of false recognitions for negative, but not for neutral, items from immediate to 1-week retrieval. Older adults tend to rely more on familiarity than on recollection in making recognition judgments (Bastin and van der Linden, 2003; Howard et al., 2006; Prull et al., 2006), which is known to increase false recognitions. Thus, the increase of false recognitions of negative items over time observed by Howe et al. in young adults may be exacerbated in older age, which may contribute to a reduced negativity effect in true recognition (discrimination) after long retention intervals.

In this study, younger and older adults underwent functional Magnetic Resonance Imaging (fMRI) during recognition of negative and neutral scenes at three occasions over 3 weeks. Here, we present behavioral and neural findings associated with recognition of negative and neutral scenes after 1 and 3 weeks of retention in relation to age. We were particularly interested in uncovering the effect of retention interval on the effect of negative emotion on memory in the presence of lures. The elaboration of an event-related fMRI design allowed us to study brain activity associated with successful, false, and true recognition.

MATERIALS AND METHODS

PARTICIPANTS

Twenty younger and 20 older adults, all right-handed, were recruited. No subject reported any previous or current psychiatric, neurological or medical disease, and none was taking psychoactive medication or abused any substances. They were paid 1,500 SEK for their participation. The study was approved and conducted in accordance with guidelines established by the regional ethics committee, and written consent was obtained from all participants prior to the start of the study. All subjects initially underwent a cognitive battery. Their performance indicated that they were representative of their age cohorts, with typical negative age differences in fluid cognitive tasks along with no age differences in crystallized cognitive tasks. Because of misunderstanding of the MRI task ($n = 2$), technical issues ($n = 1$), MR findings ($n = 1$), or too few events to be analyzed in the fMRI data ($n = 2$), 19 young and 15 old subjects were retained for analyses. Their characteristics and cognitive scores are shown in **Table 1**.

GENERAL PROCEDURE

The emotional memory task took place at three time points. At Session 1 (S1), subjects underwent intentional encoding of the material and immediate recognition. One week later, they came back and underwent the second recognition session (S2). Three weeks after S1 they undertook the third recognition session (S3). Subjects were scanned at all retrieval sessions (**Figure 1**).

MATERIALS AND TASKS

The task was displayed by means of E-prime (Psychology Software Tools Inc., Pittsburgh, PA, USA) using an IBM ThinkPad 390 computer (IBM, San Jose, CA, USA). The pictures were projected onto a screen in the scanner room using a Philips Hoper HG 20 Impact LCD projector (Philips Corp., Eindhoven, The Netherlands), positioned approximately 3 m in front of the scanner. Stimuli were

Table 1 | Participant characteristics.

	Young	Old	*t*-Tests
Number of participants (women)	19 (9)	15 (7)	
Age	25 ± 3.0	68.3 ± 2.6	
Age range	20–30	65–71	
Years of education	15.8 ± 1.8	14.2 ± 3.6*	$p = 0.11$
Vocabulary (synonym task, max = 30)	24.7 ± 2.9	26.4 ± 2.6	$p = 0.09$
Associative memory (verbal paired associates)			
Strong associates (max = 18)	16 ± 2.1	15.3 ± 1.9	$p = 0.35$
Weak associates (max = 18)	13.1 ± 3.8	7.7 ± 3.4	$p < 0.001$
Free recall (max = 16)	10.6 ± 2.7	6.6 ± 2.3	$p < 0.001$
Verbal fluency			
Category (fruits + clothes)	34.8 ± 6.7	34.5 ± 7.2	$p = 0.89$
Letter (A + F)	31.5 ± 10.9	30.1 ± 5.0	$p = 0.63$
Perceptual speed			
Figure comparison (max = 30)	21.7 ± 2.4	15.1 ± 2.9	$p < 0.001$
Letter comparison (max = 20)	9.9 ± 2.9	7.2 ± 3.3	$p = 0.02$
Working memory *n*-back			
2-Back (max = 10)	9 ± 0.8	6.6 ± 2.1	$p < 0.001$
3-Back (max = 9)	6.8 ± 1.1	4.4 ± 2.5	$p < 0.001$

*Mean ± SD; *one missing value.*

presented via a mirror system, which was placed on top of the head coil 2–5 cm from the subjects' eyes.

The material consisted of 450 pictures selected from the International Affective Picture System (IAPS, Lang et al., 2008). At encoding, 150 neutral and 150 negative pictures were presented, together with 90 null events (three black crosses on a white background with button press). Subjects were told to memorize the scenes for later retrieval, and to rate the valence of the pictures as neutral or negative. Fifty pictures of each type (neutral, negative) were shown as targets at each recognition session together with 25 lures of each type and 45 null events. The three types of events (targets, lures, null events) were inter-mixed. The order of events was identical for all subjects in order to control for between-person order effects. The pictures were presented during 3.5 s each, and were separated by a cross (on a white background) that lasted for 2–3 s. Participants responded by button presses to indicate whether or not pictures were shown during encoding (yes/no recognition). Overall, negative scenes were more arousing than neutral scenes, and these two categories (negative, neutral) also differed according to the living/non-living dimension. Importantly, within each emotional category of items, the sets of scenes did not differ on valence, arousal, and living/non-living dimensions across sessions of retrieval (no main effect of session and no interaction between emotion and session on valence, arousal, and living/non-living dimensions). Although lures were more arousing than targets, this should not have had any effect on findings as this factor did not interact with emotion or session of retrieval (**Table A1** in Appendix). The material was distributed and balanced across the retrieval sessions to reach the aforementioned criteria according to normative data and results from a pilot study.

NEUROIMAGING

The study was carried out on a GE 1.5 T MRI scanner using an eight-channel head coil. For the event-related functional scanning, an EPI (echo planar imaging) sequence was used with the following parameters: Repetition time (TR) = 2,500 ms (32 axial slices acquired in an interleaved order), echo time (TE) = 40 ms, flip angle = 90°, field of view (FOV) = 22 cm, slice thickness = 4.5 mm, in-plane resolution = 3.4 mm × 3.4 mm, interslice spacing = 0.5 mm. To avoid signals arising from progressive saturation, four dummy scans were performed prior to image acquisition. Each recognition task (S1, S2, and S3) was run within one session of 19.5 min, resulting in 482 EPI volumes per session. Structural T1-weighted images were also collected with the following parameters: TR = 24 ms (124 coronal slices acquired), TE = 6 ms, flip angle = 35°, FOV = 22 cm, slice thickness = 1.5 mm, in-plane resolution = 0.86 mm × 0.86 mm, no gap.

ANALYSES

Behavioral data

Hits (H) and FA were calculated following the procedure described by Snodgrass and Corwin (1988), where a correction was applied by adding +0.5 to H (and FA) and +1 to the number of targets (and lures), e.g., $H = (N \text{ hits} + 0.5)/(N \text{ targets} + 1)$. Discrimination was calculated by subtracting FA from H. Analyses of variance were conducted on Hits, FA, and Discrimination with the factors Age (Younger, Older), Session (S1, S2, S3), and Emotion (Neutral, Negative).

Neuroimaging data

SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London)[1] implemented in Matlab 7.13 (Mathworks, Inc., MA, USA) was used to analyze the imaging data.

Preprocessing. The structural T1 images were aligned to the standard MNI template (Montreal Neurological Institute) and voxel-based morphometry was run using the VBM8 toolbox of SPM8 (with DARTEL spatial normalization, Ashburner, 2007), using the default parameters. The normalized gray matter (GM) images were used for volumetric assessment (see Results and HC and AMG Age-Related Atrophy). Furthermore, a binary GM mask was built for use as an explicit mask in the fMRI analyses: using the ImCalc function of SPM, an average GM image was created from the individual normalized GM images of all participants, and this image was transformed into a binary mask. We also built two group-specific GM masks for within-group analyses (younger, older).

The fMRI dataset was preprocessed using the following steps: first correction for differences in slice timing was applied within each EPI volume (the middle slice was the reference slice), then the images were spatially realigned (the mean EPI image created by SPM was co-registered to the corresponding T1 image, and all volumes were realigned to the mean EPI image) and unwarped. The images were then spatially normalized to the MNI template, resampled to a voxel size of 2 mm^3, and smoothed with an 8-mm full-width at half-maximum Gaussian filter kernel.

[1] http://www.fil.ion.ucl.ac.uk/spm

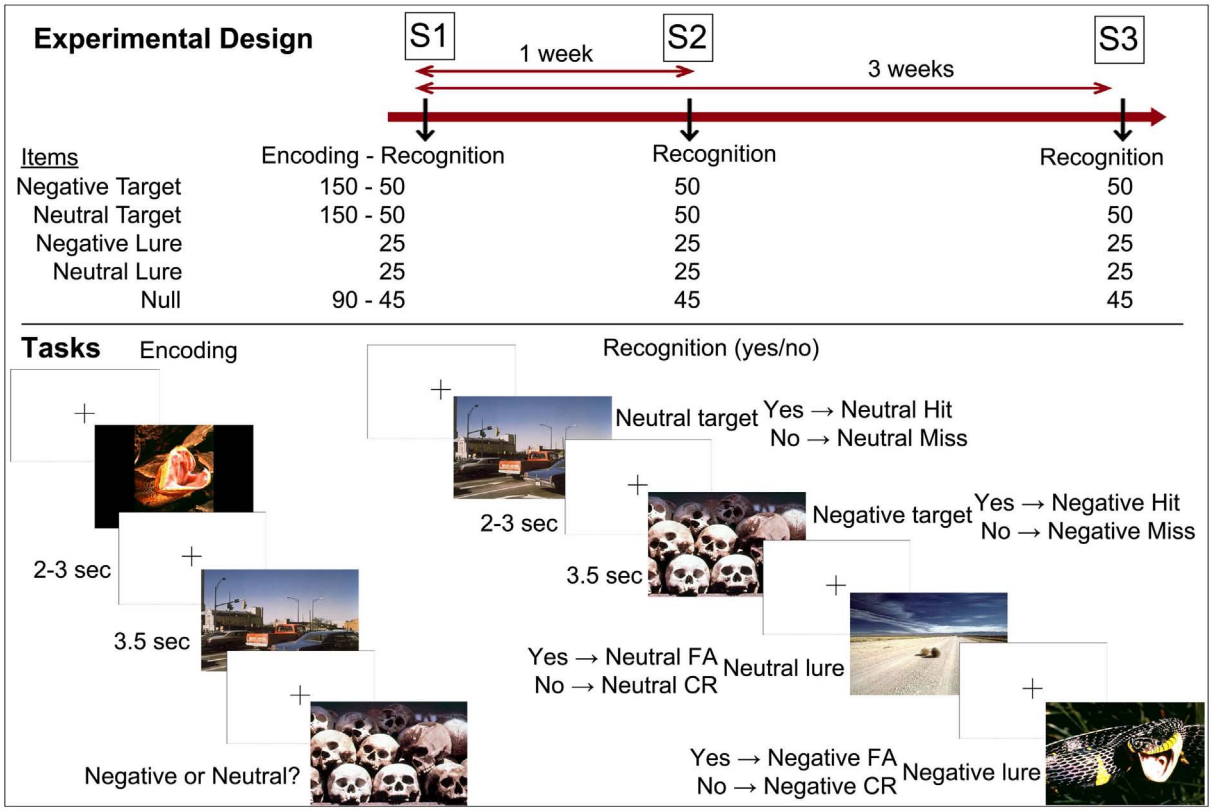

FIGURE 1 | Experimental design and tasks. Notes: S1 (Session 1) = immediate recognition; S2 (Session 2) = 1-week delay recognition; S3 (Session 3) = 3-week delay recognition. CR, correct rejection; FA, false alarm.

Statistics. For the fMRI data, single-subject contrasts were set up using the general linear model and group data were analyzed with a random-effects model. All models were convolved with a canonical hemodynamic response function as implemented in SPM. Ten regressors were constructed in order to capture the variance of all events (see bottom panel of **Figure 1**, showing the eight regressors of interest, to which two other regressors were added: baseline and no responses). All events were modeled as delta functions. Covariates of no interest included the six realignment parameters to further account for signal-changes related to inadvertent head motion. Subject analyses were run separately for each retrieval session.

At the group level, statistical parametric maps were generated voxel by voxel using factorial designs. The contrast of interest used to assess brain areas whose activity was related to successful recognition was "H − Misses (M)." The data of Session 1 were not analyzed because of too few M; therefore only the data of S2 and S3 were used in this study. Although the design of the study contains three factors, we conducted separate factorial designs with two factors each as follows: (1) two within-age-group ANOVAs were conducted with the factors Session (S2, S3) and Emotion (Neutral, Negative); (2) two within-session ANOVAs were conducted with the factors Age (Younger, Older) and Emotion (Neutral, Negative); and (3) two within-emotional-valence ANOVAs were conducted with the factors Session (S2, S3) and Age (Younger, Older). This decision was based on the fact that contrasts that do not span all conditions (or cells) at the second-level analyses are not recommended in multifactorial designs. For instance, if the three-way ANOVA was carried out and the interaction of interest (e.g., Emotion × Session) lied within the younger but not the older group, the sphericity assumption (i.e., pooled variance across all factors) may not be fulfilled. Hence, conducting two-way ANOVAs allowed testing all potential interactions without ruling out the sphericity assumption.

Brain areas related to false recognitions were assessed in the older group and only for negative items at S2 and S3. This restriction to the older group and to negative items was due to the number of events: Too few events of this type occurred in the younger group and overall in the neutral condition, precluding meaningful analyses. One older adult produced only four FA at S2 but we decided to keep this subject in the analyses (his presence did not alter the pattern of findings and he was not an outlier at the neuroimaging level). To fathom the neural basis of false recognition of negative scenes, we computed *t*-tests using the contrasts FA vs. correct rejections (CR) and H vs. FA separately for S2 and S3. Therefore, we distinguished the terms "successful recognition" and "true recognition." Successful recognition was assessed with the contrast "H vs. M," regardless of the cognitive processes or confidence with which the subjects made their recognition decision. At the cognitive level, this contrast corresponds to Hits only.

True recognition was assessed with the contrast "H vs. FA"; given the proportion of FA especially in the older adults for the negative items (see Results), it is likely that many negative Hit responses were made based on the same processes or confidence as for negative FA – thus, removing FA-related brain activity from Hit-related activity may show brain areas whose activity was related to true recognition. At the cognitive level, this contrast corresponds to discrimination.

At the voxel level, we used an uncorrected threshold of $p < 0.001$ (cluster threshold $k > 20$ contiguous voxels). For the *a priori* HC (left, right) and AMG (left, right) regions of interest (ROIs) we used a threshold of $p < 0.0125$ (i.e., $p < 0.05$ corrected for four ROIs, and $k > 20$). ROIs were taken from the WFU Pickatlas (Maldjian et al., 2003) and the AAL atlas (Tzourio-Mazoyer et al., 2002). Contrast values as displayed on the graphs were extracted from the clusters of interest (over all voxels of the given clusters) using the eigenvariate tool in SPM.

RESULTS

BEHAVIORAL DATA

Hits

As shown in **Figure 2**, no main effect of Age was found ($F < 1$). A reduction in hits from S1 through S3 was observed over age groups ($F = 191.5$, $p < 0.001$). An interaction between Age and Session ($F = 10.0$, $p < 0.001$) indicated that at S1 the younger adults produced more hits than the older adults ($F = 31.3$, $p < 0.001$), whereas no difference was found at S2 and S3 ($F < 1$ and $F = 1.9$, $p = 0.17$, respectively). Overall, higher recognition of negative scenes in comparison with neutral scenes was found ($F = 16.9$, $p < 0.001$), and there was no significant interaction between Emotion and Age ($F < 1$). There was a significant interaction effect between Session and Emotion ($F = 18.9$, $p < 0.001$): The negativity effect was significant at S2 and S3 ($F = 6.2$, $p = 0.02$ and $F = 42.2$, $p < 0.001$, respectively), but not at S1 ($F < 1$).

False alarms

The older group produced more FA than the younger group ($F = 22.9$, $p < 0.001$), and the overall proportion of FA increased over time ($F = 8.0$, $p < 0.001$), more so between S1 and S2 ($F = 7.2$, $p = 0.01$), the difference between S2 and S3 was not significant ($p = 0.15$). No significant interaction between Age and Session was observed ($F < 1$). More negative than neutral FA were produced ($F = 71.7$, $p < 0.001$). The interaction effect between Age and Emotion ($F = 23.7$, $p < 0.001$) indicated that this effect was more pronounced in the older group (Older: $F = 79.6$, $p < 0.001$; Younger: $F = 7.3$, $p = 0.01$). The significant interaction between Session and Emotion ($F = 18.9$, $p < 0.001$) reflected no increase of neutral FA over the three sessions (Fs < 1), but a significant increase of negative FA from S1 to S2 ($F = 15.9$, $p < 0.001$; S2–S3: $p = 0.15$). The three-way interaction was not significant ($p = 0.21$). These results are displayed in **Figure 2**.

Discrimination (hits − false alarms)

Taking FA into account had a significant impact on the main age effect and the negativity effect described above for hits (**Figure 2**). First, overall discrimination was higher in the younger than in the older group ($F = 22.5$, $p < 0.001$). Discrimination decreased over the three sessions ($F = 243.6$, $p < 0.001$), and the interaction between Age and Session ($F = 6.6$, $p = 0.002$) indicated significantly higher discrimination in the younger compared to the older group at S1 and S2 ($F = 40.6$, $p < 0.001$ and $F = 14.1$, $p < 0.001$, respectively), but not at S3 ($F = 1.9$, $p = 0.17$). Discrimination was higher for neutral compared to negative scenes ($F = 6.6$, $p = 0.002$). However, the significant interaction between Age and Emotion ($F = 17$, $p < 0.001$) indicated that the superiority of discrimination of neutral over negative scenes was only significant in the older group (Older: $F = 20.2$, $p < 0.001$; Younger: $F = 1.3$, $p = 0.26$). Also, linear forgetting was seen in the younger group over time for both neutral and negative scenes. Although the three-way interaction was at trend level ($F = 2.4$, $p = 0.10$), we performed follow-up tests that indicated that, in the older group, the discrimination advantage of neutral over negative scenes was significant at S1 and S2 but not at S3 (S1: $F = 10.4$, $p = 0.003$; S2: $F = 19$, $p < 0.001$; S3: $F = 2.3$, $p = 0.14$). Moreover, higher discrimination of neutral scenes in the younger compared to the older group was significant only at S1 ($F = 13.9$, $p < 0.001$), and discrimination was significantly higher in the younger group for negative scenes at S1 and S2 ($F = 55.7$, $p < 0.001$ and $F = 31.9$, $p < 0.001$, respectively), but only at trend level at S3 ($F = 3.3$, $p = 0.08$).

Over the three ANOVAs, assessment of power of the significant effects was performed, as the sample size was quite small. Considering 0.80 as the cut-off, all significant main effects and interactions were above this threshold ($0.90 <$ power < 1) except the main effect of emotion for discrimination (neutral > negative) where the power was of 0.71.

In summary, taking into account false recognitions, which greatly increased over time for negative scenes, canceled out the negativity effect that was seen for hits in both the younger and older groups, this effect being more pronounced in the old. Contrary to our prediction, no negativity effect was observed for discrimination in the two age groups.

NEUROIMAGING RESULTS

Successful long-term retrieval by age group

Hits vs. misses. As shown in **Figure 3A** (see also **Table A2** in Appendix), in the younger group, successful recognition was characterized by strong left PFC activity (ventro- and dorso-lateral) as well as activity in left lateral parietal cortex and right cerebellum. Significant activity linked to successful recognition in the young was also detected in bilateral HC and AMG. In the older group, the strongest activity for this contrast was located in posterior areas such as precuneus, posterior cingulate, and retrosplenial cortex, lateral parietal and occipito-temporal areas, as well as cerebellum. A smaller cluster located in left ventrolateral PFC (VLPFC) also showed significant activity. Bilateral HC was also significantly more activated for H than for M.

Session. In the younger group, the strongest session difference was found in occipital areas and striatum, with more activity at S2 than at S3. HC and right AMG were also more activated at S2 in comparison with S3 in the young (**Figure 3A**; **Table A2** in Appendix). In the older group, no effect of session was found.

Emotion. In the younger group, left lateral PFC was more activated in the negative condition in comparison with the neutral

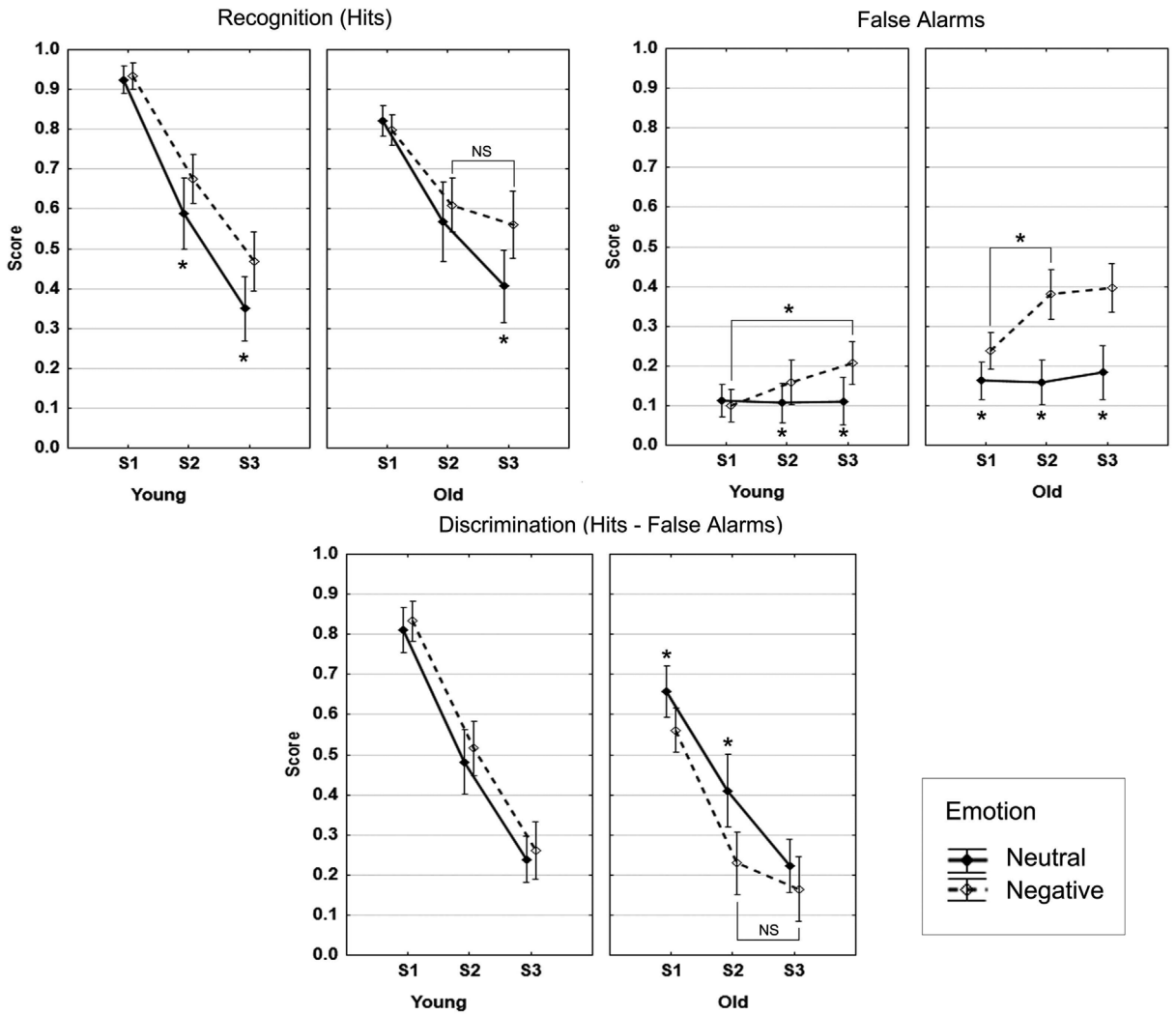

FIGURE 2 | Recognition data. Note: the bars denote 95% confidence intervals.

condition; we also found activity in left AMG but below the chosen extent threshold ($p < 0.0125$, but $k = 13$ voxels). In the older group, only an area in right HC was more activated during successful recognition of negative scenes in comparison with neutral scenes. In no case did successful recognition of neutral scenes elicit more activity than negative scenes (**Figure 3A**; **Table A2** in Appendix).

Session* × *emotion interaction. In the younger group, activity of several regions mainly located in medial temporal lobe (MTL) varied as a function of session and emotion. At the whole-brain level, activity in posterior parahippocampal cortex (bilaterally) and left lateral parietal cortex diminished from S2 to S3 for successful retrieval of neutral scenes, whereas activity in these regions increased for successful retrieval of negative scenes. At the ROI level, activity in left HC and AMG diminished from S2 to S3 for successful retrieval of neutral scenes, whereas it remained stable for successful retrieval of negative scenes (**Figure 4**; **Table 2**). In the older group, the Session × Emotion interaction was not significant for any brain region.

Successful long-term retrieval by session

Hits vs. misses. As shown in **Figure 3B** (see also **Table A3** in Appendix), activity was found at S2 in left PFC as well as in posterior cortical areas, and also in the HC bilaterally and the right AMG. By contrast, more cerebellar activity was seen at S3, where more HC activity was also revealed.

Age. The older adults showed more activity in comparison with their younger counterparts at both sessions and mostly in posterior brain areas; this effect was most pronounced at S3 (**Figure 3B**; **Table A3** in Appendix).

Emotion. At S3, successful retrieval of negative scenes elicited more activity in HC bilaterally and in right AMG in comparison with retrieval of neutral scenes. Activity in right parahippocampal/fusiform cortex, dorsomedial PFC, and precuneus showed the

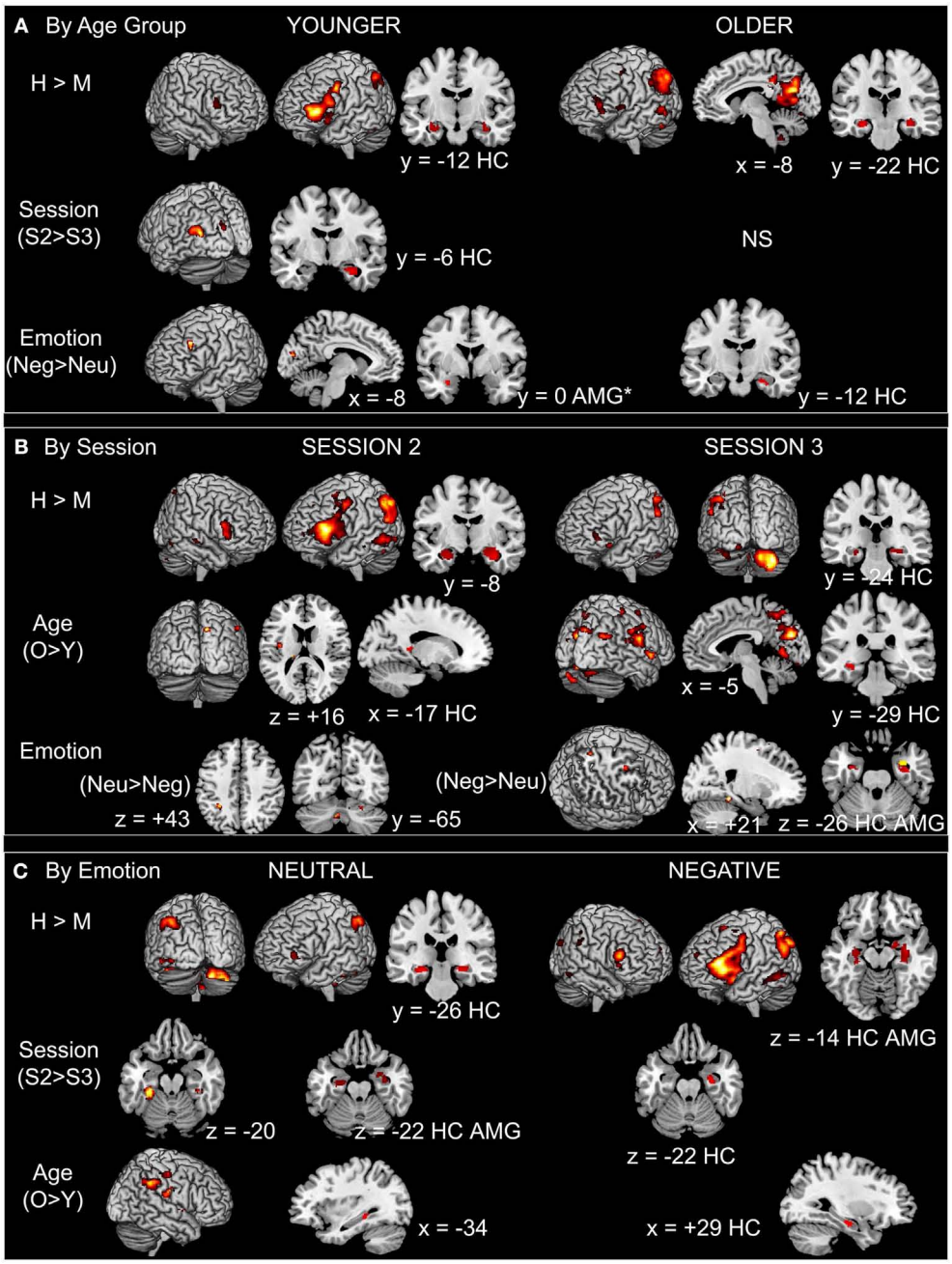

FIGURE 3 | Main effects in BOLD activation patterns by (A) age group, (B) session, and (C) emotion. Notes: AMG, amygdala; H, hits; HC, hippocampus; M, misses; Neg, negative; Neu, neutral; O, older; S2, Session 2; S3, Session 3; Y, younger. Whole-brain results shown at $p < 0.001$ uncorrected, and ROI results (HC, AMG) shown at $p < 0.0125$. *In the younger group the cluster size of the emotion effect in the AMG is below the extent threshold set for significance ($k = 13 < 20$ voxels).

same pattern. By contrast, at S2, other regions (cerebellum and inferior parietal cortex) showed more activity during retrieval of neutral in comparison with negative scenes (**Figure 3B**; **Table A3** in Appendix).

Age* × *emotion interaction. No significant effects were found at S2 and S3. Nonetheless, plotting the effect of Emotion (Negative > Neutral) described above in right AMG (**Figure 5A**) suggested the existence of an interaction effect, such that the main effect of Emotion was driven by the older group. Follow-up analyses confirmed that at S3 the difference of AMG activity between neutral and negative scenes was significant in the older group only, at $p = 0.007$, with more activity for negative scenes.

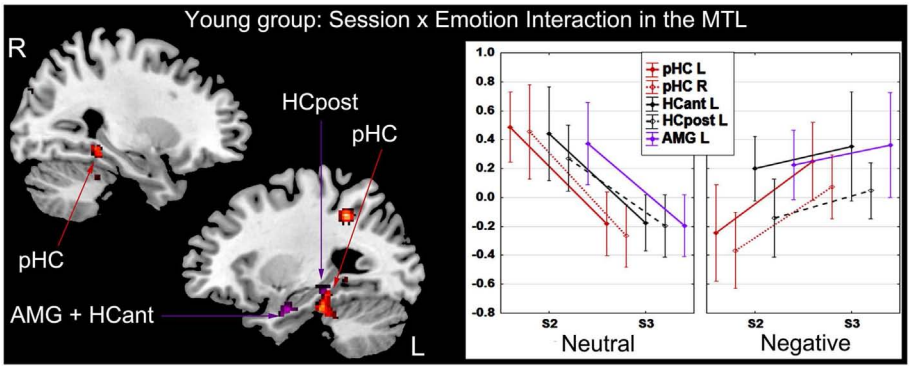

FIGURE 4 | Interaction effect between session and emotion in the younger group. There was a significant decrease of activity during successful recognition of neutral scenes from S2 to S3 in the MTL, a significant increase of activity in posterior parahippocampal cortex bilaterally and stable activity over time in left hippocampus and amygdala during successful recognition of negative scenes. The *Y*-axis of the graph represents contrast values (Hits − Misses). L, left; R, right; HCant, anterior hippocampus; HCpost, posterior hippocampus; pHC, parahippocampal cortex; AMG, amygdala; MTL, medial temporal lobe; S2, Session 2 (1-week delay); S3, Session 3 (3-week delay).

Table 2 | Interaction between retrieval session and emotion in the younger group.

Brain areas	BA	MNI coordinates			*t*	*k*	*F*-tests	
		x	*y*	*z*			Neutral (S2 > S3)	Negative (S3 > S2)
ROI HC L		−32	−32	−12	3.65	63	$p = 0.003$	NS
		−30	−6	−28	2.93	36	$p = 0.002$	NS
ROI AMG L		−28	−4	−24	2.80	23	$p = 0.004$	NS
ParaHC, fusiform L	37, 30	−32	−32	−16	4.16	220	$p = 0.0004$	$p = 0.008$
ParaHC, fusiform R	37, 30	22	−40	−12	4.10	190	$p = 0.0001$	$p = 0.01$
Parietal inferior L	40	−28	−46	42	4.09	82	$p = 0.01$	$p = 0.002$
Parietal superior L	7	−22	−72	48	3.43	64	$p = 0.0001$	NS
DMPFC L	6	−22	0	52	3.67	35	$p = 0.02$	$p = 0.01$
Postcentral R	3	58	−16	44	3.61	26	$p = 0.0002$	NS

All results shown at $p < 0.001$ except ROI analyses at $p < 0.0125$ for HC (first cluster: peak at $p < 0.001$; second peak at $p = 0.002$) and AMG (peak at $p = 0.003$). AMG, amygdala; BA, Brodmann Area; DMPFC, dorsomedial prefrontal cortex; HC, hippocampus; L, left; MNI, Montreal Neurological Institute; NS, no significant; ParaHC, parahippocampal cortex; R, right; ROI, region of interest; S2, Session 2 (1-week retention interval); S3, Session 3 (3-week retention interval).

Successful long-term retrieval by emotional valence

Hits vs. misses. As shown in **Figure 3C** (and **Table A4** in Appendix), for both the neutral and negative scenes, HC was activated bilaterally, whereas AMG was activated only for negative scenes, especially in the right hemisphere (subthreshold in the left, $k = 13$ voxels). Although activity was found in similar regions for both types of scenes such as VLPFC and parietal areas with a strong asymmetry toward the left hemisphere, more widespread activity was found for the negative scenes where other areas were also activated (cingulate gyrus, occipital and temporal regions, and thalamus).

Session. At the whole-brain level, only a small region in right cerebellum showed increased activity at S3 in comparison with S2 for the negative scenes. Further, activity in HC dropped from S2 to S3 for both types of scenes, but the effect was much more pronounced for the neutral scenes: Although only a small portion of right HC showed decreased activity for negative scenes, larger HC areas bilaterally showed such a decrease for neutral scenes. Moreover, although AMG was not activated for the main effect (H − M), we found decreased activity over time in right AMG for the neutral (but not the negative) scenes (**Figure 3C**; **Table A4** in Appendix).

Age. For both types of scenes, older adults showed more activity in comparison with younger adults. This effect was seen in posterior brain regions (occipital, parietal, and lateral temporal regions) and to a lesser extent in HC (**Figure 3C**; **Table A4** in Appendix).

Session × age interaction. No brain area showed a significant interaction for the neutral scenes. For negative scenes, activity of right VLPFC (BA 45) increased from S2 to S3 in the older group, whereas it decreased in the younger group over time (**Figure 5B**; **Table A4** in Appendix). To verify whether this effect was truly unilateral, we used a more permissive threshold, $p < 0.005$. Left VLPFC became significant ([−36; 36; 6], $t = 3.19$), likely suggesting bilateral VLPFC activity modulation according to session and

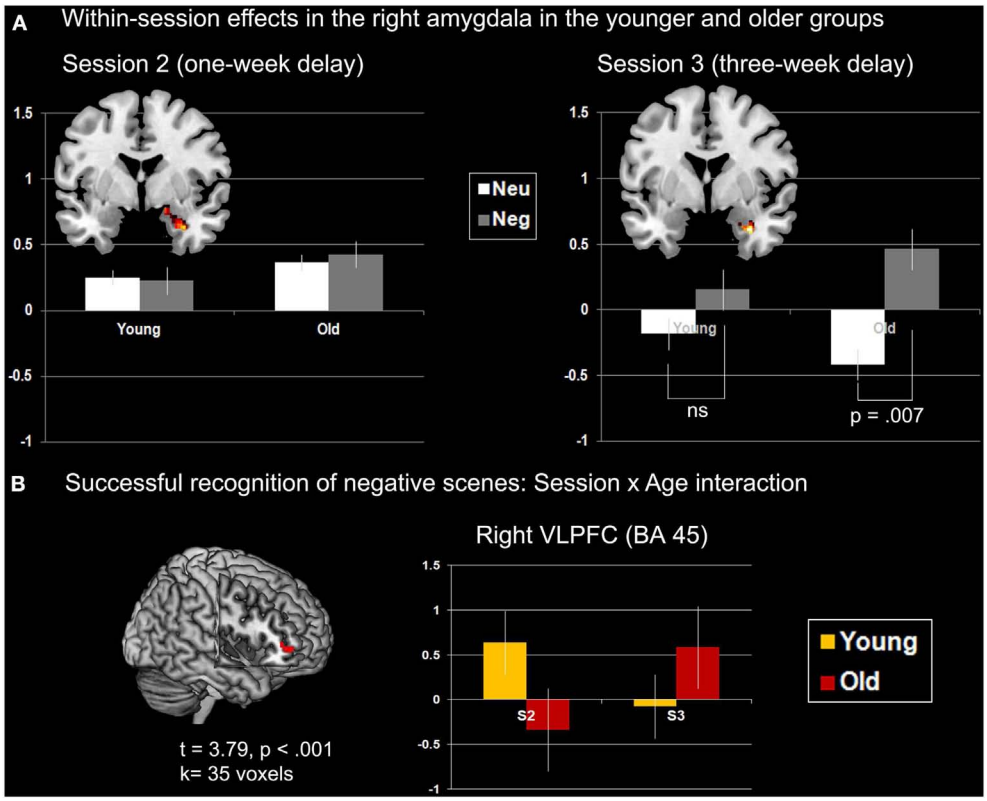

FIGURE 5 | Interaction effects with age in AMG and VLPFC. (A) Within-session effects in right AMG (coronal slices, $y = 0$). The main effect of successful retrieval (H > M) at S2 is plotted on the left. No modulation of AMG activity was found according to Age and Emotion. The main effect of Emotion (negative > neutral) at S3 in plotted on the right. Modulation of AMG activity differed across Age: in the younger group the effect of emotion was not significant ($p = 0.23$), although it was reliable in the older group ($p = 0.007$). The *Y*-axis of the graphs represents contrast values (H > M) which have been extracted individually over all voxels of the cluster (eigenvalues). Bars represent standard errors. **(B)** Age × Session interaction for successfully recognized negative scenes. The *Y*-axis of the graph represents contrast values (H > M). Peak coordinates are [46; 46; 0].

age. Bilateral involvement may reflect complementary processes according to the nature of the material (visual and verbal).

Correlational analyses

Correlations were performed between activity in AMG, VLPFC, and HC, and between activity in these areas and performance for negative scenes, both Hits and Discrimination. Four older individuals were considered as outliers in these analyses as their brain data were >2 SDs and were therefore excluded from these analyses. Results are shown in **Table 3**, but should be considered cautiously due to the small sample size.

In the younger group at S2, positive correlations were found between activity in AMG and VLPFC. As VLPFC was significantly activated at the group level, the significant correlations with AMG activity indicate that these two regions may interact during successful recognition of negative scenes. Correlations with performance mostly indicate that left- but not right-sided structures (HC, VLPFC) contributed to performance, except for right AMG whose activity was positively linked to performance. However, the fact that right HC and VLPFC were significantly correlated with AMG suggests an indirect contribution to performance. At S3, activity in AMG was positively correlated with performance (negative hits), but in contrast with S2, right (but not left) VLPFC activity was negatively correlated with the proportion of negative hits. However, at this session, VLPFC was not significantly activated during retrieval of negative scenes at the group level. Therefore, it can be hypothesized that mainly automatic mechanisms as subserved by the AMG (as opposed to controlled processes subserved by the PFC) are involved in successful recognition of negative scenes in younger adults. The opposite role of these two regions was substantiated with the negative correlation between activity in AMG and right VLPFC. In contrast with S2, HC activity did not correlate with any of the other measures at S3, suggesting diminished contribution of this structure to performance with increasing retention interval.

In the older group, at S2, activity in right AMG did not correlate with performance, whereas right (but not left) VLPFC activity correlated positively with negative hits, suggestive of beneficial controlled mechanisms, in interaction with right HC, whose activity was also correlated with right VLPFC. However, right VLPFC was not significantly activated at the group level during successful retrieval of negative scenes, which goes against a compensatory interpretation. VLPFC was activated only at S3, suggesting delayed involvement of this region compared with the younger group.

Table 3 | Within-group and within-session correlations between brain activity and performance.

	Younger		Older	
	S2	**S3**	**S2**	**S3**
AMG R				
VLPFC R	0.49*	−0.53*	−0.30	−0.13
VLPFC L	0.68**	−0.16	0.32	−0.02
HC R	0.56**	0.41	0.26	0.15
HC L	0.49*	0.36	0.03	−0.26
Neg hits	0.54*	0.62**	−0.16	0.18
Neg disc	0.53*	0.40	−0.32	0.43
VLPFC R				
HC R	0.46*	−0.25	0.64*	0.33
HC L	0.02	−0.28	0.42	0.24
Neg hits	−0.03	−0.60**	0.67**	−0.01
Neg disc	0.08	−0.23	0.37	0.02
VLPFC L				
HC R	0.59**	−0.05	0.37	0.17
HC L	0.71**	−0.05	0.40	0.22
Neg hits	0.40	−0.42	0.35	−0.09
Neg disc	0.53*	−0.23	0.41	0.29
VLPFC R – VLPFC L	0.52*	0.66**	0.41	0.31
HC R				
Neg hits	0.24	0.14	0.37	−0.40
Neg disc	0.35	0.15	0.28	−0.33
HC L				
Neg hits	0.61**	0.25	0.20	−0.26
Neg disc	0.60**	0.22	0.14	−0.34
HC R–HC L	0.53*	0.58**	0.68**	0.65**

$*p \leq 0.05$, $**p \leq 0.01$. Younger: N = 19. Older Session 2: N = 14 for correlations involving AMG R, N = 13 for correlations involving HC, otherwise N = 15. Older Session 3: N = 14 for correlations involving AMG R, N = 14 for correlations involving VLPFC, N = 13 for the correlations between AMG R and VLPFC, otherwise N = 15. AMG, amygdala; HC, hippocampus; L, left; Neg Disc, negative discrimination; R, right; S2, Session 2 (1-week delay); S3, Session 3 (3-week delay); VLPFC, ventrolateral prefrontal cortex.

However, the lack of correlation with AMG indicates that these two regions may not interact in older adults. Actually, at S3, no correlation was significant in the older group, although there was a trend toward a positive relationship between AMG activity and discrimination of negative scenes ($r = 0.43$, $p = 0.13$). If this trend is meaningful, one can hypothesize that successful retrieval of negative scenes at S3 is mainly driven by automatic processes subserved by AMG activity in older adults.

Finally, while in the younger group activity between left- and right-sided structures was significantly correlated (HC, VLPFC), only activity between left and right HC was correlated in the older group, suggestive of a functional frontal disconnection in aging.

Overall, AMG activity was positively correlated with performance in the younger group in the two retrieval sessions, suggesting a specific role of the AMG in successful recognition of negative scenes regardless of time, and a trend toward a similar relationship in the older group was only seen after 3 weeks retention. Interestingly, at Session 2, only activity in left VLPFC and HC was associated with performance in the young group. Regarding activation of left and right VLPFC in the older group at S3, no relationship was found with either AMG activity or performance, suggesting no compensation or increased emotional regulation at retrieval.

Successful, false, and true recognition of negative scenes in the older group

As shown in **Figure 6** and **Table 4**, at S2, same areas were activated during successful (H > M) and false (FA > CR) recognition, including right HC and left fronto-parietal regions. Consequently, the direct comparison between H and FA showed very few differences, suggestive of similar neurocognitive processes involved in successful and false retrieval. At S3 the pattern of results was different. More activity in several regions was found during successful in comparison with false recognition. The direct contrast between H and FA, thought to unveil brain areas associated with true recognition, showed more activity for H in lateral occipito-temporal areas, left temporo-parietal junction, and left HC.

HC and AMG age-related atrophy

Because age-related differences were observed in the fMRI data for HC and AMG, we examined whether these effects could be due to local atrophy. There were two reasons for these additional analyses: first, several recent studies have demonstrated that more, or less, brain activity in older adults was partly driven by gray-matter losses, thus providing a biological underpinning for activity difference in aging (e.g., Kalpouzos et al., 2012; for review, see Kalpouzos and Nyberg, 2012); second, as noted in the introduction, a previous study on emotional memory in aging (St Jacques et al., 2009b) showed an hemispheric asymmetry in AMG activity in younger and older adults (more left activity in the young and more right activity in the old) that is difficult to explain. The current fMRI results showed: (1) More HC activity in older compared to younger adults, (2) Bilateral AMG involvement in the young, but mostly right AMG activity in the old (as in the St Jacques et al.'s study). After transformation of the functional HC and AMG clusters into ROIs, we overlaid the newly created binary masks on the individual unsmoothed, MNI-normalized and modulated gray-matter images preprocessed with the VBM8 toolbox as mentioned in the Section "Materials and Methods," and extracted with MRIcroN the mean intensity for each cluster of interest, representing GM volume in this specific area[2]. We found no significant atrophy in the investigated HC areas that showed more activity in the older compared to the younger group [Clusters: (1) Age effect in Session 2: $t = 0.69$, $p = 0.49$; (2) Age effect in Session 3: $t = 1.73$, $p = 0.09$; (3) Age effect in Negative condition: $t = 1.73$, $p = 0.09$; and (4) Age effect in Neutral condition: $t = 1.74$, $p = 0.09$]. Similarly, we found no evidence for atrophy in right AMG, but left AMG showed significant gray-matter volume loss in the older group [Clusters for left AMG: (1) Emotion × Session interaction

[2]http://www.mccauslandcenter.sc.edu/mricro/mricron/

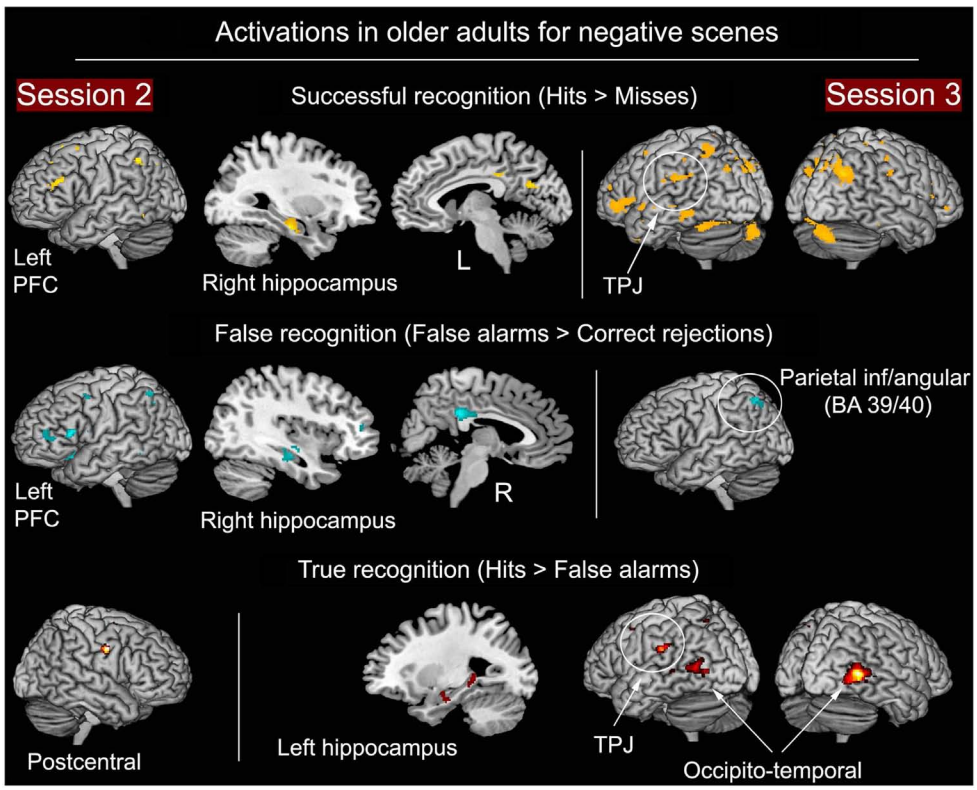

FIGURE 6 | Successful, false, and true recognition of negative scenes in the older group at S2 and S3. Notes: all results shown at $p < 0.001$ (whole-brain analyses), except HC ($p < 0.0125$, ROI analyses).

in the younger group: $t = 2.2$, $p = 0.03$; (2) Negative − Neutral in the younger group: $t = 3.45$, $p = 0.001$; and (3) H − M in the Negative condition: $t = 2.04$, $p = 0.05$. Clusters for right AMG: (1) Negative − Neutral for Session 3: $t = 0.96$, $p = 0.34$; (2) H − M in Negative condition: $t = 1.94$, $p = 0.06$; and (3) Session 2 − Session 3 in Neutral condition: $t = 0.95$, $p = 0.35$]. These findings suggest that the age-related HC over-activation is unlikely to be driven by gray-matter losses, and that the lateralization effect seen in AMG may be due to structural deterioration of left AMG in aging. Specifically, in this task context only the structurally intact right AMG may be used to perform the emotional recognition task in older adults.

DISCUSSION

The main aims of this study were to test the negativity effect over 1 and 3 weeks in younger and older adults, and to investigate the brain correlates of long-term successful, false, and true recognition. In long-term recognition, the negativity effect found for hits was canceled out when taking into account false recognitions, and this effect was present in both groups with a magnification of the effect in the older adults. MTL activity, including HC and AMG, was present in general during successful recognition of negative scenes, but its activity was modulated according to session of retrieval and age. Findings related to brain regions involved during successful and false recognition of negative scenes in older adults are discussed in terms of impaired recollection processes.

TESTING THE NEGATIVITY EFFECT

Although previous studies showed a robust negativity effect in young adults such that negative items are better remembered than neutral items, findings are mixed in older adults, with a trend toward a reduced negativity effect in true recognition. However, in most of these studies, the delay of retention was short (for meta-analysis, see Murphy and Isaacowitz, 2008). Here we show that, for hit rates, where no age-related difference was found in performance, both younger and older adults showed a negativity effect that increased over time. Further, more false recognitions of negative scenes were observed over time; this effect was especially marked in the old. Thus, H and FA canceled each other out, resulting in an absence of a negativity effect in the younger group in terms of discrimination, and higher discrimination of neutral than negative scenes in the older group over the three retrieval sessions. Also, global discrimination was higher in the younger group, except after 3 weeks of retention where age differences no longer were observed.

These results are in accordance with the view that negative emotional stimuli are more prone to memory distorsion than neutral stimuli. This may reflect that emotional items generally have a higher semantic cohesiveness; they share more characteristics within categories than neutral items (Maratos et al., 2000; Marchewka et al., 2008). Indeed, contrary to the neutral scenes, the negative scenes in the IAPS can be grouped into categories like "snakes," "guns," and "blood" (**Figure 1**). In line

Table 4 | Brain activity during successful (H > M), false (FA > CR), and true (H > FA) recognition of negative scenes in older adults at Session 2 and Session 3.

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
Session 2: Neg H > Neg M							
HC R ROI		28	−16	−22	3.98	91	0.001
Parietal inferior L	40	−42	−50	46	5.10	37	
VLPFC L	45	−44	32	24	4.76	53	
Cingulate middle/posterior L	23	−6	−32	34	4.52	37	
Precuneus/cuneus L	23	−6	−64	24	4.52	38	
Session 3: Neg H > Neg M							
Occipital middle/superior, precuneus LR	19, 7	34	−70	34	11.45	1730	
Anteromedial PFC/cingulate anterior L	32, 10	−2	52	14	8.03	186	
Cingulate anterior L	32	−10	34	18	6.69	157	
Cerebellum crus 1, 2 R		24	−82	−38	6.59	908	
Rostromedial PFC R	10	4	56	10	6.11	28	
VLPFC, insula L	45, 47	−48	34	0	5.81	354	
Cingulate middle LR	23	6	−10	28	5.74	77	
Temporo-parietal junction L	22, 40	−54	−42	28	5.67	79	
VLPFC R	45	42	28	24	5.51	25	
Parietal inferior R	40	32	−46	34	5.44	37	
Rostrolateral PFC L	10	−26	58	14	5.36	46	
Precuneus L	5	−10	−52	68	5.18	56	
Lingual L	18	−14	−52	0	5.13	38	
Rostrolateral PFC L	10	20	64	8	5.08	26	
Temporal inferior L	37	−56	−54	−10	5.01	81	
Temporal superior L	22	−56	−2	−4	5.00	25	
Precuneus R	5	4	−46	60	4.98	24	
Parietal superior L	7	−30	−60	60	4.85	96	
Superior frontal sulcus L	6	−32	6	52	4.66	32	
Cingulate posterior LR	26	0	−30	24	4.64	122	
VLPFC L	45	−44	44	18	4.63	23	
Postcentral R	3	32	−30	56	4.58	24	
VLPFC L	47	−36	26	28	4.44	22	
Lingual L	17	−6	−70	6	4.41	36	
Session 2: Neg FA > Neg CR							
HC R ROI		36	−16	−14	5.34	175	<0.001
Cingulate middle/posterior LR	23	2	−34	30	6.78	278	
VLPFC L	45	−52	24	10	6.74	71	
Precuneus L	23	−10	−64	30	6.13	49	
Insula, HC R		40	−12	−12	5.6	92	
VLPFC L	47	−36	20	−16	5.34	33	
VLPFC R	45	50	24	8	5.09	25	
Parietal inferior L	40	−46	−56	54	4.95	28	
VLPFC L	47	−38	40	4	4.52	56	
Session 3: Neg FA > Neg CR							
Parietal inferior/angular L	39/40	−42	−62	54	7.03	51	
Session 2: Neg H > Neg FA							
Postcentral R	4	56	−2	36	4.98	44	
Session 2: Neg FA > Neg H							
Insula R		40	−12	−12	4.64	20	
Session 3: Neg H > Neg FA							
HC L ROI		−24	−40	4	5.77	70	<0.001
		−30	−8	−16	3.39	36	0.002

(Continued)

Table 4 | Continued

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
AMG L ROI		−28	−8	−12	2.72	1	0.008*
Occipito-temporal R	37, 19	52	−66	6	6.05	408	
Lingual L	18	−8	−60	−4	5.42	45	
Occipito-temporal L	37, 19	−48	−84	4	5.37	116	
Temporo-parietal junction L	48	−56	−38	26	5.14	86	
Calcarine, precuneus L	17	−4	−68	10	4.78	27	
Session 3: Neg FA > Neg H							
	–						

**At p < 0.05: AMG L 15 voxels; AMG R [32; 2; −22], t = 2.26, p (peak) = 0.02, k = 15 voxels. AMG, amygdala; BA, Brodmann Area; CR, correct rejections; FA, false alarms; H, hits; HC, hippocampus; L, left; MNI, Montreal Neurological Institute; Neg, negative; R, right; ROI, region of interest; VLPFC, ventrolateral prefrontal cortex.*

with our hypothesis, the findings suggest that older adults, relatively to younger adults, are more prone to falsely recognize a negative scene because they may base their recognition on categories or more general features rather than on perceptual detail.

Second, our results extend Howe et al.'s (2010) findings on young adults to older adults, showing that the increase of false emotional memories over time is magnified in aging. This disproportionate increase of FA in the older group was striking; the percentage of negative FA was 40% at both S2 and S3. Although the results suggest stabilization of performance from week 1 to 3 with no further forgetting of negative scenes, no further increasing proportion of false negative recognitions in the older adults, and normalization of performance in comparison with the younger group over the last 2 weeks, these effects were likely a consequence of a floor effect. Indeed, older adults displayed a rapid decline of performance already at Session 2, reaching a very low discrimination score (but not proportion of hits) at Session 3. Overall, memory accuracy for negative scenes was not better than that of neutral scenes, especially in older adults, thus supporting Socioemotional selectivity theory in aging (Mather, 2012).

However, a recent study from our lab with a retention interval of 1 year demonstrated better memory accuracy for negative compared to neutral scenes in both younger and older adults (Gavazzeni et al., 2012). This further highlights the importance of retention intervals and might reflect that very long-term consolidation of negative scenes may result in a re-established negativity effect in both age groups. Perhaps more importantly, the lack of negativity effect in the younger group on long-term memory accuracy may be due to the material used. As aforementioned, IAPS contains many items that can easily be grouped into semantic categories. Information regarding this possible grouping of items into categories is usually not provided in previous studies, and differences on this dimension across studies may explain discrepant findings. Indeed, in their study on false memory, Howe et al. (2010) showed, in young adults, no valence effects for unrelated lures on FA rates, but significant higher FA rates for related negative emotional lures than for related neutral lures, substantiating the importance to consider this factor in emotional memory studies.

EMOTION AND SESSION OF RETRIEVAL MODULATE MTL ACTIVITY

The involvement of HC has been the focus of studies in which retention interval has been manipulated (Andreasen et al., 1995; Stark and Squire, 2000; Dupont et al., 2001; Bosshardt et al., 2005a,b; Takashima et al., 2006, 2009; Janzen et al., 2008; Suchan et al., 2008; Viskontas et al., 2009). A controversy exists in the literature, with two opposing theories: Multiple trace theory claims that HC is systematically engaged when retrieving information from long-term memory whatever the remoteness, whereas the standard model posits that HC disengages with increasing remoteness (for review, see Winocur and Moscovitch, 2011). Research has largely ignored the role of emotion in modulating the effect of passage of time on HC activity. Our findings underscore the point that emotion modulates the engagement of the MTL during recognition of scenes over time, but only in young adults (**Figure 4**). For HC and other MTL structures (posterior parahippocampal cortex bilaterally and left AMG), activity decreased over time for successful recognition of neutral scenes, in agreement with the standard model. However, activity remained stable or increased for successful recognition of negative scenes, in line with Multiple trace theory. Additional correlations between HC activity and performance during successful recognition of negative scenes revealed that increased activity in left HC was associated with higher performance in young adults after 1 week but not after 3 weeks of retention, indicative of reduced function of the structure at the cognitive level with increasing remoteness.

AGING EFFECTS ON THE NEURAL SUBSTRATES OF LONG-TERM SUCCESSFUL RETRIEVAL

Both the younger and older groups showed activity in brain areas typically associated with successful episodic retrieval such as fronto-parietal areas and HC (**Figure 3**). This pattern of activity was strongly left-lateralized regarding neocortical regions. Retrieval in episodic memory has been traditionally related to right-sided activity notably in the PFC (Tulving et al., 1994); however a recent meta-analysis showed that *successful* retrieval elicited more left-lateralized regions (Spaniol et al., 2009). The left-sided preference found here could also reflect task difficulty. Some previous studies showed a hemispheric modulation according to the difficulty of the task and the specific cognitive processes needed to

solve such tasks (Nolde et al., 1998; Cabeza et al., 2003). Although we used a recognition task, supposedly easy to carry out, the 1- and 3-week delays of retention may have contributed to increased task difficulty, where subjects may have had to generate more cues in order to decide whether a scene had been seen or not 1 and 3 weeks ago.

Overall age-related effects

Generally, more BOLD activity was found in the older compared with the younger group. This pattern varied by session and emotion. The most pronounced age difference was seen for Session 3 in posterior areas, notably the precuneus, which is known to be involved in imagery processes and episodic retrieval (Huijbers et al., 2011). Two invariant patterns were observed across the different conditions: Older individuals systematically activated HC more than the young, whereas PFC over- or under-activation in aging was generally not evidenced. The latter result goes against many studies on age-related differences in functional brain activity, particularly in episodic memory, often showing more recruitment of PFC in aging (Rajah and D'Esposito, 2005). This may be due to the fact that, unlike most previous assessments, the retrieval sessions here were delayed, making the task more difficult, even for younger subjects, as substantiated by the recruitment of left PFC in the main effect of successful retrieval (**Figure 3A**). More HC activity is a rare finding in normal aging, although it has been shown in persons with mild cognitive impairment (Putcha et al., 2011): Over-activation, in that case, was seen as compensatory for structural MTL deterioration. As no evident hippocampal atrophy was found, the over-recruitment of the old found here may be due to the length of the retention interval and accompanying increase in difficulty. One study showed that increased cognitive demands during an associative encoding task increased both PFC and HC activity similarly in younger and older adults (Leshikar et al., 2010), corroborating the hypothesis that task difficulty, due to the length of retention interval, resulted in minimal age differences in PFC activity and slightly increased HC activity in the older group.

Right amygdala activity in older adults after 3 weeks of retention for successful recognition of negative scenes

While AMG engagement during perception and encoding of negative stimuli is well established (Murty et al., 2010; Sabatinelli et al., 2011), its involvement during emotional episodic retrieval is not obvious, and even less so during *successful* retrieval. The present study, in which an event-related fMRI design was used, showed that over the two groups, right AMG activity was present for successful retrieval of negative scenes but not for neutral scenes (**Figure 3C**). Within-group analyses further showed that left AMG displayed more activity during successful recognition of negative in comparison with neutral scenes in younger adults (**Figure 3A**), with a modulation effect according to session (**Figure 4**), whereas no significant effect of emotion on AMG activity could be demonstrated in older adults.

When considering the retrieval sessions separately over the two groups, an effect of negative emotion was revealed after 3 weeks of retention in right AMG, but not after 1 week (**Figure 3B**). Thus, AMG activity was specifically involved in successful long-term retrieval of negative scenes (Dolcos et al., 2005). Examining the effect of emotion for Session 3 further revealed that this effect was mainly driven by the older adults, who showed a significant difference for this session between successful negative and neutral scene recognition (**Figure 5A**). Specifically, after a long delay, right AMG was especially activated during successful retrieval of negative scenes in older individuals, suggesting that automatic mechanisms, as mediated by AMG, may be activated after a certain time in older adults during successful recognition of negative information. Although the positive correlation observed in this group between AMG activity and discrimination of negative scenes was only at trend level, significant positive associations found in the younger group support the hypothesis of AMG involvement in recognition memory of negative scenes after 1 and 3 weeks of retention. For the older group, however, it is difficult to state that increased right AMG activity for successfully recognized negative scenes compared with neutral scenes subtended a delayed negativity effect: Considering the discrimination findings, although performance seemed to stabilize compared to S2 in the old, and normalize compared to the younger group, the fact that performance was low prevents firm conclusions. However, a beneficial effect of AMG activity on performance can be hypothesized when considering hits only, where the negativity effect appeared at S3 in the older group (see also Gavazzeni et al., 2012).

VLPFC involvement during successful recognition of negative scenes

An interaction between Age and Session for successful recognition of negative scenes was observed in right VLPFC (and left VLPFC at a more liberal threshold): activity in this region decreased from S2 to S3 in the younger group, while it increased in the older group. In other words, VLPFC was engaged in the younger, but not older adults at S2, while it was engaged at S3 in the older but not in the younger group (**Figure 5B**). Right VLPFC has been shown to play a role in response inhibition and selective attention (Aron et al., 2003, 2004), especially in relation to episodic memory retrieval (Kuhl et al., 2007, 2008; for review see Anderson and Weaver, 2009), where this region is thought to select the correct representation among several plausible alternatives (by inhibiting irrelevant options). Given the nature of the task (yes-no recognition with targets and lures), the latter function seems plausible. In the younger group, left and right VLPFC were activated at S2 (not at S3), and activity in these regions was positively correlated with AMG activity, but only left VLPFC was correlated with performance. This suggests a direct contribution of left VLPFC to performance, and an indirect beneficial effect of right VLPFC on performance, via AMG, whose activity was positively linked to successful recognition of negative scenes (**Table 3**). The same conclusion can be drawn for HC: at S2, only left HC was correlated with performance, suggesting a direct contribution to performance, and the significant correlations between right HC and AMG (as well as left and right VLPFC) may indicate an indirect contribution of these right-lateralized structures on performance via AMG activity. If we consider theoretical models on hemispheric asymmetries, left structures being more involved in episodic and/or verbal processes and right structures being more engaged in visual processes (Kalpouzos and Nyberg, 2010), our findings suggest a direct contribution of episodic/verbal processes subserved by left

VLPFC and HC on successful recognition, and indirect contribution of the contralateral structures subserving visual mechanisms via the right AMG, which directly contributed to successful recognition of negative scenes. Also, and as aforementioned in Section "Overall Age-Related Effects," increased task difficulty due to long retention interval may have been a factor of the involvement of left brain areas, directly influencing performance via additional episodic, verbal-related processes.

In the older group, activity in VLPFC was delayed in comparison with the younger group, as activity was seen only at S3. Nonetheless, at S3, no significant correlation was seen between VLPFC and AMG activity, and performance did not correlate with VLPFC activity in the old. Hence, increased activity in VLPFC in the older group did not seem to play a role during successful recognition of negative scenes, and may therefore reflect a failed attempt of either compensation or emotion regulation, which is in disagreement with previous studies where PFC activity in older adults was interpreted as compensatory (Murty et al., 2009) or reflecting increased regulation of emotional processes (St Jacques et al., 2009a). This does not exclude the hypothesis of increased regulation of emotion at encoding (Mather, 2012). Nevertheless, the absence of correlation between AMG and VLPFC activity in the old is partly in line with St Jacques et al.'s (2009b) functional connectivity findings, where a decrease in functional connectivity between AMG and VLPFC was found in older compared with younger adults, but an increase in functional connectivity between AMG and dorsolateral PFC. These differences highlight the need to consider age effects on different regions of the PFC (see also Ebner et al., 2012 for an investigation of a differential involvement of dorso- and ventro-medial PFC in emotion in younger and older adults; for review, see Mather, 2012).

Interestingly, interhemispheric correlations suggest a preserved age-related functional connectivity between left and right HC, but a functional disconnection between contralateral VLPFC areas, the latter indicating reduced interhemispheric information flow between these anterior regions. Anterior callosal integrity has been shown to be crucial for interhemispheric functional connectivity of the frontal lobes (Davis et al., 2012). Age-related structural deterioration of the corpus callosum may contribute to the observed diminished relationship between activity in left and right VLPFC as observed in the present study. Future studies combining fMRI and Diffusion Tensor Imaging in emotional pictorial memory could address this hypothesis.

BRAIN CORRELATES OF SUCCESSFUL, FALSE, AND TRUE RECOGNITION OF NEGATIVE SCENES IN OLDER ADULTS

Similar regions were engaged during successful recognition (as assessed using the H − M contrast) and false recognition (FA − CR), including left VLPFC, middle-posterior cingulate and HC at S2, and left lateral parietal cortex at S2 and S3 (**Figure 6**). Left VLPFC has been associated with retrieval of semantic information (Tulving et al., 1994), contributing to episodic memory retrieval (see also Aging Effects on the Neural Substrates of Long-Term Successful Retrieval of the present discussion). The fact that the direct comparison between hits and FA did not show differential activity in this region suggests that, in both successful and false recognition, left VLPFC is linked to semantic operations during episodic retrieval by providing categorical or general information, but does not, in the present case, contribute to true recognition. Failure to find significant correlations between left VLPFC activity and accurate recognition in the old group partly substantiate this interpretation (**Table 3**).

Brain areas differentially activated for successful and false recognitions were mostly seen at S3. Lateral occipito-temporal cortex was more activated for H than for FA for negative scenes in the older group. This region has been previously shown to be specific to sensory-perceptual processing of detail that enables recognition of negative stimuli based on recollection (Mickley and Kensinger, 2008). Contrary to S2, at S3 left HC activity was more pronounced during successful in comparison with false recognition (**Figure 6**), which does not support previous findings where no HC activity difference was found between true and false memories (Cabeza et al., 2001). The HC has been shown to be involved in recollection rather than familiarity-based retrieval in episodic memory (Suchan et al., 2008). Moreover, the study by Suchan et al. showed consistent HC activity for recollection at immediate retrieval but also after 3- and 6-week retention intervals. In line with the hypothesis that false recognitions are more likely to be based on general features rather than on perceptual detail, these findings suggest that some brain areas such as the HC and lateral occipito-temporal areas whose activity also differed between hits and FA may reflect a dissociation between recollection and familiarity-based retrieval. Toward this end, the marked increase of FA for negative scenes in the older participants could be due to impairment in recollection processes (Comblain et al., 2004). Besides the aforementioned brain areas whose activity distinguished between successful and false recognition, the temporo-parietal junction, which is a main substrate of bottom-up attention to memory for detection of relevant information (Corbetta and Shulman, 2002; Cabeza et al., 2008) also characterized true recognition.

We did not find more activity in AMG for false recognitions in comparison with CR, and no difference was revealed in the direct comparison between hits and FA, which indicates that AMG activity is not modulated by memory accuracy. However, one study showed left AMG activity during successful recognition of negative items but not during false recognitions, supporting the hypothesis that AMG may be involved in accurate recognition of visual detail (Kensinger and Schacter, 2007). Other studies also found more AMG activity for successfully retrieved items based on recollection rather than familiarity (Sharot et al., 2004; Dolcos et al., 2005). It is possible that our analyses lacked statistical power. An alternative explanation may be that our analyses were conducted on the older group only, where gray-matter loss in left AMG was found, which may have induced dysfunction of this structure. Nonetheless, setting a more liberal threshold in our analyses ($p < 0.05$, uncorrected) indeed revealed more bilateral AMG activity for negative H than for negative FA (**Table 4**).

Thus, all regions highlighted in the direct comparison between successful and false recognition at S3 have been shown to have a role in retrieval based on recollection processes. A reason why these regions showed differential activity at S3 and not at S2 may be that, after long delays of retention, negative scenes are recognized based on recollection of detail, although the number of accurately recognized items has diminished. This hypothesis finds support

in some previous studies showing that item recognition is based more on recollection after long than after short retention intervals, thus reflecting consolidation of these memories (Sharot et al., 2007; Sharot and Yonelinas, 2008).

CONCLUSION

After delays of 1 and 3 weeks, an increased rate of false recognitions that was specific to negative scenes canceled out, in both younger and older adults, the negativity effect present for hits only. This effect was more pronounced in older adults, who nonetheless showed right AMG engagement during successful recognition of negative compared to neutral scenes, after 3 weeks delay of retention, possibly reflecting activation of relatively automatic processes during negative emotional retrieval. In the older adults, the significant higher discrimination of neutral, relative to negative scenes could be interpreted as an enhancement of the positivity effect, which overall supports Socioemotional selectivity theory. However, inclusion of positive scenes in future investigations would be more optimal to study the two sides of the effect (positive and negative, relative to neutral).

A direct comparison of activity related to successful and false recognition of negative scenes after the 3-week delay in older adults showed that regions that have been related to recollection rather than familiarity (HC and lateral occipito-temporal cortex) were more engaged for hits, indicating consolidation and true recognition of detail for negative scenes. Future studies should confirm this possibility by assessing recollection vs. familiarity in the present task situation. Another important issue raised by this study is the need to control for the semantic relatedness between targets and lures, as emotional items are in general, and particularly in the IAPS database, more likely to be grouped into categories than neutral items, which can dramatically modify memory accuracy. This issue becomes even more critical in event-related fMRI paradigms, where many items are to be used. Increased activity in VLPFC in older adults during successful recognition of negative scenes after 3 weeks retention was not related to performance or AMG activity, rejecting the hypothesis of successful compensation or emotion regulation at retrieval via VLPFC in aging. However, future studies should specifically address functional connectivity differences in aging during retrieval of emotional information between MTL and prefrontal regions. All the present findings hold for transient brain activity, and thus need to be validated by future investigations.

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APPENDIX

Table A1 | Picture material characteristics.

Session	Type	Emotion	*N*	Valence*	Arousal*	Living/non-living**
				Mean	Mean	Mean
S1	Target	Neutral	50	5.27	3.57	0.56
		Negative	50	2.68	5.71	0.90
	Lure	Neutral	25	5.33	3.82	0.60
		Negative	25	2.82	6.04	0.84
S2	Target	Neutral	50	5.27	3.58	0.50
		Negative	50	2.84	5.55	0.88
	Lure	Neutral	25	5.25	3.68	0.56
		Negative	25	2.67	5.76	0.84
S3	Target	Neutral	50	5.30	3.63	0.52
		Negative	50	2.64	5.64	0.86
	Lure	Neutral	25	5.34	3.73	0.56
		Negative	25	2.74	5.95	0.88

**Based on normative IAPS data. **Binary rating (0 = non-living; 1 = living).*

Analysis of variance on Valence with factors Session (S1, S2, S3), Type of item (target, lure), Emotion (neutral, negative): no significant main effects and interaction effects (all Fs < 1) except main effect of Emotion ($F = 1759.7$, $p < 0.001$).

Analysis of Variance on Arousal: significant main effects of Type of item ($F = 6.8$, $p = 0.009$) and Emotion ($F = 648.3$, $p < 0.001$). No significant main effect of Session ($F = 1$, $p = 0.36$) and interaction effects (all Fs < 1).

Analysis of variance on living/non-living dimension: significant main effect of Emotion ($F = 54.4$, $p < 0.001$). No other significant main or interaction effects (all Fs < 1).

Table A2 | Neuroimaging results.

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
YOUNGER GROUP							
Hits > misses main effect							
HC L ROI		−16	−32	−6	3.74	33	<0.001
		−16	−4	−20	3.52	188	<0.001
HC R ROI		28	−28	−8	4.02	171	<0.001
		22	−2	−22	2.98	21	0.002
AMG L ROI		−16	−4	−18	3.33	27	0.001
AMG L ROI		−30	−2	−28	3.24	22	0.001
AMG R ROI		18	4	−16	3.49	29	<0.001
		26	−2	−28	3.09	19	0.001
Ventrolateral PFC, dorsolateral PFC L	6, 44, 45, 47	−44	40	4	6.64	1943	
Ventrolateral PFC R	45	56	30	16	3.76	73	
Paracingulate L	32	−6	34	40	4.95	170	
Cingulate posterior L	23	−2	−32	34	4.07	37	
Angular, parietal inferior L	39, 40	−42	−58	48	5.04	545	
Temporal inferior R	37	44	−56	−14	4.46	98	
Fusiform L	19	−42	−68	−12	3.92	26	
HC R		28	−28	−8	4.02	26	
HC L		−16	−32	−6	3.74	23	
Caudate L		−10	12	−2	4.33	113	
Ventral striatum R		8	2	−2	4.01	30	
Ventral striatum R		16	6	−14	4.00	20	
Cerebellum crus 1, 2 R		34	−70	−32	4.18	308	
Cerebellum lobule 6 L		−42	−52	−26	4.13	54	
Session 2 > Session 3							
HC L ROI		−30	−14	−20	2.55	20	0.006
HC R ROI		26	−6	−22	3.66	131	<0.001
AMG R ROI		28	−4	−20	3.07	30	0.001
Occipital middle L	37, 39	−36	−68	16	4.51	302	
Calcarine R	19	28	−56	8	4.38	75	
Calcarine L	17	−8	−64	12	3.74	73	
Cuneus L	18	−8	−88	22	3.60	106	
Cingulate middle R	23	12	−28	44	4.13	54	
Temporo-parietal junction R	41, 42	52	−34	22	3.64	40	
Putamen L		−32	−8	2	4.39	119	
Putamen R		34	4	4	4.38	80	
Ventral striatum R		6	22	4	4.25	125	
Session 3 > Session 2							
	–						
Negative > Neutral							
AMG L ROI		−28	2	−20	2.70	13	0.004
PFC lateral L	45, 46	−40	34	36	3.67	46	
Calcarine L	18	−8	−84	16	3.49	21	
Neutral > Negative							
	–						
Session x emotion interaction (neutral drop, negative rise)							
HC L ROI		−32	−32	−12	3.65	63	<0.001
		−30	−6	−28	2.93	36	0.002
AMG L ROI		−28	−4	−24	2.80	23	0.003
Parahippocampal, fusiform L	37, 30	−32	−32	−16	4.16	220	

(Continued)

Table A2 | Continued

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
Parahippocampal, fusiform R	37, 30	22	−40	−12	4.10	190	
Parietal inferior L	40	−28	−46	42	4.09	82	
Parietal superior L	7	−22	−72	48	3.43	64	
Dorsomedial PFC (posterior) L	6	−22	0	52	3.67	35	
Postcentral R	3	58	−16	44	3.61	26	
Session x emotion interaction (negative drop, neutral rise)							
	–						
OLDER GROUP							
Hits > misses main effect							
HC L ROI		−26	−26	−14	4.03	290	<0.001
HC R ROI		32	−24	−14	3.45	185	0.001
Precuneus, cingulate posterior, cuneus, retrosplenial, calcarine, lingual LR	26, 29, 30, 23, 7, 17, 18	−8	−68	22	6.56	2270	
Occipital mid/sup, cuneus, precuneus R	19, 7	36	−70	30	5.79	897	
Fusiform, temporal inferior/middle L	20, 37	−44	−54	−24	5.54	924	
Lingual, retrosplenial R	19, 30	22	−50	−6	3.90	80	
Temporal inferior R	20, 37	50	−46	−18	4.07	194	
Temporal superior R	38	62	2	−4	3.95	33	
Temporal superior R	22	68	−34	16	3.70	20	
Angular, parietal inferior L	39, 40	−38	−64	42	5.46	2312	
Supramarginal R	40, 2	62	−28	40	4.22	241	
Parietal inferior R	40	54	−52	48	3.91	29	
VLPFC L	45, 46	−46	44	8	4.27	149	
VLPFC L	45	−54	14	0	3.66	63	
HC L		−26	−30	−14	4.14	115	
Thalamus LR		0	−12	4	4.00	68	
Rolandic operculum R	48	48	−12	20	3.81	22	
Cerebellum crus 1 R		38	−70	−38	5.12	674	
Cerebellum lobule 6 L		−18	−74	−16	4.76	328	
Cerebellum lobule 9 L		−10	−50	−50	3.80	45	
Session 2 > Session 3							
	–						
Session 3 > Session 2							
	–						
Negative > Neutral							
HC R ROI		26	−8	−26	2.82	43	0.003
Neutral > Negative							
	–						
Session x emotion							
	–						

ANOVAs by Age group. All results shown at $p < 0.001$ except ROI analyses at $p < 0.0125$ for HC and AMG. AMG, amygdala; BA, Brodmann Area; HC, hippocampus; L, left; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; R, right; ROI, region of interest.

Table A3 | Neuroimaging results.

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
SESSION 2							
Hits > Misses main effect							
HC L ROI		−28	−22	−18	3.85	411	<0.001
HC R ROI		32	−12	−22	4.36	514	<0.001
AMG R ROI		20	−4	−16	3.44	114	0.001
Ventrolateral PFC, dorsolateral PFC L	44, 45, 46, 47, 10, 6	−46	40	10	6.88	2400	
Angular, parietal inferior, parietal superior, temporal middle, occipital middle L	39, 40, 21, 19, 7	−36	−66	42	6.34	2330	
Cingulate middle/posterior LR	23	−2	−32	34	5.99	286	
Retrosplenial, precuneus, calcarine L	17, 18, 30, 23	−8	−56	18	5.26	460	
Temporal inferior/middle, occipital inferior, fusiform L	20, 37, 19	−42	−66	−10	5.18	1519	
Ventrolateral PFC R	45	56	30	18	4.97	158	
Temporal inferior R	20, 37	48	−56	−12	4.66	142	
Parietal superior, occipital superior R	7, 19	20	−74	42	4.44	278	
HC, parahippocampal R	28, 35, 36, 20	32	−12	−22	4.36	245	
Cingulate anterior dorsal L	32	−4	38	24	4.34	235	
Ventral striatum R	25	10	6	−8	4.26	77	
Ventral striatum L	25	−12	10	−8	4.25	91	
Thalamus LR		−2	−12	0	4.08	89	
parahippocampal, HC (posterior) R	27, 30	22	−34	−4	4.06	157	
Parietal superior R	7	24	−68	56	3.88	90	
Thalamus L		−18	−26	16	3.85	26	
Precuneus ventral R	30	12	−54	14	3.81	53	
Cerebellum crus 1, 2 R		22	−70	−32	3.62	46	
Younger > Older							
	–						
Older > Younger							
HC L ROI		−14	−36	8	2.87	20	0.003
Precuneus R	7	14	−70	42	4.28	62	
Thalamus L		−18	−26	16	3.99	29	
Insula L		−38	−12	18	3.89	22	
Rolandic operculum L		−36	−28	20	3.66	22	
Parietal inferior R	40	56	−52	44	3.63	28	
Temporal superior L	41	−44	−36	12	3.58	25	
Negative > Neutral							
	–						
Neutral > Negative							
Cerebellum lobule 8 L		−6	−64	−36	4.02	34	
Parietal inferior L	40	−30	−44	44	3.87	41	
Cerebellum lobule 6 R		24	−64	−22	3.55	40	
Age x emotion interaction							
	–						
SESSION 3							
Hits > misses main effect							
HC L ROI		−26	−28	−12	3.19	60	0.001
HC R ROI		30	−22	−10	3.21	38	0.001
Cerebellum crus 1, 2 R		34	−72	−36	5.87	1382	
Cerebellum crus 1, 2 L		−40	−54	−28	4.78	333	
Parietal inferior, angular L	39, 40	−40	−56	50	4.67	475	
Vermis		0	−62	−34	4.09	112	

(Continued)

Table A3 | Continued

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
Ventrolateral PFC L	47	−48	22	−10	4.09	22	
Thalamus LR		−2	−8	6	4.01	96	
Lingual L	18	−14	−86	−14	3.97	71	
Ventrolateral PFC L	45	−48	44	−2	3.77	37	
Younger > Older							
	–						
Older > Younger							
HC L ROI		−34	−32	−6	3.33	77	0.001
Precuneus, cuneus, cingulate middle LR	7, 18, 23	−4	−76	24	5.00	1852	
Supramarginal, rolandic operculum, temporal superior R	48, 2, 42	52	−18	22	4.81	1112	
Temporal superior L	22	−60	−2	−2	4.70	165	
Lingual, cerebellum lobule 6 L	18	−10	−62	−16	4.59	567	
Temporal superior, supramarginal L	42, 40	−64	−32	22	4.44	159	
Occipital middle R	19	34	−68	28	4.19	60	
Supplementary motor area R	6	8	−12	66	4.15	64	
Occipital middle, angular R	39	40	−68	28	4.12	70	
Cerebellum crus 1, 2 L		−24	−82	−30	4.11	128	
Postcentral R	3	34	−22	58	3.88	66	
Cerebellum crus 1 R		20	−76	−24	3.75	111	
Postcentral R	3	34	−34	54	3.70	26	
Precentral R	6	44	−10	58	3.62	33	
Precuneus L	5	−12	−44	56	3.60	25	
Postcentral L	3	−28	−38	50	3.51	24	
Negative > Neutral							
HC L ROI		−30	−6	−26	3.10	99	0.001
HC R ROI		34	−10	−24	3.03	53	0.002
AMG R ROI		30	−2	−26	2.93	36	0.002
Parahippocampal, fusiform R	30	20	−36	−12	4.46	32	
Dorsomedial PFC R	8	26	4	58	3.94	52	
Precuneus R	5	8	−46	68	3.89	30	
Cingulate middle L	23	−10	−22	38	3.66	27	
Neutral > Negative							
	–						
Age x emotion interaction							
	–						

ANOVAs by Session. All results shown at $p < 0.001$ except ROI analyses at $p < 0.0125$ for HC and AMG. AMG, amygdala; BA, Brodmann Area; HC, hippocampus; L, left; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; R, right; ROI, region of interest.

Table A4 | Neuroimaging results.

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
NEGATIVE							
Hits > misses main effect							
HC L ROI		−30	−18	−20	4.16	309	<0.001
HC R ROI		30	−14	−22	4.38	362	<0.001
AMG L ROI		−30	−4	−22	2.89	13	0.003
AMG R ROI		32	−4	−28	3.41	73	0.001
Ventrolateral PFC L	45, 47, 44, 6	−42	42	14	6.88	3090	
Ventrolateral PFC R	45	56	30	16	5.70	275	
Dorsomedial PFC L	8	−14	20	60	4.31	55	
Cingulate anterior dorsal L	24, 32	−6	34	30	5.98	599	
Cingulate anterior dorsal R	24, 32	8	38	16	4.22	64	
Cingulate middle/posterior LR	23	−2	−32	34	5.48	373	
Cingulate middle/posterior L	23	0	−10	32	4.23	102	
Cingulate posterior, cuneus R	18, 23	16	−60	18	3.82	91	
Occipital middle, angular, parietal inferior L	19, 39, 40	−38	−72	38	5.94	1700	
Cuneus, precuneus, calcarine L	23, 7, 18	−8	−68	22	4.96	626	
Occipital superior, cuneus, precuneus R	19, 7	20	−76	42	4.48	326	
Supramarginal R	40	66	−32	32	3.65	23	
Temporal inferior L	37, 20	−44	−54	−24	4.31	668	
Temporal inferior R	37	58	−54	−10	3.58	48	
Thalamus medial LR		−4	−10	0	5.11	731	
Caudate L		−10	12	−4	5.27	264	
HC, parahippocampal L		−30	−18	−20	4.16	112	
HC, parahippocampal R		30	−14	−22	4.38	170	
Retrosplenial L	27	−14	−36	−4	3.89	68	
Cerebellum crus 1/2 R		36	−74	−36	3.81	40	
Session 2 > Session 3							
HC R ROI		30	−14	−22	2.95	60	0.002
Session 3 > Session 2							
Cerebellum lobule 6 R		−4	−64	−34	3.65	22	
Younger > Older							
	–						
Older > Younger							
HC R ROI		28	−16	−18	2.74	80	0.004
Dorsolateral PFC L	9	−28	28	34	3.93	33	
Precentral R	6	60	6	24	3.59	38	
Precuneus/cuneus R	7, 18	12	−68	36	4.50	183	
Precuneus/cuneus L	7, 18	−6	−74	26	4.00	140	
Rolandic operculum R	48	50	−12	18	4.37	196	
Rolandic operculum L	48	−60	2	6	4.23	25	
Temporal superior L	22	−60	−2	−2	4.15	24	
Temporal superior/supramarginal L	42	−64	−26	20	3.54	21	
Postcentral L	43	−52	−10	26	3.70	34	
Session × Age interaction (younger drop, older rise)							
Ventrolateral PFC R	45	46	46	0	3.79	35	
Ventrolateral PFC L*	45, 47	−36	36	6	3.19		
Session × Age interaction (younger rise, older drop)							
	–						

(Continued)

Table A4 | Continued

Brain areas	BA	MNI coordinates			*t*	*k*	*p* (ROI-peak)
		x	*y*	*z*			
NEUTRAL							
Hits > misses main effect							
HC L ROI		−26	−26	−14	3.66	168	<0.001
HC R ROI		24	−28	−10	3.17	186	0.001
Ventrolateral PFC L	45, 46	−46	46	0	3.82	55	
Angular, parietal inferior L	7, 39, 40	−40	−64	44	4.71	757	
Temporal inferior R	37	46	−60	−10	4.22	117	
HC, parahippocampal L		−24	−30	−12	3.87	75	
Cerebellum crus 1 L		−16	−68	−32	3.82	36	
Cerebellum crus 1/2, lobule 6 R		14	−80	−30	5.62	966	
Cerebellum lobule 6, fusiform L	37	−40	−52	−26	5.24	952	
Vermis		−4	−60	−34	4.44	356	
Vermis		−2	−50	−12	3.74	69	
Session 2 > Session 3							
HC L ROI		−20	−14	−22	3.78	97	0.002
HC R ROI		22	−34	−4	3.78	97	<0.001
HC R ROI		26	−2	−26	3.27	92	0.001
AMG R ROI		30	4	−28	4.43	58	<0.001
Fusiform, parahippocampal L	30, 37	−28	−34	−18	5.05	284	
Fusiform, parahippocampal R	30, 37	22	−36	−12	4.21	89	
Fusiform, parahippocampal R	20	36	−32	−20	4.01	32	
Temporal inferior L	20	−46	−46	−14	3.62	26	
AMG R		30	4	−28	4.43	28	
Parietal superior L	7	−20	−72	54	3.99	43	
Occipital superior L	18	−24	−92	26	3.85	33	
Putamen L		−30	−12	2	4.02	35	
Postcentral R	3	40	−18	34	3.66	35	
Postcentral L	4	−54	−18	50	3.43	22	
Session 3 > Session 2							
	–						
Younger > Older							
	–						
Older > Younger							
HC L ROI		−36	−34	−6	3.16	59	0.001
Precuneus R	5	10	−46	56	4.52	109	
Parietal inferior, supramarginal, angular R	40, 39	60	−44	38	4.23	284	
Supramarginal R	48	52	−18	26	4.21	135	
Calcarine, lingual L	17	−8	−66	2	4.15	105	
Rolandic operculum L	48	−30	−30	14	3.81	21	
Postcentral R	3	30	−40	54	4.30	88	
Postcentral R	3	48	−18	52	3.81	21	
Session × Age interaction							
	–						

*ANOVAs by Emotion. All results shown at $p < 0.001$ except ROI analyses at $p < 0.0125$ for HC and AMG. *Left ventrolateral PFC significant at $p < 0.005$. AMG, amygdala; BA, Brodmann Area; HC, hippocampus; L, left; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; R, right; ROI, region of interest.*

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Neural mechanisms of reading facial emotions in young and older adults

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The ability to read and appropriately respond to emotions in others is central for successful social interaction. Young and older adults are better at identifying positive than negative facial expressions and also expressions of young than older faces. Little, however, is known about the neural processes associated with reading different emotions, particularly in faces of different ages, in samples of young and older adults. During fMRI, young and older participants identified expressions in happy, neutral, and angry young and older faces. The results suggest a functional dissociation of ventromedial prefrontal cortex (vmPFC) and dorsomedial prefrontal cortex (dmPFC) in reading facial emotions that is largely comparable in young and older adults: Both age groups showed greater vmPFC activity to happy compared to angry or neutral faces, which was positively correlated with expression identification for happy compared to angry faces. In contrast, both age groups showed greater activity in dmPFC to neutral or angry than happy faces which was negatively correlated with expression identification for neutral compared to happy faces. A similar region of dmPFC showed greater activity for older than young faces, but no brain-behavior correlations. Greater vmPFC activity in the present study may reflect greater affective processing involved in reading happy compared to neutral or angry faces. Greater dmPFC activity may reflect more cognitive control involved in decoding and/or regulating negative emotions associated with neutral or angry than happy, and older than young, faces.

Keywords: emotion, faces, aging, medial prefrontal cortex, amygdala, affective processing, cognitive control

INTRODUCTION

Humans are social-emotional beings. From early on and throughout our life, we are surrounded by social and emotional stimuli that are crucial for our survival and well-being. The ability to correctly interpret other peoples' feelings, intentions, and behavior, and then respond appropriately and remember such social and emotional information, correctly, is central for successful social interaction (Baron-Cohen et al., 2000; Grady and Keightley, 2002; Adolphs, 2003). Successful and satisfying social interactions and avoiding social isolation have important consequences for our subjective and objective health and well-being across the entire lifespan (Cornwell and Waite, 2009; Cacioppo et al., 2011). In addition, our interpretation of facial expressions in others has been shown to influence how we attend to, and how well we remember, faces (Ebner and Johnson, 2009; Ebner et al., 2011c).

The effect of aging on reading facial emotions has recently received considerable interest. As summarized in a meta-analysis by Ruffman et al. (2008) that considered data from 962 young (mean age 24 years) and 705 older (mean age 70 years) participants, the predominant pattern was age-related decline in identification of facial emotions (largely comparable findings were also reported for voices, bodies, and matching faces to voices). In particular, compared to young adults, older adults are worse at identifying facial expressions of anger, sadness, and fear. For happiness and surprise, these age-group differences go in the same direction, but are substantially smaller. When interpreting these results, however, one needs to consider that most previous studies have used only one positive expression among various negative expressions. Assuming negative emotions are more difficult to distinguish from each other than from positive emotions, findings of age differences in reading facial emotions may simply reflect older compared to young adults' greater difficulty in discriminating among more similar negative emotions (Ebner and Johnson, 2009; Ebner et al., 2011c).

In addition, the meta-analysis by Ruffman et al. (2008) suggests that each age group is more accurate in identifying certain expressions than others. In particular, older adults have more difficulty identifying anger, sadness, and fear, compared to disgust, surprise, and happiness, whereas young adults have more difficulty identifying fear and disgust, followed by anger, surprise, sadness, and happiness (Ebner and Johnson, 2009; Murphy and Isaacowitz, 2010; see Isaacowitz et al., 2007, for another meta-analysis).

The literature discusses at least three explanations for age-group differences in reading facial expressions.

(a) *Age-related change in motivational orientation*: According to *Socio-emotional Selectivity Theory* (Carstensen et al., 1999;

Carstensen, 2006), due to an increase in perception of future time as limited, older adults become more motivated to maximize positive affect and minimize negative affect in the present, as an adaptive emotion regulation strategy. This is assumed to result in a greater attentional and memory-related focus on, and preference for, positive over negative information (Carstensen and Mikels, 2005; Mather and Carstensen, 2005). This age-related change may be reflected in older adults' impaired ability to identify negative expressions, whereas the recognition of positive expressions may improve (or at least remain unaffected) with age. This pattern of results is at least partly consistent with the overall literature (see Ruffman et al., 2008). However, findings that older adults are sometimes worse in labeling positive expressions than young adults, and that they are not always worse in recognition of negative expressions (e.g., disgust), are somewhat inconsistent with this theoretical account.

(b) *General age-related cognitive decline*: This account is based on evidence that older adults experience declines in cognition across various functional domains. For instance, normal aging is accompanied by a relative sparing of crystallized abilities (e.g., vocabulary). However, there is broad evidence of age-related declines in processes that involve greater mental effort, self-initiation, inhibitory control, information complexity, novelty, processing speed, and/or working memory (i.e., fluid abilities; Salthouse, 2000; Lustig and Hasher, 2001; Hedden and Gabrieli, 2004). Such age-related changes in general cognitive functioning may have a negative impact on older adults' ability to identify facial expressions. The little research to date investigating this account does not support this assumption. Rather, the existing studies show that age differences in facial emotion identification remain when accounting for fluid intelligence. For example, age-related reductions in labeling negative expressions were shown to be independent of general age-related cognitive changes in processing speed, basic face processing abilities, and reasoning about non-face stimuli (Sullivan and Ruffman, 2004; Keightley et al., 2006).

(c) *Age-related structural and functional brain changes*: The third account discussed in the literature pertains to evidence that some regions involved in emotional face processing, such as frontal and temporal regions, show substantial structural (Raz and Kennedy, 2009) and functional (Iidaka et al., 2001; Gunning-Dixon et al., 2003; Fischer et al., 2005; Wright et al., 2007) changes with age. These changes may contribute to age-related deficits in the accuracy and speed of reading facial emotions (see Calder et al., 2003; Ruffman et al., 2008). The empirical examination of such effects, however, is still very sparse and the current knowledge about the specific neural processes underlying these effects and potential differences in the neural mechanisms between young and older adults is still very limited.

The particular focus of the present study was on the neural underpinnings of *expression identification of faces* in samples of young and older adults. To our knowledge, only very few fMRI studies to date have explicitly addressed this question as outlined in more detail below (Gunning-Dixon et al., 2003; Williams et al., 2006; Keightley et al., 2007; for a broader discussion of functional neuroimaging evidence on aging and emotion, see St Jacques et al., 2009; Samanez-Larkin and Carstensen, 2011). Importantly, due to design-related issues, none of these previous studies could directly relate young and older adults' brain activity during facial emotion reading to accuracy or speed of performance. Thus, the present study set out to fill this gap by identifying brain activity in young and older adults during facial emotion reading with happy, neutral, and angry faces, including both young and older faces. Our design allowed us to directly examine the relationship between brain response during task engagement and accuracy and speed of responding in both young and older adults.

Evidence so far suggests involvement of a wide range of neural systems in processing facial emotions, independent of the specific valence, and/or emotion displayed (see Ruffman et al., 2008, for an overview). At the same time, certain brain areas seem to particularly contribute to the processing of individual emotional facial displays and/or seem to be differentially involved in reading positive vs. neutral or negative facial expressions. This suggests that at least partially distinct neural circuits subserve individual emotions and/or different valence of facial expressions.

Ventromedial prefrontal cortex (vmPFC) has been shown to be associated with processing happy faces, possibly in conjunction with amygdala (Keightley et al., 2007; see also Ruffman et al., 2008). This may be due to vmPFC's function in assessing and representing reward (O'Doherty et al., 2001; Kringelbach and Rolls, 2004). Dorsomedial prefrontal cortex (dmPFC), in contrast, has been shown to be sensitive to various negative expressions (Williams et al., 2006; Keightley et al., 2007). Another area that has been shown to be recruited in emotional face processing is the cingulate cortex (Taylor et al., 1998; Bush et al., 2000; Whalen et al., 2001; Keightley et al., 2003). Both anterior and posterior cingulate cortex are associated with identifying facial expressions of happiness (Salloum et al., 2007), anger (Blair and Cipolotti, 2000), and sadness (Killgore and Yurgelun-Todd, 2004; Salloum et al., 2007).

The majority of neuroimaging studies with young adults have found amygdala activation during viewing of negative faces (and in particular fear and anger but also sadness; Morris et al., 1996; Whalen et al., 2001; Anderson et al., 2003). However, some studies also show increased amygdala activity to positive faces in young adults (Hamann et al., 2002; Pessoa et al., 2002; Winston et al., 2003; Zald, 2003), suggesting that amygdala may have a more general role in directing attention to socially and emotionally relevant cues (Cunningham et al., 2004; Vuilleumier, 2005) than simply and exclusively responding to negative information.

Most neuroimaging studies of processing of positive, neutral, and negative facial expressions conducted so far have limited their investigation to samples of young adults (cf. Gunning-Dixon et al., 2003; Williams et al., 2006; Keightley et al., 2007). Examination of comparable mechanisms between young and older adults as well as differences among the age groups, as both addressed in the present study, will shed more light on the neural and cognitive processes involved in reading facial emotions and their relation to fast and correct facial expression identification. In an investigation of the neural processes involved in facial expression identification in a sample of young and older adults, both structural and functional

age-related changes in brain areas associated with this task should be important, as addressed next.

Gradual atrophy is widespread in the brain in aging (Raz et al., 2005; Raz and Kennedy, 2009). At the same time, there is evidence that age-related brain volume reductions and metabolic decline occur earlier and more rapidly in frontal, and particularly in lateral compared to medial frontal, brain regions (Dimberger et al., 2000; Allen et al., 2005; Grieve et al., 2005; Phillips and Henry, 2005). In addition to mPFC, temporal regions such as the amygdala decline less rapidly. Still these areas experience linear volume reductions with age (Mu et al., 1999; Grieve et al., 2005; Wright et al., 2006; Zimmerman et al., 2006).

In addition to age-related structural changes in brain areas associated with processing facial emotions, there also is some evidence of important functional brain changes with age. Consistent evidence of reduced subcortical activity accompanied by increased cortical involvement in older compared to young adults has been shown across various tasks, such as passive viewing of angry and neutral faces (Fischer et al., 2005), gender discrimination of positive, neutral, and negative faces (Iidaka et al., 2001), matching facial emotions of angry and fearful faces (Tessitore et al., 2005), and also age and emotion identification of happy, sad, angry, fearful, disgusted, and neutral faces (Gunning-Dixon et al., 2003; see also Williams et al., 2006; Keightley et al., 2007). This age-related shift toward prefrontal-based and away from amygdala-based facial emotion processing has been interpreted as reflecting more deliberative, controlled processing of emotional information in older than young adults (Satpute and Lieberman, 2006; Williams et al., 2006; see Mather et al., 2004; St Jacques et al., 2010, for similar evidence with scenes and objects) and may reflect age-related increased emotion regulation strategies mediated by frontal brain regions (see St Jacques et al., 2009, for an overview and a discussion).

In particular, using an emotional face viewing task (followed by a facial expression identification task outside the scanner) with blocks of happy and fearful faces in an fMRI study, Williams et al. (2006) found a linear decrease in dmPFC (MNI: $x = -18$, $y = 22$, $z = 54$) activity to happy faces and a linear increase in dmPFC (MNI: $x = -14$, $y = 36$, $z = 42$) activity to fearful faces with increasing age. This finding was interpreted as further support of greater effort and increased controlled processing of negative compared to positive faces with advancing age. Importantly, this shift in mPFC activity for processing positive vs. negative faces was associated with emotional stability: Less dmPFC response to happy faces and more dmPFC response to fearful faces during the face viewing task predicted greater self-reported emotional stability (i.e., lower levels of self-reported neuroticism).

Williams et al.'s (2006) findings are in line with another study that examined differences between young and older adults' brain activity in the context of a facial expression identification task and that explicitly differentiated happy from various negative expressions. Keightley and colleagues (Keightley et al., 2007) conducted an event-related fMRI study with faces depicting anger, disgust, fear, happiness, sadness, and surprise. To avoid verbal responses and the high memory load of a multiple-alternative forced-choice response format, participants overtly labeled the faces prior to entering the scanner. They then saw each face again during the scanner task and were asked to silently (re-)label each of them. Largely in line with the literature (Isaacowitz et al., 2007; Ruffman et al., 2008; Ebner and Johnson, 2009), young and older adults performed equally well in identifying happy faces, with ceiling performance in both groups. In addition, young adults outperformed older adults in identifying sadness, anger, and disgust but there were no differences in identifying surprise, fear, or neutral faces.

With respect to the fMRI data, Keightley et al. (2007) reported various findings. One pattern that distinguished happy from other expressions, largely driven by *young adults*, was characterized by greater activity in vmPFC, among other areas (i.e., anterior and posterior cingulate gyrus, left postcentral gyrus, and bilateral middle frontal gyri, bilateral cuneus, precuneus, inferior parietal lobe, and superior temporal gyrus). This was accompanied by decreased activity in left dorsal anterior cingulate gyrus for happy compared to other facial expressions. In addition, at a lower threshold, for young (but not older) adults, there was greater activity in small regions of bilateral amygdala and greater activity in left hippocampus for happy compared to other expressions. A second pattern distinguishing happy from other expressions was largely driven by *older adults*, and was characterized by greater activity in vmPFC among other areas (i.e., lingual gyrus and bilateral premotor cortex; for older adults brain activity in these areas was greater for happy and, to a lesser degree, also disgusted faces when compared with all other expressions). In addition, there was less activity in dorsal anterior cingulate among other areas (i.e., middle and inferior frontal gyrus, somatosensory cortex, middle temporal gyrus, and insula) to happy (and disgust) faces than all other expressions.

Both these brain patterns supported a dorsal/ventral distinction in mPFC that differentiated happy from other facial expressions (note that Keightley et al., 2007, did not differentiate further between the various negative expressions). Importantly, for young and older adults, there was greater activity for happy than other expressions in very similar areas of vmPFC, and, at the same time, greater activity for all other facial expressions compared to happy (and disgust) in very similar regions of dorsal anterior cingulate cortex. Thus, young and older adults partly used different brain networks during (re-)labeling emotional faces. At the same time, however, there was great overlap in the networks recruited by young and older adults, suggesting that the neural processes underlying facial expression identification change little with age. No direct correlational findings between brain activity and accuracy or speed of facial expression reading were reported in the paper.

Taken together, so far most aging studies on processing facial emotions have not explicitly differentiated between different emotions or valences in their analyses (Gunning-Dixon et al., 2003), or have focused exclusively on (different) negative but not positive expressions (Fischer et al., 2005; Tessitore et al., 2005). Moreover, the few studies that have considered both positive and negative faces either did not use facial emotion identification as their orienting task (Iidaka et al., 2001), or conducted facial expression identification outside the scanner (prior to scanning: Keightley et al., 2007; or post scanning: Williams et al., 2006), and thus could not assess correlations between brain activity during task engagement and behavioral performance. There is some evidence in the literature, however, of age differences in attention to, and

preference for, positive vs. negative information (Mather and Carstensen, 2005; Isaacowitz et al., 2006; cf. Murphy and Isaacowitz, 2008, for a recent meta-analysis that finds only limited support for a general "positivity effect" in aging). Thus, valence of the expression display is likely to be central for understanding the neural mechanisms involved in facial emotion reading in young and older adults. For example, studies that have used emotional scenes or objects (not faces) have shown greater recruitment of amygdala during the processing of positive than negative scenes in older compared to young adults (Mather et al., 2004; Moriguchi et al., 2011). Also, older compared to young adults were found to recruit vmPFC to a greater extent during processing of positive than negative objects (Leclerc and Kensinger, 2008). And, as reported above, older adults show increased dmPFC activity to negative faces and decreased dmPFC activity to positive faces (Williams et al., 2006). This evidence points to the importance of considering valence as an explicit factor in the design when examining the neural processes involved in reading facial emotions, and when exploring neural-behavioral correlations in samples of young and older adults.

Another important factor, largely ignored in previous studies, is the age of the presented faces. All of the imaging studies on facial emotion reading so far have exclusively used faces of young, and some middle-aged, adults but none has examined the neural mechanisms underlying age differences in reading facial emotions by systematically varying young and older adult faces. However, there is increasing behavioral and neuroimaging evidence of age-of-face effects on processing of faces, such as on attention (e.g., Ebner and Johnson, 2010; Ebner et al., 2011b), evaluation (Ebner et al., 2011a), age estimation (Voelkle et al., 2012), and memory (see Rhodes and Anastasi, 2012, for a meta-analysis; see also Ebner and Johnson, 2009; He et al., 2011). In particular, recent behavioral studies that examined the impact of the age of the face on young and older adults' ability to correctly identify facial emotions suggest that performance in both age groups is better for young than older faces (Ebner and Johnson, 2009; Ebner et al., 2011c; Riediger et al., 2011). One possibility is that expressions in young compared to older faces are easier to read because emotion cues are more explicit and less ambiguous in young than (more wrinkled and thus more complex) older faces (see Ebner and Johnson, 2009; Ebner et al., 2011b).

The present study had the following two major aims (see **Table 1** for a summary): *Research Aim 1* was to examine brain activity in vmPFC, dmPFC, and amgydala during facial expression identification as a function of facial expression and age of face, respectively, across young and older adults. As outlined above, previous neuroimaging evidence suggests a role of vmPFC and dmPFC in facial expression reading in young and older adults and amygdala involvement in young adults (Keightley et al., 2007). Moreover, behavioral studies suggest that happy and young faces are easier to read than angry (or neutral) and older faces for young and also older adults (Ebner and Johnson, 2009; Ebner et al., 2011c). Based on this previous evidence, *Hypothesis 1a* predicted greater activity in vmPFC to happy than angry (or neutral) faces, and similarly to young than older faces, for both young and older adults. Even though various studies suggest amygdala activation during viewing of negative faces (Whalen et al., 2001), Keightley et al. found greater amygdala activation, at least in young adults, to happy than various other (negative) facial expressions in a facial expression identification task quite similar to the one used in the present study. Thus, *Hypothesis 1b* predicted greater amygdala activity to happy than angry (or neutral) faces, and also to young than older faces, for both young and older adults. *Hypothesis 1c* predicted greater dmPFC activity to angry (or neutral) than happy faces, and to older than young faces, across both young and older adults. Based on previous literature, reviewed above, suggesting some age-group differences in vmPFC, dmPFC, and amygdala activity during facial expression reading (Gunning-Dixon et al., 2003; Williams et al., 2006; Keightley et al., 2007), *Hypothesis 1d* predicted greater dmPFC activity to angry (or neutral) than happy faces in older than young participants. This age difference may be due to increased controlled processing of negative relative to positive information with age (Williams et al., 2006) and/or older adults' particular difficulty decoding anger from faces (Ruffman et al., 2008; see also Ebner and Johnson, 2009; Ebner et al., 2011c).

The expected ventral/dorsal distinction in mPFC (see *Hypotheses 1a* and *1c*) may reflect greater "ease" of (i.e., less controlled) processing of happy than angry (or neutral) faces and young than older faces (see Williams et al., 2006). Consequently, *Research Aim 2* was to examine the brain-behavior correlations in vmPFC, dmPFC, and amygdala for the facial expressions in relation to each other as well as young vs. older faces in samples of young and older adults. In particular, *Hypothesis 2a* predicted a positive correlation between vmPFC activity to happy relative to angry (or neutral) faces and accuracy, as well as speed, of identifying happy relative to angry (or neutral) expressions in both young and older adults. A similar pattern was predicted for young compared to older faces. In addition, comparable correlations were expected for amygdala activity (*Hypothesis 2b*). *Hypothesis 2c*, in contrast, predicted a negative correlation between dmPFC activity to angry (or neutral) relative to happy faces and accuracy, as well as speed, of identifying angry (or neutral) relative to happy expressions in both young and older participants. Again, a comparable pattern was predicted for older compared to young faces.

The focus of the present paper on mPFC and amygdala as regions of interest (ROI) was motivated by evidence outlined above that these areas appear to be particularly involved in facial emotion reading in young and older adults (Keightley et al., 2007). In addition, these regions have been shown to be involved in thinking about the self in both young and older adults (Gutchess et al., 2007; Mitchell et al., 2009; Ebner et al., 2011a). That is, areas of mPFC are recruited when young (Amodio and Frith, 2006; Mitchell, 2009; Van Overwalle, 2009) and older (Gutchess et al., 2007; Ebner et al., 2011a) adults "mentalize" about their own or other people's intentions, thoughts, feelings, and preferences, or empathize with them (Völlm et al., 2006), which are processes that appear particularly relevant when attempting to decode other people's emotions and feelings from facial displays as in the present study. In addition, these brain regions show only moderate age-related structural changes (Raz and Kennedy, 2009) and show largely intact functional patterns in older adults (Gutchess et al., 2007; Wright et al., 2008; Ebner et al., 2011a, in preparation), even in studies that find overall lower activity in these regions in older than young adults (Mather et al., 2004; Mitchell et al., 2009). Also,

Table 1 | Overview of the central research aims and study predictions.

Research aim	Specific study prediction	Previous evidence
Research Aim 1: Brain activity in vmPFC, dmPFC, and amgydala during facial expression identification as a function of facial expression and age of face in young and older adults	*Hypothesis 1a*: Greater vmPFC activity to happy than angry (or neutral) faces and to young than older faces across age groups *Hypothesis 1b*: Greater amygdala activity to happy than angry (or neutral) faces and to young than older faces across age groups *Hypothesis 1c*: Greater dmPFC activity to angry (or neutral) than happy faces and to older than young faces across age groups *Hypothesis 1d*: Greater dmPFC activity to angry (or neutral) than happy faces in older than young adults	e.g., Gunning-Dixon et al. (2003), Williams et al. (2006), Keightley et al. (2007), Ruffman et al. (2008), Ebner and Johnson (2009), Ebner et al. (2011c)
Research Aim 2: Brain-behavior correlations in vmPFC, dmPFC, and amygdala for different facial expressions and different age of faces in young and older adults	*Hypothesis 2a*: Positive correlations between vmPFC activity to happy relative to angry (or neutral) faces and ability of identifying happy relative to angry (or neutral) faces in young and older adults; similar pattern predicted for young relative to older faces *Hypothesis 2b*: Positive correlations between amygdala activity to happy relative to angry (or neutral) faces and ability of identifying happy relative to angry (or neutral) faces in young and older adults; similar pattern predicted for young relative to older faces *Hypothesis 2c*: Negative correlations between dmPFC activity to angry (or neutral) relative to happy faces and ability of identifying angry (or neutral) vs. happy faces in young and older adults; similar pattern predicted for older relative to young faces	e.g., Williams et al. (2006), Ruffman et al. (2008), Ebner et al. (2011c)

as discussed above, there is evidence of an age-related shift from amygdala to more frontal regions with aging during processing of facial emotions (Iidaka et al., 2001; Gunning-Dixon et al., 2003; Fischer et al., 2005; St Jacques et al., 2009). This evidence combined makes mPFC and amygdala particularly interesting candidates in an examination of the neural mechanisms underlying facial emotion reading in samples of young and older adults.

MATERIALS AND METHODS

PARTICIPANTS

Participants were healthy young adults [$n = 30$ (16 females), $M = 25.1$ years (SD = 3.4; range = 20–31)] and healthy, active, independently living older adults [$n = 32$ (18 females), M age = 68.2 years (SD = 2.5; range = 65–74)]. Due to technical problems with the response pad, behavioral data for the task were lost for one older woman and one older man. Thus, all behavioral data were based on $N = 60$ participants. Young [$M = 14.8$ years (SD = 2.1; range = 12–19)] and older [$M = 14.5$ years (SD = 3.7; range = 9–27)] participants did not differ in their years of education [$F(1,59) = 0.21$, $p = 0.652$, $\eta_p^2 = 0.00$]. **Table 2** presents descriptive information and age-group differences in cognitive and affective measures for both age groups. There were no differences on MMSE scores, verbal fluency, depression, or anxiety. However, young participants scored better than older participants in processing speed, episodic memory, and working memory, and older participants scored better in vocabulary than young participants. Participants were all in good health, with no known history of stroke, heart disease, or primary degenerative neurological disorder, and were right-handed native Swedish speakers. They all had normal or corrected-to-normal vision (using MR-compatible eyeglasses) and none were known to take psychotropic medications. A radiologist screened both a T1-weighted and T2-weighted structural image of the older participants to rule out gray and white matter lesions and/or abnormal amount of atrophy.

STIMULI

Stimuli were taken from the FACES database (for detailed information, see Ebner et al., 2010). Face stimuli were digital, high-quality, color, front-view head shots on gray background, all standardized in terms of production and general selection procedure. Each participant saw 32 happy, 32 neutral, and 32 angry faces, each a unique identity, with equal numbers of young (18–31 years) and older (69–80 years) male and female faces. Stimulus presentation and response collection (accuracy and response time) were controlled using E-Prime (Schneider et al., 2002).

PROCEDURE, MEASURES, AND DESIGN

The ethics committee at the Karolinska Institute approved the protocol; informed consent was obtained from all participants at the beginning of the study session. The data reported here were

Table 2 | Means (*M*) and standard deviations (SD) and age-group differences for cognitive and affective measures.

Measures	Young participants *M* (SD)	Older participants *M* (SD)	Age-group differences
COGNITIVE FUNCTIONING			
MMSE	29.3 (0.69)	28.9 (0.91)	$F(1, 59) = 3.08$, $p = 0.084$, $\eta_p^2 = 0.05$
LCT	11.0 (2.06)	8.44 (2.01)	$F(1, 59) = 25.6$, $p < 0.001$, $\eta_p^2 = 0.29$
FWRT	10.0 (2.34)	7.16 (1.85)	$F(1, 59) = 28.4$, $p < 0.001$, $\eta_p^2 = 0.33$
2-Back	8.44 (1.38)	6.27 (1.95)	$F(1, 57) = 24.2$, $p < 0.001$, $\eta_p^2 = 0.30$
SST	22.6 (3.68)	26.1 (2.53)	$F(1, 59) = 19.5$, $p < 0.001$, $\eta_p^2 = 0.25$
VF	15.1 (4.97)	16.5 (6.95)	$F(1, 59) = 0.9$, $p = 0.348$, $\eta_p^2 = 0.02$
AFFECTIVE FUNCTIONING			
GDS	1.37 (1.63)	1.45 (2.51)	$F(1, 59) = 0.02$, $p = 0.877$, $\eta_p^2 = 0.02$
STAI	30.5 (5.35)	28.3 (6.61)	$F(1, 58) = 1.98$, $p = 0.165$, $\eta_p^2 = 0.03$

MMSE, Mini Mental State Examination; dementia screening; maximum possible = 30 (higher score representing better cognitive performance); Folstein et al. (1975). LCT, Letter Comparison Task; processing speed; mean number of correct comparisons of two letter strings within 30 s; Salthouse and Babcock (1991). FWRT, Free Word Recall Task; episodic memory; recall of a list of 16 words (e.g., envelope, guitar) after 120 s; newly developed. 2-Back, 2-Back Digits Task; working memory; mean number of correct responses; maximum possible = 10; Kirchner (1958). SST, Swedish Synonym Task; underlining of one synonym to target word out of four choices; maximum possible = 30; Dureman (1960). VF, Verbal Fluency Task; verbal fluency; mean number of correctly generated words starting with a given letter (A and F, respectively), within 60 s; Lezak (1995). GDS, Geriatric Depression Scale; depression screening; maximum possible = 20 (higher scores represent more depressive symptoms); Brink et al. (1982); Gottfries (1997; Swedish version). STAI, State-Trait Anxiety Inventory; state and trait anxiety; maximum possible = 80 (higher scores representing greater state-trait anxiety); Spielberger et al. (1983). There were missing data for questionnaires and covariate measures for one older woman; missing data for 2-Back for one young man and one older woman; missing data for STAI for one young man.

embedded in a larger project. Only a subset of variables is reported in this paper. In the first session, approximately one week before scanning, participants filled in several paper-and-pencil questionnaires (i.e., Demographic Questionnaire, MMSE, GDS, STAI) and worked on various computer tasks (i.e., LCT, FWRT, 2-Back, SST, VF; see **Table 2**).

During the second session (fMRI), participants worked on the *Facial Expression Identification Task* (**Figure 1**). This task had a mixed 2 (*age of participant*: young, older) × 3 (*facial expression*: happy, neutral, angry) × 2 (*age of face*: young, older) factorial design, with *age of participant* as a between-subjects factor and *facial expression* and *age of face* as within-subjects factors. As shown in **Figure 1**, participants saw faces, one at a time. Each face was presented for 3500 ms. Participants were asked to indicate whether the displayed face showed a happy, neutral, or angry expression by pressing one of three response buttons on a button box (index finger for "happy," middle finger for "neutral," and ring finger for "angry" expressions) as fast and accurately as possible. Response options appeared in black on a gray background below the faces and were always presented in the same order. In between faces, a black fixation cross appeared on a gray background on the screen. The inter-stimulus interval (ISI) pseudo-randomly varied between 3000 and 4000 ms in 250 ms increments (mean ISI = 3500 ms). In one-third of the trials (48 out of a total of 144 trials), "low-level baseline events" of three black Xs on a gray background were presented. Participants pressed any one of the three buttons that they also used for labeling the facial expressions to indicate appearance of a low-level baseline trial.

The presentation order of face identities was identical for each participant with facial expressions counterbalanced across participants (each participant only saw each face with one expression). Lists were pseudo-randomized with the constraints that no more than two faces of the same category (i.e., age, gender, facial expression) were repeated in a row. The presentation order of faces and low-level baseline events was pseudo-randomized with the constraint that no more than three faces and no more than two baseline trials were presented in a row. The task started with four practice trials. It was split into two runs, each of them lasting for 8.4 min. At the end of the session, participants were debriefed and financially compensated for participation.

IMAGING DETAILS

Images were acquired using a 3T Siemens Magnetom Trio-Tim scanner at Huddinge Hospital, Stockholm, Sweden. After localizer scans, two runs of 160 functional images each were acquired with a T2*-weighted echo-planar sequence (ep2d_bold; TR = 2500 ms, TE = 40 ms, flip angle = 90°, FoV = 230 mm, voxel size = 3 mm × 3 mm × 3 mm). Thirty-nine oblique axial slices were positioned parallel to the AC-PC line, and acquired interleaved. A 1 mm × 1 mm × 1 mm T1-weighted image was used for co-registration with functional images (MP-RAGE; TR = 1900 ms, TE = 2.52 ms, FoV = 256 mm).

fMRI ANALYSES

Data from this event-related fMRI study was analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience). Pre-processing included slice timing correction, motion correction, co-registration of functional images to the participant's anatomical scan, spatial normalization, and smoothing [9 mm full-width half maximum (FWHM) Gaussian kernel]. Spatial normalization used a study-specific template brain composed of the average of the young and older participants' T1 structural images (detailed procedure for creating this template is available from the authors). Functional images were re-sampled to 3 mm isotropic voxels at the normalization stage, resulting in image dimensions of 53 × 63 × 46.

For the fMRI analysis, first-level, single-subject statistics were modeled by convolving each trial with the SPM canonical hemodynamic response function to create a regressor for each condition

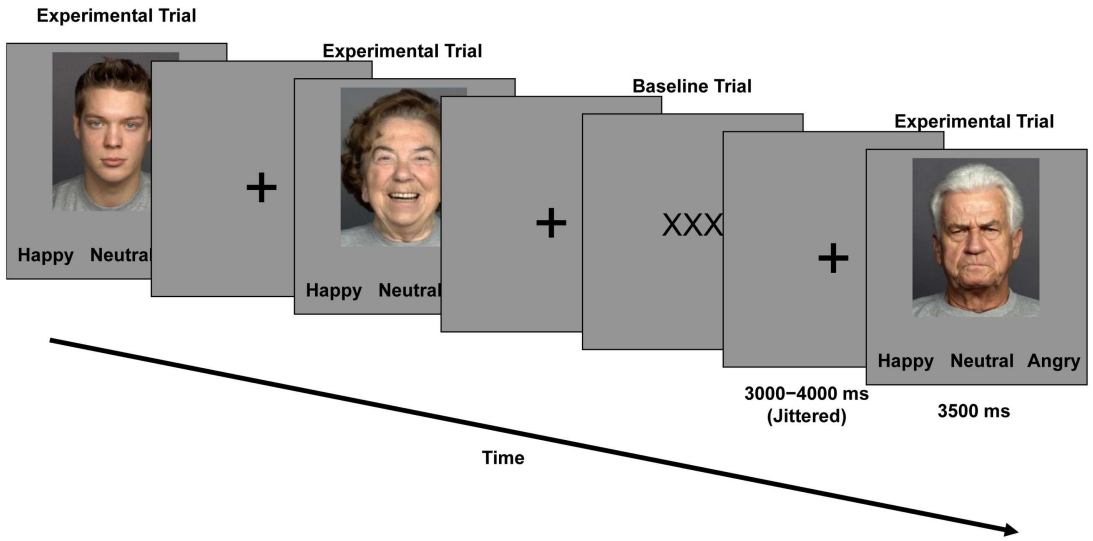

FIGURE 1 | Trial event timing and sample faces used in the *Facial Expression Identification Task*.

(young happy, young neutral, young angry, older happy, older neutral, older angry). Parameter estimates (beta images) of activity for each condition and each participant were then entered into a second-level random-effects analysis using a mixed 2 (*age of participant*) × 3 (*facial expression*) × 2 (*age of face*) ANOVA, with *age of participant* as a between-subjects factor and *facial expression* and *age of face* as within-subjects factors. From within this model, the following six *T*-contrasts were specified across the whole sample to address *Hypotheses 1a–1c* (see **Table 1**): (a) *happy faces* > *neutral faces*, (b) *happy faces* > *angry faces*, (c) *neutral faces* > *happy faces*, (d) *angry faces* > *happy faces*, (e) *young faces* > *older faces*, (f) *older faces* > *young faces*. In addition, the following two *F*-contrasts examining interactions with *age of participant* were conducted to address *Hypothesis 1d* (see **Table 1**): (g) *happy faces* vs. *neutral faces by age of participant*, (h) *happy faces* vs. *angry faces by age of participant*. Analyses were based on all trials, not only on those with accurate performance. Young and older participants' accuracy of reading the facial expressions was quite high for all conditions (ranging between 98.5 and 88.5%; see **Table 3**); that is, only few errors were made. Nevertheless, consideration of all, and not only correct, trials in the analyses leaves the possibility that for some of the facial expressions the subjective categorization may have differed from the objectively assigned one (see Ebner and Johnson, 2009, for a discussion).

We conducted four sets of analyses on selected *a priori* ROIs defined by the WFU PickAtlas v2.4 (Maldjian et al., 2003, 2004[1]; based on the Talairach Daemon) and using different thresholds: (1) For all *T*-contrasts listed above, we used a mPFC ROI mask that comprised bilateral medial frontal gyrus and anterior cingulate gyrus based on the anatomic labels specified in the WFU PickAtlas. For this set of analyses we used a threshold of 10 contiguous voxels each significant at $p < 0.001$, uncorrected for multiple comparisons. (2) All *T*-contrasts were also examined using an amygdala ROI mask comprising bilateral amygdala as specified in the WFU PickAtlas. For examination of this circumscribed, small ROI, we used a threshold of $p < 0.05$, uncorrected, with the number of contiguous voxels unspecified. (3) For all *F*-contrasts (i.e., interactions with participant age), we used the mPFC ROI at a threshold of 10 contiguous voxels, each significant at $p < 0.05$, uncorrected. This lowered threshold was used to increase the sensitivity to detect significant interaction effects with *age of participant*. (4) Finally, for all *F*-contrasts, assessing interactions with participant age, we also conducted analyses using the amygdala ROI, again at a lowered threshold ($p < 0.05$, uncorrected, number of contiguous voxels unspecified).

For each region of activation identified by a contrast, beta values were extracted for each participant to produce a single value for each condition of interest. These values are depicted in the bar graphs and the scatter plots of **Figures 3–5**. In the fashion of

Table 3 | Means (*M*) and standard deviations (SD) for accuracy (%) and response time (ms) in expression identification of happy, neutral, and angry young and older faces for young and older participants.

	Accuracy (%) *M* (SD)		Response time (ms) *M* (SD)	
	Young participants	Older participants	Young participants	Older participants
HAPPY FACES				
Young faces	95.8 (9.5)	98.5 (3.6)	1077 (145)	1234 (241)
Older faces	94.6 (10.6)	96.7 (5.9)	1159 (216)	1250 (212)
NEUTRAL FACES				
Young faces	92.1 (11.9)	96.0 (6.0)	1292 (241)	1318 (228)
Older faces	90.2 (10.7)	91.3 (9.9)	1469 (295)	1567 (267)
ANGRY FACES				
Young faces	94.8 (9.6)	94.6 (10.2)	1340 (251)	1527 (288)
Older faces	88.5 (12.9)	91.9 (9.9)	1451 (295)	1638 (293)

[1]http://www.nitrc.org/projects/wfu_pickatlas/

follow-up F- and t-tests in analysis of variance (ANOVA), subsequent statistical comparisons of these values ($p < 0.05$) were conducted using IBM SPSS Statistics Version 20 to aid interpretation of the activations. Montreal Neurological Institute (MNI) coordinates are reported. Anatomical localization were verified using the Talairach Daemon (Lancaster et al., 1997, 2000) on coordinates transformed using *icbm2tal*,[2] and labels were confirmed visually using the Talairach and Tournoux (1988) atlas.

RESULTS

BEHAVIORAL DATA

Compliance with the task in the scanner was high, with a button press on 97% of the faces trials (76% of low-level baseline trials). In a first step, we conducted separate mixed 2 (*age of participant*: young, older) × 3 (*facial expression*: happy, neutral, angry) × (*age of face*: young, older) repeated-measures ANOVAs on accuracy and response time of accurate responses, respectively (see **Table 3**; **Figure 2**). For accuracy, neither of the three- or two-way interactions was significant. The only significant effects were the main effects for *facial expression* [$F(2,57) = 16.56$, $p < 0.001$, $\eta_p^2 = 0.37$; **Figure 2A**] and *age of face* [$F(1,58) = 23.10$, $p < 0.001$, $\eta_p^2 = 0.29$; **Figure 2B**]. Overall, participants were very good at identifying the facial expressions. Moreover, they were better at reading happy ($M = 96.4\%$, SD = 7.5) than neutral ($M = 92.4\%$, SD = 8.8) or angry ($M = 92.4\%$, SD = 9.3) expressions and were better at reading young ($M = 95.3\%$, SD = 8.0) than older ($M = 92.2\%$, SD = 7.8) faces.

For speed of responding (see **Table 3** and **Figure 2C**), the main effects for *facial expression* [$F(2,57) = 98.56$, $p < 0.001$, $\eta_p^2 = 0.78$], *age of face* [$F(1,58) = 103.66$, $p < 0.001$, $\eta_p^2 = 0.64$], and *age of participant* [$F(1,58) = 5.12$, $p = 0.027$, $\eta_p^2 = 0.08$] were significant. There also were significant interactions for *facial expression* × *age of face* [$F(2,57) = 17.94$, $p < 0.001$, $\eta_p^2 = 0.39$], *facial expression* × *age of participant* [$F(2,57) = 3.21$, $p < 0.048$, $\eta_p^2 = 0.10$], and *facial expression* × *age of face* × *age of participant* [$F(2,57) = 3.12$, $p < 0.052$, $\eta_p^2 = 0.10$]. Although young and older participants did not show a behavioral performance difference with respect to accuracy, older participants ($M = 1422$ ms, SD = 208) were overall slower to respond than young participants ($M = 1298$ ms, SD = 218). In particular, older compared to young participants were slower in responding to happy (young participants: $M = 1118$ ms, SD = 166; older participants: $M = 1242$ ms, SD = 219) and angry (young participants: $M = 1395$ ms, SD = 263; older participants:

[2]http://www.brainmap.org/icbm2tal/

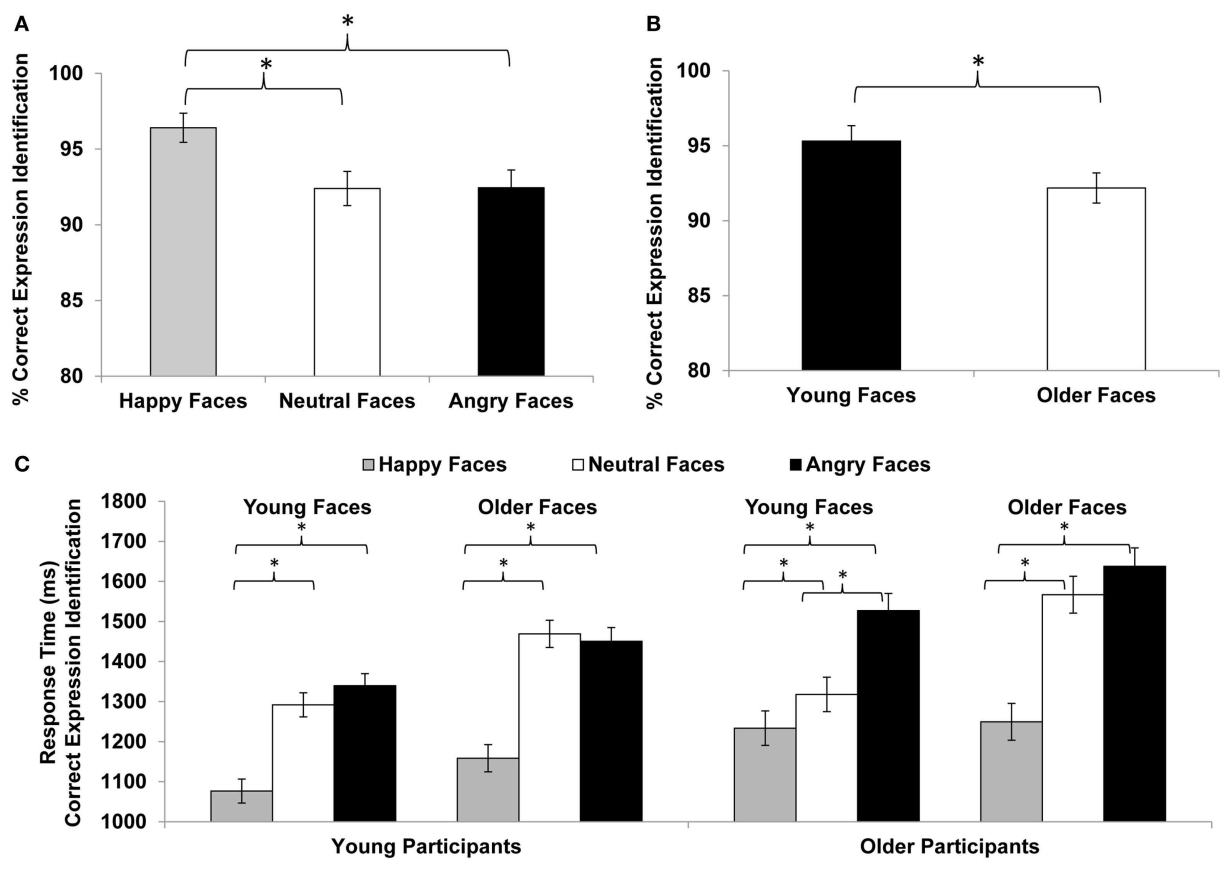

FIGURE 2 | Facial expression identification (% correct) for (A) happy, neutral, vs. angry faces and (B) young vs. older faces. (C) Response time (ms) for facial expression identification in young and older participants for happy, neutral, and angry young and older faces. Error bars represent standard errors of condition mean differences; $^*p \leq 0.05$.

$M = 1582$ ms, SD = 276) but not neutral (young participants: $M = 1381$ ms, SD = 254; older participants: $M = 1442$ ms, SD = 230) faces. In line with the accuracy data, response time to young faces ($M = 1298$ ms, SD = 212) was faster than response time to older faces ($M = 1422$ ms, SD = 237). And, collapsed across young and older adults, response time to happy faces ($M = 1180$ ms, SD = 203) was faster than response time to neutral faces ($M = 1411$ ms, SD = 242), which was faster than response time to angry faces ($M = 1489$ ms, SD = 283). However, the significant difference between neutral and angry faces held only for older [$t(29) = -3.29$, $p = 0.003$] but not young [$t(29) = -0.61$, $p = 0.550$] participants and was driven by a faster responses to young neutral than young angry faces [$t(29) = -4.55$, $p < 0.001$]; the difference between older neutral and older angry faces was not significant [$t(29) = -1.38$, ns; see **Figure 2C**].

fMRI DATA

The results section is structured along the two central aims of the study (see **Table 1**). We start by reporting results pertaining to brain activity in vmPFC, dmPFC, and amgydala during facial expression identification as a function of the facial expression and the age of the face, respectively, across the whole sample (*Research Aim 1*). This is followed by an examination of the correlations between brain response in vmPFC, dmPFC, and amygdala and behavioral performance in the facial expression identification task for the different facial expressions and different age of faces, respectively, in both young and older participants (*Research Aim 2*).

Brain activity in vmPFC, dmPFC, and amygdala

Happy faces > neutral faces and happy faces > angry faces and young faces > older faces across the whole sample. As a first step, we were interested in testing whether vmPFC activity was greater to happy than neutral or angry faces across the whole sample (see **Table 1**; *Hypothesis 1a*). As presented in **Table 4** (section A, Analysis across whole sample), similar areas of bilateral *vmPFC* showed greater BOLD response to happy compared to neutral (MNI: $x = -3, y = 63, z = 0$) and happy compared to angry (MNI: $x = -3$, $y = 57$, $z = -3$) faces. **Figure 3A** shows brain activity in

Table 4 | Results of ROI analyses: activity in mPFC and amygdala during facial expression identification to happy relative to neutral or angry and young relative to older faces (across whole sample and in interaction with participant age).

Hemi	BA	Anatomical area	Activation peak			*T*-value/*F*-value	# Vox
			x	*y*	*z*		
(A) Analysis across whole sample							
Happy faces > neutral faces across whole sample							
B	10	Medial frontal gyrus	−3	63	0	5.68	164
R		Amygdala	24	−9	−12	2.75	6
Happy faces > angry faces across whole sample							
B	**10**	**Medial frontal gyrus, anterior cingulate**	**−3**	**57**	**−3**	**5.11**	**49**
R		Amygdala	24	−9	−18	1.87	3
Young faces > older faces across whole sample							
–							
Neutral faces > happy faces across whole sample							
B	**8, 6**	**Superior frontal gyrus, medial frontal gyrus**	**−6**	**24**	**48**	**5.33**	**69**
Angry faces > happy faces across whole sample							
L	6	Superior frontal gyrus, medial frontal gyrus	−6	15	51	6.46	312
Older faces > young faces across whole sample							
B	**8, 32**	**Medial frontal gyrus, anterior cingulate gyrus, superior frontal gyrus**	**−3**	**33**	**39**	**4.94**	**102**
(B) Interaction with participant age							
Happy faces vs. neutral faces by participant age							
R	24	Cingulate gyrus	6	9	27	8.32	11
Happy faces vs. angry faces by participant age							
R	**24**	**Anterior cingulate, medial frontal gyrus**	**12**	**39**	**−3**	**7.67**	**52**
B	**8, 6**	**Medial frontal gyrus, superior frontal gyrus**	**−6**	**27**	**51**	**9.50**	**23**
R	6	Medial frontal gyrus	15	3	54	8.45	19

*Analyses across whole sample (T-contrasts) used a threshold of 10 contiguous voxels, each at $p < 0.001$, uncorrected, for mPFC and $p < 0.05$, uncorrected, with number of contiguous voxels unspecified for amygdala. Age of participant interaction analyses (F-contrasts) used a threshold of 10 contiguous voxels, each at $p < 0.05$, uncorrected, for mPFC and $p < 0.05$, uncorrected, with number of contiguous voxels unspecified for amygdala. Areas printed in **bold** are shown in **Figures 3–5**, respectively. MNI coordinates (x, y, z) and maximum T-value/F-value are given for the peak voxel (local maximum) within each region of activation. Hemi, hemisphere; L, left; R, right; B, bilateral; BA, Brodmann area; # vox, number of voxels in cluster. Areas are presented by contrast and within a contrast sorted from anterior to posterior and from ventral to dorsal. Full activation maps for all areas shown in the table are available from the authors.*

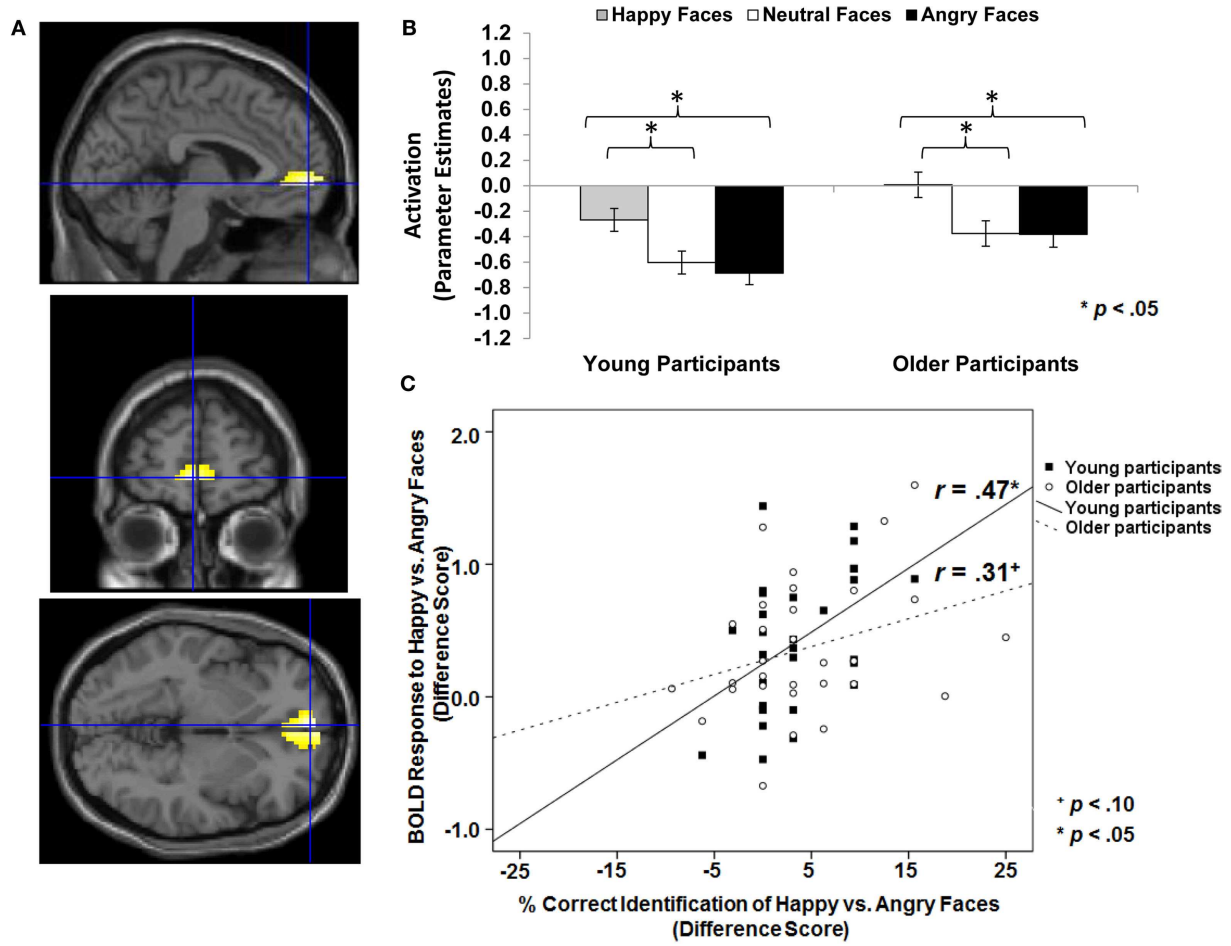

FIGURE 3 | Area of vmPFC where happy faces > angry faces (*T*-contrast): (A) Left ventral medial frontal gyrus, anterior cingulate (BA 10; MNI: $x = -3$, $y = 57$, $z = -3$; cluster size: 49 voxels; maximum *T*-value for cluster: 5.11). The region of activation represents the *T*-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(B)** Bar graphs show the mean left vmPFC parameter estimates (beta values) separately for facial expression and age of participant (across age of face); betas for this region of activation identified by the *T*-contrast *happy faces > angry faces* were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively. **(C)** Mean difference in participants' left vmPFC BOLD response to happy relative to angry faces in relation to the percentage of correctly identified happy relative to angry faces for young and older participants, respectively.

left vmPFC (MNI: $x = -3$, $y = 57$, $z = -3$) for the contrast *happy faces > angry faces*. Follow-up paired-sample *t*-tests collapsed across the whole sample on extracted beta values at the peak voxel of activation showed that left vmPFC activity was greater for happy than angry [$t(61) = 6.32$, $p < 0.001$] and neutral [$t(61) = 5.01$, $p < 0.001$] faces. **Figure 3B** presents these extracted beta values separately for young and older adults. The pattern of results was quite comparable for the two age groups with both young [$t(29) = 4.45$, $p < 0.001$] and older [$t(31) = 4.42$, $p < 0.001$] participants showing greater left vmPFC activity for happy than angry faces. Note that vmPFC deactivation is often seen during cognitive tasks and vmPFC activation during rest (Raichle et al., 2001). Self-relevant and/or emotional processing has been associated with activation in vmPFC (Johnson et al., 2006) or with less deactivation (Ames et al., 2008), as observed in the present study.

Next, we were interested in examining *amygdala* activity to happy compared to neutral or angry faces across the whole sample (see **Table 1**; *Hypothesis 1b*). As show in **Table 4** (section A, Analysis across whole sample), somewhat similar to the findings in vmPFC, we found significant right amygdala activity for *happy faces > neutral faces* (MNI: $x = 24$, $y = -9$, $z = -12$) and for *happy faces > angry faces* (MNI: $x = 24$, $y = -9$, $z = -18$). Follow-up tests collapsed across the whole sample on extracted beta values at the peak voxel of activation showed that right amygdala activity (MNI: $x = 24$, $y = -9$, $z = -12$) was greater for happy than neutral faces [$t(61) = 2.97$, $p = 0.004$]. Again, the pattern of results was comparable for the two age groups: young [$t(29) = 2.26$, $p = 0.031$] and, marginally, older [$t(31) = 1.97$, $p = 0.058$] participants showed greater amygdala activity for happy than neutral faces. Note that contrasting *young faces > older faces* resulted in

no significant brain activity in any area of the examined ROIs (see *Hypotheses 1a* and *1b*).

Neutral faces > happy faces, angry faces > happy faces, and older faces > young faces across the whole sample. The next set of analyses addressed whether there was greater dmPFC activity to neutral or angry compared to happy faces and to older compared to young faces across the whole sample (see **Table 1**; *Hypothesis 1c*). As shown in **Table 4** (section A, Analysis across whole sample), when contrasting neutral or angry with happy faces, a region of left *dmPFC* showed greater BOLD response. This dmPFC region was very similar for both neutral greater than happy faces (MNI: $x = -6$, $y = 24$, $z = 48$; note that for this contrast, the activity was bilateral) and angry greater than happy faces (MNI: $x = -6$, $y = 15$, $z = 51$). **Figure 4A** shows activity in dmPFC for the contrast *neutral faces > happy faces* (MNI: $x = -6$, $y = 24$, $z = 48$). Follow-up tests across the whole sample on extracted beta values at the peak voxel of activation showed that left dmPFC activity was greater for neutral [$t(61) = 4.38$, $p < 0.001$] and angry [$t(61) = 5.85$, $p < 0.001$] than happy faces. **Figure 4B** shows comparable results when examining young and older participants separately with both young [$t(29) = 4.15$, $p < 0.001$] and older [$t(31) = 2.59$, $p = 0.014$] participants showing greater dmPFC activity for neutral than happy faces.

In addition, for *older faces > young faces* bilateral *dmPFC* showed greater BOLD response to older than young faces (see **Table 4**, section A, Analysis across whole sample). This region of dmPFC (MNI: $x = -3$, $y = 33$, $z = 39$) was very similar to the dmPFC region (MNI: $x = -6$, $y = 24$, $z = 48$) reported above for *neutral faces > happy faces*. **Figure 4D** shows this activity in dmPFC (MNI: $x = -3$, $y = 33$, $z = 39$) for the contrast *older faces > young faces*. Follow-up paired-sample t-tests across the whole sample on extracted beta values at the peak voxel of activation showed that activity in left dmPFC was greater for older than young faces [$t(61) = 4.60$, $p < 0.001$]. **Figure 4E** presents the data separately for young and older adults and shows that for older [$t(31) = 4.90$, $p < 0.001$], but only marginally young [$t(29) = 1.96$, $p = 0.060$], participants left dmPFC activity was greater for older than young faces. Note that even at the lower threshold ($p < 0.05$ uncorrected, number of contiguous voxels unspecified), there was no significant amygdala activation for this set of contrasts.

Happy faces vs. neutral faces and happy faces vs. angry faces in interaction with participant age group. Based on previous research, for a next set of analyses we had the specific hypothesis that there would be greater dmPFC activity to neutral or angry than happy faces in older than young adults (see **Table 1**; *Hypothesis 1d*). We also examined participant age-group differences in vmPFC and amygdala activity, but we did not have specific hypotheses for these analyses given rather mixed previous literature (see, e.g., Leclerc and Kensinger, 2008; St Jacques et al., 2009). **Table 4** (section B, Interaction with participant age) summarizes the areas of mPFC that showed age-group differences in activity to happy vs. neutral and/or happy vs. angry faces (F-contrasts). These analyses suggest that, even though we saw similar patterns of brain activity between young and older adults in the analyses reported above, there also were some age-group differences in the recruitment of subregions of vmPFC and dmPFC in the present task: In particular, as shown in **Figure 5A**, for the F-contrast *happy faces* vs. *angry faces by age of participant*, a region of vmPFC (MNI: $x = 12$, $y = 39$, $z = -3$), that was slightly more posterior and more lateral than the vmPFC regions presented in **Figure 3A** (MNI: $x = -3$, $y = 57$, $z = -3$), showed greater activity to happy than angry faces [$t(29) = 2.99$, $p < 0.001$] and also to neutral faces [$t(29) = 3.18$, $p = 0.004$] in young adults. For older adults, however, brain activity in this more posterior and lateral region of vmPFC did not differ between happy and angry [$t(31) = -0.54$, $p = 0.593$] nor happy and neutral [$t(31) = 0.095$, $p = 0.925$] faces (see **Figure 5B**). By contrast, as shown in **Figure 5C**, activity in an area of dmPFC (MNI: $x = -6$, $y = 27$, $z = 51$), that was largely overlapping with the dmPFC region presented in **Figure 4A** (MNI: $x = -6$, $y = 24$, $z = 48$), was greater in response to angry than happy [$t(31) = -4.98$, $p < 0.001$], as well as to neutral than happy [$t(31) = -2.60$, $p = 0.014$] faces in older participants. Note that activity in this area of dmPFC in young participants was only marginally greater in response to angry than happy faces [$t(29) = -1.92$, $p = 0.065$], but was significantly greater in response to angry than neutral faces [$t(29) = -3.28$, $p = 0.003$; see **Figure 5D**]. There was no significant amygdala activity for these contrasts, even when lowering the threshold ($p < 0.05$ uncorrected, number of contiguous voxels unspecified).

Brain-behavior correlations

With respect to the brain-behavior correlations, we were particularly interested in examining whether brain responses to one facial expression in relation to another were correlated with the ability to read one expression in relation to another. This approach required use of difference scores. That is, brain activity resulting from contrasting one facial expression with another (e.g., *happy faces > angry faces*) was correlated with behavioral performance (accuracy and speed, respectively) for one facial expression (e.g., happy) contrasted with another (e.g., angry).

First, we tested whether there were positive correlations between *vmPFC* activity to happy relative to neutral or angry faces and accuracy and speed, respectively, of identifying happy relative to neutral or angry faces across the whole sample as well as for young and older adults separately. We tested the same pattern of findings for young vs. older faces (see **Table 1**; *Hypothesis 2a*). As expected, the difference in BOLD response to happy vs. angry faces in the observed area of left vmPFC (MNI: $x = -3$, $y = 57$, $z = -3$) was positively correlated with the difference in accuracy in reading facial emotions of happy relative to angry faces across participants (Pearson $r = 0.36$, $p = 0.005$). As shown **Figure 3C**, examining young and older participants separately, this positive correlation was significant in young (Pearson $r = 0.47$, $p = 0.010$), but only marginally in older (Pearson $r = 0.31$, $p = 0.092$), participants. In addition, the greater the BOLD response to happy relative to angry faces in this region of left vmPFC, the faster young participants (response time: Pearson $r = -0.46$, $p = 0.011$) were able to read happy relative to angry facial expressions. This correlation was not significant in the older participants and was not significant when collapsing across the whole sample.

Next, we examined whether there were positive correlations between *amygdala* activity to happy relative to neutral or angry

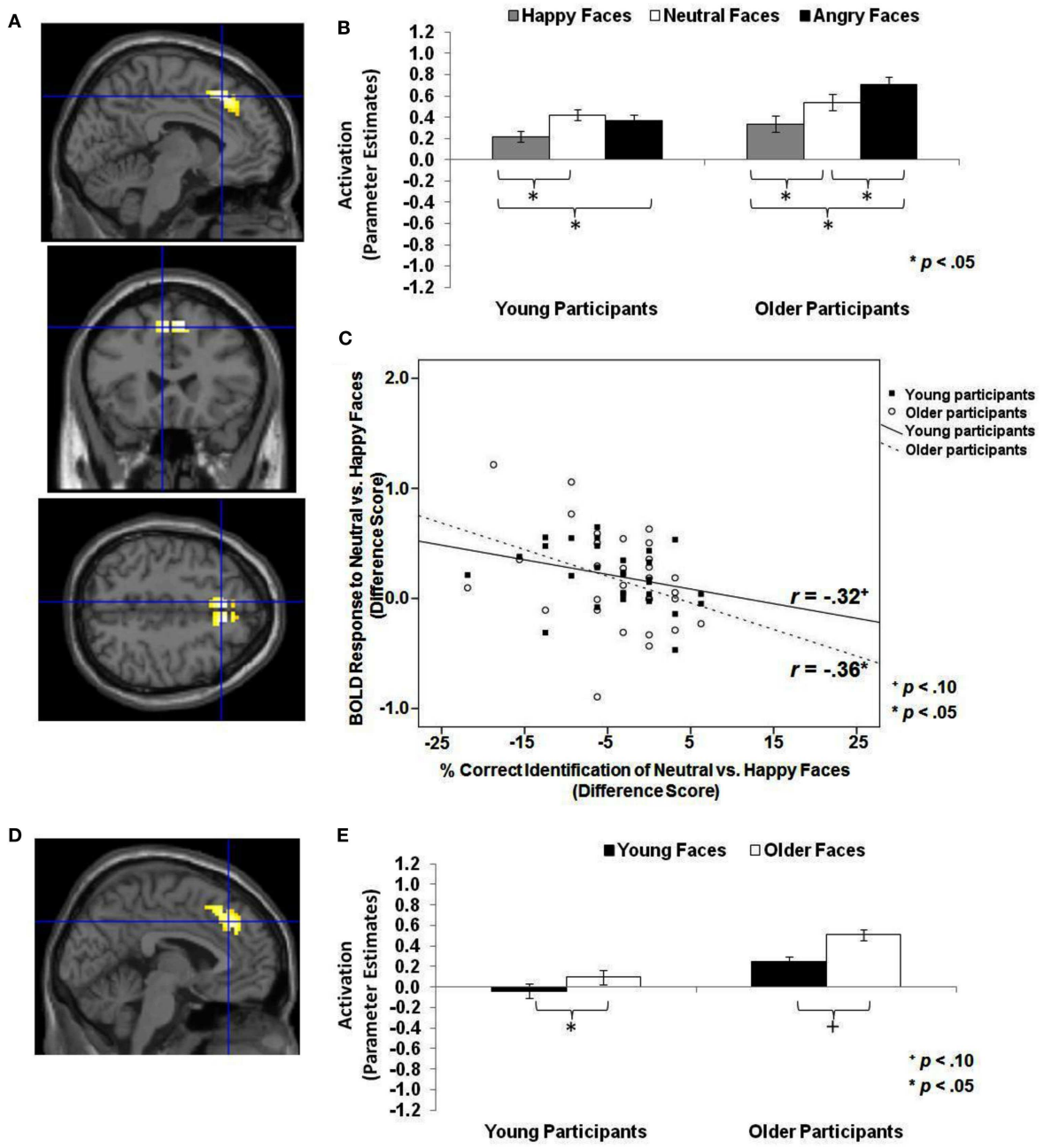

FIGURE 4 | Area of dmPFC where neutral faces > happy faces and older faces > young faces (*T*-contrasts): neutral faces > happy faces: (A) Left superior frontal gyrus, medial frontal gyrus (BA 8, 6; MNI: $x = -6$, $y = 24$, $z = 48$; cluster size: 69 voxels; maximum *T*-value for cluster: 5.33). The region of activation represents the *T*-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(B)** Bar graphs show the mean left dmPFC parameter estimates (beta values) separately for facial expression and age of participant (across age of face); betas for this region of activation identified by the *T*-contrast *neutral faces* > *happy faces* were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively. **(C)** Mean difference in participants' left dmPFC BOLD response to neutral relative to happy faces in relation to the percentage of correctly identified neutral relative to happy faces for young and older participants, respectively. *older faces* > *young faces*: **(D)** Left medial frontal gyrus, anterior cingulate, superior frontal gyrus (BA 8, 32; MNI: $x = -3$, $y = 33$, $z = 39$; cluster size: 102 voxels; maximum *T*-value for cluster: 4.94). The region of activation represents the *T*-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(E)** Bar graphs show the mean left dmPFC parameter estimates (beta values) separately for age of face and age of participant (across facial expression); betas for this region of activation identified by the *T*-contrast *older faces* > *young faces* were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively.

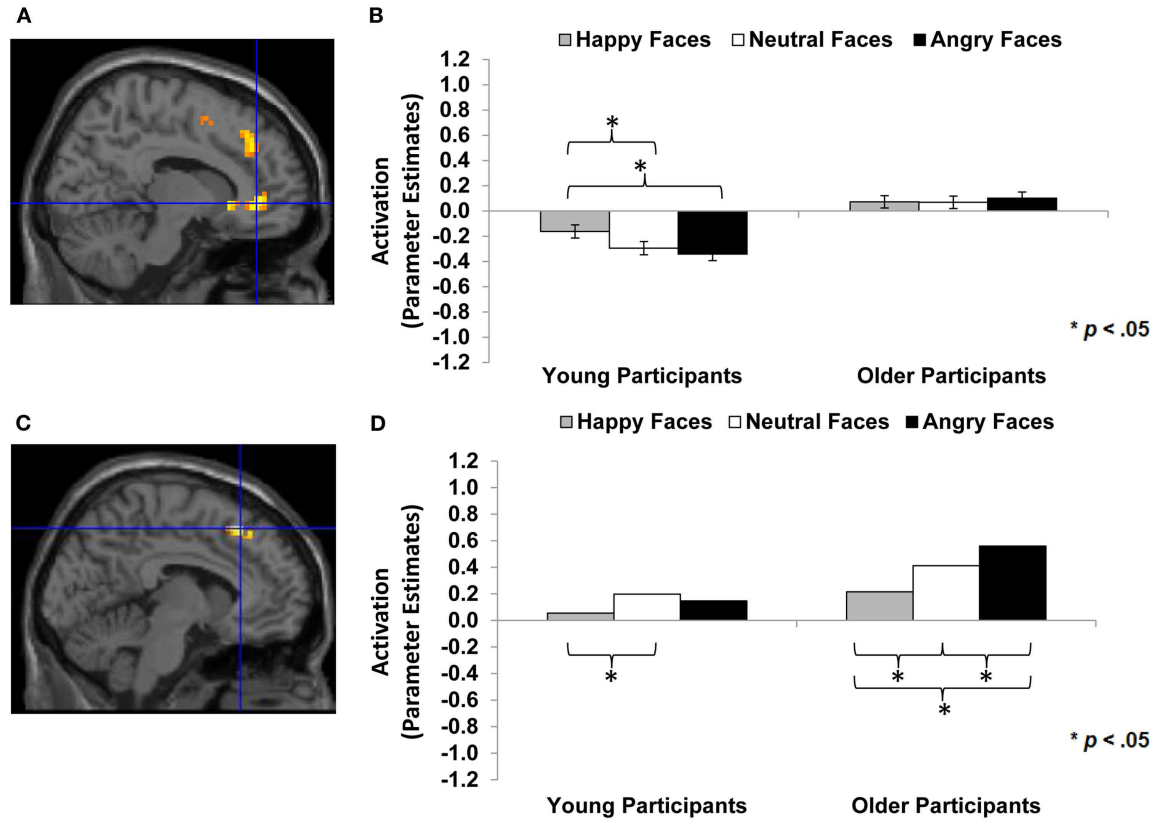

FIGURE 5 | Area of vmPFC and dmPFC showing happy vs. angry faces by age of participant interaction (*F*-contrast): (A) Right medial frontal gyrus, anterior cingulate (BA 24; MNI: $x = 12$, $y = 39$, $z = -3$; cluster size: 52 voxels; maximum *F*-value for cluster: 7.67). The region of activation represents the *F*-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(B)** Bar graphs show the mean right vmPFC parameter estimates (beta values) separately for facial expression and age of participant (across age of face); betas for this region of activation identified by the *F*-contrast *happy* vs. *angry faces by age of participant* were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively. **(C)** Left medial frontal gyrus, superior frontal gyrus (BA 8, 6; MNI: $x = -6$, $y = 27$, $z = 51$; cluster size: 23 voxels; maximum *F*-value for cluster: 9.50). The region of activation represents the *F*-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(D)** Bar graphs show the mean left dmPFC parameter estimates (beta values) separately for facial expression and age of participant (across age of face); betas for this region of activation identified by the *F*-contrast *happy* vs. *angry faces by age of participant* were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively.

faces and accuracy and speed of identifying happy relative to neutral or angry faces across the whole sample and for young and older adults separately. Again, we tested the same pattern of findings for young vs. older faces (see **Table 1**; *Hypothesis 2b*). BOLD response to happy relative to angry faces in right amygdala (MNI: $x = 24$, $y = -9$, $z = -18$) was positively correlated with participants' accuracy (Pearson $r = 0.35$, $p = 0.006$) in reading facial expressions of, and the faster they were in responding to (response time: Pearson $r = -0.25$, $p = 0.05$), happy compared to angry faces. Investigating young and older participants separately, we found positive correlations for older (Pearson $r = 0.39$, $p = 0.03$), but only marginally for young (Pearson $r = 0.31$, $p = 0.10$), participants in their accuracy in reading facial expressions of happiness relative to anger, but no significant correlations with speed of responding.

Finally, we examined whether there were negative correlation between *dmPFC* activity to neutral or angry faces relative to happy faces and accuracy and speed of identifying neutral or angry faces relative to happy faces across the whole sample, as well as for young and older adults separately. The same pattern of findings was tested for older relative to young faces (see **Table 1**; *Hypothesis 2c*). The difference in BOLD response to neutral relative to happy faces in left dmPFC (MNI: $x = -6$, $y = 24$, $z = 48$) was negatively correlated with participants' accuracy in reading neutral relative to happy facial expressions (Pearson $r = -0.38$, $p = 0.008$), and the greater the brain activity in left dmPFC, the slower were participants in giving their responses (response time: Pearson $r = 0.41$, $p = 0.002$). As shown in **Figure 4C**, examining young and older participants separately, this difference in BOLD response to neutral relative to happy faces in left dmPFC was negatively correlated with older (Pearson $r = -0.36$, $p = 0.049$), but only marginally with young (Pearson $r = -0.32$, $p = 0.086$), participants' accuracy in reading neutral compared to happy facial expressions. In addition, the greater the BOLD response to neutral relative to happy

faces in this region of left dmPFC, the slower older (response time: Pearson $r = 0.51$, $p = 0.004$) but not young participants read neutral relative to happy expressions. Note that we found no significant correlations with BOLD response to *young faces > older faces* or *older faces > young faces* in any of the examined regions and behavioral performance, neither across young and older participants, nor for the age groups separately (see *Hypotheses 2a–2c*).

DISCUSSION

The central goal of the present study was to increase knowledge of the neural mechanisms underlying identification of positive, neutral, and negative expressions in young and older adult faces. In particular, we were interested in investigating samples of young and older adults with respect to the neural correlates of reading facial emotions. The study examined the role of mPFC and amygdala, brain areas associated with facial emotion processing, while young and older adults engaged in facial expression identification. Targeting the functional role of these selected brain regions, the study directly examined the correlations between activity in mPFC as well as amygdala to specific facial expressions relative to others, and young and older adults' ability to correctly read one expression over the other. The present study provides converging evidence for previous observations and reports several novel findings.

YOUNG AND OLDER ADULTS WERE BETTER AND FASTER AT READING EMOTIONS FROM HAPPY AND YOUNG FACES

Young and older adults in the present study did not differ in their accuracy of reading facial emotions. This finding differs somewhat from previous studies (see Ruffman et al., 2008, for an overview). However, in contrast to previous studies, the present study only used three different facial expressions (i.e., happy, neutral, angry). This was done to increase comparability in stimulus and response variety for positive and negative expressions, that is, to better equate task complexity for positive and negative expressions (as compared to using one positive along with various negative expressions, which likely results in qualitatively different tasks for identification of positive and negative expressions; see Ebner et al., 2011c). Thus, overall, the present task was likely easier than paradigms used in previous work, as reflected in the high accuracy and fast response under all conditions for both young and older adults in the present study (see **Figure 2** and **Table 3**).

Importantly, even though there were no age-group differences in accuracy, in line with age-related decline in the ability to read facial expressions, older compared to young adults were slower in responding to happy and angry, but not neutral, faces. Moreover, consistent with prior studies (Ebner and Johnson, 2009; Ebner et al., 2011c; Riediger et al., 2011), both young and older adults were more accurate and faster in reading happy than neutral or angry faces. Both age groups were also more accurate and faster in reading expressions in young than older faces. That is, in line with previous work (Ebner and Johnson, 2009; Ebner et al., 2011c), young adults were better at reading expression of faces of their own-age group, but for older adults', there was no indication of an own-age advantage in facial emotion reading. Similar findings have been explained in terms of greater complexity and more ambiguity of neutral and angry compared to happy (Ebner and Johnson, 2009) and older compared to young (Ebner et al., 2011b) faces. Slower response time to angry than neutral faces for older but not young participants (and only for young but not older faces; see significant three-way interaction in **Figure 2C**) suggests that for older adults, it may be particularly hard differentiating neutral from angry young but not older faces, maybe because anger is an expression that an older person would not expect to see or is reluctant to attribute to a young person's face.

Taken together, in line with the literature, the present study provides supporting evidence of both young and older adults' greater ability to read emotions from happy compared to neutral or angry and from young compared to older faces.

VENTRAL/DORSAL DISTINCTION IN mPFC DURING READING FACIAL EMOTIONS IN YOUNG AND OLDER ADULTS AND BRAIN-BEHAVIOR CORRELATIONS

Importantly, the behavioral differences in the ability to read expressions of happy, neutral, and angry young and older adult faces were reflected in young and older adults' neural responses. In particular, there was greater *vmPFC* activity in response to happy than neutral or angry faces in both young and older participants. In addition, this greater vmPFC activity to happy compared to angry faces was positively correlated with the ability to read happy relative to angry faces. Specifically, greater vmPFC activity to happy relative to angry faces was positively correlated with accuracy of reading facial happiness opposed to facial anger in both young and older participants. In addition, the greater the vmPFC activity to happy relative to angry faces, the faster young participants were able to read happy compared to angry faces. These findings are consistent with the idea that happy expressions, compared to other expressions, are readily available and easy to process. Salience may derive, in part, from a reward value associated with happy faces. That is, it is possible that activity in this area of vmPFC reflects *affective response*, and in particular, positive affective response, to "good" cues, such as the happy compared to the neutral or angry faces in the present task. Support for this interpretation comes from Mitchell et al. (2009), who found greater activity in a very close area of vmPFC (MNI: $x = 0$, $y = 52$, $z = -11$) during self-relevant thought in both young and older adults, and in particular, showed greater activity in this region of vmPFC when young adults thought about more positive compared to negative personal agendas. It is also supported by Kim and Johnson (2012), who found greater activity in a largely overlapping subregion of vmPFC (MNI: $x = 2$, $y = 52$, $z = -4$) when young participants were randomly assigned objects compared to when objects were assigned to another person, and, importantly, found an association of this vmPFC activity with increased preference for objects assigned to the self.

Similar to the findings for vmPFC, there was greater *amygdala* activity to happy than neutral or angry faces in both age groups. Also, amygdala activity to happy compared to angry faces was positively related to accuracy in, and faster response during, reading of happy relative to angry faces. This finding may appear somewhat counter-intuitive in light of findings that angry (and fearful) faces typically activate amygdala more than neutral or happy faces (Whalen et al., 2001), and that amygdala has been discussed as involved in processing ambiguity in faces (Davis and Whalen, 2001). However, our finding is in line with results by Keightley et al.

(2007) and other studies that provide evidence that amygdala is also responsive to positive faces (Hamann et al., 2002; Yang et al., 2003; Zald, 2003). Thus, the direction of our amygdala finding further supports the notion of greater positive affective response to happy compared to neutral or angry faces. It is in accord with evidence of greater amygdala response to faces that are associated with more positive evaluations, greater familiarity, and more self-relevance (see Van Bavel et al., 2008; Wright et al., 2008; Ebner et al., in preparation), like the happy compared to the neutral or angry faces in the present context. Thus, this finding lends further support to a role of amygdala, and possibly in connection with vmPFC, in a wider range of emotional processing than simply processing of negative information (see also Shaw et al., 2005; Keightley et al., 2007). Our findings of greater amygdala response to happy than angry (or neutral) faces, instead of greater amygdala activity to negative than positive stimuli (Whalen et al., 2001), is furthermore in line with Lieberman et al.'s (2007) finding of diminished amygdala activity during labeling compared to passively viewing of emotional faces in a sample of young adults. In line with Lieberman et al.'s interpretation, it is possible that in our study, the more cognitively demanding process of identifying angry and neutral than happy expressions dampened amygdala response. This process may be modulated by mPFC, and in particular, dmPFC as discussed below (cf. Lieberman et al., 2007).

By contrast, comparison of brain activity to neutral or angry with that associated with happy faces resulted in greater *dmPFC* activity for both age groups. Exploring again the brain-behavior correlations, we found that greater dmPFC activity to neutral than happy faces was associated with less accurate and slower expression identification for neutral relative to happy faces. Importantly, a very similar region of dmPFC also showed greater activity for older than young faces, with no correlations between brain activity and behavioral performance.

Taken together, the pattern of findings observed in the present study suggests an important functional dissociation between vmPFC, possibly in interaction with amygdala, and dmPFC in facial emotion reading. And importantly, this functional dissociation is quite comparable between young and older adults. There is evidence that vmPFC is associated with affective and valenced evaluative processing (Bush et al., 2000; Cunningham et al., 2004; Ochsner et al., 2005; Lebreton et al., 2009; Kim and Johnson, 2012). In contrast, there is evidence that dmPFC is recruited during more cognitively complex processing (see also Amodio and Frith, 2006; Northoff et al., 2006; Van Overwalle, 2009). In particular, dmPFC and dorsal anterior cingulate have been found to be involved in a variety of tasks requiring cognitive control (Bush et al., 2000; Carter et al., 2001; Paus, 2001). Thus, increased activity in dmPFC to neutral and angry compared to happy faces likely reflects *increased cognitive control* to identify (and perhaps differentiate between) angry and neutral expressions. It is possible that this differential dmPFC activity in response to happy vs. angry or neutral faces directly interacts with vmPFC and amygdala response to these stimuli. In particular, the greater mental effort of identifying angry or neutral relative to happy faces, which is associated with greater dmPFC activity, may result in decreased affective response (reflected in decreased vmPFC and amygdala activity) to angry or neutral compared to happy faces.

Very interesting in the context of the present study was also the highly overlapping pattern of brain activation for angry/neutral relative to happy faces and older relative to young faces, respectively, for both young and older participants. This is particularly intriguing as angry/neutral and older faces were the faces that were harder to read for both young and older adults. Thus, this further supports that the ventral/dorsal mPFC dissociation seen in the present study (and similarly in Keightley et al., 2007) reflect differences in demands for cognitive control, perhaps due to differences in the availability of facial cues necessary for accurate expression identification in happy compared to neutral or angry faces.

Thus, overall, the observed ventral/dorsal distinction in mPFC was quite comparable in young and older adults. However, at the same time, we also saw some informative differences in young and older adults' brain response during the present study's facial expression identification task: In particular, young but not older adults showed greater activity in a more posterior, more lateral subregion of vmPFC (**Figure 5A**) in response to happy compared to angry faces. This suggests that there may be a functional difference between this more posterior, more lateral vmPFC region and the more anterior and less lateral vmPFC region in which young and older adults showed largely the same pattern (**Figure 3A**). Also, it is possible that in older compared to young adults, a less extensive subregion of vmPFC (the more anterior, more medial part of vmPFC) is involved in differentiating between happy, neutral, and angry expressions.

Importantly, we also found further evidence that increased activity in dmPFC to angry (and neutral) compared to happy faces was more pronounced in older than young adults. This age-group difference is in accord with our hypothesis that greater dmPFC activity to angry than happy faces in older compared to young adults may reflect older adults' particular difficulty reading angry faces (Ebner and Johnson, 2009; Ebner et al., 2011c; see also Ruffman et al., 2008), as identification of angry faces requires more complex judgment. Alternatively, this finding is in line with evidence of an age-associated increase in controlled regulatory processing of negative than positive faces (Williams et al., 2006), a finding consistent with an increased positivity bias in older compared to young adults as suggested by *Socio-emotional Selectivity Theory* (Carstensen et al., 1999; Carstensen, 2006).

Our observed age-group differences seem at odds with results reported by Gutchess et al. (2007) and by Leclerc and Kensinger (2008). Gutchess et al. found greater dmPFC activity in older (but not young) adults during processing of (self-referential) positive than negative information. Leclerc and Kensinger, in line with our findings, found greater vmPFC activity during processing of positive than negative information in older adults, but found greater vmPFC activity during processing of negative than positive information in young adults. Also, previous studies observed a subcortical to cortical shift with age during emotion processing (Iidaka et al., 2001; Gunning-Dixon et al., 2003; Fischer et al., 2005; Tessitore et al., 2005), whereas the present study found increased amygdala, in addition to increased vmPFC, activity to happy compared to neutral or angry faces for both young and older adults. When comparing these studies, it is important to consider that they differed substantially in design (e.g., block- vs. event-related design, orienting tasks and stimulus material used). Gutchess et al.

for instance, used positive vs. negative person-descriptive adjectives in the context of a self- and other-evaluation task, and Leclerc and Kensinger used images of positive and negative objects in the context of an object categorization task not related to valence.

The studies by Keightley et al. (2007) and Williams et al. (2006) are most similar in approach to the present study and they produced quite comparable results. At the same time, there also were some design-related differences between their studies and ours that may explain some differences in the findings. For instance, different from Keightley et al. and Williams et al., the present study focused on happy, neutral, and angry facial expressions. Limiting the investigation to only these three facial expressions resulted in sufficient trials to allow direct comparison of each expression. Also, focusing on only three expressions, and the fact that we used an event-related design not a block-design as in Williams et al., made corresponding button presses feasible in the scanner. This allowed us to directly link brain activity during task engagement to behavioral responses, instead of having to refer to outside-the-scanner (re-)labeling of the facial expressions. Also, faces did not have to be presented twice (prior/post and during scanning), which may have induced participants to try to remember which expression they had assigned to a face when initially presented with it. Furthermore, in the present study, the identical face identities were presented in all three emotion expressions, counterbalanced across participants. This increased the control over varying levels of complexity of the face stimuli as a function of the different emotions displayed. The present study examined a larger sample of young and older adults than the other two studies, contributing to the reliability of the findings. And, importantly, whereas all previous fMRI studies on age-group differences in facial expression identification exclusively used young and no older faces, the present study systematically varied the age of the presented faces and thus could explicitly address age-of-face effects.

CONCLUSION AND OUTLOOK

The specific focus of the present study was to examine the neural mechanisms involved in reading emotions. Extending previous work, we examined neural correlates of facial expression identification in two populations (young and older adults) and with respect to faces that differed in valence (happy, neutral, and angry faces) as well as age (young and older faces). Thus, we were able to examine the comparability as well as the differences in the neural underpinnings of facial emotion reading between young and older adults as a function of the facial expression and the age of the faces, respectively. In addition, our design allowed us to directly examine correlations between brain activity and behavioral task performance.

The present study adds to the knowledge about the neural mechanisms of facial expression identification in young and older adults and extends earlier work in several important ways. It provides important new evidence of a *ventral/dorsal distinction in mPFC, possibly in interaction with amygdala, during facial emotion reading in both young and older adults*: Increased vmPFC and amygdala activity may reflect increased affective processing, and maybe positive affective processing in particular, of the more salient, unambiguous, and positive happy faces. In contrast, increased dmPFC activity may reflect increased cognitive effort to decode the more ambiguous and complex neutral or angry as well as older faces and/or to regulate negative emotions associated with such faces, particularly in older adults. And it is possible that this increased effort in identifying neutral and angry compared to happy faces results in dampened response in vmPFC and amygdala. The interpretation of affective vs. cognitive processing in vmPFC vs. dmPFC, respectively, was further supported by brain-behavior correlations: There was a positive correlation between vmPFC activity to happy relative to angry faces and a negative correlation between dmPFC activity to neutral relative to happy faces and the ability to read the respective facial expression over the other, with largely comparable correlations in young and older adults.

There are various promising routes to take this work in the future: One such future direction is to examine age-related changes in brain structure, such as reductions in gray volume and/or white matter integrity in regions of the brain associated with facial emotion reading, and their correlations with functional brain changes and behavioral performance. This approach may be particularly interesting given evidence that the vmPFC and amygdala only undergo relatively modest structural changes with age (Shimamura, 1994; West, 1996; Hedden and Gabrieli, 2004). Moreover, there are suggestions that vmPFC vs. dmPFC show somewhat different rates of structural and functional age-related decline, with dmPFC (like lateral PFC regions) exhibiting earlier and somewhat more rapid decline in normal aging than other regions of PFC (Daigneault and Braun, 1993; Shimamura, 1994; West, 1996). The empirical work on structure-function relations in the context of facial expression identification in young and older adults is, to date, still very limited. Williams et al. (2006) found support for age-related gray matter volume declines in mPFC, while there was comparative preservation of the amygdala and the basal ganglia caudate region. However, even though the age-related loss of mPFC gray matter predicted decline in correct post-scan identification of fearful faces, no correlation between structural and functional brain changes were observed. Another important future avenue is to address the predictive value of brain activity during, and performance in, facial emotion reading assessed in the laboratory context for successful real-life social interactions, social embeddedness, and socio-emotional well-being. Investigation of these effects may be particularly interesting in adults of different ages as well as in clinical populations that experience particular difficulties with reading facial expressions (e.g., autism) or that have a particular bias toward certain emotions (e.g., depression). Finally, a better understanding of the mechanisms involved in correct interpretation vs. misinterpretation of emotional facial expressions in others, and how certain confusions of facial emotions may differently influence (hinder or promote) attention to, and memory for, faces in young and older adults (see Ebner and Johnson, 2009; Ebner et al., 2011c) is warranted in the future.

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Happily distracted: mood and a benefit of attention dysregulation in older adults

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Positive mood states are believed to broaden the focus of attention in younger adults, but it is unclear whether the same is true for older adults. Here we examined one consequence of broader attention that has been shown in young adults: that memory for distraction is greater for those in a positive mood. In the current study, positive and neutral moods were induced in older adults ($M = 67.9$) prior to a 1-back task in which participants were instructed to attend to relevant pictures and ignore distracting words. Following a 10-min filled interval, participants performed a word fragment completion task that tested implicit memory for the distracting words from the 1-back task. Older adults in the positive mood group showed greater implicit memory for previous distraction compared to those in the neutral mood group. These findings suggest that affect influences the ability to regulate attention in a similar manner for younger and older adults.

Keywords: aging, positive affect, mood, attention regulation, distraction, inhibition

INTRODUCTION

Affective states are believed to serve a variety of functions including regulating the bandwidth of attention. Relative to negative states, positive affective states broaden both spatial (Schmitz et al., 2009) and temporal attention (Vermeulen, 2010), possibly because positive affect is a signal of relative safety to explore the environment (Fredrickson, 1998; Friedman and Förster, 2010).

However, attentional broadening can also have negative effects on cognition which can manifest in a number of ways, including increased susceptibility to distraction. For example, positive affect can increase interference from distractors during both flanker (Rowe et al., 2007) and set switching tasks (Dreisbach and Goschke, 2004) relative to neutral or negative affect. As well, positive affect decreases performance on tasks requiring inhibitory control, such as directed forgetting (Bäuml and Kuhbandner, 2009) and negative affective priming (Goeleven et al., 2007). Therefore, it seems plausible that positive affect may impair the ability to ignore irrelevant distraction by slackening inhibitory control.

Given the apparently increased attention paid to distractors as a result of positive mood, it is also possible that positive affect can actually enhance performance should previously irrelevant items later become relevant. Previous research demonstrated that younger adults in both naturally occurring (Biss et al., 2010) and experimentally induced positive moods (Biss and Hasher, 2011) showed greater implicit use of previous distraction compared to those in more neutral moods. Older adults, a population considered to have reduced inhibitory control abilities relative to younger adults (Hasher et al., 1999), also show greater implicit memory for distraction (Rowe et al., 2006).

An open question is whether the tendency for positive affect to broaden attention and increase the implicit use of distraction also extends to older adults who generally show less control over attention than their younger counterparts (Rowe et al., 2006).

In the current study, we tested whether mood influences older adults' ability to ignore distraction in the same manner as we have demonstrated in younger adults. We used a paradigm that has previously been used to demonstrate mood differences in implicit memory for distraction among younger adults (Biss and Hasher, 2011) as well as age differences in priming for distraction (Rowe et al., 2006). Positive and neutral affect were induced in older adults prior to a 1-back task in which participants responded to relevant pictures and were instructed to ignore superimposed irrelevant words. Following a 10-min filled delay, we tested implicit knowledge of the previously distracting words using a fragment completion task. If positive affect increases susceptibility to distraction in older adults as it appears to in younger adults, then older adults in an induced positive affect group should show enhanced priming for previous distraction compared to those in a neutral affect group.

MATERIALS AND METHODS

PARTICIPANTS

Sixty older adult participants ($M = 67.9$, SD $= 4.6$) were recruited from the community and paid for their participation. Participants were randomly assigned to either the positive ($n = 30$) or neutral ($n = 30$) mood induction condition. All participants were free of neurological or psychiatric illness, and were native English speakers or had learned English by age 6. In keeping with the goal of assessing implicit memory for distraction, we replaced data from participants who reported being aware of the connection between the 1-back and fragment completion tasks (three in the neutral condition). In addition, we replaced participants

who appeared to focus directly on the distraction, either by being very slow (more than 2.5 SDs slower than the group mean; one participant in the positive condition) or very inaccurate on the 1-back task (50% accuracy or below; three each in the positive and neutral conditions) relative to the majority of participants tested here and in prior work (Rowe et al., 2006; Biss and Hasher, 2011). The remaining participants had an average of 17.1 years of education (SD = 4.4), and scored 35.3 (SD = 3.5) on the Shipley (1946) vocabulary test. Mood groups did not differ based on age, education, or vocabulary scores, ts < 1. The experimental procedures were approved by the Social Sciences, Humanities, and Education Research Ethics Board at the University of Toronto, and informed consent was obtained from all participants prior to the experiment.

MATERIALS

Mood induction

One hundred forty-six pictures were selected from the International Affective Picture System (IAPS; Lang et al., 2008) based on the norms provided in the IAPS database. Pictures selected for the neutral condition had valence ratings between 4.5 and 5.5 ($M = 5.1$, SD = 0.3), while pictures selected for the positive affect induction had valence ratings of seven or higher ($M = 7.5$, SD = 0.3). Arousal ratings did not differ between neutral ($M = 4.1$, SD = 0.9) and positive pictures ($M = 4.2$, SD = 0.5), $t(144) < 1$. Although these IAPS norms include ratings from younger adults only, other normative data suggests that older adults' valence ratings of IAPS pictures are strongly associated with normative ratings collected in younger adults (Grühn and Scheibe, 2008). Sound clips free of verbal material were also selected for use in the mood induction. In the neutral affect condition, a sound clip with ambient street sounds was played. In the positive affect condition, participants heard a jazzy version of Bach's *Brandenberg Concerto No. 3* that has previously been used to induce positive mood in young adults (e.g., Rowe et al., 2007; Biss and Hasher, 2011).

Mood ratings

Participants rated the pleasantness of their moods on a nine-point scale adapted from Rowe et al. (2007), ranging from 1 (*not at all pleasant*) to 9 (*extremely pleasant*). They also rated arousal on a nine-point scale that ranged from 1 (*very calm*) to 9 (*very aroused*).

1-back task pictures

Fifty-five nameable line drawings were selected from Snodgrass and Vanderwart (1980) and colored red. Fifty of these pictures were superimposed with distraction: 30 with non-words, 10 with critical primed words, and 10 with filler words, which were used to reduce awareness of the connection between tasks.

Word stimuli and fragments

Two lists of 10 words and their corresponding fragments were chosen, and were matched for the number of letters in both the provided fragment and critical solution word, as well as based on previously collected baseline completion rates (Ikier, 2005). Lists were counterbalanced such that each participant was exposed to one list as critical primed words in the 1-back task, and solved fragments from both lists in the fragment completion task. Completion from the control list not seen in the 1-back task was used to calculate baseline completion for critical words. The critical words were between five and eight letters long ($M = 6.0$, SD = 1.1), and fragments contained between two and five letters ($M = 3.4$, SD = 0.8). All fragments had multiple solutions (e.g., B _ T T _ _ S could be solved using BUTTERS, BATTLES, or BUTTONS), only one of which (e.g., BUTTONS) was presented during the course of the experiment. Ten easy filler fragments also appeared in the fragment completion task in order to limit participants' awareness of the connection between tasks and to ensure that they felt successful about their fragment completion performance.

PROCEDURE

Before the experimental tasks began, participants rated their mood pleasantness and arousal. A 6-min mood induction procedure followed, during which participants viewed the IAPS pictures and listened to the corresponding sound clip using headphones. Each picture appeared on the computer screen for 5 s. Participants were instructed to relax and think about how the pictures and sounds made them feel. Participants rated their mood pleasantness and arousal again after the mood induction in order to determine its effectiveness.

The 1-back task followed. Participants were instructed to attend to a series of line drawings presented individually on the computer screen, pressing a key whenever consecutive pictures were identical, and to ignore the words and non-words that were superimposed over the pictures. Each overlapping picture and word/non-word appeared for 1000 ms, with an ISI of 500 ms. There were 10 pictures that repeated, requiring a key press; these repeated pictures occurred randomly amid novel pictures, with lags of two to six pictures in between repeated picture trials. Picture and word stimuli were assigned randomly to repeated trials, and no words were repeated during the task. Responses on these trials were recorded to calculate accuracy and RT. The 55 total trials proceeded in the following sequence: five pictures presented alone, eight pictures with superimposed non-words, 34 pictures superimposed with either non-words, filler words, or primed words, and eight pictures with superimposed non-words.

Participants then performed a non-verbal filler task for 10 min. Following the filler task, participants rated their mood pleasantness and arousal.

During the fragment completion task, participants viewed 30 word fragments, each presented individually on the computer screen for 3000 ms, with an ISI of 500 ms. They were instructed to respond out loud with the first word that came to mind, and the experimenter recorded their responses. The fragments included 10 easy filler fragments, 10 primed items presented as distraction during the 1-back task, and 10 control items from the list not seen in the 1-back task.

Following the fragment completion task, participants rated their mood pleasantness and arousal a final time. Participants were then given an awareness questionnaire to ensure that the test was implicit for all participants: they were asked if they had noticed a connection between any of the experimental tasks, and if so, to describe the connection. Finally, participants completed

a background questionnaire and were debriefed. All participants watched a brief comedic video clip before leaving as a mood reinstatement.

RESULTS

Mood pleasantness and arousal ratings made during the experiment are reported in **Figure 1**. Mood pleasantness ratings were entered into an ANOVA with mood group (neutral, positive) as a between-subject factor and rating time (baseline, post-induction, pre-fragment, post-fragment) as a within-subject factor. Greenhouse–Geisser corrections for degrees of freedom were used whenever appropriate. Both the absence of a main effect for mood, $F < 1$, and the presence of an effect of rating time, $F(2.3,134) = 48.35$, $p < 0.001$, were qualified by an interaction between mood group and rating time, $F(2.3, 134) = 3.98$, $p = 0.02$, $\eta_p{}^2 = 0.06$. Planned comparisons showed that participants in the positive mood condition had higher pleasantness ratings following the mood induction, $t(58) = 2.34$, $p = 0.02$, $d = 0.61$, but not at any other point during the experiment, $ps > 0.10$. Arousal ratings were also entered into a mood group x rating time ANOVA. Neither of the main effects nor the interaction was significant, $ps > 0.22$.

There was no difference in accuracy on the 1-back task for participants in the neutral ($M = 91\%$, SD = 12%) and positive affect ($M = 90\%$, SD = 11%) groups, $t(58) < 1$. Similarly, there was no difference in 1-back task RTs between the neutral ($M = 599$ ms, SD = 128) and positive ($M = 619$ ms, SD = 111) groups, $t(58) < 1$.

Performance on the word fragment completion task is shown in **Table 1**. Affect groups did not differ in completion of filler or control fragments, $ts < 1$. Priming scores were calculated using group baseline data, by taking each individual's primed fragment completion and subtracting average control fragment completion for their affect group. Consistent with our prediction, priming for distraction was greater among older adults in the positive affect compared to the neutral affect condition, $t(58) = 1.99$, $p = 0.05$, $d = 0.51$.

To further investigate how mood influenced priming for distraction, we analyzed whether there was an association between mood ratings and fragment completion performance when baseline mood was controlled. Across all participants, there was a significant partial correlation between post-induction pleasantness ratings and priming for distraction, pr = 0.33, p = 0.01. Post-induction pleasantness ratings were not associated more generally with fragment completion performance, as indexed by partial correlations with control fragment completion, pr = 0.15, $p = 0.25$ or with filler fragment completion, pr = 0.20, $p = 0.14$. Mood at retrieval was not associated with priming: There was no partial correlation between pleasantness ratings made prior to the fragment completion task and priming for distraction, pr = 0.18, $p = 0.16$.

DISCUSSION

Older adults in an induced positive mood showed greater priming for distraction compared to age mates in a neutral mood

Table 1 | Mean percentage completion (SD) on the fragment completion task.

Measure	Affect group	
	Positive	**Neutral**
Filler fragment completion	71 (18)	67 (17)
Primed fragment completion	19.3 (13)	15.7 (10)
Control fragment completion	8.3 (11)	10.7 (9)
Priming	11.0 (13)	5.0 (11)

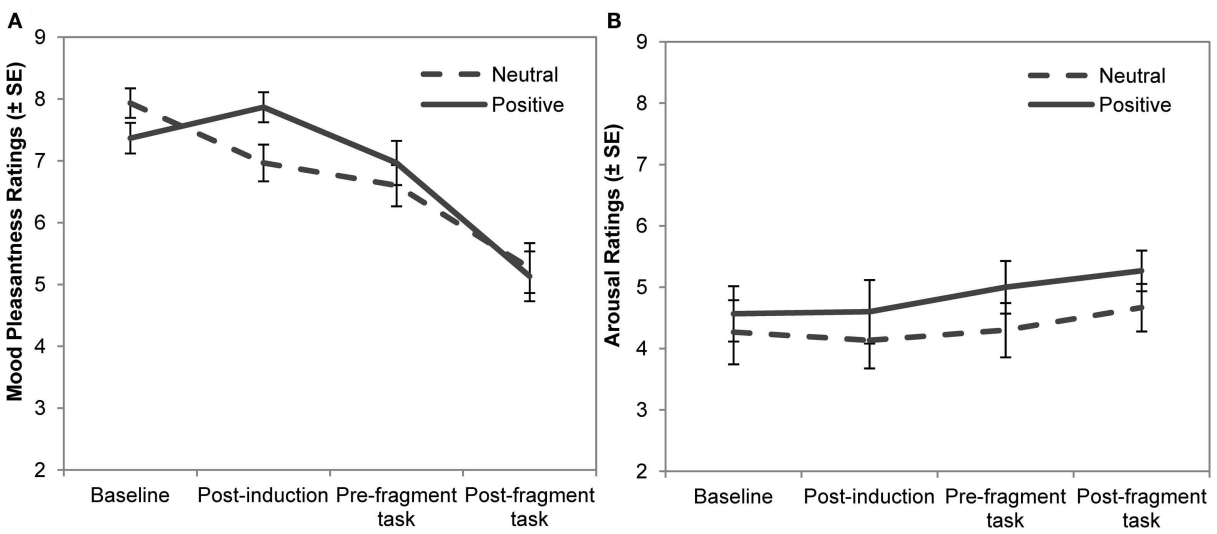

FIGURE 1 | Ratings made at various points during the experiment for (A) mood pleasantness, and (B) arousal. Error bars indicate standard error of the mean.

condition. Although the two mood groups did not differ in 1-back task performance, they did differ in subsequent knowledge for distraction presented during that task. In addition, mood pleasantness ratings made prior to the 1-back task were associated with the extent of priming when baseline mood was controlled. Ratings made at other times did not differ between mood groups, and had no influence on priming for distraction. Thus, the effect of mood was specific to attention at encoding, and in particular, there was no evidence that mood at retrieval mattered. Our results suggest that positive mood in older adults results in increased encoding of information that was never relevant to a task.

These findings support the idea that positive affect relaxes attentional control processes that otherwise restrict goal-irrelevant information from reaching the focus of attention (Hasher et al., 1999), an effect that is generally considered an impairing effect of emotion on attentional selectivity (e.g., Dreisbach and Goschke, 2004; Goeleven et al., 2007; Rowe et al., 2007). Here, we have shown that reduced inhibitory control and broadening of attention under positive affect (Fredrickson, 2001) can also have an enhancing effect. This enhancement was seen here on an implicit memory task which tested for tacit knowledge of previous distraction. Given the similarity of these results to those shown by younger adults (Biss and Hasher, 2011), positive affect appears to have a similar effect on the downstream benefits of distractibility among both younger and older adults.

Taken together with evidence that aging is associated with increased positive affect (e.g., Mroczek and Kolarz, 1998; Stone et al., 2010; Carstensen et al., 2011; Reed and Carstensen, 2012), our results suggest that age differences in affect may contribute to at least some age differences in cognition. Older adults generally have difficulty down-regulating the processing of irrelevant information, and show greater implicit knowledge about previous distraction compared to younger adults (Rowe et al., 2006). Given the evidence here that positive affect modulates older adults' processing of distraction, greater positive affect among older adults may partially contribute to this age difference in attentional control. There is evidence that positive affect also influences the magnitude of age differences for other attention processes: Positive affect mediates the extent of age differences in alerting efficiency (Noh et al., 2012). Affective state may also contribute to age differences on the Tower of London task, a measure of executive function (Phillips et al., 2002). Phillips and colleagues found that, under induced neutral mood, there were no age differences in the ability to plan moves on the task. In contrast, positive mood decreased both younger and older adults' planning ability, with older adults particularly disrupted relative to younger adults. This work highlights the importance of considering emotional and motivation influences on cognitive performance when studying age differences in cognition (see also Biss and Hasher, 2011; Hess et al., 2012 for a similar perspective).

Positive affective shifts associated with age may operate in parallel with normative changes in the structure and function of the brain (see Grady, 2008), potentially amplifying the cognitive consequences of these neural changes. Positive affect is thought to influence recruitment of prefrontal cortex and cingulate regions associated with executive control (Mitchell and Phillips, 2007), possibly via increased dopamine levels in these regions (Ashby et al., 1999). In particular, positive affect may influence the interaction between ventral emotional processing regions involved in automatic processing of salient information and dorsal control regions that downregulate processing of goal-irrelevant information from the environment (Drevets and Raichle, 1998; Dolcos and McCarthy, 2006). There is mounting evidence in favor of a functional dissociation between the dorsal executive control network and ventral emotion processing regions (see Dolcos et al., 2011). Dolcos and McCarthy (2006) found that poor working memory performance in the face of emotional distraction was associated with increased activity in ventral regions and decreased activity in dorsal regions, suggesting a trade-off between emotional and executive processes. Given recent fMRI evidence that younger and older adults recruit ventral affective areas during viewing of positive stimuli and dorsal executive control regions during viewing of negative stimuli (Ebner et al., 2012), it seems possible that positive affect's impairing effect on attention is related to decreased blood flow to executive regions and increased blood flow to affective processing regions.

Prefrontal control regions have been implicated in age differences in susceptibility to distraction (e.g., Chao and Knight, 1997; Jonides et al., 2000; Gazzaley et al., 2008). While performing a 1-back task similar to that used here, older adults showed less activation in a frontoparietal control network than younger adults when instructed to ignore irrelevant words, and decreased activity in this control network was associated with greater priming for the irrelevant words later on (Campbell et al., 2012). Thus, positive emotion's impairing effect on attention selectivity and enhancing effect on tacit knowledge of past distraction may amplify the effects of normal aging. Positive affect may act via ventral emotion processing regions to modulate older adults' recruitment of prefrontal control regions that are already associated with age-related reductions, thus facilitating automatic or implicit processing of distraction. Ventral areas of the prefrontal cortex are likely to play a larger role in this process than are basic emotion areas such as the amygdala, considering recent event-related potential evidence suggesting that older adults' visual attention is not modulated by the amygdala as is seen in younger adults (Pollock et al., 2012).

In a general sense, both positive affect and aging may result in a cognitive shift toward a more diffuse mental state that involves disengagement of executive control and greater reliance on more automatic processes. While there may be substantial cognitive costs, such as greater distractibility, there likely are also tangible benefits to this broadened mode of processing, including enhanced tacit knowledge of past distraction, as we have shown here.

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Emotion potentiates response activation and inhibition in masked priming

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Previous studies have shown that emotion can have 2-fold effects on perception. At the object-level, emotional stimuli benefit from a stimulus-specific boost in visual attention at the relative expense of competing stimuli. At the visual feature-level, recent findings indicate that emotion may inhibit the processing of small visual details and facilitate the processing of coarse visual features. In the present study, we investigated whether emotion can boost the activation and inhibition of automatic motor responses that are generated prior to overt perception. To investigate this, we tested whether an emotional cue affects covert motor responses in a masked priming task. We used a masked priming paradigm in which participants responded to target arrows that were preceded by invisible congruent or incongruent prime arrows. In the standard paradigm, participants react faster, and commit fewer errors responding to the directionality of target arrows, when they are preceded by congruent vs. incongruent masked prime arrows (positive congruency effect, PCE). However, as prime-target SOAs increase, this effect reverses (negative congruency effect, NCE). These findings have been explained as evidence for an initial activation and a subsequent inhibition of a partial response elicited by the masked prime arrow. Our results show that the presentation of fearful face cues, compared to neutral face cues, increased the size of both the PCE and NCE, despite the fact that the primes were invisible. This is the first demonstration that emotion prepares an individual's visuomotor system for automatic activation and inhibition of motor responses in the absence of visual awareness.

Keywords: emotion, masking, motor priming, fearful faces, activation, inhibition

EMOTION POTENTIATES RESPONSE ACTIVATION AND INHIBITION IN MASKED PRIMING

Previous studies have shown that emotion can have 2-fold effects on visual perception. At the visual object level, emotional stimuli benefit from a stimulus-specific boost in the allocation of visual attention which occurs at the relative expense of spatially or temporally competing stimuli (Fox et al., 2001; Bocanegra and Zeelenberg, 2009a). At the visual feature level, recent findings indicate that emotion facilitates the fast processing of coarse visual features (Phelps et al., 2006; Bocanegra and Zeelenberg, 2009b, 2011) and inhibits the slower processing of small visual details (Bocanegra and Zeelenberg, 2009b, 2011). In the present study, we investigated whether emotion influences covert visuomotor processing that occurs in the absence of overt visual perception.

Many authors have suggested that the primary function of affective reactions is to enhance an organism's preparedness for action (Dolan, 2002; Phelps and LeDoux, 2005; Hajcak et al., 2007; Yiend, 2010; Bradley et al., 2012). Indeed, it has been shown that the perception of fearful faces enhances corticospinal motor tract excitability (Schutter et al., 2008). Consistent with these ideas, emotion influences response times (RTs) in various experimental paradigms, such as visual search and cueing tasks. For example, many studies indicate that a task-irrelevant emotional cue can influence RTs to a visual feature of a subsequent target (such as, location, color, shape, or orientation) (Mogg and Bradley, 1999; Fox et al., 2001; Yiend and Mathews, 2001; Mathews et al., 2003).

It has been proposed that, emotion influences RTs to visual stimuli either by speeding up access to visual awareness (e.g., by engaging attention to a stimulus or a certain stimulus feature) or by enhancing the processes responsible for maintaining visual awareness (e.g., by sustaining attention to a stimulus or stimulus feature). Within most theoretical frameworks, emotional cues are thought to modulate the perceptual processing stages that result in the overt identification of a feature, which in turn influences the downstream activation of motor codes and subsequent response execution (for an overview, see Yiend, 2010, for a direct emotion modulation in motor processing, see Schutter et al., 2008; Bradley et al., 2012). If visual stimuli access or occupy overt stages of perception more readily, this, in turn, could accelerate or increase the build-up of response activation triggered by a response-contingent stimulus feature.

A modulation in visual perception provides a natural explanation of how emotion might influence RTs to a stimulus. As a general rule one can say that as the perceptual strength of a visual feature is increased or decreased, detection or identification times also decrease or increase respectively (Teichner and Krebs, 1974). However, several studies, which were not concerned with the impact of emotion on action, now indicate that

the initial stages of motor responding do not depend causally on the conscious perception of the stimulus feature specifying the response to be executed. Instead, it is well-established that simple stimulus features (such as color, shape, or orientation) can trigger motor responses prior to visual identification (Klotz and Neumann, 1999; Eimer and Schlaghecken, 2003; Sumner et al., 2006). These covert visuomotor responses have generated much interest because they demonstrate that sensory information can trigger motor responses directly, by-passing the perceptual mechanisms that support conscious visual perception.

In the standard motor priming paradigm, a prime stimulus is backward-masked and followed by a clearly visible target stimulus. On congruent trials, prime and target are mapped on the same response, whereas on incongruent trials they are mapped on different responses. Although participants are unable to visually identify the masked primes, it has been shown that reaction-times differ for congruent vs. incongruent trials (e.g., Klotz and Neumann, 1999). Typically, prime and target are presented in rapid succession and positive congruency effects (PCEs) are observed (i.e., congruent trials are faster than incongruent trials). Surprisingly, however, when the prime-target stimulus onset asynchrony (SOA) is increased beyond 100 ms, the PCE turns into a negative congruency effect (NCE) where congruent trials are *slower* than incongruent trials (see **Figure 1**) (Eimer and Schlaghecken, 2003; Sumner et al., 2006). The initial PCE and subsequent NCE have been interpreted as an activation-followed-by-inhibition sequence reflecting the workings of low-level motor control mechanisms (Schlaghecken et al., 2006). Initially, the prime-induced response activation facilitates responding to the target on congruent trials, compared to incongruent trials. However, when the mask suddenly removes the sensory signal supporting the prime response, this specific motor response is actively inhibited which leaves the opposite response relatively more active. If a target is presented during this inhibition phase incongruent trials will be facilitated compared to congruent trials. This inhibitory mechanism has been interpreted as an "emergency brake" mechanism in covert visuomotor processing (Schlaghecken et al., 2006).

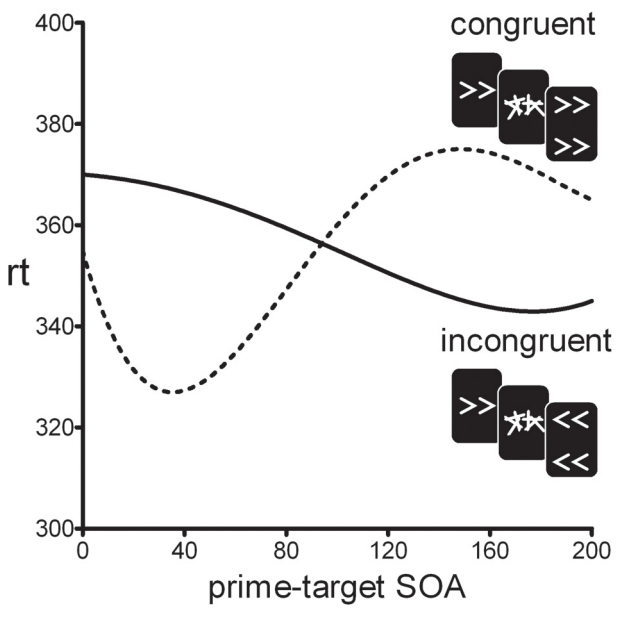

FIGURE 1 | Typical time-course of the positive congruency effect (PCE ≈0–100 SOA) and the negative congruency effect (NCE ≈100–250 SOA).

In light of these findings, an intriguing unexplored question is whether emotion modulates covert visuomotor processing *prior* to the overt perception of a visual stimulus. Conceivably, emotion might influence RTs in two distinct ways. On the one hand, emotion might modulate the perceptual strength of the conscious percept of a visual feature (Phelps et al., 2006; Bocanegra and Zeelenberg, 2011), and as a result of this, influence the build-up of motor activation that is initiated once the response-contingent stimulus feature is overtly identified. On the other hand, emotion might also influence covert visuomotor responses that are initiated prior to the identification of the initiating visual feature, which could influence RTs-independent of conscious visual perception (Vorberg et al., 2003). A crucial difference between these possibilities is that an overt perceptual mechanism predicts that RT-effects should depend critically on the response-contingent stimulus feature having been identified faster or more accurately (see Phelps et al., 2006; Bocanegra and Zeelenberg, 2009b), whereas covert visuomotor mechanisms predicts that RT-effects should be obtained even if the response-contingent feature of the stimulus has not been processed fully enough to be visually identified. Previous emotional studies did not address this distinction because in these paradigms motor responses were always elicited by a clearly visible suprathreshold stimulus (Yiend, 2010) or were elicited by a non-visual TMS pulse applied directly over the motor cortex (Schutter et al., 2008). Here, we employed a novel emotional cueing paradigm where a subthreshold prime is rendered invisible through pattern-masking in order to tap into the early activation phase and subsequent inhibition phase of covert visuomotor processing.

EXPERIMENT 1

In order to tap into covert visuomotor processing and minimize the effect of overt visual perception on RT, we used a masked priming paradigm where participants performed speeded responses to target arrows that were preceded by masked prime arrows (see **Figure 2**). On any given trial, the masked prime elicited either the same response as the target (congruent trials), or a different response (incongruent trials). By comparing the RT-differences between congruent and incongruent trials we assessed the covert visuomotor processing triggered by the masked prime through its effect on the subsequent target. Specifically, we assessed the PCE at a short prime-target SOA (20 ms) and the NCE at a long prime-target SOA (170 ms). To test whether emotion modulates covert visuomotor processing, we presented an emotional face cue concurrently with the prime and assessed the magnitude of the PCE and NCE. If emotion modulates covert visuomotor processing, larger prime-target congruency effects are expected when the prime is accompanied by an emotional face cue, compared to a neutral face cue.

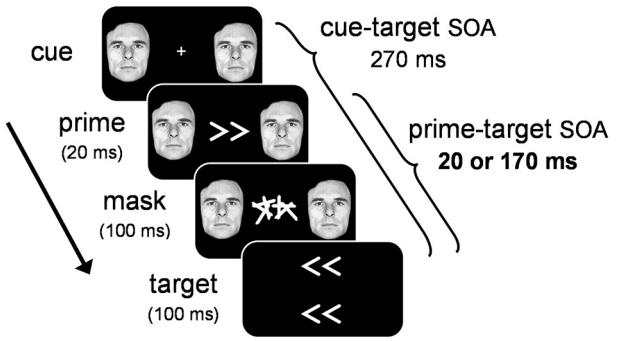

FIGURE 2 | Illustration of the general trial sequence for Experiments 1–3. Target arrows were not presented in Experiment 3. See text for details.

METHODS

PARTICIPANTS

Twenty undergraduate students at the Erasmus University Rotterdam participated for course credit or a small monetary reward. All were naïve as to the purpose of the study, reported normal or corrected-to-normal vision, and gave informed consent.

STIMULUS MATERIALS, APPARATUS, AND PROCEDURE

Stimuli were presented on a gamma-corrected Iiyama 21-in. (100 Hz refresh-rate; 1600 × 1200 pixel resolution). A white fixation cross (0.8° × 0.8°) was presented at the center of a uniform black background for 500 ms prior to the stimulus sequence (see **Figure 1**). To manipulate emotion, we selected 11 *fearful* and *neutral* facial expressions from the Picture of Facial Affect (Ekman and Friesen, 1976). Cue displays consisted of a bilateral pair of fearful or neutral facial cut-outs of the same person (6.5° in diameter), presented left and right of fixation at 8° eccentricity. We chose to manipulate emotional significance with fearful facial expressions because previous studies have shown that this expression reliably activates the amygdala (Whalen et al., 1998), and has been shown to modulate perceptual processing throughout the visual system (Vuilleumier, 2005). Primes consisted of white left-pointing or right-pointing double arrows (<< and >>; size 3.5° × 1.8°) presented at fixation for 20 ms. A mask was presented for 100 ms immediately following the prime. Masks consisted of two white characters covering the entire area where primes had been presented. Targets consisted of two left-pointing or right-pointing arrow-pairs (3.5° × 1.8°), presented at 1.5° eccentricity above and below the center of the mask. The cue-target SOA was held constant (270 ms), and the prime-target SOA was either short (20 ms) or long (170 ms). Please note that by equalizing the cue-target SOA across the two prime-target SOA conditions, we created an inherent methodological confound between prime-target SOA and cue-prime SOA. Ten different mask characters were constructed, each consisting of four randomly oriented lines. To minimize prime-mask feature-overlap (Lleras and Enns, 2004), none of the lines in the mask shared the angular orientation of the prime. For each of the two mask positions, a character was sampled randomly from the set of ten mask characters.

Participants viewed the display at a distance of approximately 60 cm, maintaining central eye fixation, responding as quickly and accurately as possible to the direction of the target by pressing the "*z*" key for left and the "*m*" key for right. The experiment consisted of two blocks, one for the short SOA (20 ms) and one for the long SOA (170 ms). Each block was divided up into 5 experimental sub-blocks of 88 trials each. All experimental conditions within each sub-block were equiprobable and were presented in a randomized order. The order of the blocks was counterbalanced across participants.

DATA ANALYSIS

Incorrect responses were excluded from the analysis (<5% in all conditions). Mean RTs were calculated for correct responses, removing trials with RTs of less than 200 ms or more than 800 ms (1.6% of all trials). The same outlier criterion was used in all experiments reported here. A repeated-measures analyses-of-variance was conducted that included the factors prime-target SOA (20 ms vs. 170 ms), cue-type (fearful vs. neutral) and prime-target congruency (congruent vs. incongruent).

RESULTS AND DISCUSSION

Figure 3 shows RTs as a function of prime-target SOA, cue-type and prime-target congruency. As expected, we found a cross-over interaction effect between prime-target congruency and SOA, $F_{(1,\ 19)} = 100.93$, $p < 0.001$, $\eta_p^2 = 0.84$. At the short prime-target SOA, we observed a PCE, $t_{(19)} = 5.92$, $p < 0.001$; congruent trials were 18 ms faster than incongruent trials. At the long prime-target SOA, we observed a NCE, $t_{(19)} = 7.89$, $p < 0.001$; congruent trials were 26 ms slower than incongruent trials.

Importantly, we observed a two-way interaction between cue-type and prime-target congruency, $F_{(1,\ 19)} = 8.51$, $p < 0.001$, $\eta_p^2 = 0.31$, indicating that the covert effect of the prime stimulus on target responding depended on the emotional significance of the cue stimulus. In addition, we obtained a three-way interaction between prime-target SOA, cue-type and prime-target congruency, $F_{(1,\ 19)} = 20.36$, $p < 0.001$, $\eta_p^2 = 0.52$. Cue-type and prime-target congruency interacted at the short SOA, $F_{(1,\ 19)} = 27.00$, $p < 0.001$, $\eta_p^2 = 0.59$. Specifically, this shows that the PCE was larger for fearful cues (27 ms; $t_{(19)} = 8.15$, $p < 0.001$) than for neutral cues (10 ms; $t_{(19)} = 2.68$, $p = 0.015$). The NCE, however, was not affected by the emotional status of the face cues, as indicated by the lack of a cue-type × prime-target congruency interaction at a long SOA, $F < 1$, $p > 0.75$. Thus, the main finding of Experiment 1 was that the presentation of a bilateral fearful face cue potentiated the activation of the visuomotor response elicited by the masked prime.

EXPERIMENT 2

Why was the PCE enhanced by emotion whereas the NCE was not? It has recently been proposed that the NCE may partly depend on global inhibitory processes that occur *between* response-channels (Praamstra and Seiss, 2005; Schlaghecken et al., 2006). In Experiment 1, the presentation of a bilateral

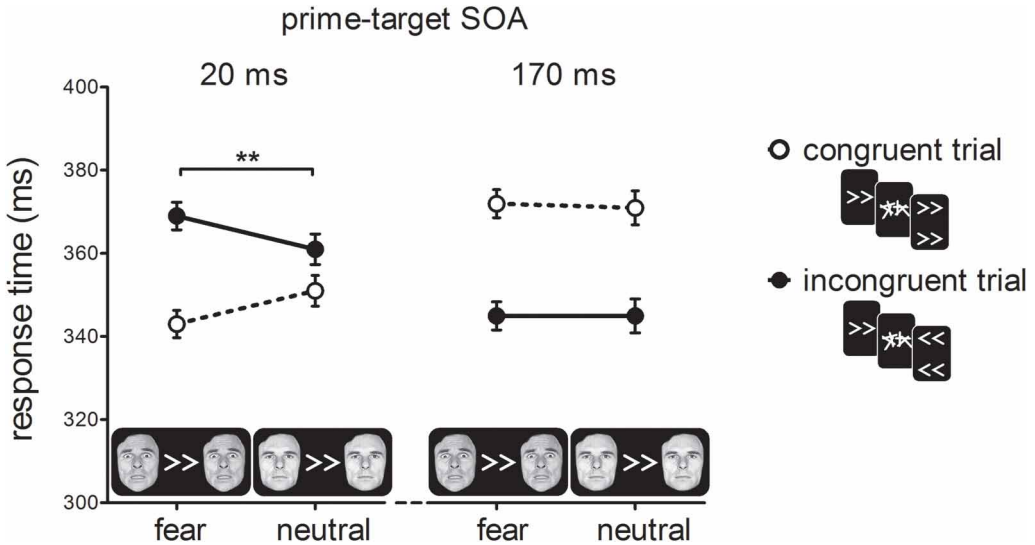

FIGURE 3 | Response times in milliseconds (ms) for the experimental conditions in Experiment 1. For compatible trials, prime, and target arrows elicited the same response, whereas for incompatible trials they elicited different responses. Error-bars indicate within-subject standard errors of the mean difference (Loftus and Masson, 1994). $^{**}p < 0.01$ (interaction).

fearful cue may have resulted in the same inhibitory balance between the response-channels as a bilateral neutral cue. If the NCE depends partly on the relative balance of lateral inhibition between the left vs. right response-channels, the symmetrical bilateral cues we used in Experiment 1 may not have been optimal in order to influence reciprocal inhibition between response-channels.

In order to test the possibility that emotion also enhances the NCE we presented the emotional stimulus unilaterally in order to influence the inhibitory balance between the response-channels (Praamstra and Seiss, 2005). In our second experiment, we did this by constructing cues consisting of a fearful face paired with a neutral face and varied their location (see Mogg and Bradley, 1999; Yiend and Mathews, 2001). Critically, if emotion enhances covert visuomotor processing, priming effects should be larger when the fearful face is presented in the hemifield that matches the primed response, compared to when the fearful face is presented in the hemifield that mismatches the primed response.

METHODS

Twenty students participated in the experiment. All experimental aspects were identical to Experiment 1 except for the type of cue displays used. Cue displays consisted of a fearful face paired with a neutral face that were presented left and right of fixation. On half of the trials the fearful face was presented left of fixation and the neutral face was presented right of fixation. On the other half of the trials the location of fearful and neutral faces was reversed. This resulted in two cue-types: cues where the location of the fearful face was congruent with the direction of the prime response (congruent fear cue), and cues where the location of the fearful was incongruent with the direction of the prime response (incongruent fear cue). Incorrect responses were again excluded (<6% in all conditions), and RTs were trimmed (1.6% of all trials).

RESULTS AND DISCUSSION

Figure 4 shows RTs as a function of prime-target SOA, cue-type and prime-target congruency. As in Experiment 1, and consistent with previous reports (e.g., Eimer and Schlaghecken, 2003), we found a cross-over interaction effect between prime-target congruency and SOA, $F_{(1,\ 19)} = 32.37$, $p < 0.001$, $\eta_p^2 = 0.63$. At the short prime-target SOA, we observed a PCE, $t_{(19)} = 4.53$, $p < 0.001$; congruent trials were 18 ms faster than incongruent trials. At the long prime-target SOA, we observed a NCE, $t_{(19)} = 4.54$, $p < 0.001$; congruent trials were 13 ms slower than incongruent trials.

Importantly, we observed a two-way interaction between cue-type and prime-target congruency, $F_{(1,\ 19)} = 7.95$, $p = 0.01$, $\eta_p^2 = 0.30$, indicating that the covert effect of the prime stimulus on target responding depended on the emotional significance of the cue stimulus. Although the three-way interaction between prime-target SOA, cue-type and prime-target congruency failed to reach significance, $F_{(1,\ 19)} = 2.15$, $p = 0.16$, $\eta_p^2 = 0.10$, we tested the two-way interactions between cue-type and prime-target congruency separately for the two SOA conditions to determine which of the SOAs was driving the two-way interaction between cue-type and prime-target congruency. Cue-type and prime-target congruency did not interact at the short SOA, $F < 1$, $p > 0.50$, but did at the long SOA, $F_{(1,\ 19)} = 11.42$, $p < 0.01$, $\eta_p^2 = 0.38$, suggesting that the NCE was larger for fearful cues (18 ms; $t_{(19)} = 5.21$, $p < 0.001$) than for neutral cues (9 ms; $t_{(19)} = 2.79$, $p = 0.01$). Thus, the covert visuomotor inhibition of the motor response elicited by the masked prime was larger when the peripheral fearful face was presented in the hemifield that matched the response-channel activated by the prime.

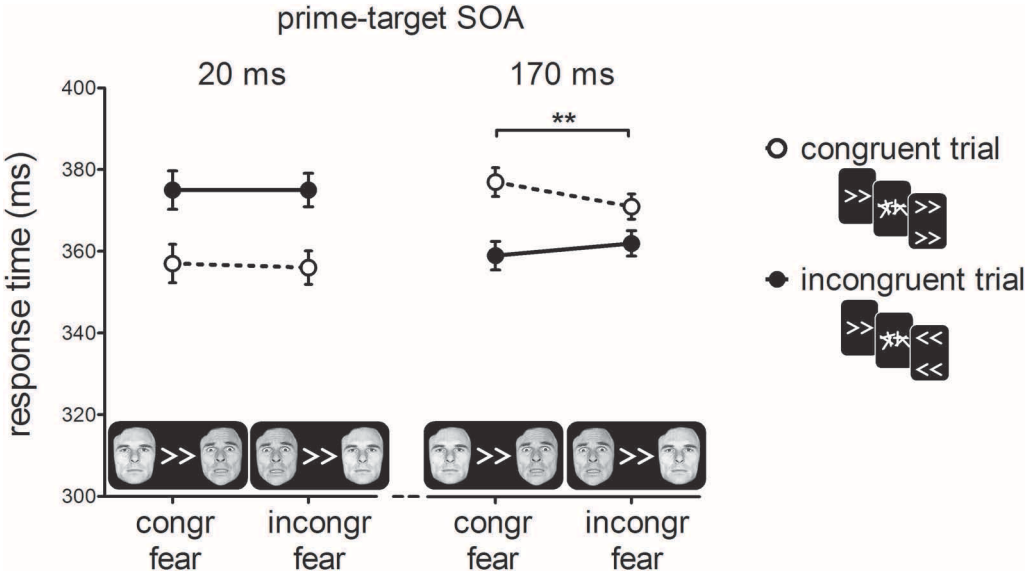

FIGURE 4 | Response times in milliseconds (ms) for the experimental conditions in Experiment 2. For congruent fear cues, the fearful face was presented on the same side as the direction of the prime, whereas for incongruent fear cues the fearful face appeared on the opposite side. Error-bars indicate within-subject standard errors of the mean difference (Loftus and Masson, 1994). $^{**}p < 0.01$ (interaction).

EXPERIMENT 3

Our findings in Experiments 1 and 2 suggest that emotion enhances the activation and inhibition of covert visuomotor responses elicited by an invisible masked stimulus. In Experiment 1, the presentation of a fearful face cue enhanced covert response activation and in Experiment 2 the peripheral presentation of a fearful face potentiated covert response inhibition when it was presented in the hemifield that matched the response-channel activated by the prime. Although none of the participants in Experiments 1 and 2 reported having seen any of the prime arrows, the different cue-types might have differentially affected any residual prime visibility. Conceivably, this could have influenced the magnitudes of the PCE and NCE (see Sumner et al., 2006). In order to address this possibility, we assessed prime identification performance for the cue displays used in Experiments 1 and 2.

METHODS

Ten additional students participated in the experiment. Participants performed a non-speeded prime identification task, indicating the direction of the primes by pressing "*z*" for left and "*m*" for right. It has been shown that the presence of a trailing target during a prime identification task makes it virtually impossible for participants to follow task instructions (Eimer and Schlaghecken, 2003). Thus, we excluded the target in order to prevent artificially reduced performance levels. Also, we included a short response delay (2 s) after mask presentation in order to ensure that identification performance would not be contaminated by any short-lived covert responses elicited by the masked primes (see Klapp and Hinkley, 2002). All other experimental aspects were identical to the previous experiments. Observers performed 2 blocks of 176 trials, one block containing the fearful and neutral cues, and the other containing the match and mismatch cues. Although the number of trials and participants are less than those included in Experiments 1 and 2, these numbers are comparable to other control experiments that have been published in the motor priming literature (Naccache and Dehaene, 2001; Klapp and Hinkley, 2002; Kiesel et al., 2007). The order of the blocks was counterbalanced across participants.

RESULTS AND DISCUSSION

Prime identification accuracy did not differ between the four different cue-types, $F < 1$, $p > 0.8$ (see **Figure 5**). In addition, identification accuracy did not differ significantly from chance performance (50%) in any of the cue-type conditions (all ts < 0.9, ps > 0.4), In addition, we calculated the JZS Bayes factor for all four conditions. Bayes factors can be used to provide confirmative evidence for the null-hypothesis of no effect by estimating how much more likely the null-hypothesis is given the data relative to the alternative hypothesis (Rouder et al., 2009). We found that for all cue-type conditions *JZS-BF*s >3, which is typically considered positive evidence in favor of the null-hypothesis by researchers advocating the use of Bayesian statistics. This suggests that the results of Experiments 1 and 2 were not mediated by the effect of the cues on prime visibility.

GENERAL DISCUSSION

In the present study, we investigated whether emotion potentiates visuomotor responses that are initiated *prior* to the conscious visual identification of a stimulus. Specifically, we assessed the initial activation phase and subsequent inhibition phase of motor responses elicited by an invisible masked stimulus. In accordance with previously reported findings, we obtained a positive

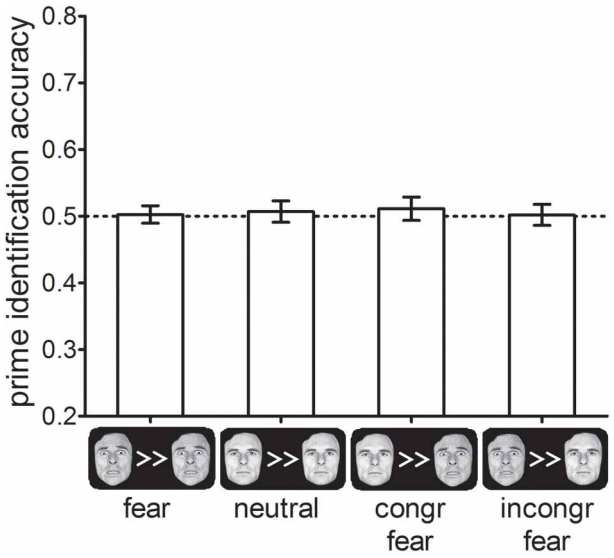

FIGURE 5 | Percentage correctly identified primes as a function of cue-types in Experiment 3. Error-bars indicate standard errors of the mean.

congruency effect (PCE) at a short (20 ms) SOA and a negative congruency effect (NCE) at a long (170 ms) SOA (for an overview, see Eimer and Schlaghecken, 2003). More important, in Experiment 1, the presentation of a bilateral fearful face cue, compared to a bilateral neutral face cue, increased the size of the PCE. The size of the NCE, however, was not affected by the emotional status of the face cue. In Experiment 2, we presented cues consisting of both a neutral face and a fearful face, and varied the location of the neutral and fearful face (e.g., left face: neutral, right face: fearful). The presentation of a fearful face cue at the location of the primed response, compared to a fearful face cue at the opposite location, increased the size of the NCE. Combined, these findings suggest that the presentation of fearful face cues potentiate both early facilitatory and later inhibitory stages of covert visuomotor processing, Experiment 3 indicated that prime visibility was at chance performance for each of the different cue-types used in Experiments 1 and 2, which suggests that our findings were not mediated by an effect of emotional cueing on prime visibility.

A reviewer pointed out to us that the lack of an emotional modulation of the NCE in Experiment 1 may have been due to an intrinsic experimental confound. In our stimulus sequence, we equalized the cue-target SOA for the short and long prime-target SOA conditions. In doing so, we inherently created an experimental confound between the prime-target SOA and the cue-prime SOA: the cue-prime was always shorter in the long prime-target SOA condition, compared to the short prime-target SOA condition. Thus, if the emotional modulation due to the bilateral fearful cues requires some time to build-up, the prime presentation in the long prime-target condition may have been too soon after cue-onset to be modulated by emotion. It is thus possible that with bilateral cues the NCE would also be modulated by emotional face cues if a longer cue-prime SOA is used. However, these considerations do not invalidate our primary conclusion that emotion modulates visuomotor processing prior to visual awareness.

Interestingly, a previous study has demonstrated that a masked subthreshold emotional cue presented outside visual awareness can nonetheless influence RTs to a subsequent target (Mogg and Bradley, 1999). A pair of emotional and neutral face stimuli were briefly displayed and masked in a dot-probe task. RTs were faster when the spatial location of the emotional face matched the location of the subsequent target compared to when it mismatched. This finding shows that emotional facial expressions may rapidly engage and release attention (see also Santesso et al., 2008; Maratos, 2011), and suggests that these attentional effects of emotion may also operate prior to overt visual awareness. Indeed, our results in Experiment 2 may have due to covert spatial attentional mechanisms. Although the (Mogg and Bradley, 1999) study relates to our finding in the sense that emotion may influence the allocation of attention prior to visual awareness, there is a critical difference with our study. In the Mogg and Bradley (1999) study, the task-irrelevant emotional face cue was masked whereas in our study the prime was masked (but face cues were clearly visible). Thus, in contrast to our study, the response initiating stimulus was always clearly visible in the Mogg and Bradley study (1999). In sum, where Mogg and Bradley (1999) showed that a subthreshold emotional cue enhances the visual identification of a subsequent stimulus at the cued location, our study shows that the presentation of an emotional cue enhances the visuomotor processing of subthreshold stimulus *prior* to visual identification.

An emotional boost of covert visuomotor processing could serve to facilitate the quick activation and inhibition of ready action triggers in situations in which there is time-pressure to respond and a more elaborate visual identification of a stimulus is costly. Initially, emotion potentiates the automatic activation of a visuomotor response. However, if the sensory evidence supporting this response is suddenly removed the motor activation is quickly inhibited (Schlaghecken et al., 2006). It has been suggested that the inhibition of a masked prime-induced response may be partly determined by competitive interactions between response-channels where alternating cycles of activation and inhibition continue until one response is selected and all the competing responses are deselected (Praamstra and Seiss, 2005). In this manner, we might speculate that an emotional modulation in visuomotor activation and inhibition may help to facilitate both the rapid selection of correct responses and rapid deselection of erroneous responses during threatening situations.

An interesting question is whether the emotional modulation in visuomotor processing observed in our study is restricted to specific types of emotional stimuli or whether it reflects a more general emotional mechanism. Do our findings extend to other types of visual stimuli (e.g., other emotional facial expressions, affective pictures), and does the pattern of results depend on the specific affective state of the participants? As with most previous studies investigating the influence of emotion on visual processing (Pourtois et al., 2004; Phelps et al., 2006; Bocanegra and Zeelenberg, 2009a,b), we used fearful faces because they have consistently been shown to activate the amygdala

(Vuilleumier, 2005). However, it would be interesting to test whether these results extend to other emotional expressions such as anger, happiness, or disgust.

Importantly, the covert visuomotor mechanisms uncovered in the present study constitute a significant conceptual departure from current theorizing in emotion research. Currently, emotional influences on responding are thought to result either from facilitated access or maintenance in visual perception (Yiend, 2010; Bradley et al., 2012). Here, we provide evidence that emotion facilitates visuomotor responding-independent of the perceptual mechanisms that support visual identification. Future accounts of emotional influences in visual RTs may want to incorporate the distinction between covert visuomotor and overt perceptual influences on action.

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Neural mechanisms underlying the effects of face-based affective signals on memory for faces: a tentative model

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In our daily lives, we form some impressions of other people. Although those impressions are affected by many factors, face-based affective signals such as facial expression, facial attractiveness, or trustworthiness are important. Previous psychological studies have demonstrated the impact of facial impressions on remembering other people, but little is known about the neural mechanisms underlying this psychological process. The purpose of this article is to review recent functional MRI (fMRI) studies to investigate the effects of face-based affective signals including facial expression, facial attractiveness, and trustworthiness on memory for faces, and to propose a tentative concept for understanding this affective-cognitive interaction. On the basis of the aforementioned research, three brain regions are potentially involved in the processing of face-based affective signals. The first candidate is the amygdala, where activity is generally modulated by both affectively positive and negative signals from faces. Activity in the orbitofrontal cortex (OFC), as the second candidate, increases as a function of perceived positive signals from faces; whereas activity in the insular cortex, as the third candidate, reflects a function of face-based negative signals. In addition, neuroscientific studies have reported that the three regions are functionally connected to the memory-related hippocampal regions. These findings suggest that the effects of face-based affective signals on memory for faces could be modulated by interactions between the regions associated with the processing of face-based affective signals and the hippocampus as a memory-related region.

Keywords: fMRI, face, memory, amygdala, orbitofrontal cortex, insula

INTRODUCTION

Facial stimuli convey various types of information in human society, and are very important in non-verbal communication with others. For example, when we encounter someone for the first time, we try to read their feelings from their face. The facial information that can provide us with impressions of people includes many factors such as trustworthy, caring, responsible, emotionally stable, sociable, attractive, intelligent, confident, dominant, happy, aggressive threatening, mean, or weird features (Oosterhof and Todorov, 2008; Todorov and Engell, 2008; Todorov et al., 2008b), and it is also influenced by racial information (Stanley et al., 2011, 2012). Among them, three possible factors of facial expression, attractiveness, or trustworthiness are particularly important in forming the impressions of people and in selecting which people should be remembered, because the response times for the attractiveness and trustworthiness judgments were almost identical and faster than the response times for judgments of competence, likeability, and aggressiveness (Willis and Todorov, 2006). However, there is little evidence of the neural mechanisms underlying this psychological process. The aims of this article are to review psychological and cognitive neuroscience studies related to the effects of face-based affective signals on memory for faces, particularly those concerning facial expressions, attractiveness, and trustworthiness, and to propose a tentative framework for understanding the neural mechanisms of memory for faces in the context of human social interaction.

EFFECTS OF FACE-BASED AFFECTIVE SIGNALS ON MEMORY FOR FACES: PSYCHOLOGICAL STUDIES

The first main factor of face-based affective signals is facial expression. Previous psychological studies have reported that positive facial expressions such as smiling have a beneficial effect on remembering faces (D'Argembeau et al., 2003; D'Argembeau and van der Linden, 2004, 2007; Laroi et al., 2006; Shimamura et al., 2006; Ebner and Johnson, 2009). For example, Shimamura and his colleagues found that faces encoded with smiling expressions were remembered more accurately than those with other expressions, including surprise, anger, or fear (Shimamura et al., 2006). However, there is also evidence from psychological studies that positive facial expressions have no selective advantage on memory for faces. One study showed better remembering of faces with fearful expressions than of those with happy expressions (Righi et al., 2012), whereas another study reported memory enhancement for faces with positive and negative expressions, compared to those with neutral expressions (Foa et al., 2000). Taken together, both positive and negative facial expressions could contribute to the enhancing effects on memory for faces.

The second main factor of affective signals conveyed from faces is facial attractiveness. The beneficial power of facial attractiveness has been observed in several studies investigating the recognition of other people. For example, adults (Langlois et al., 2000) as well as infants (Langlois et al., 1987) show a preference for attractive faces. Also, compared to facially unattractive people, facially attractive people are likely to show enhanced positive behavior in a social way (Langlois et al., 2000), and to be judged people with better personality by others (Dion et al., 1972). The positive bias toward attractive faces has been identified in memory for faces, in which attractive faces are better remembered than unattractive faces (Cross et al., 1971; Marzi and Viggiano, 2010). However, there is evidence from psychological studies that the distinctiveness in attractive faces is low, and the low distinctiveness of faces has little beneficial effect on memory for faces (Light et al., 1981). Thus, the effect of facial attractiveness on memory for faces may be advantageous, but the mechanisms underlying it and its efficiency in terms of remembering faces are still controversial.

The third main factor of face-based affective signals enhancing the memory processing of faces is facial trustworthiness. There is evidence from psychological studies that facial untrustworthiness has a beneficial power on memory for faces. For example, one psychological study demonstrated that the recognition of faces with untrustworthy impressions was better than that of faces with neutral or trustworthy impressions (Mealey et al., 1996). Another psychological study found that the faces of trustworthy-looking people with bad personality traits were remembered more accurately than those of untrustworthy-looking people with bad personality traits (Suzuki and Suga, 2010). In this study, 58 college students played a debt game, where they learned to discriminate among good, neutral, and bad lenders, who respectively charged no, moderate, and high interest on the debt. Each lender had either a trustworthy- or untrustworthy-looking faces. The findings of better memory for people associated with an untrustworthy impression or bad personality, which depends on the face-based first impression or on the later contextual information of personality, suggest that humans could be equipped with protective mechanisms against people with really bad personality traits (Suzuki and Suga, 2010).

ROLES OF THE AMYGDALA IN THE PROCESSING OF FACE-BASED AFFECTIVE SIGNALS

The first candidate region associated with the processing of face-based affective signals is the amygdala (**Figure 1**). Previous functional neuroimaging studies have reported that the amygdala shows significant activations during the processing of face-based negative and positive signals including happy, sad, and fearful expressions (Fusar-Poli et al., 2009). For example, activity of the amygdala was greater during perceiving high-intensity expressions than low-intensity expressions, and the activity was identified in relation to both positive and negative signals from faces (Winston et al., 2003). This suggests that activity of the amygdala could be modulated by affective intensities of facial expressions. However, there is functional neuroimaging evidence linking amygdala activities to the processing of negative facial expressions (Vuilleumier and Pourtois, 2007). For example, one functional MRI (fMRI) study demonstrated that the amygdala showed greater activity during the processing of negative facial expressions than of neutral facial expressions (Iidaka et al., 2001). Amygdala responses selective to negative facial expressions have been observed in other functional neuroimaging and lesion studies (Adolphs et al., 1994; Morris et al., 1996; Broks et al., 1998). The amygdala, in which the activity is modulated by affective intensities of facial expressions, could be involved in the processing of both positive and negative facial expressions, but the involvement could be biased toward more negative expressions. However, given that a meta-analysis study showed no effect of angry and disgusted expressions on amygdala activations (Fusar-Poli et al., 2009), further investigations would be required to clarify whether the amygdala activations are modulated only by specific types of facial expressions, rather than affective intensities of facial expressions.

The contribution of the amygdala to the processing of facial attractiveness or trustworthiness has also been demonstrated in cognitive neuroscience studies (Bzdok et al., 2011). Several functional neuroimaging studies have reported greater amygdala activity in the processing of highly attractive and unattractive faces than of middle-ranked attractive faces (Winston et al., 2007; Cloutier et al., 2008; Liang et al., 2010). Additionally, there is functional neuroimaging evidence that amygdala activity increased during the processing of both trustworthy and untrustworthy faces, compared to that of neutral faces (Todorov, 2008). For example, one fMRI study found that the amygdala showed greater responses to highly trustworthy as well as to highly untrustworthy faces than to neutral faces (Said et al., 2009). The non-linear amygdala responses to face-based affective signals suggest that this region could be involved in sensing the value of social stimuli including both positive and negative affects of faces. However, other functional neuroimaging studies have demonstrated that the amygdala response to faces increased as their perceived untrustworthiness increased (Winston et al., 2002; Engell et al., 2007; Todorov et al., 2008a), and this amygdala response to untrustworthy faces was supported by a lesion study (Adolphs et al., 1998). Taken together, amygdala responses to facial attractiveness and trustworthiness could be possibly modulated by both good and bad impressions of the two factors, but the responses could be biased to more negative signals conveyed from faces. However, further studies would be required to clarify whether the amygdala activity is modulated by facial impressions or by affective intensities of presented pictures.

ROLES OF THE ORBITOFRONTAL CORTEX IN THE PROCESSING OF FACE-BASED AFFECTIVE SIGNALS

The second candidate region associated with the processing of face-based affective signals is the medial orbitofrontal cortex (OFC: **Figure 2**). The involvement of the medial OFC region in the processing of facial expressions has been identified when the facial expression is happy or smiling. For example, activity of the medial OFC region was enhanced in the processing of happy facial expressions, compared to that of facial expressions of disgust (Gorno-Tempini et al., 2001). The medial OFC responses to happy facial expressions have also been found in other functional neuroimaging studies (O'Doherty et al., 2003; Minagawa-Kawai

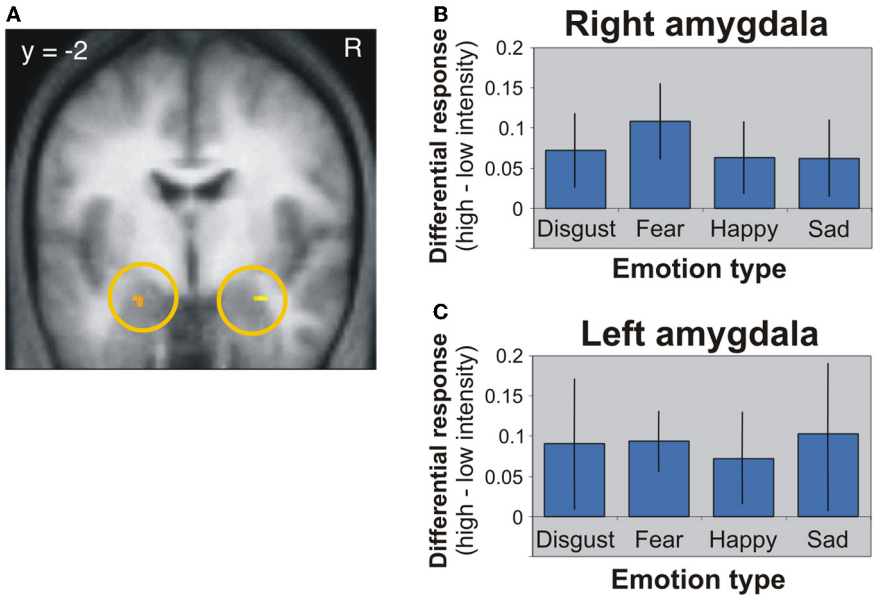

FIGURE 1 | Amygdala activation in response to different facial expressions (Winston et al., 2003). (A) Activation image of the amygdala during the processing of high-intensity expressions compared to low-intensity expressions. **(B)** Activation profiles of the right amygdala. **(C)** Activation profiles of the left amygdala. This figure was reused with the permission.

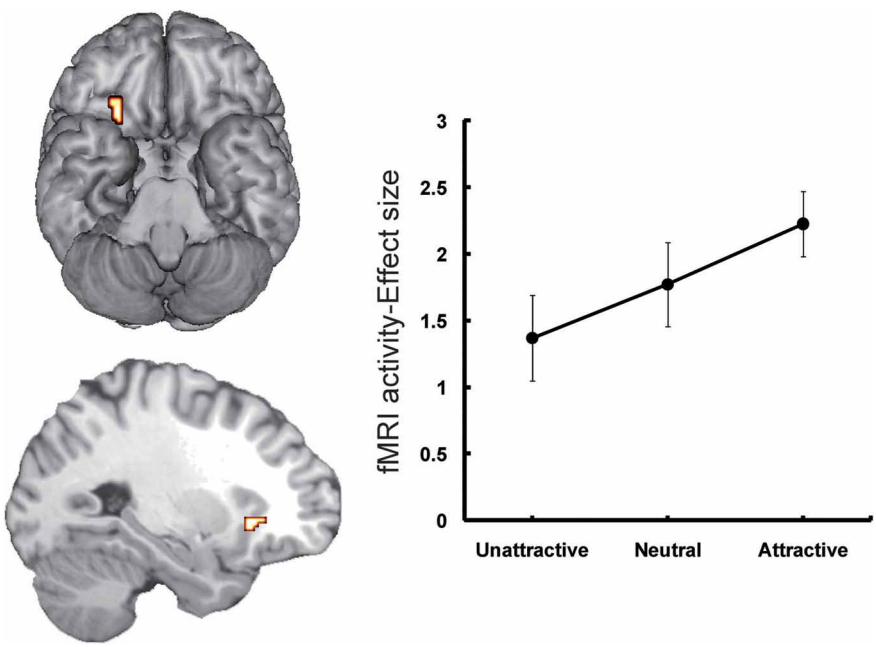

FIGURE 2 | Orbitofrontal activations in response to attractive faces (Tsukiura and Cabeza, 2011a). Activity of the OFC reflected an increasing function of facial attractiveness. This figure was reused with the permission.

et al., 2009). However, given that a meta-analysis study failed to identify significant activations in the medial OFC region during the processing of happy facial expressions (Fusar-Poli et al., 2009), it is possible that a greater response of this region to happy facial expressions may be limited in some specific situations, such as the explicit processing of happy facial expressions (Gorno-Tempini et al., 2001) or the social processing of smiling faces (Minagawa-Kawai et al., 2009).

Moreover, functional neuroimaging studies have linked the medial OFC regions to the processing of attractive faces as

one of the positive affective signals from faces (Aharon et al., 2001; O'Doherty et al., 2003; Kranz and Ishai, 2006; Bray and O'Doherty, 2007; Ishai, 2007; Winston et al., 2007; Cloutier et al., 2008; Liang et al., 2010; Tsukiura and Cabeza, 2011a,b). The roles of this region in the processing of face-based positive signals have also been observed when the personality traits estimated from faces are trustworthy. For example, medial OFC activity reflected an increasing function of trustworthiness for self-resembling faces (Platek et al., 2009), and of personality traits estimated from sentences describing hypothetical actions (Tsukiura and Cabeza, 2011b). Taken together, activity of the medial OFC region could be modulated by facial attractiveness and positive attributes of personality estimated from faces.

The important role of the medial OFC in the processing of rewards has been demonstrated by cognitive neuroscience studies involving animal and human subjects (Rolls, 2000; Martin-Soelch et al., 2001; McClure et al., 2004; O'Doherty, 2004). For example, single unit recording studies with non-human primates have shown that the medial OFC contributes to the coding of reward values of stimuli (Rolls et al., 1989; Critchley and Rolls, 1996). Likewise, functional neuroimaging studies involving human subjects have reported that activity in the medial OFC region is associated with coding rewards from a variety of sensory modalities, including taste, olfaction, somatosensory, auditory, and vision, as well as more abstract rewards such as money (O'Doherty, 2004). In addition, one study found greater activity in this region when subjects viewed beautiful paintings than when they viewed ugly paintings, regardless of the category of painting (Kawabata and Zeki, 2004). Thus, the response bias toward affectively positive signals from faces could be strongly associated with reward-related activity in the medial OFC region. This implication is supported by functional neuroimaging evidence, in which attractive faces increased activations in the medial OFC as well as the nucleus accumbens comprising the putative reward circuit (Cloutier et al., 2008).

However, several studies have implied that roles in the OFC region may be dissociable between medial and lateral portions of this region. For example, one fMRI study reported that activity in the medial OFC region was positively correlated with an increasing function of facial attractiveness, whereas the lateral OFC region showed a reverse pattern of activity (O'Doherty et al., 2003). Another fMRI study, which investigated activations associated with the onset or offset of emotional expressions, demonstrated that the medial OFC region showed greater activity during the processing of positive expressions (offset of angry expression), and that activity in the lateral OFC region reflected both conditions of negative (onset of angry expression and offset of happy expression) and positive expressions (offset of angry expression) (Muhlberger et al., 2011). These findings suggest that roles of the lateral OFC in the processing of face-based affective signals may be different from those of the medial OFC, but the precise roles in the lateral OFC region are still controversial.

ROLES OF THE INSULAR CORTEX IN THE PROCESSING OF FACE-BASED AFFECTIVE SIGNALS

The third candidate region associated with the processing of face-based affective signals is the insular cortex (**Figure 3**). Cognitive neuroscience studies have reported that the insular cortex is involved in the processing of affectively negative facial expressions, in particular expressions of disgust (Phillips et al., 1997, 1998; Sprengelmeyer et al., 1998; Sambataro et al., 2006). Additionally, insular activations during the processing of negative facial expressions have been identified in association with expressions of pain (Botvinick et al., 2005), or with the offset of happy expressions and the onset of angry expressions (Muhlberger et al., 2011). There is also functional neuroimaging evidence that the insula shows greater activity during the processing of unattractive faces than during that of attractive faces (O'Doherty et al., 2003; Krendl et al., 2006; Tsukiura and Cabeza, 2011b), and during the processing of untrustworthy faces than of trustworthy faces (Winston et al., 2002; Krendl et al., 2006; Tsukiura et al., 2012). Thus, insular activities could be modulated by face-based negative signals, which include both external features, such

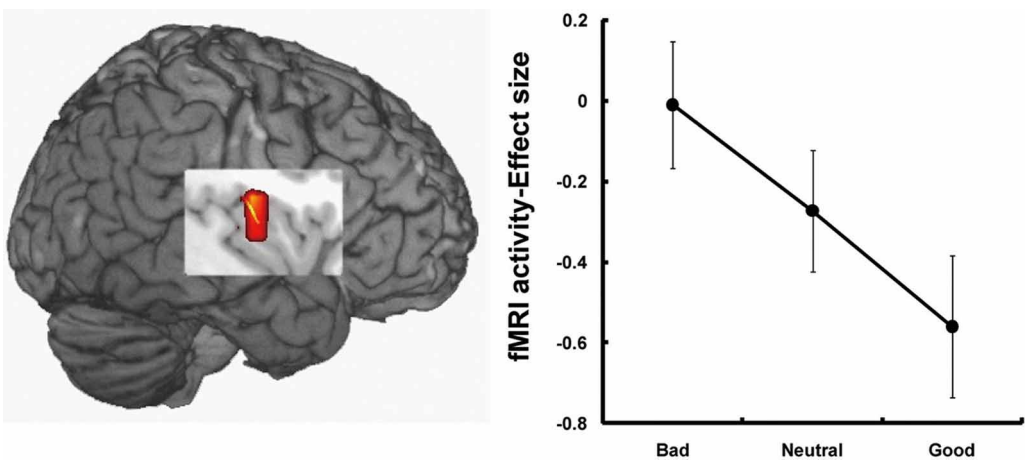

FIGURE 3 | Insular activations in response to untrustworthy faces (Tsukiura et al., 2012). Activity of the insular cortex was greater during the processing of faces with an impression of untrustworthiness. This figure was reused with the permission.

as negative facial expressions or unattractiveness of faces, and negative personality traits, such as untrustworthiness.

Functional neuroimaging studies have demonstrated that the insular cortex shows increasing activity associated with a variety of negative social situations, including social exclusion (Eisenberger et al., 2003), unfairness (Sanfey et al., 2003), and unreciprocated cooperation (Rilling et al., 2008). The insular activity has also been linked to the processing of pain (Critchley et al., 2000) and aversive conditioning (Seymour et al., 2004). These findings suggest that the insular cortex could contribute to an avoidance response away from people with face-based negative signals. The link between insular cortex and avoidance responses is consistent with findings that insular activity is involved in the anticipation of threat (Seymour et al., 2007), the avoidance of risky options in decision-making tests (Kuhnen and Knutson, 2005), and individual differences in avoidance learning (Samanez-Larkin et al., 2008).

ROLES OF THE HIPPOCAMPUS AND FUSIFORM GYRUS IN MEMORY FOR FACES

One of the important regions in memory for face-related information is the hippocampus. Functional neuroimaging studies have reported that the hippocampus as the medial temporal lobe (MTL) memory system is involved in the encoding and retrieval of episodic memory details including contextual information of an event (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007). The importance of this region have also been observed in the encoding and retrieval of face-related memories (Small et al., 2001; Sperling et al., 2001, 2003; Paller et al., 2003; Zeineh et al., 2003; Kirwan and Stark, 2004; Chua et al., 2007; Tsukiura et al., 2008, 2011). For example, one fMRI study showed hippocampal activations during the successful retrieval of both face-name associations and face-job title associations, and the hippocampal activations were significantly declined in older adults, compared to young adults (Tsukiura et al., 2011). In addition, hippocampal contributions to face-related memories have been identified in the processing of memory for face-scene associations (Hayes et al., 2010), or face-face and face-laugh associations (Holdstock et al., 2010). These findings suggest that the hippocampus could be involved in memory for details of face-related information.

Another important region in face memories is the right fusiform region, in which a region selective to the processing of face information is known as the fusiform face area (FFA; Kanwisher et al., 1997). Functional neuroimaging studies have reported that both FFA and hippocampal regions show significant activations during the successful encoding or retrieval of facial stimuli (Prince et al., 2009; Skinner et al., 2010). One theory of episodic memory consolidation proposes that components forming episodic memories are stored in unimodal or heteromodal association cortices, and that the hippocampus binds these components with event-specific contextual information (Alvarez and Squire, 1994; Mishkin et al., 1997; Nadel and Moscovitch, 1997; Fujii et al., 2000; Shastri, 2002; Norman and O'Reilly, 2003). Taken together, face memories could be successfully encoded or retrieved by the FFA-hippocampal network, in which facial stimuli processed in FFA are bound with the specific contextual information by the hippocampus.

NEURAL MECHANISMS UNDERLYING THE EFFECTS OF FACE-BASED AFFECTIVE SIGNALS ON MEMORY FOR FACES

The importance of the amygdala, medial OFC, and insula in the processing of face-based affective signals has been identified in cognitive neuroscience studies. These studies have demonstrated that the amygdala contributes to the processing of both positive and negative affective signals from faces, and that medial OFC activity shows biased responses to positively affective signals from faces, whereas insular activity is modulated by negatively affective signals from faces. In addition, recent advances in effective connectivity analysis in functional neuroimaging studies have shown that the effective connectivity between the amygdala and medial OFC contributes to the differentiation of positive and neutral facial expressions from negatively valenced angry, disgust, and fear expressions (Liang et al., 2009), and that the effective connectivity between the amygdala and insula is associated with the processing of facial expressions of disgust (Tettamanti et al., 2012). Another fMRI study revealed that activities in the medial OFC region, which is involved in the processing of facial attractiveness and personality goodness, were negatively correlated with activities in the insular cortex, which is involved in the processing of facial unattractiveness and personality badness (Tsukiura and Cabeza, 2011b). These findings suggest that the amygdala-medial OFC-insula network could contribute to forming impressions of people by face-based affective signals. The amygdala could act as a primary system of face-based affective signals by responding to their intensity, and could adjust interacting activities between the medial OFC, which is involved in the processing of positively valenced signals from faces, and insula, which is involved in the processing of negatively valenced signals from faces (**Figure 4**).

The modulatory effects of face-based affective signals on memory for faces could be mediated by an interaction between

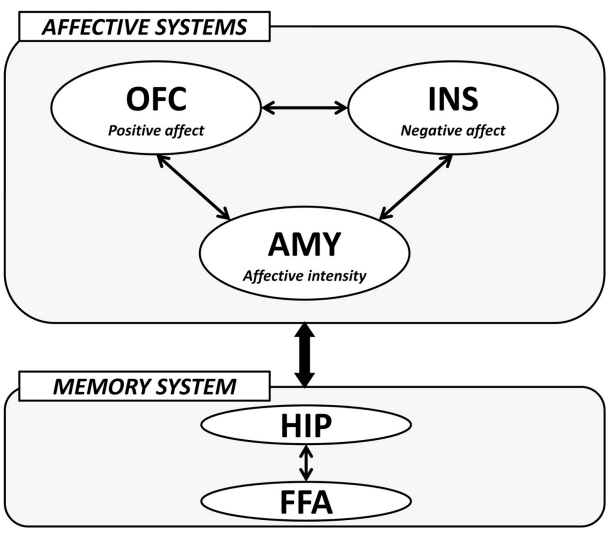

FIGURE 4 | A hypothetical model of the neural mechanisms underlying the effect of face-based affective signals on memory for faces. AMY, amygdala; OFC, orbitofrontal cortex; INS, insular cortex; HIP, hippocampus; FFA, fusiform face area.

affective systems including the amygdala, medial OFC, and insula, and *memory system* including the hippocampus and FFA (**Figure 4**). For example, functional neuroimaging studies have reported that both hippocampal and FFA regions show significant activations during the encoding and retrieval of faces (Prince et al., 2009; Skinner et al., 2010), and that faces with emotional expressions are remembered more accurately than those with neutral expressions by an effect of the affect-related amygdala (Fenker et al., 2005) or medial OFC (Tsukiura and Cabeza, 2008) activities on the memory-related hippocampal activities. The effects of face-based affective signals on memory for faces have also been identified in the processing of attractive faces, better memory for which is modulated by an interaction between activities in the medial OFC and hippocampus (Tsukiura and Cabeza, 2011a). Moreover, an interaction between the insula, which is associated with the processing of untrustworthy impressions, and the hippocampus is important in the enhancement of memory for untrustworthy faces (Tsukiura et al., 2012). These findings suggest that the amygdala, medial OFC, and insula as *affective systems* could directly or indirectly interact with the hippocampus-FFA network as *memory system*, and that the functional connection could contribute to the enhancement of memory for faces by face-based affective signals. Given that the interactions between affect-related regions and memory-related regions were identified in encoding (Tsukiura and Cabeza, 2011a; Tsukiura et al., 2012), retrieval (Fenker et al., 2005), or both (Tsukiura and Cabeza, 2008), the functional connection could be shared between these processes.

However, the possible interaction between regions as *affective systems* and *memory system* in memory for (affective) faces has been identified in memory for other affective stimuli such as affective pictures (LaBar and Cabeza, 2006; Dolcos et al., 2012). Thus, the model presented here is preliminary or tentative, because evidence whether an interaction between *affective*- and *memory*-related regions in our model is applied only to the memory for faces or to the affective memory in general is still scarce. Additional supports by future studies would be needed to clarify the neural mechanisms involved in the modulatory effects of face-based affective signals on memory for faces, and which of these mechanisms are specific to facial stimuli.

CONCLUSION

This review article outlined the neural mechanisms underlying the effects of facial impressions on memory for faces by discussing previous functional neuroimaging findings. Information related to face-based affective signals consists of several factors such as facial expression, facial attractiveness, and trustworthiness, and is mediated by the amygdala, medial OFC, and insular regions as the affective system. Behaviorally, memory for faces is often enhanced by these kinds of face-based affective signals, and the memory enhancement is explained in terms of the modulatory effects of affect-related regions on the memory-related hippocampal region. In our daily lives, we have some impression of others on the basis of face-based affective signals, and the impression of others is important in deciding whether they should be approached or avoided. These effects of enhancement (approach) and impairment (avoidance) on perceiving people are influential in memory for faces. Face-based affective signals, as well as interpersonal relationship (Cacioppo and Cacioppo, 2012; Powers and Heatherton, 2012), could be important in remembering who should be approached or avoided in the context of social interaction.

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Characterizing socially avoidant and affiliative responses to social exclusion

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Humans have a fundamental need for social relationships. From an evolutionary standpoint, the drive to form social connections may have evolved as an adaptive mechanism to promote survival, as group membership afforded the benefits of shared resources and security. Thus, rejection from social groups is especially detrimental, rendering the ability to detect threats to social relationships and respond in adaptive ways critical. Previous research indicates that social exclusion alters cognition and behavior in specific ways that may initially appear contradictory. That is, although some studies have found that exclusionary social threats lead to withdrawal from the surrounding social world, other studies indicate that social exclusion motivates affiliative social behavior. Here, we review the existing evidence supporting accounts of avoidant and affiliative responses, and highlight the conditions under which both categories of responses may be simultaneously employed. Then, we review the neuroimaging research implicating specific brain regions underlying the ability to detect and adaptively respond to threats of social exclusion. Collectively, these findings are suggestive of neural system highly attuned to social context and capable of motivating flexible behavioral responses.

Keywords: social exclusion, need to belong, withdrawal, affiliation, social brain, self-esteem, medial prefrontal cortex, ventral anterior cingulate cortex

INTRODUCTION

Humans have a fundamental need for social groups (Bowlby, 1969; Baumeister and Leary, 1995). From an evolutionary perspective, group membership affords the benefits of shared resources and security. Because social exclusion poses critical challenges for survival, the drive to maintain social relationships may have evolved for adaptive purposes. As a basic human motive, the need to belong activates behavior and influences cognition and emotion. Failure to satisfy this need for close social connections has been associated with a variety of adverse consequences, including self-defeating behaviors, negative moods, and mental and physical health complications (Twenge et al., 2001; Cacioppo et al., 2006).

The need to belong theory is supported by evidence that people feel anxious when facing actual or potential exclusion from social groups (Baumeister and Tice, 1990). According to social exclusion theory, people are socially excluded for reasons of immorality, incompetence, or unattractiveness. Breaking group norms and rules, which is the essence of immorality, threatens group structure; incompetence provides a drain on group resources; and being physically unattractive or having a stigmatizing condition may suggest inferior genes.

In order to induce experiences of social exclusion in the laboratory, researchers have utilized a variety of manipulations, including playing the virtual ball-tossing game Cyberball, receiving fictitious predictions that their future lives will be isolated and lonely, and recalling past experiences of rejection (for comprehensive reviews of the various methodologies, we point interested readers to Baumeister et al., 2007, and DeWall et al., 2011a). Results of previous behavioral research indicate that experiencing social exclusion alters cognition and behavior in specific ways that may initially appear contradictory. That is, although some studies have found that social exclusion leads to withdrawal from the surrounding social world and emotional numbness (e.g., Twenge et al., 2003; Baumeister et al., 2007), other studies suggest that social exclusion actually motivates affiliative social behavior (e.g., Gardner et al., 2000; Pickett et al., 2004; Maner et al., 2007). Here, we review the existing evidence supporting both avoidant and affiliative responses, and highlight the conditions under which both categories of responses may be simultaneously employed. Furthermore, given the importance of group inclusion, there ought to be mechanisms for detecting as well as adaptively responding to threats of social exclusion (Heatherton, 2011). After reviewing the behavioral findings, we discuss the neuroimaging research implicating the specific brain regions underlying the ability to detect and adaptively respond to threats of social exclusion.

AVOIDANCE OF SOCIAL INFORMATION

Prior research suggests that social exclusion motivates withdrawing from the surrounding social world and produces feelings of emotional detachment (Twenge et al., 2003; DeWall and Baumeister, 2006; Baumeister et al., 2007). Specifically, Twenge et al. (2003) demonstrated that social exclusion results in lethargy, avoidance of self-awareness, and emotional numbness. Additional support for emotional numbness following exclusion

is abundant, as excluded participants repeatedly fail to report occurrences of negative mood or aversive emotions (e.g., Twenge et al., 2001, 2002, 2003, 2007; Baumeister et al., 2002; DeWall and Baumeister, 2006; Maner et al., 2007; DeWall et al., 2009). Moreover, when differences are found, they do not mediate the observed behavioral effects, suggesting that experiencing social exclusion results in a state of emotional numbness, rather than acute emotional distress. Withdrawal and emotional numbness may help avoid the initial pain of an experience of rejection, as well as protect the self from further experiences of social distress (Baumeister et al., 2007).

One consequence of this withdrawal is the apparent failure to demonstrate concern for others. Following receiving fictitious feedback about having a lonely future life, participants donated less money to student funds, expressed disinterest in volunteering for future lab experiments, and picked up fewer dropped pencils (Twenge et al., 2007). Moreover, social exclusion decreases motivation to attend to the emotional states of others. Indeed, excluded participants report less empathic concern for the social misfortunes of others, such as being rejected by a romantic partner (DeWall and Baumeister, 2006; Twenge et al., 2007).

Such a disinterest in other people and failure to consider their emotional states may even lead to aggressive interpersonal behaviors. Across several studies, excluded participants were more likely to provide negative job evaluations (Twenge et al., 2001), deliver an aversive noise (Twenge et al., 2001), administer excessive amounts of hot sauce to participants who dislike spicy food (DeWall et al., 2010), and force others to listen to an annoying tape (Buckley et al., 2004).

On a broader level, these responses may represent failures of regulatory efforts to exert self-control (Baumeister et al., 2007). The capacity to properly regulate behavior and control impulses, and to put the needs of the group above one's own, is critical for maintaining social relationships and group cohesion (Heatherton, 2011). From this perspective, effectively regulating behavior is closely related to social acceptance, as failure to do so may lead to undesirable outcomes, such as eviction from social groups (Twenge et al., 2001; DeWall et al., 2011a). Several studies have further probed this link by investigating how social exclusion directly affects self-regulatory performance. Exclusion appears to impair self-regulatory efforts, as measured by decreased performance on intelligence tests and tasks requiring executive function (Baumeister et al., 2002, 2005) and an increased tendency to eat unhealthful foods (Baumeister et al., 2005). It should be noted that providing additional motivations to regulate behaviors (e.g., offering a cash incentive) reverses these effects, suggesting that exclusion renders people unwilling, but not unable, to exert self-regulatory control (DeWall et al., 2011a). Thus, the impaired regulatory performance described above suggests that excluded individuals may simply not care about gaining positive impressions (and ultimately, social acceptance) from others.

In summary, experiencing social exclusion has been shown to result in withdrawal and emotional numbness. Consequently, people have a diminished desire to empathize with others, occasionally even engaging in aggressive behaviors. These behavioral tendencies are consistent with the reasoning that exclusion leads to a lack of concern for others, resulting in reduced motivation to regulate behavior in desirable ways and obtain social acceptance.

ATTENTION TO SOCIAL INFORMATION

In contrast to the withdrawal pattern, other work suggests that social exclusion alters cognition and behavior in more socially affiliative ways. Notably, social exclusion appears to bias cognitions such that people can more readily identify social information (see also Cacioppo and Cacioppo, 2012). Gardner et al. (2000) investigated the saliency of social information following social exclusion. Participants engaged in a simulated chat room experience during which they were accepted or rejected by supposed peers. Following this experience, participants read diary entries containing social and nonsocial information, and were administered a surprise memory test for events in the diaries. Results revealed that socially excluded participants displayed enhanced memory for social information and events. Similarly, Pickett et al. (2004) provided evidence that the desire to have a lot of social relationships heightens attention paid to the surrounding social world. Specifically, people who reported having a strong desire to belong to social groups demonstrated greater accuracy in identifying emotional facial expressions, as well as the valence of spoken words.

Just as important as identifying social information is determining its authenticity. Indeed, socially excluded people can more readily distinguish between real and fake ("Duchenne") smiles (Bernstein et al., 2008) and display a preference for real smiles (Bernstein et al., 2010), suggesting a heightened ability to decode social information.

These studies offer the possibility that social information becomes more salient following social exclusion because it signals potential affiliation opportunities. In line with this reasoning, Maner et al. (2007) demonstrated that social exclusion leads people to view others in a more positive light (e.g., as more friendly and desirable) and to display an increased desire to work with others in groups rather than working alone. Such biased cognitions may generalize to generally seeking out more positive stimuli. Indeed, DeWall et al. (2011b) demonstrated that excluded participants spontaneously recalled more positive events than those who did not experience exclusion. Moreover, exclusion leads people to group words together based on positive emotional connotations (e.g., matching "puppy" with "parade" instead of "beetle"), and to complete more word stems with words depicting positive emotions.

Additional research has investigated the overt behavioral responses resulting from these cognitive biases. Specifically, excluded people appear motivated to engage in affiliative social behavior. Maner et al. (2007) performed a series of studies examining behavior following manipulations of social exclusion. They found that social exclusion leads to a greater desire to make new friends and form social bonds, and to work cooperatively with others on tasks.

Together, this research illustrates how social exclusion can bias cognitive processes in socially affiliative ways. These behaviors are likely driven by the desire to re-establish social bonds, and ultimately, may increase the likelihood of gaining acceptance from others (DeWall et al., 2011a).

SIMULTANEOUSLY EMPLOYED PROCESSES

For years, these seemingly contradictory accounts of responses to social exclusion prevailed. However, recent evidence suggests that responses to social exclusion may be more nuanced than simply avoiding or approaching others. Instead, people might simultaneously employ both defensive and affiliative strategies, allowing them to avoid further distress while also encouraging the establishment of positive social connections (Hess and Pickett, 2010). This line of reasoning is supported by an eye-tracking study by DeWall et al. (2009) in which socially excluded participants displayed decreased attention to negative social stimuli while selectively attending to signs of social acceptance. Moreover, exclusion results in differential attempts to infer the mental states of others. Specifically, people apparently display a preference for mentalizing about positive social information and avoid considering negative aspects of their social world (Powers et al., in press).

This interpretation converges nicely with one of the earliest models of self-regulation (Carver and Scheier, 1982), in which people regulate their behaviors in adaptive and profitable ways when favorable outcomes are expected, but escape from self-awareness and withdraw when unfavorable outcomes are expected. Indeed, unfavorable outcomes following social exclusion (e.g., thinking about the mental states of potential social threats) are met with mental withdrawal, while favorable outcomes (e.g., re-establishing social ties) are met with continued, possibly enhanced efforts.

SOCIAL EXCLUSION AND SELF-ESTEEM

If humans have a fundamental need to belong, then there ought to be dedicated mechanisms for detecting threats to social inclusion (Leary et al., 1995; Heatherton, 2011). Put another way, given the fundamental importance of group inclusion to mental and physical health, humans need to be especially sensitive to signs that the group might exclude them. According to the sociometer model, self-esteem functions as a monitor of the status of interpersonal relationships and the possibility of social exclusion. When people behave in ways that increase the likelihood they will face exclusion, they experience a reduction in state self-esteem (Leary et al., 1995).

According to the sociometer theory, people likely vary in terms of how their sociometers are calibrated (Leary et al., 1995). For instance, high self-esteem individuals generally feel accepted and included and expect others to like them. Therefore, they may be less concerned with interpersonal evaluation than people with moderate or low self-esteem (Leary and Downs, 1995). Indeed, when asked to estimate occurrences of positive and negative feedback, individuals with high self-esteem reported receiving more positive feedback than those with low self-esteem. Moreover, those with high self-esteem consistently overestimated the amount of positive feedback they received, while those with low self-esteem were generally accurate in their estimations (Somerville et al., 2010b). Although people with high self-esteem apparently do experience a reduction in feelings of state self-esteem when excluded, they may not drop to a level that suggests they are in imminent danger of being excluded. By contrast, people with low self-esteem have a tendency to more readily perceive rejection, and this is reflected in the relative calibration of their sociometers (Leary et al., 1995).

ASSOCIATED BRAIN MECHANISMS

Given the importance of group inclusion for survival, various brain mechanisms may be particularly attuned to information about the social world. From this perspective, there ought to be neural mechanisms for detecting threats of social exclusion, as well as adaptively responding to them (Heatherton, 2011). Indeed, neuroimaging research has revealed that specific brain regions support these dissociable processes.

Studies examining neural responses during the experience of social exclusion have consistently revealed activation in the anterior cingulate cortex (ACC), although some studies implicate more dorsal ACC regions (e.g., Eisenberger et al., 2003), while others observed more ventral activations (e.g., Somerville et al., 2006). The ACC is involved in a variety of cognitive and affective processes (see Bush et al., 2000), and debate in the field still exists regarding the exact region of the ACC involved in detecting threats of social exclusion; however we note the extant literature that implicates ventral ACC in emotional and social processes and disorders including depression (Drevets et al., 1997; Mayberg et al., 2005; Moran et al., 2006). Other brain regions that have been shown to respond to social exclusion include the ventrolateral prefrontal cortex (vlPFC), which may be involved in the regulation of distress, and the insula, which has been implicated in processing the sensory components of physical pain (Eisenberger et al., 2003; Eisenberger and Lieberman, 2005).

During adolescence, the salience of peer interactions and an increased desire to be accepted by others suggest that the brain may uniquely respond to experiences of social exclusion (Somerville et al., 2010a; Masten et al., 2011). Masten et al. (2009) scanned adolescents during an experience of social exclusion and found activation in the insula. However, they noted that experiencing social exclusion failed to recruit the dorsal ACC or vlPFC, as has been previously reported in adults. Other studies have consistently revealed involvement of the ventral ACC in adolescents experiencing social exclusion (Gunther Moor et al., 2010; Sebastian et al., 2011). Taken together, neural responses in adolescents to social exclusion appear to be marked by engagement of the ventral ACC and insula. That the vlPFC is not implicated in adolescents as it is in adults is may be indicative of a differential sensitivity to social exclusion across the lifespan (Pfeifer and Blakemore, 2012). Alternatively, the ongoing maturation of the PFC during adolescence may lead to activation patterns that would differ from that of adults.

To the extent that self-esteem functions as a monitor of the likelihood of social exclusion, this ought to be reflected by differential neural responses. Somerville et al. (2010b) examined functional brain activity in response to evaluative social feedback as a function of self-esteem. They found that activity within ventral ACC is modulated by self-esteem, such that individuals with low self-esteem display enhanced activity to positive versus negative feedback. Ventral ACC activity did not distinguish between positive and negative feedback for individuals with high self-esteem. This finding suggests a neural mechanism underlying the particular sensitivity of individuals with

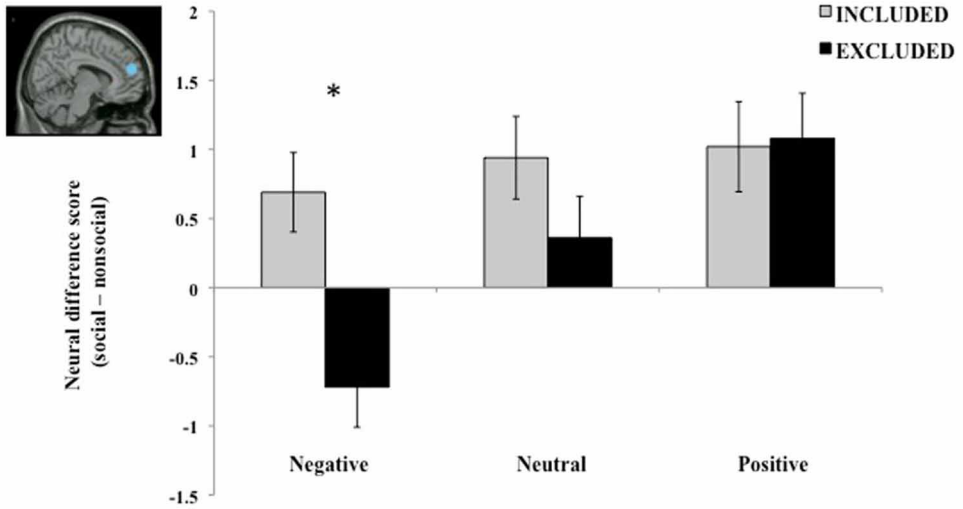

FIGURE 1 | Following social exclusion, activity in dmPFC, a brain region involved in mentalizing, (1) is reduced when viewing negative social scenes, and (2) increases in a linear fashion across valence categories (from negative to neutral to positive). Inset displays location of dmPFC ROI (6, 54, 21). Thus, people may be motivated to mentalize about the positive aspects of their social worlds following rejection, but avoid doing so for negative social information (Powers et al., in press).

low self-esteem to cues indicative of social standing, and further implicates the ventral ACC as critical in the representation of social relations.

This work highlights the neural mechanisms involved in detecting threats of social exclusion. Recently, in order to more clearly understand the cognitive processes underlying the differential behavioral reactions to social exclusion detailed above, we explored neural responses immediately following an experience of social exclusion (Powers et al., in press). We employed a modified version of a social exclusion manipulation used in previous behavioral research (see Twenge et al., 2001), in which participants were provided with fictitious feedback indicating that their futures would be filled with long-lasting, stable relationships (social inclusion) or that they would be isolated and lonely (social exclusion). Participants were then scanned while viewing a series of pictures varying in social (i.e., with people, without people) and emotional (i.e., negative, neutral, positive) content. We found that socially excluded individuals failed to recruit dorsomedial prefrontal cortex (dmPFC), a brain region consistently implicated in mentalizing, for negative social scenes. Critically, dmPFC was still engaged when viewing positive social scenes. Moreover, following social exclusion, dmPFC demonstrated a linear effect of valence, with greater activity to positive social scenes compared to negative social scenes (see **Figure 1**). Importantly, there was no effect of social exclusion on dmPFC response to nonsocial scenes. Our results suggest that people are motivated to mentalize about the positive aspects of their social worlds following rejection, but avoid doing so for negative social information. Thus, the behavioral strategies engaged in response to social exclusion may reflect differential engagement of brain regions involved in understanding the mental states of others.

Taken together, this evidence suggests that neural activity differs depending on whether people are actively being excluded or responding to a very recent experience. While open questions remain, as neuroimaging research in this field is still in its infancy, these findings do highlight the sensitivity of the brain to social context and the status of interpersonal relationships, and offer insight into developmental changes.

SUMMARY

Emotional threats can enhance or impair social cognition. Responses to social exclusion seem to engender categorically oppositional reactions to socially relevant stimuli and situations, with research showing both that social exclusion motivates withdrawal from the surrounding social world and antisocial behaviors and also that excluded people appear highly attuned to social information, specifically that which is positive, and display a propensity to engage in prosocial behaviors. That is, people may concurrently employ avoidant and affiliative strategies in an effort to most adaptively respond to social threats. In this way, people may protect themselves from further distress while simultaneously attempting to form positive social connections with others. Neuroimaging research has revealed that specific neural regions, notably the ACC and mPFC, support the ability to detect and adaptively respond to social threats. Across these responses, a clear pattern of social specificity emerges. That is, converging behavioral and neuroimaging evidence reveals that both affiliative and avoidant responses to social exclusion are specific to social stimuli. Considered in concert, these findings are suggestive of neural system highly attuned to social context and capable of motivating flexible behavioral responses.

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Decoding the invisible forces of social connections

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By its 20th anniversary, social neuroscience has witnessed an incredible rise in the number of studies demonstrating the effects of perceived social isolation (e.g., loneliness, ostracism), and inversely, the beneficial effects of social bonding (e.g., love, desire, attachment) on social perception, cognition, and behavior and on mental and physical health. The current review underscores the importance of two factors in this literature: (1) where an individual falls along the continuum of isolation/bonding from feelings of rejection and neglect to feelings of strong, stable, trusted social bonds, and (2) whether gauging an individual's general feeling of social isolation/bonding or the specific feeling of isolation/bonding toward the person with whom the individual is interacting. Evidence shows that these factors are related to brain and cognition, including embodied social cognition—a system integrating past self-related actions from which simulation mechanisms can be used to access other people's minds and anticipate their actions. The neurophysiological mechanisms underlying sensorimotor mapping between interacting individuals offers an empirical opportunity to investigate the interpersonal forces that operate on individuals at a distance. This multilevel integrative approach provides a valuable tool for investigating the brain networks responsible for understanding acute and chronic social disorders.

Keywords: social neuroscience, loneliness, bonding, mimicry, synchrony, embodied cognition, interdependence, social isolation

Social species form organizations that extend beyond the individual. The goal of social neuroscience is to investigate the biological mechanisms that underlie these social structures, processes, and behavior and the influences between social and neural structures and processes (Cacioppo and Berntson, 1992; Cacioppo et al., 2000). The forces operating between individuals to create these superorganismal structures form connections that vary in strength and valence. Whether comparing different individuals at a given point in the lifespan or the same individuals across the lifespan, these social forces vary along a continuum of isolation/bonding from feelings of rejection and neglect to feelings of strong, stable social bonds.

Like the forces between chemical elements, the forces operating between individuals are difficult to observe directly but become visible through their effects on individuals. In the present article, we review some of the visible signs that one can use to identify where individuals fall along the continuum of perceived social isolation/bonding. The traditional way of determining where a person falls along the continuum of perceived social isolation to perceived social bonding is through the use of psychometrically validated questionnaires, such as the UCLA loneliness scale (Russell, 1996). One can also decode social bonds at a distance, for instance, by looking at a person's body language, but doing so involves a multitude of processes that are subject to various other influences. For this reason, validated questionnaires remain the most common and effective way of identifying a person's position on this isolation/bonding continuum. In this review, we focus on the effects on brain and cognition, including embodied cognitive operations such as sensorimotor perception, imitation/mimicry, and interpersonal synchrony. Embodiment here refers to the notion that thoughts, feelings, and behaviors are grounded in sensory experiences and bodily states (for reviews see Semin and Smith, 2002; Niedenthal et al., 2005; Barsalou, 2008; Schubert and Semin, 2009; Meier et al., 2012). We begin by reviewing the effects of perceived social bonding/isolation on health.

SOCIAL ISOLATION/BONDING AND HEALTH

A person's position along the continuum of perceived social isolation/bonding to others is associated with a variety of physical and mental health effects (see **Figure 1**). Perhaps most striking, people who subjectively feel they are isolated or have few if any strong connections to others (in blue on the spectrum; **Figure 1**) live shorter lives than those who feel they have strong, dependable, meaningful social bonds (Cacioppo and Patrick, 2008; Cacioppo and Cacioppo, 2012; Luo et al., 2012; Perissinotto et al., 2012). The increased risk of mortality is evident even when objective social isolation and health behaviors are statistically controlled (Luo et al., 2012). Meta-analyses of the odds ratio for increased mortality for perceived social isolation/bonding in humans is 1.45—larger than found for marriage or physical activity, approximately double the odds ratio for increased mortality for obesity, and quadruples the odds ratio for air pollution (Holt-Lunstad et al., 2010).

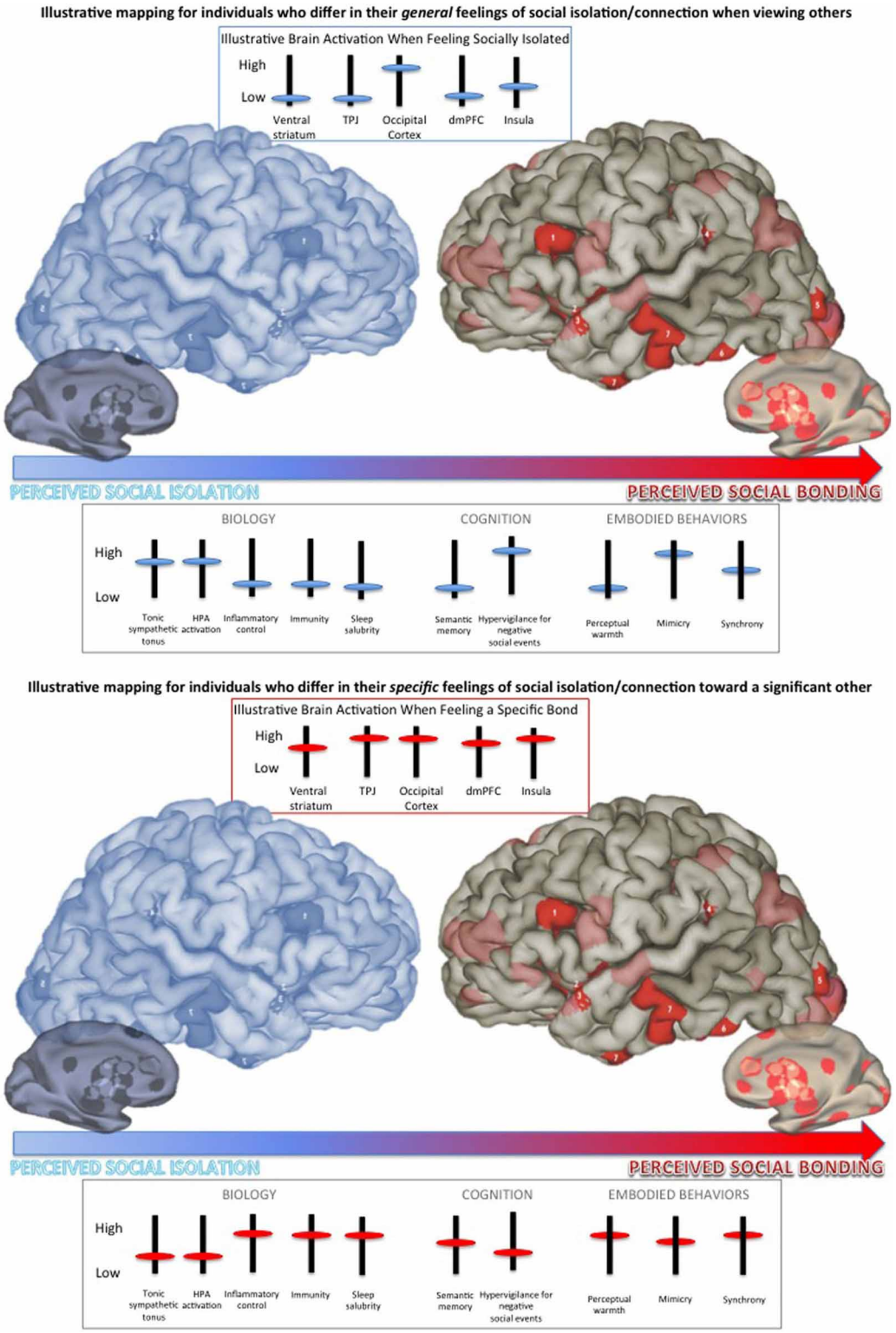

FIGURE 1 | Schematic representation of the continuum of social isolation/bonding from feelings of social isolation or neglect (in blue) to feelings of strong, salubrious social bonds (in red). Brain and behavioral responses differ depending on an individual's general feeling of social isolation/connection and specific feeling of isolation/connection to the person with whom one is interacting. **Top Panel**: Illustrative mapping for individuals who differ in their *general* feelings of social isolation/connection when viewing others (see Cacioppo and Patrick, 2008). **Bottom Panel**: Illustrative mapping for individuals who differ in their *specific* feelings of social isolation/connection toward (e.g., love for) a significant other (see Ortigue et al., 2010; Cacioppo et al., 2012; Brain Graphic by James W. Lewis, West Virginia University published in the Scientific American Mind).

Perceived isolation in humans, as measured using the UCLA loneliness scale, and the experimental manipulation of social isolation in nonhuman animals have been associated with a number of effects, including increased hypothalamo-pituitary adrenocortical activation, tonic sympathetic tonus, depressive behavior, and prepotent responding, and decreased inflammatory control, viral immunity, and expression of genes regulating glucocorticoid responses (**Figure 1**, **top panel**; see review by Cacioppo et al., 2011). Both cross-sectional and longitudinal studies have also demonstrated that perceived isolation in humans increases sleep fragmentation and daytime fatigue (Cacioppo et al., 2002, 2011).

Interestingly, animal work suggests that social connection constitute a stimulus that can have direct effects not only on physical and mental health but on brain structures and function. Consider the desert locust (Schistocerca gregaria) as a case in point. The desert locust has an asocial and a social state. The asocial state is the more typical condition, during which period the locust tends to avoid conspecifics. Under specifiable conditions, however, the locusts transform from a solitary to a swarming phase, at which point the brains of these locusts grow approximately 30% larger, presumably to accommodate the additional information processing demands of their now more complicated social environment (Ott and Rogers, 2010). The deprivation of these social connections leads to a return to the asocial phase, along with a consequent reduction in brain volume.

Social processes were once thought to have been incidental to human learning and cognition, but the social complexities and demands of primate species are now thought to have contributed to the evolution of the neocortex and various aspects of human cognition (Dunbar and Shultz, 2007; Dunbar, 2011, 2012). In line with this reasoning, cross-species comparisons have revealed that the evolution of large and metabolically expensive brains is more closely associated with social than ecological complexity (Dunbar and Shultz, 2007). Moreover, although human toddlers and chimpanzees have similar cognitive skills for engaging and interacting in the physical world, toddlers show more sophisticated cognitive skills than chimpanzees for engaging the social world (Hermann et al., 2007).

For any member of a social species, it is dangerous to be on the social perimeter (Cacioppo and Patrick, 2008). Social species can vary in terms of the position along a continuum of social isolation (e.g., neglect, exclusion) to social connection or bonding. In nonhuman animals, where an individual falls along this continuum is typically manipulated experimentally by housing the animal in isolation or with conspecifics for an extended period of time. Given the complex social ties that characterize human existence, the irrepressibly meaning-making nature of humans, and the ethical constraints against experimentally isolating individuals for an extended period, a large literature has developed showing that *perceived* social isolation in normal samples is a more important predictor of a variety of adverse behavioral, psychological, and health outcomes than is objective social isolation. For instance, where an individual falls along the continuum of perceived social isolation/bonding—whether acute or chronic—may also have important consequences for cognitive abilities. Feeling socially isolated or excluded appears to increase attention to social information, especially negative information. For instance, research shows that people, who feel socially rejected, show an increase in memory for selected social information (Gardner et al., 2000), and are more sensitive to emotional vocal tone and are more accurate on a facial emotion detection task (Pickett et al., 2003) than people who feel accepted by a group. Studies using the social Stroop task have also shown that the interference in the Stroop task produced by negative social words is a direct function of how socially isolated the participants feel, whether the feelings of social isolation were experimentally manipulated (acute) or dispositional (chronic; Cacioppo and Hawkley, 2009; see, also, Powers and Heatherton, 2012; Tsukiura, 2012).

Importantly, prospective longitudinal studies of older adults also show that perceived isolation is a risk factor for general cognitive decline (e.g., Tilvis et al., 2004) and Alzheimer Disease (Wilson et al., 2007). Illustrative of the latter is a large prospective study conducted by Wilson et al. (2007) in 823 older adults free of dementia at enrollment. They found that the more the participants felt socially isolated, the poorer their later cognitive performance in semantic memory, perceptual speed, and visuo-spatial skills (compared to baseline as assessed by an extensive battery of cognitive measures). Furthermore, Cox proportional hazards models that controlled for age, sex, and education indicated that perceived social isolation significantly increased the risk of clinical Alzheimer Disease: 76 individuals developed dementia during the 65 month study period. This association was unchanged when objective social isolation, depressive symptomatology, or other demographic and health-related factors served as covariates.

SOCIAL ISOLATION/BONDING AND BRAIN MECHANISMS

From a neuro-functional viewpoint, recent evidence from both human and nonhuman animal studies investigating the biochemistry and brain activity associated with social isolation/bonding point to specific patterns of activation elicited by social stimuli. Cacioppo et al. (2009) identified a specific brain signature associated with perceived isolation in a brain imaging study in which participants performed a categorical judgment task. In the scanner, participants viewed pictures chosen from the International Affective Picture System (IAPS) that varied in their emotional (i.e., negative/unpleasant, positive/pleasant) and social (i.e., nonsocial, social) content, and participants specified whether each picture was pleasant, neutral, or unpleasant. Results showed that the closer participants were to the social isolation anchor of the continuum, the greater the activation of the ventral striatum to pleasant nonsocial, in contrast to social pictures, whereas the closer participants were to the social bonding anchor, the greater the activation of the ventral striatum to the pleasant social, in contrast to nonsocial, pictures.

Individuals who fell near the socially isolated end of the continuum showed greater activity in the dorsal mPFC to pleasant nonsocial, relative to social, stimuli, whereas individuals who fell near the socially bonded end of the continuum showed the greatest activity in this region to pleasant social, compared to nonsocial, stimuli. Prior functional neuroimaging work on thinking about the characteristics of people (e.g., Jenkins et al., 2008) and deciding to be altruistic toward another person (Waytz et al., 2012) has reliably shown the dorsal mPFC to be involved.

Together, these data fit the notion that the more individuals feel socially isolated from others, the greater the emphasis on self-preservation and maintaining a safe psychological distance from others.

For unpleasant pictures, the closer participants were to the social isolation anchor of the continuum, the greater the activation of the visual cortex to *social*, in contrast to nonsocial pictures, whereas the closer participants were to the social bonding anchor, the less the difference in the activation of the visual cortex to the social and nonsocial pictures. These neuroimaging data parallel the behavioral findings from the social Stroop task. It is dangerous on the social periphery. Humans who feel socially isolated and nonhuman animals who are experimentally isolated increase behaviors that promote predator evasion and self-preservation. Interestingly in this context, the closer participants were to the social isolation anchor of the continuum, the less the difference in the activation of the temporo-parietal junction to social, in contrast to nonsocial pictures, whereas the closer participants were to the social bonding anchor, the greater the activation of the temporo-parietal junction to the social and nonsocial pictures—consistent with the notion that the former are more likely to focus on self-preservation and, therefore, reflect less on the perspective of others in a negative social context.

Powers et al. (2012) extended these results by reinforcing the role of the dMPFC in social isolation/bonding during the processing of social and non-social stimuli. Powers et al. manipulated social exclusion in 32 female undergraduates, who then viewed social and non-social pictures selected from the IAPS, and categorized them as indoor or outdoor scene. Their results revealed that the dmPFC was significantly modulated by social exclusion. Consistent with Cacioppo et al. (2009), socially excluded participants showed no differences in activation of the dmPFC for social and nonsocial scenes, whereas socially included participants showed greater dmPFC activity to social than non-social scenes.

Thus far, we have dealt with regional brain activation in individuals who vary in their feeling of social isolation/bonding in response to pictures of *unfamiliar* people in positive or negative circumstances (**Figure 1**, **top panel**). A related literature has emerged investigating the regional brain activation in individuals who vary in their feeling of social isolation/bonding in response to pictures of a specific significant other (**Figure 1**, **bottom panel**). This work suggests that the feeling of love (disdain) for and closeness to (distance from) a significant other elicits both common and unique neural processes.

Brain mapping of individuals who feel social bonding with a significant other activates the subcortical brain areas that are associated with euphoria, reward, and motivation as well as the cortical brain areas that are involved in social cognition and self-representation (such as anterior cingulate cortex, middle frontal gyrus, superior temporal gyrus, precentral gyrus, temporo-parietal junction, and occipo-temporal cortices; Ortigue et al., 2010; Cacioppo et al., 2012). The deactivation of subcortical dopaminergic-rich areas during experiences of social isolation/bonding is in line with psychological studies defining social connections as a rewarding, positive, and motivating experience. Interestingly, the co-activations of these subcortical emotion-related areas with cortical areas that mediate more complex cognitive functions (e.g., social knowledge, mentalizing, body image, mental associations, and self-awareness and understanding others) reinforces the top-down neuro-functional model of interpersonal relationships, which suggest that associative cortical regions may be priming the emotion-related areas and visual cortex to be more sensitive to certain kinds of information—in essence, instructing the eyes on what kind of person is perceived as socially positive or negative, and telling the emotional centers what to feel. From these results, one may consider social isolation/bonding on a spectrum that calls for a hypo- to hyper-activation of the same network for social bonding.

Interestingly, a growing body of neuroimaging studies suggests several overlapping areas (e.g., prefrontal areas, insula) between the network sustaining social isolation/bonding, and that sustaining embodied cognitive behaviors. As a distinct knowledge domain, embodied cognition recruits a bilateral network of cortical brain regions including this inferior fronto-parietal network (i.e., inferior parietal lobule, inferior frontal gyrus) as well as the bilateral posterior superior temporal sulcus, dorsal premotor cortex, and ventral premotor cortex (Grafton, 2009). Within this bilateral network, embodied cognition acts as a special knowledge system with dedicated encoding and retrieval processes, which play a role in the interaction between what we do and what we perceive. Along these lines, it makes sense that the way individuals perceive others and their connections with others may also modulate the way they perceive their actions, imitate them and/or synchronize with others.

Within the brain network sustaining embodied behaviors, the discovery of the inferior fronto-parietal mirror neuron system (MNS), which includes a type of neurons (i.e., mirror neurons) that are activated both by the execution and the observation of object-related actions, may play a role in mimicry, synchrony, and embodied behaviors more generally (see Semin and Cacioppo, 2009 for review). Neurophysiological and functional neuroimaging studies suggest the existence of a motor resonance mechanism in the premotor and the posterior parietal cortices that is activated during motor imitation (Jackson et al., 2006) and when participants observe goal-directed actions executed by another individual (e.g., Grafton et al., 1996; Jackson et al., 2006). These data have generally been interpreted as evidence for the direct-matching hypothesis, which states that we understand actions by mapping the visual representation of the observed action onto a sensorimotor representation (Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2008; Semin and Cacioppo, 2009). If the MNS is involved in the embodied signs of social isolation/bonding, as has been postulated, then the activation of this system should not be seen simply as a response to an observed action but should be powerfully modulated by the nature of the social connection between the actor and observer. How this brain network is modulated as a function of where the individuals fall along the continuum of perceived social isolation/bonding is an open question at this point. We turn next to behavioral research on this question.

SOCIAL ISOLATION/BONDING AND SENSORIMOTOR PERCEPTION

Recent research on embodied cognition has shown that feelings of social warmth or coldness can be induced by experiences of physical warmth or coldness, and vice versa. This is consistent with a growing body of research on embodied cognition as well as work underscoring the centrality of interpersonal warmth (vs. coldness) in person perception (Asch, 1946; Kelley, 1950; Cacioppo and Gardner, 1999; Bargh and Shalev, 2012). One explanation for the power of the warm-cold dimension in person perception is that somatosensorial experiences (such as temperature perception) constitute an "embodied ground" for social proximity and abstract and psychological concepts and metaphors (such as interpersonal warmth; Asch, 1958; see also Semin and Smith, 2008; Bargh and Shalev, 2012 for reviews). For instance, people often describe their feelings as "warm" when they are thinking about a trustworthy and loving individual and "cold" when they are thinking about a detached, distant individual (Asch, 1946; Fiske et al., 2007; IJzerman and Semin, 2010).

Interestingly, where people fall along the social isolation/bonding continuum has been shown to be related to their estimates of the room temperature. For instance, Ijzerman and Semin (2009) found that participants seated in a warm room reported feeling interpersonally closer to the experimenter compared to participants seated in a colder room. Together these studies show that experiences of physical warmth produce concomitant feelings of social warmth. Reciprocally, IJzerman and Semin (2010) showed that physically (or verbally) induced experiences of closer social proximity/warmth produced changes in the perception of room, and led to higher estimates of room temperature. On the other end on the continuum of perceived social isolation/bonding, Zhong and Leonardelli (2008) demonstrated that individuals who felt socially isolated estimated room temperature to be lower than those who felt socially bonded, and they also showed greater desire for warm food (hot soup) and drinks (hot coffee), but not for the two control foods (apples and crackers) and the control drink (icy soda). Bargh and Shalev (2012) hypothesized that individuals who feel socially isolated might tend to self-regulate their feelings of social warmth through applications of physical warmth. Consistent with this reasoning, Bargh and Shalev found significant positive associations between perceived social isolation and both the frequency of bathing and the typical duration of a bath or shower, as well as a trend for individuals who felt socially isolated to prefer warmer water temperature. In sum, there is growing evidence that the association between physical warmth/coldness and social warmth/coldness share a common representation or code (Meyer-Lindenberg, 2008).

SOCIAL ISOLATION/BONDING AND MIMICRY/SYNCHRONY

The idea of embodiment and behavior matching in social settings is not new. Scholars have long observed that people tend to mirror the emotional and motor expressions of others (Smith, 1759/1976; James, 1890/1950; Hatfield et al., 1994). For instance, it has been shown that couples who have been married for a long period of time tend to resemble each other in their expressions and actions more than random couples of the same age, and married couples resemble each other even more than they did when they were first married (Zajonc et al., 1987; Mondillon et al., 2007). Studies of motor and emotional contagion also illustrate how people automatically mimic others (e.g., contagious yawning and laughter, body inclination, for a review, see Hatfield et al., 1994). The nature of the connection linking these individuals has been found to matter, however (Lakin and Chartrand, 2005; Lakin et al., 2008). Lakin et al. (2008), for instance, found that people who felt excluded by an in-group mimicked a confederate who was an in-group member more than a confederate who was an out-group member (Lakin et al., 2008).

The ability of individuals to automatically mimic others has been assumed to facilitate the transmission of known behaviors from one individual to another (and so from one generation to the next), and also to be involved in the discovery and incorporation of innovative behaviors into a group's behavioral repertoire. In this sense, imitation is thought to facilitate social learning, cohesion and tradition (the transmission of known behaviors among individuals; Hatfield et al., 1994). Accordingly, it has been suggested that imitation of close others might serve the adaptive function of increasing affiliation, liking, and rapport between people (see Hatfield et al., 1994; Lakin and Chartrand, 2005).

Interpersonal *mimicry* refers to the similarity in form of the actions between individuals, whereas interpersonal *synchrony* refers to the coordination of movement that occurs between individuals, featuring both similarity in form and the temporal alignment of the actions. As illustrated by the Social Cognition model (from Semin and Cacioppo, 2009), synchronization is "time-locked to the observed stimulus." Like mimicry, interpersonal synchrony increases the social connection felt between individuals. For instance, synchrony has been shown to facilitate relationship formation (Vacharkulksemsuk and Fredrickson, 2012), to improve group cohesion (McNeil, 1995), to foster cooperation (Wiltermuth and Heath, 2009), and to breed compassion (Valdesolo and DeSteno, 2011), emotional support satisfaction (Jones and Wirtz, 2007), elevated pain thresholds (Cohen et al., 2010) and affiliation (Hove and Risen, 2009). There is some evidence that the affiliative effects are not dependent on an individual's awareness of the interpersonal synchrony (e.g., see review by Hatfield et al., 1994).

According to emotional contagion theory (Hatfield et al., 1992, 1994), people spontaneously mimic facial and bodily expressions, especially with whom they feel a close social connection to the person (Hatfield et al., 1994; Mondillon et al., 2007). Consistent with this notion, recent research shows that people who are "psychologically experiencing self-other overlap as a result of self-disclosure" are more likely to synchronize their body movements (Vacharkulksemsuk and Fredrickson, 2012). Social motivation plays an important modulating role. For instance, Lakin and Chartrand (2005) showed that individuals who feel socially isolated/excluded, and who therefore are motivated to create new connections with others, mimic strangers more than people who do not feel socially excluded. Subsequent research indicates that people who feel socially isolated not only display greater mimicry with a stranger, but they show an advantage in decoding nonverbal cues (e.g., fake smile vs. real smile; Bernstein et al., 2008) and, specifically, cues that may indicate rejection (Pickett and Gardner, 2005).

In sum, embodied mechanisms are not a pre-requisite to act, connect or understand others, but the extant literature suggests that embodied behaviors offer new ways to investigate social perception, cognition, and behavior (e.g., Semin and Smith, 2002; Semin and Cacioppo, 2009; Schubert and Semin, 2009; Meier et al., 2012). Aron and Aron's (1986) self-expansion model, which posits that others toward whom one feels a close social bond can be incorporated into the representation of one's self, and the relational model of communal sharing and cognitive interdependence (see Fiske, 2004; Smith, 2007; IJzerman and Semin, 2010), which posits that self-representations that incorporate aspects of others also foster interdependent behavior, are consistent with the notion that social bonds are grounded in people's actions. Recent advances in the neurosciences make it possible to investigate whether an individual's position along the continuum of social isolation/bonding modulates shared sensorimotor representations and visible embodied behaviors.

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Do surrounding figures' emotions affect judgment of the target figure's emotion? Comparing the eye-movement patterns of European Canadians, Asian Canadians, Asian international students, and Japanese

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Although the effect of context on cognition is observable across cultures, preliminary findings suggest that when asked to judge the emotion of a target model's facial expression, East Asians are more likely than their North American counterparts to be influenced by the facial expressions of surrounding others (Masuda et al., 2008b). Cultural psychologists discuss this cultural variation in affective emotional context under the rubric of holistic vs. analytic thought, independent vs. interdependent self-construals, and socially disengaged vs. socially engaged emotion (e.g., Mesquita and Markus, 2004). We demonstrate that this effect is generalizable even when (1) photos of real facial emotions are used, (2) the saliency of the target model's emotion is attenuated, and (3) a specific amount of observation time is allocated. We further demonstrate that the experience plays an important role in producing cultural variations in the affective context effect on cognition.

Keywords: Asian Canadians, Asian international students, cognition, culture, emotion, European Canadians, Japanese, the affective context effect

Previous studies suggest that East Asians tend to holistically pay attention to both focal and contextual information, while North Americans are more likely to pay attention to the focal objects (Nisbett et al., 2001; Nisbett, 2003; Nisbett and Masuda, 2003; Nisbett and Miyamoto, 2005). Under the rubric of analytic vs. holistic thought, Nisbett and his colleagues speculated that North Americans and East Asians epistemologically apply different strategies to the viewing of scenes. Researchers have in fact demonstrated systematic cultural variations in attentional patterns. For example, East Asians are more likely than their North American counterparts to describe contextual and relational information and to remember objects in relation to context (Masuda and Nisbett, 2001); to be good at finding the change in the spot-the-difference task (Masuda and Nisbett, 2006; Miyamoto et al., 2006); to perform well on a task that requires attention to context (Kitayama et al., 2003); and to perform less well on a task that requires attention to focal objects (Ji et al., 2000; Masuda et al., 2008a).

However, the effect of context on Europeans' and North Americans' cognitive judgment has also been reported. Researchers have shown that Western participants' judgment of target facial emotions is influenced by descriptions of concrete situations in which a particular facial emotion occurred (Russell and Fehr, 1987; Russell, 1991; Carroll and Russell, 1996). For example, Carroll and Russell (1996) demonstrated that Canadian participants' categorization of facial emotion was influenced by situational information. In their experiment, participants were sequentially presented with the description of a situation, and then a target facial emotion. In this paradigm, the contextual information was mismatched with the target models' facial expression. That is, anger-provoking situations (e.g., having a hubcap stolen from their car) were paired with fearful faces; fear-provoking situations (e.g., bumping into a bear while hiking) were paired with angry faces; and disgust-provoking situations (e.g., finding a rotten garbage bag in a kitchen after a long trip) were paired with sad faces. Participants then engaged in the judgment task. They were asked to select from a list of emotion words that best described the target model's feeling (happiness, anger, sadness, surprise, fear, or disgust). The results indicated that 70% of participants were influenced by the emotional valence of the situations, rather than the actual facial expression. In general, these findings suggest that Westerners treat the salient context information, rather than the facial expression, as the dominant element when judging the target's facial emotion. According to James Russell, a leading researcher on the effect of context on facial emotion judgment, "judgment of emotion in a facial expression is not a simple straightforward registration of the meaning of that face. The face is judged not in an absolute manner but relative to the context of judgment" (Russell, 1991, p. 150).

The literature of the affective priming paradigm supports the findings of the context effect, indicating that affectively salient contextual information influences people's judgment. For example, in a typical affective priming experiment, participants are

briefly presented with various affectively salient stimuli (e.g., a beach under a clear blue sky, or a ruined building), and then categorize positive, neutral, or negative target stimuli (see Fazio, 2001, for a review). Participants' judgment is influenced by affective contexts in the prime, to the extent that the participants tend to respond faster to the target when the prime and the target are affectively congruent than when the two are incongruent. Several studies suggest that such an affective context effect is observable even when the contextual information is conveyed through words (Fazio et al., 1986); images of landscape scenery (Hietanen et al., 2007); nonverbal sounds (Carroll and Young, 2005); odors (Leppänen and Hietanen, 2003); attractive faces (Olson and Marshuetz, 2005); humorous cartoons (Strick et al., 2009); or recollection of outrageous events (Baumann and DeSteno, 2010). However, the extent to which people's cognition (judgment of the target face) is influenced by the affective context, and whether there are systematic cultural variations in the degree of context effect, have not been fully examined.

Extending the theoretical framework advocated by Nisbett and his colleagues (e.g., Nisbett and Masuda, 2003), this paper examines whether East Asians' context sensitivity is stronger than that of North Americans, even when the contextual information is the facial expressions of actual models. Whereas the independent/analytic understanding of the world is dominant in North American cultures, people in East Asian cultures are more likely to show sensitivity to multiple others' emotion in a given situation, and the contexts where the complex interpersonal activities are taking place. Another line of discourse in cultural psychology suggests that cultural variation in the sensitivity to context should be particularly intensified in social contexts, because East Asians and North Americans have qualitatively different perceptions of the role of social others (Markus and Kitayama, 1991; Kitayama and Markus, 1999). In fact, previous findings indicate that the types of stimuli have different impacts on people across cultures. That is, North Americans tend to regard an individual as a distinct agent whose emotions are socially disengaged and whose state of mind is a strictly personal phenomenon (Markus and Kitayama, 1994, 2010; Mesquita and Markus, 2004; Mesquita and Leu, 2007). Given North Americans' agentic understanding of emotions, the presence of social others' emotions should be less important for North Americans' interpretation of the target model's facial emotions. That is, North Americans would be likely to consider emotions as manifestations of private states impervious to the emotions of others. By contrast, East Asians tend to share the cultural belief that individuals' emotional states are strongly tied with those of social others who are significant in their lives. Thus the presence of social others' emotions would be easily merged into East Asians' interpretation of the target model's facial emotions, whereas such an effect would be less pronounced among North Americans.

In the preliminary investigation, we asked participants to watch a series of cartoon images in which a protagonist, who showed a specific facial expression, stood out from people in the background, who also showed specific facial expressions. Participants were asked to judge the protagonist's facial expression. Here we manipulated the combination of emotional expressions of the center model and background models: congruent images (e.g., happy center and happy backgrounds) vs. incongruent images (e.g., happy center and sad backgrounds). The results indeed showed partial evidence that surrounding figures' emotions strongly affected Japanese participants' judgment of target figure's emotions, while such manipulation had little effect on European Americans' judgment (Masuda et al., 2008b). The findings suggest a systematic variation in the affective context effect between Japanese and European Americans.

However, it is only recently that researchers have begun to test the generalizability of the findings to real emotion faces, to different cultural groups, and to different age groups (e.g., Ko et al., 2011). In addition, the number of studies investigating the relationship between behavioral patterns (cognitive judgment) and psycho-physiological patterns is limited (e.g., Chua et al., 2005). Furthermore, there are several methodological weaknesses in our preliminary investigation (Masuda et al., 2008b). For example, Masuda et al. (2008b) used cartoon images as the experimental stimuli. It is important to replicate the findings using photographs of real faces, which provide a closer representation of how people process information in everyday interpersonal relationships. In addition, familiarity with cartoon faces may vary culturally, and this factor should be controlled. Second, Masuda et al. intentionally made the target model large so that participants could easily identify the target of judgment. However, such a manipulation might have indirectly conveyed the message to North Americans that they should focus only on the target face during the task. To reduce this effect, the target model's saliency needs to be attenuated. Third, the amount of presentation time in Masuda et al. was not well controlled. As a result, there remains a possibility that North Americans quickly made a judgment by focusing only on the target model's face, whereas East Asians allocated enough time for their judgment by alternating their attention from the target model's face to surrounding others' faces. To control the above confounds, the current study examined whether a similar cultural variation in the effect of surrounding emotions on judgment is observable even when participants judge real facial expressions.

We also maintain that this investigation has an important implication. Recent findings in culture and neuroscience suggest that there are substantial cultural variations in neural activities in visual perception (Gutchess et al., 2006; Goh et al., 2007; Hedden et al., 2008; Lewis et al., 2008). Furthermore, researchers report that there are cultural variations in the increased magnitude of the N400 response associated with incidental or incongruent events (Goto et al., 2010; Na and Kitayama, 2011). Our aim in conducting this research is to produce a cross-culturally usable set of stimuli to further advance the research on culture and neuroscience.

We created 60 images, each of which consisted of one center model and four background models, while manipulating the combination of emotional expressions of the center model and background models: congruent images (e.g., happy center and happy backgrounds) vs. incongruent images (e.g., happy center and sad backgrounds). To test the robustness of the effect of culture, we also reduced the saliency of the protagonist, so that his/her size was now identical to that of the surrounding

others. Third, we had all participants observe the stimulus image for a full 10 s, so they would have an equal amount of time to allocate their attention to the surrounding others. Finally, in addition to European Canadians as a representative group of North Americans, and Japanese as a representative group of East Asians, we collected data from Asian Canadians and Asian international students in Canada, which allowed us to test whether the pattern of attention acquired through experience is malleable rather than static. We hypothesized that (1) the degree of context effect would be strongest for the Japanese data, and weakest for the European Canadian data, and (2) Asian Canadian data and Asian international data would fall between these two extremes, but each would also differ from the other.

METHOD

PARTICIPANTS

Forty-four European Canadian students (30 females, 14 males, age $M = 18.72$, $SD = 1.47$); 44 Asian Canadian students (33 females, 11 males, age $M = 19.55$, $SD = 3.57$); and 34 Asian international students (24 females, 10 males; age $M = 22.06$, $SD = 5.05$) were recruited at University of Alberta, Canada. Forty-four Japanese students (27 females, 17 males, age $M = 18.63$, $SD = 0.69$) were recruited at Hokkaido University, Japan. European Canadians, Asian Canadians, and Asian international students were recruited from the University of Alberta psychology participation pool on the basis of their ethnic backgrounds and citizenship. Japanese students were recruited through the Hokkaido University research participation system. European Canadians, Asian Canadians, and half of the Asian international students received credits to fulfill a course requirement; Japanese students and the rest of the Asian international students received monetary compensation of 10 Canadian dollars for their participation.

MATERIALS

A pilot study was conducted to ensure that all models' facial expressions were interpreted as intended and had a similar meaning across cultures when presented without any background. First, we took portraits of 20 student models[1]. These models imitated Ekman and Friesen's (1975) images of happy, sad, and neutral expressions. In addition to the neutral expressions, we asked the models to produce both extreme and moderate versions of happy and sad facial expressions (a total of five expressions per model). Based on the clarity of their facial expressions, we selected the portraits of six Caucasian models (3 females and 3 males) and six Japanese models (3 females and 3 males). Then, 42 European Canadian students (25 females and 17 males) at University of Alberta, and 21 Japanese students (16 females and 5 males) at Hokkaido University judged the 12 models' intensity of happiness and sadness based on their facial expression on a 10-point Likert scale ranging from 0 (*not at all*) to 9 (*extremely*). Participants' judgments of each figure's facial expressions indicated that overall these facial expressions were clearly and equally understood by both Canadians and Japanese[2]; thus, we confirmed that there were no effects of culture on the participants' judgments of the single models' emotional expression without backgrounds. Using these models, we created 60 images in the Photoshop 7. Each image consisted of one center model (target) and four background models.

PROCEDURE

After signing the consent form, participants were asked to sit in front of the eye tracker (Tobii 1750) and were told that their overall task was to judge the central persons' emotions based on their facial expressions. All participants in Canada (European Canadians, Asian Canadians, International students) received instructions in English, and Japanese participant received instructions in Japanese. To maintain the equivalency in translation, we applied the procedure used by Masuda et al. (2008b), in which the word "*feeling*" was translated into "*kimochi*," and the word "*emotion*" was translated into "*kanjo*."

The participants sat on an adjustable chair, and placed their chins on a chin rest to standardize the distance (30 cm) between the monitor and their faces. The 60 stimuli were presented in two different orders (1–60 or 60–1) using Clearview 2.5.1 software, with the Tobii 1750 eye tracker on a 17-inch (43 cm) monitor. The 50 Hz eye tracker allows us to measure participant's eye movement every 20 ms. Based on the threshold criteria used by Masuda et al. (2008a), we define the fixation threshold to be the attention held within a circle 20 pixels in diameter for two consecutive measurement units (40 ms). Saccadic eye movement below this threshold was not measured.

Participants were first asked to observe each image for 10 s. During this process, the participants' patterns of eye-movement were measured by the eye tracker. After a 500 msec interval, they were presented with the same image again and were asked to state out loud their judgments of each central model's happiness and sadness respectively using the 10-point Likert scale ranging from 0 (*not at all*) to 9 (*extremely*) (see **Figure 1**). For each central model, participants were asked to provide the happiness rating first and the sadness rating second, so that the experimenter could easily record the evaluations. At the end of the experiment, participants were asked (1) whether they noticed that the emotional expression of the background figures changed, and (2) whether the background figures' emotional expressions influenced their judgments. They were then asked to fill out the demographic questionnaires and were debriefed.

RESULTS

MANIPULATION CHECK

The majority of European Canadians (97.73%), Asian Canadians (93.18%), Asian international students (96.97%) and Japanese (97.73%) said that they noticed changes in the expression of the background figures, and the cultural differences did not reach

[1]All the models agreed to let the researchers use their portraits for research purposes. The models were not professional models but were students who were recruited through a school flyer.

[2]Canadian and Japanese participants' judgment was statistically different regarding the neutral expression of only one model, $t_{(59)} = 2.07$, $p = 0.043$. Other than that, there was no cultural variation in judgment between Canadian and Japanese participants.

FIGURE 1 | Experimental procedure.

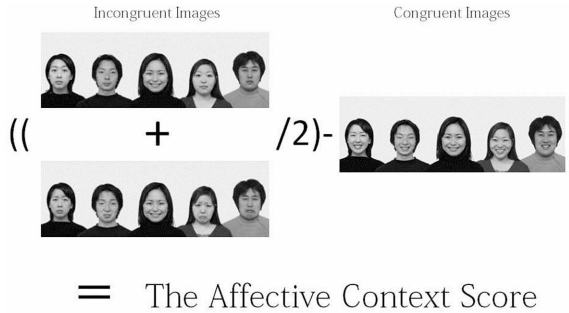

FIGURE 2 | Formula used for computing the affective context score.

significance, $\chi^2(3, 166) = 1.795$, $p = 0.616$. This can be interpreted as a check that the manipulation was clearly observed in all groups.

SUBJECTIVE PERCEPTION OF THE EFFECT OF CONTEXT

Our first hypothesis was that in judging the intensity of the central person's facial expressions, Japanese participants would be more likely than their North American counterparts to be influenced by the emotions of the other people. When we asked the participants whether changes in the background figures' emotional expressions influenced their judgments, we found that 59.09% of European Canadians, 59.09% of Asian Canadians, 79.41% of Asian international students, and 86.36% of Japanese stated that their judgment was indeed influenced by the surrounding others. There was a cultural difference, $\chi^2(3, 166) = 12.13$, $p = 0.007$.

JUDGMENT DATA

To examine participants' judgment styles, we collapsed the factors of models' gender and ethnicity, as well as types of target emotion, and subtracted the average judgment scores of congruent images [e.g., (happy-center and happy-background images)] from those of incongruent background images (e.g., [(happy-center and sad-background images) + (happy-center and neutral-background images)]/2; see **Figure 2**)[3]. A One-Way ANOVA was applied to the difference values. The results indicated that there was a main effect of culture, $F_{(1, 166)} = 4.53$, $p = 0.004$, $\eta^2 = 0.077$. The results suggest that the more the participants were exposed to the East Asian cultural worldview, the more their judgments were influenced by changes in background figures' facial expression. In fact, the results of multiple t-tests revealed that Japanese ($M = -0.47$) were more likely than European Canadians ($M = 0.01$) and Asian Canadians ($M = -0.19$) to be influenced the affective contexts, $t_{(166)} = 3.73$, $p < 0.01$; $t_{(166)} = 2.17$, $p < 0.05$, respectively. The Japanese score was marginally different from that of Asian international students ($M = -0.02$), $t_{(166)} = 1.96$, $p < 0.10$. The Asian Canadian and Asian international student scores were only marginally different from the European Canadian score, $t_{(166)} = 1.55$, $p < 0.20$; $t_{(166)} = 1.52$, $p < 0.20$. When we tested whether the score of each cultural group significantly deviated from zero, the results indicated that the scores of Japanese participants, Asian international students, and Asian Canadians were all significantly different from zero, $t_{(44)} = 3.06$, $p < 0.01$. $t_{(34)} = 2.40$, $p < 0.03$; $t_{(44)} = 2.27$, $p < 0.03$, respectively. However, significance was not observed for European Canadians' score, $t_{(44)} < 1$, ns (see **Figure 3**).

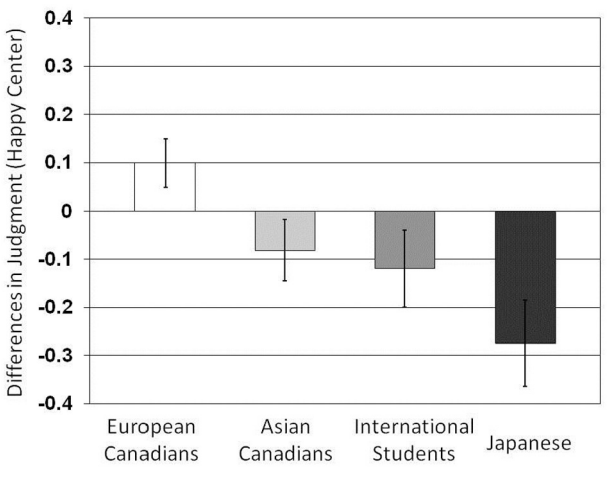

FIGURE 3 | Comparison of affective context scores for the four cultural groups.

EYE TRACKING DATA

We again collapsed the factors of models' gender and ethnicity as well as the types of target emotion and further analyzed the eye tracking data during the first 10 s of observation. We divided the image into two areas: the center area and the background area. The number of fixations and sums of fixation durations falling in each area were measured (see **Figure 4**).

[3]We also carried out a full factorial model of the types of target emotion, model's gender, and ethnicity. The results indicated an effect of types of target emotion. In general, the differences in score between congruent facial expressions and incongruent expressions is larger when participants judged targets' happy faces than when they judged targets' sad faces, $F_{(1, 162)} = 10.77$, $p = 0.001$, $\eta^2 = 0.062$. However, there were no effects of model's gender or models' ethnicity, $F_{(1, 162)} = 1.55$, ns, $F < 1$, respectively. In addition, no interaction terms produced statistically significant results. We therefore are confident regarding the equivalence of image quality used in this study.

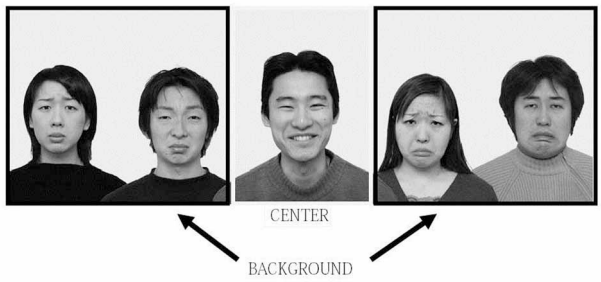

FIGURE 4 | Example of the division between the center area and the background area in an experimental image. The total number of fixations and fixation duration for each of the two areas were recorded separately.

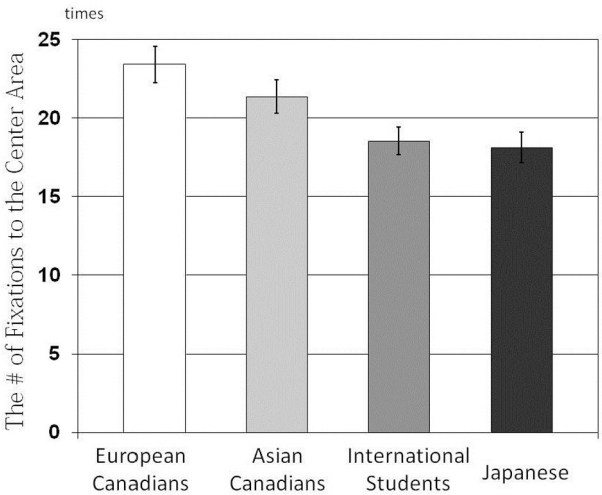

FIGURE 5 | Comparison of the number of fixations to the Center Area for the four cultural groups.

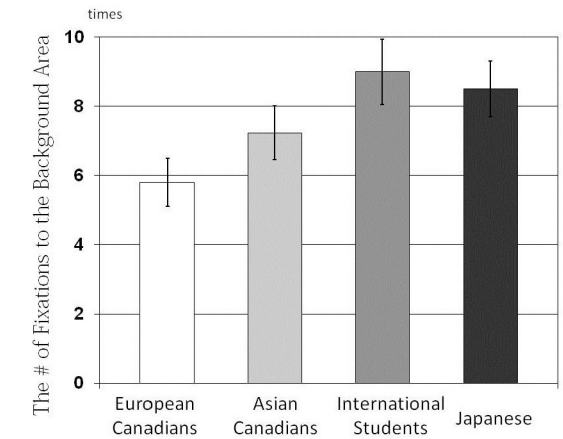

FIGURE 6 | Comparison of the number of fixations to the Background Area for the four cultural groups.

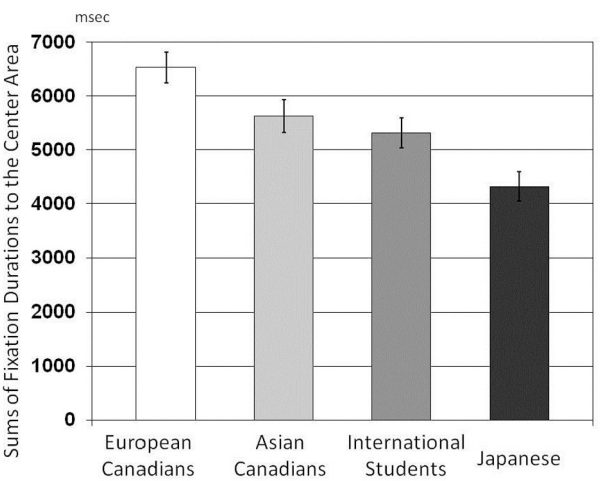

FIGURE 7 | Comparison of sums of fixation durations to the Center Area for the four cultural groups.

Number of fixations

The results of a One-Way ANOVA applied to the number of fixations indicated that there were main effects of culture on the number of fixations, $F_{(3,\ 162)} = 5.88$, $p < 0.001$, $\eta^2 = 0.098$ for the Center Area (**Figure 5**); $F_{(3,\ 162)} = 3.14$, $p < 0.03$, $\eta^2 = 0.055$ for the Background Area (**Figure 6**). The results of multiple t-tests revealed that European Canadians ($M = 23.42$) and Asian Canadians ($M = 21.37$) were more likely than their Japanese counterparts ($M = 18.11$) to allocate their attention to the Center Area, $t_{(166)} = 3.72$, $p < 0.001$, $t_{(166)} = 2.29$, $p < 0.05$, respectively. In addition, European Canadians were more likely than Asian international students to allocate their attention to the center area, $t_{(166)} = 3.19$, $p < 0.01$. Furthermore, Japanese ($M = 8.51$) and Asian international students ($M = 9.00$) were more likely than European Canadians ($M = 5.80$) to allocate their attention to the background area, $t_{(166)} = 2.46$, $p < 0.01$, $t_{(166)} = 2.71$, $p < 0.01$, respectively.

Sums of fixation durations

The results of a One-Way ANOVA applied to the number of fixations indicated that there were main effects of culture on sums of fixation durations, $F_{(3,\ 162)} = 10.73$, $p < 0.001$, $\eta^2 = 0.166$ for the Center Area (**Figure 7**); $F_{(3,\ 162)} = 4.03$. $p = 0.008$, $\eta^2 = 0.069$ for the Background Area (**Figure 8**). The results of multiple t-tests for the Center Area revealed that European Canadians ($M = 6533.89$) were more likely than Japanese ($M = 4322.46$), Asian international students ($M = 5314.56$) and Asian Canadians ($M = 5626.61$) to allocate their attention to the center area, $t_{(166)} = 5.62$, $p < 0.001$, $t_{(166)} = 2.89$, $p < 0.01$, $t_{(166)} = 2.31$, $p < 0.05$, respectively. And, Asian Canadians and Asian international students were more likely than and Japanese to allocate their attention to the center area, $t_{(166)} = 3.31$, $p < 0.01$, $t_{(166)} = 2.35$, $p < 0.05$, respectively. Furthermore, Japanese ($M = 1568.19$) and Asian international students ($M = 1878.20$) were more likely than European Canadians ($M = 1154.17$) to allocate their attention to the background area, $t_{(166)} = 2.02$, $p < 0.05$, $t_{(166)} = 3.29$, $p < 0.01$, respectively. Asian international

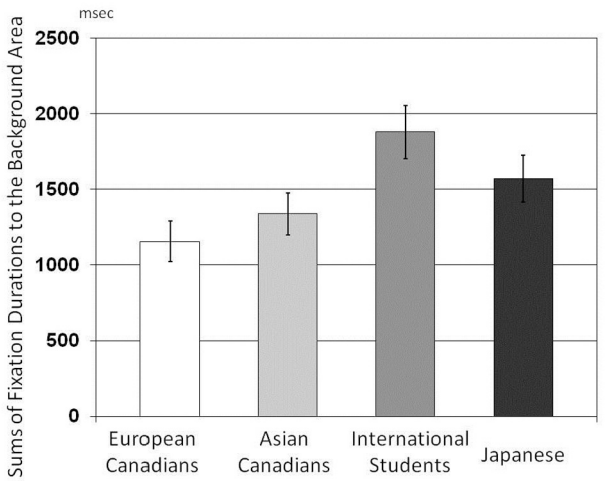

FIGURE 8 | Comparison of sums of fixation durations to the Background Area for the four cultural groups.

students were more likely than Asian Canadians to allocate their attention to the background area, $t_{(166)} = 2.46$, $p < 0.02$.

In sum, the results of eye tracking data analyses suggest that (1) Japanese attended more than their European Canadian counterparts to background figures; (2) Canadians, especially European Canadians, were more likely than Japanese to attend to the central figure; (3) Asian international students in Canada were more likely than European Canadians to allocate their attention to the background figures; and (4) Asian Canadians' eye movement data fell between the two extreme groups (European Canadians and Japanese). This suggests that the emotional context effect of the Asian Canadian and Asian international student data, although weaker than that of the Japanese data, still display the patterns of attention dominant in East Asia. Furthermore, the results indicated that participants' attention to background positively correlated with their judgment styles. The more a person paid attention to the background (as indicated by increased number of fixations and longer fixation duration), the larger the discrepancy in judgment between congruent and incongruent images, $r_{(166)} = -0.19$, $p < 0.02$ for number of fixations, $r_{(166)} = -0.16$, $p < 0.05$ for fixation duration.

This suggests that the cultural variation in emotional context effect on judgment is not grounded in superficial differences in judgment patterns but heavily grounded in participants' voluntary eye movement patterns.

GENERAL DISCUSSION

The findings suggest that although the influence of some types of affective cues in context is observable across cultures, affective contexts used in the current study had the greatest influence on Japanese participants' judgment and the least influence on European Canadians' judgment. We maintain that the cultural variation in affective context effect observed in this study is due to differences in worldview shared by the respective cultural communities. For East Asians, the world is complex and everything is interrelated. Therefore, East Asians epistemologically apply a holistic strategy to capture the scenes, paying attention not only to the focal information but also to surrounding information that might be considered peripheral by North Americans. East Asians' interdependent tendency also facilitates the holistic pattern of attention. The results suggest that, instead of assuming that one's facial expressions are generated from his or her inner feelings, East Asians assume that facial expressions are a product of complex interpersonal relationships. Therefore, for East Asians, it is informative to attend to surrounding others' facial expressions and incorporate them into their judgment of the target model's facial expression. By contrast, North Americans share a worldview in which the world consists of discrete things that are independent from each other. Therefore, North Americans epistemologically apply an analytic strategy to capture the scenes, detecting focal faces in the scenes while differentiating them from peripheral information. North Americans' independent tendency also facilitates the analytic pattern of attention. The results suggest that North Americans assume that one's facial expression is generated from the person's inner feelings. Therefore, for North Americans, it is informative to focus only on the target agent to be assessed.

LIMITATIONS

There are some limitations in the current studies. First, because of the technological constraints, we could not capture participants' saccadic eye movement below the threshold (40 ms and 20 pixels). However, it is possible that there are systematic cultural variations in participants' saccade. Although it is beyond the scope of the current research, it will be worthwhile to investigate this aspect using a more advanced eye-tracking device. Second, although the forced attention method used in this study overcame the shortcomings of previous work (Masuda et al., 2008b), it is still possible that there are substantial cultural variations in participants' judgment speed. North Americans might make a judgment faster than Japanese while viewing images for 10 s. Therefore it is advisable to test, in a future study, whether Japanese are influenced by changes in background when they view the image for a very short period of time, for example, shorter than that of North Americans' fastest judgment time. In fact, the findings of Masuda et al. (2008b) partially suggested this possibility. That is, Japanese participants' attention started to deviate from the center after 1 s. However, in combination with the current experimental design—forcing North Americans to view images much longer than their regular judgment speed—an experimental design that uses a shorter viewing time will further elucidate the relationship between culture, judgment speed, and the context effect.

IMPLICATIONS

The current findings address a variety of research questions which future research needs to investigate. First, as aforementioned, current findings in neuroscience indicate that substantial cultural variations in the increased magnitude of the N400 response associated with incidental and incongruent pieces of information (Goto et al., 2010; Na and Kitayama, 2011). On the basis of these neuroscientific findings that indicate the cultural specificity of the N400 response (e.g., Goto et al., 2010), we assume that East Asians will be more likely than North Americans to

have an increase in the magnitude of the N400 response when they observe an image in which the target facial expression is incongruent with that of the background figures. Future neuroscientific research should investigate this possibility so as to further elucidate cultural variations in the mechanism of information processing.

Second, it is advisable to further discuss the issue from the gerontological perspective. For example, Ko et al. (2011) found that cultural variation in context sensitivity was observed only among young adults and not among older adults. They interpreted this to mean that the ability to incorporate background information declines with age. However, the background images and foreground images used by Ko et al. are visually dissociated from each other (e.g., a target human face detached from the body was placed against a picture of a snake, the texture and resolution of which were quite different from those of the target face), which increases the difficulty of perceptually integrating them. The stimuli used in the current study, however, use the same texture and resolution for both the background and foreground images, which may allow participants to easily integrate these pieces of information. We suggest that our stimuli be used in future research to examine whether the cultural variation in context sensitivity is observable even in older adults.

Third, the issue of malleability of attention need to be investigated. Is one's pattern of attention static? We maintain that this is unlikely. From an early age, a person learns the dominant worldview of a given society through interaction with people in that culture (Nisbett, 2003; Duffy and Kitayama, 2010), and if that person moves to a new culture, his or her way of thought gradually blends the worldview of the host culture with that of the original culture. Much cross-cultural research that involves both monocultural and bicultural participants has reported such a blending pattern. That is, the bicultural group's performance falls somewhere between that of two monocultural groups (Kitayama et al., 1997; Heine and Lehman, 2004; Tsai et al., 2004; Heine and Hamamura, 2007; Cheung et al., 2011). These findings suggest that patterns of behavior are not static, but blend malleably into new circumstances. Some data indeed indicate that one's patterns of attention are learned (Kitayama et al., 2003; Duffy et al., 2009) and malleable (Miyamoto et al., 2006). The current paper demonstrated that the affective context effect observed in Asian Canadians' and Asian international students' data was somewhat weaker than the Japanese data, and somewhat stronger than the European data. In fact, although the affective context effect was weaker for Asian Canadians and international students than for their Japanese counterparts, both judgment data and most of eye tracking data show that Asian Canadians' and international students' patterns of judgment and patterns of attention reside between those of the two extremes (European Canadians and Japanese).

Several attempts have been initiated to further test the compatibility with previous findings and to articulate the cross-cultural variations and similarities of the affective context effect. In this line of studies, researchers have attempted to determine the conditions in which the affective context effect is observed, that is, what types of judgment tasks and what types of affective stimuli accentuate or attenuate the affective context effect. For example, Ito and Masuda (submitted) used stimuli in which the target model's face was presented against either affectively congruent or incongruent scenes (e.g., the target's happy facial expression against a beautiful beach as background, vs. the same facial expression shown against a dirty toilet). Results of the rating task indicated that even North Americans experienced the affective context effect. Using the same stimuli, Ito et al. (2012) asked participants to simply make a quick categorization of the valence (positive vs. negative) of the target facial expression, and again demonstrated that that European Canadians and Japanese equally responded faster when targets' facial emotions were affectively congruent with contextual information than when they were incongruent. The findings of these two studies indicated that affective context effects are indeed observable across cultures, but that cultural variation in the affective context effect is accentuated only when the task involves deliberate rating of the target models' facial expression and when the target agents are surrounded by social others. We maintain that this line of investigation is important for future research because it will contribute to an understanding of cultural variations and universals in neural substrates of psychological processes. We also maintain that this research paradigm will shed light on individual differences in sensitivity to social others. For example, it will be informative to examine what types of personality characteristics and clinical attributes are associated with stronger or weaker affective context effects, and what causes these variations in judgment (e.g., Risko et al., 2012).

SUMMARY

In sum, while reducing potential confounding variables in Masuda et al. (2008b), the current findings suggest that cultural variation in emotion judgment is substantial even when real facial expressions are used. This finding has many implications for research on emotion, cognition, and neuroscience. Current findings in neuroscience indicate that substantial cultural variations in the increased magnitude of the N400 response associated with incidental and incongruent pieces of information (Goto et al., 2010; Na and Kitayama, 2011). On the basis of these findings, we assume that East Asians will be more likely than North Americans to have an increase in the magnitude of the N400 response when they observe an image in which the target facial expression is incongruent with that of the background figures. Future neuroscientific research should investigate this possibility so as to further elucidate cultural variations in the mechanism of information processing. In addition, the current set of real face stimuli will contribute to further advance research on emotions and corresponding facial expressions. Because many researchers have focused on the consistency between emotion and facial expression, they tended to put less importance on external factors such as the context effect on emotion judgment (e.g., Ekman and Friesen, 1975). However, various researchers have discussed the importance of context for one's emotion judgment (e.g., Carroll and Russell, 1996; Hietanen et al., 2007). Along with these findings, the current paper will facilitate the discussion regarding the malleability of context attention across age (e.g., Miyamoto et al., 2006; Duffy et al., 2009; Ko et al., 2011), and the magnitude of the context effect across situations (e.g., Ito et al., 2012).

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Issues in localization of brain function: The case of lateralized frontal cortex in cognition, emotion, and psychopathology

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The appeal of simple, sweeping portraits of large-scale brain mechanisms relevant to psychological phenomena competes with a rich, complex research base. As a prominent example, two views of frontal brain organization have emphasized dichotomous lateralization as a function of either emotional valence (positive/negative) or approach/avoidance motivation. Compelling findings support each. The literature has struggled to choose between them for three decades, without success. Both views are proving untenable as comprehensive models. Evidence of other frontal lateralizations, involving distinctions among dimensions of depression and anxiety, make a dichotomous view even more problematic. Recent evidence indicates that positive valence and approach motivation are associated with different areas in the left-hemisphere. Findings that appear contradictory at the level of frontal lobes as the units of analysis can be accommodated because hemodynamic and electromagnetic neuroimaging studies suggest considerable functional differentiation, in specialization and activation, of subregions of frontal cortex, including their connectivity to each other and to other regions. Such findings contribute to a more nuanced understanding of functional localization that accommodates aspects of multiple theoretical perspectives.

Keywords: emotion, motivation, frontal cortex, lateralization, localization

Across decades of research to identify the functions served by various brain regions, using non-invasive, low-density scalp EEG recording, emphasis on large brain regions was understandable, because more localized inferences were rarely feasible. Proposals about broad functional differences in the cerebral hemispheres were common. A prominent literature in that tradition attempted to assign functions differentially to left- and right-frontal or posterior cortex, and much attention was spent on frontal lateralization and frontal specialization with respect to emotion and emotion-related psychopathology such as depression.

The emotion literature more generally has yet to settle on a dominant set of concepts for mapping emotion phenomena, with various definitions of and time courses for emotion, affect, mood, and motivation in use (e.g., Gendron and Barrett, 2009; Lindquist et al., 2013). For example, central or peripheral physiology associated with emotion is commonly treated as a *response to* emotion, but some have proposed that the physiology is *part of* emotion (e.g., Lang, 1979; Niedenthal, 2007). Thus, what it means to "have" an emotion is, in part, having the relevant physiology. Definitions as well as relevant psychological and biological mechanisms overlap for emotion, motivation, etc. The diversity of conceptualizations of emotion adds methodological and interpretive variance to the literature on frontal lateralization of function.

TWO MODELS OF FRONTAL LATERALIZATION

The present review contends that key assumptions in the debate about frontal lateralization are untenable in light of recent research on frontal cortex. A longstanding literature has argued that frontal differences in activation track emotional valence or mood, with left-frontal activation associated with positive stimuli or mood and right-frontal activation associated with negative stimuli or mood (e.g., Heller and Levy, 1981; Tucker, 1981; Davidson, 1983, 1984, 1992; Heller, 1990; Heller et al., 1998). A growing literature has argued for a different interpretation of lateralized frontal activity, with approach and avoidance (or the closely related concept of withdrawal) motivation as the relevant dichotomy (for reviews, see Davidson, 2003; Harmon-Jones, 2003; Harmon-Jones et al., 2010). Davidson (1983) proposed that frontal asymmetry is not related fundamentally to the valence of an emotional stimulus but to the motivational system that is engaged by that stimulus. He posited that left prefrontal cortex (PFC) is involved in a system facilitating approach to appetitive stimuli and right PFC in a system facilitating avoidance of aversive stimuli. In this model, it is not processing related to emotional valence itself that is lateralized in PFC. Rather, emotion-related lateralization is observed because emotions involve approach and/or avoidance components. Therefore, emotion will be associated with a left or right

lateralization depending on the extent to which it is accompanied by approach or avoidance motivation (Davidson, 1983). Several related dichotomies have been proposed, including Dickinson and Dearing's (1979) Aversive/Attractive systems, Gray's (1994) Behavioral Activation/Behavioral Inhibition systems, and Lang et al.'s (1990) Appetitive/Defensive systems (for reviews, see Lang et al., 1990; Davidson and Irwin, 1999; Elliot and Covington, 2001).

Wacker et al. (2003) noted that the valence perspective on frontal asymmetry had persisted for two decades with very little direct examination of whether related constructs such as motivation or behavioral activation/inhibition would do as well or better. More recently the literature has attempted to choose between those interpretations (e.g., Spielberg et al., 2008; Carver and Harmon-Jones, 2009b; Herrington et al., 2009). Here it is argued that no such choice is needed, if a finer degree of cortical granularity is considered.

EVOLVING CONCEPTUALIZATIONS OF THE FUNCTIONAL ROLE OF EEG ALPHA

Much of the evidence that forms the foundation of these two traditional views of lateralized function rests on EEG studies of hemispheric asymmetries in alpha-band activity. This research has long relied on the view that alpha-band activity is inversely related to the level of nearby regional brain activity. Besides some well-known methodological challenges (Allen et al., 2004), there are substantive challenges to this traditional view, beginning with the functional role of alpha. Rather than being simply a non-specific index of regional activity, alpha and other low-frequency oscillations foster communication between brain regions, whereas high-frequency oscillations facilitate coordination within cell assemblies on a much smaller scale (Kopell et al., 2000; von Stein and Sarnthein, 2000). Klimesch et al. (2007) argued that reduced alpha facilitates relatively unfiltered throughput, whereas increased alpha facilitates processing of specific features of a current stimulus or of an accessed memory relevant to the current task or goal state. Furthermore, cross-frequency coupling (frequency-specific, correlated oscillations in distributed networks) has been proposed as an index of network interaction across brain regions (Siegel et al., 2012). These distinct distant/local roles can converge, for example when there is cross-frequency coupling between alpha phase and gamma amplitude, in the form of alpha driven by region X modulating gamma in region Y. This so-called phase-amplitude coupling can be quantified as a phase-locking value relating the phase of activity in one frequency band to the amplitude of activity in another (typically higher) frequency band (Lachaux et al., 1999). Voytek et al. (2010, p. 191) identified phase-amplitude coupling as reflecting a "... means through which multiple overlapping long-range networks can communicate by statistically biasing the extracellular membrane potential in local cortical regions such that neurons will be more likely to fire during particular phases or phase network ensembles of low-frequency oscillations."

This richer and more functionally specific perspective on alpha activity provides a means to re-examine longstanding assumptions as well as to develop new predictions about cognition-control regions modulating activity in emotion-control regions (at least to the extent that cognition and emotion can be distinguished; Miller, 1996; Pessoa, 2005; Duncan and Barrett, 2007; Mohanty et al., 2007; Dolcos et al., 2011). For example, region-specific correlations between alpha phase and gamma amplitude might be observed in regions related to emotion regulation, given that alpha oscillations modulate the state of sensory brain regions to direct the flow of information and optimize performance (Jensen and Mazaheri, 2010; White et al., 2010; Hanslmayr et al., 2011; Popov et al., 2012a,b) and that large-scale cortical interactions in the alpha/beta range influence gamma activity (Siegel et al., 2012). Thus, although EEG alpha conceived as a nonspecific activity metric has been the dominant tool in the debate over valence/arousal and approach/avoidance constructs regarding frontal lateralization, it provides a problematic foundation on which to base conclusions about regional brain organization.

LATERALIZATION IN FRONTAL LOBES AS THE UNIT OF ANALYSIS AND OF CONCEPTUALIZATION

A second substantive challenge to the traditional use of alpha in studies of frontal lateralization is that the notion of "brain region" is problematic in this context, such as when two sets of neurons are treated as anatomically and functionally quite distinct (and the neurons within a "region" are treated as functionally homogenous). Consensus has not been reached on how to segment even the gross structural or functional anatomy of the brain, particularly in the face of individual differences (Brett et al., 2002). Although the psychological functions served by specific regions cannot themselves be anatomically localized (Miller, 2010; see also Lindquist et al., 2013), there is considerable momentum to view demarcated brain regions as serving or implementing distinct, specific functions. Granting that such an oversimplification can be an appropriate methodological expedient, a question of granularity arises: how big (small) a region to treat as a functional unit?

Surely fruitful answers to the granularity question will vary by psychological function, by brain region, and by research method. The extensive literature on functional laterality in frontal cortex has commonly treated the left- and right-frontal lobes as the units of analysis, and the amount of EEG alpha recorded over them has typically, as reviewed above, been interpreted as an (inverse) index of neural activity in those units. Accordingly, differences in EEG recorded over left- and right-frontal cortex have been used to infer lateralized specialization or function. The following discussion examines a particular line of research by the authors and their colleagues for evidence about the appropriate granularity for the literature on frontal lateralization in emotion and suggests that hemisphere-level models of functional differentiation are no longer viable.

PRACTICAL CHALLENGES TO HEMISPHERE-LEVEL MODELS

As noted above, implicitly and sometimes explicitly the literatures arguing for valence or approach interpretations have often treated the left- and right-frontal lobes as single functional units. This assumption was understandable given that, until recently, much of the research involved scalp EEG studies relying on what are

now considered low-density montages or, less commonly, lesion patients with uncertain or inconsistent trauma. Dense-array EEG recording montages can provide more precise localization of activity. However, the frontal lobes pose particular challenges to EEG source localization, especially in the absence of hypotheses about specific, dipolar sources, typically leading to reliance on the relatively low spatial localization precision of methods aimed at identifying distributed sources. Many studies were undertaken without individual structural MRI (which would allow for individual differences in brain structure) and before dense-array EEG recording was widely available. EEG source analysis was rarely attempted, and inferences beyond the level of hemisphere, cortical quadrants, or gross superior/inferior distinctions were rarely advanced.

The frontal-laterality EEG literature faces additional challenges, including reliance on resting data with little knowledge of or control over what subjects are doing as well as methodological disputes about choice of reference site, inter-session replicability, and laterality quantification metrics (e.g., Allen et al., 2004; Davidson, 2004). Davidson (2004) suggested that the frontal cortex is a large territory with considerable, if controversial, functional differentiation. Considerable research addressing the valence/motivation dispute, with much better localization of findings, has subsequently accrued. On balance it provides partial support to both views, in that different regions of frontal cortex are associated both with different functions and with functionally different networks of brain regions. Even a very selective review of recent fMRI studies demonstrates quite diverse functions associated with different regions of frontal cortex. The present review draws on a program of research using color-word and emotion-word variants of the Stroop task, not only to limit the scope of the review but to demonstrate that support for diverse functions and diverse localizations can be observed even within a single task in a single line of study.

EXPERIMENTAL CHALLENGES TO HEMISPHERE-LEVEL MODELS

Wager et al. (2003) reviewed hemodynamic neuroimaging studies of emotion, finding little support for valence-specific lateralization of emotion, including in frontal cortex. However, Herrington et al. (2009) noted that inclusion of a hemisphere factor in analyses is remarkably rare in the fMRI literature, even though it is often essential when making claims about lateralization. Herrington et al. (2005) provided the first fMRI demonstration of left-frontal lateralization associated with positive valence. As illustrated in **Figure 1**, Herrington et al. (2005) reported both Valence and Valence × Hemisphere effects for an empirically defined region of interest (ROI) in left vs. right dorsolateral prefrontal cortex (DLPFC). Using an independent sample, Herrington et al. (2010) replicated this finding (**Figure 2**, upper panels). Herrington et al. (2010) identified a separate DLPFC region that showed enhanced rightward lateralization in depression (**Figure 3**). These fMRI studies thus support earlier EEG literature drawing the same conclusions—positive valence associated with left-frontal activation and depression associated with right-frontal activation. However, Herrington et al. (2010) found another area of DLPFC showing a contrary lateralization, with response to negative words more left-lateralized (**Figure 2**, lower panels). Such results suggest that a hemisphere- or cortical-quadrant-level view of frontal lateralization is inadequate.

Engels et al. (2007) replicated the leftward lateralization in DLPFC associated with positive stimuli. In addition, they identified a distinct, non-overlapping left inferior frontal gyrus (IFG) ROI that was sensitive to worry/anxious apprehension (**Figure 4**). The determination that anxious apprehension and positive valence are associated with distinct left PFC regions puts to rest an apparent contradiction that traditional, low-density EEG studies (e.g., Heller et al., 1997; Nitschke et al., 1999) could not address, that a negative emotion (worry) seemed

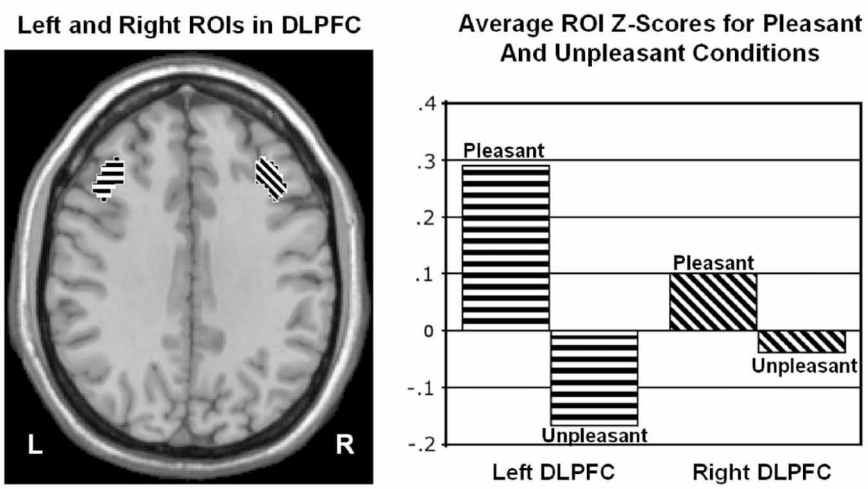

FIGURE 1 | Region yielding a Valence × Hemisphere interaction in middle frontal gyrus of dorsolateral prefrontal cortex (DLPFC). Left panel: Regions of interest (ROIs) used to quantify activity in left (L) and right (R) dorsolateral prefrontal cortex at Talairach $z = 34$ mm. **Right panel**: Mean z scores for pleasant and unpleasant word conditions in left and right DLPFC. From Herrington et al. (2005). Copyright by the American Psychological Association. Reprinted with permission.

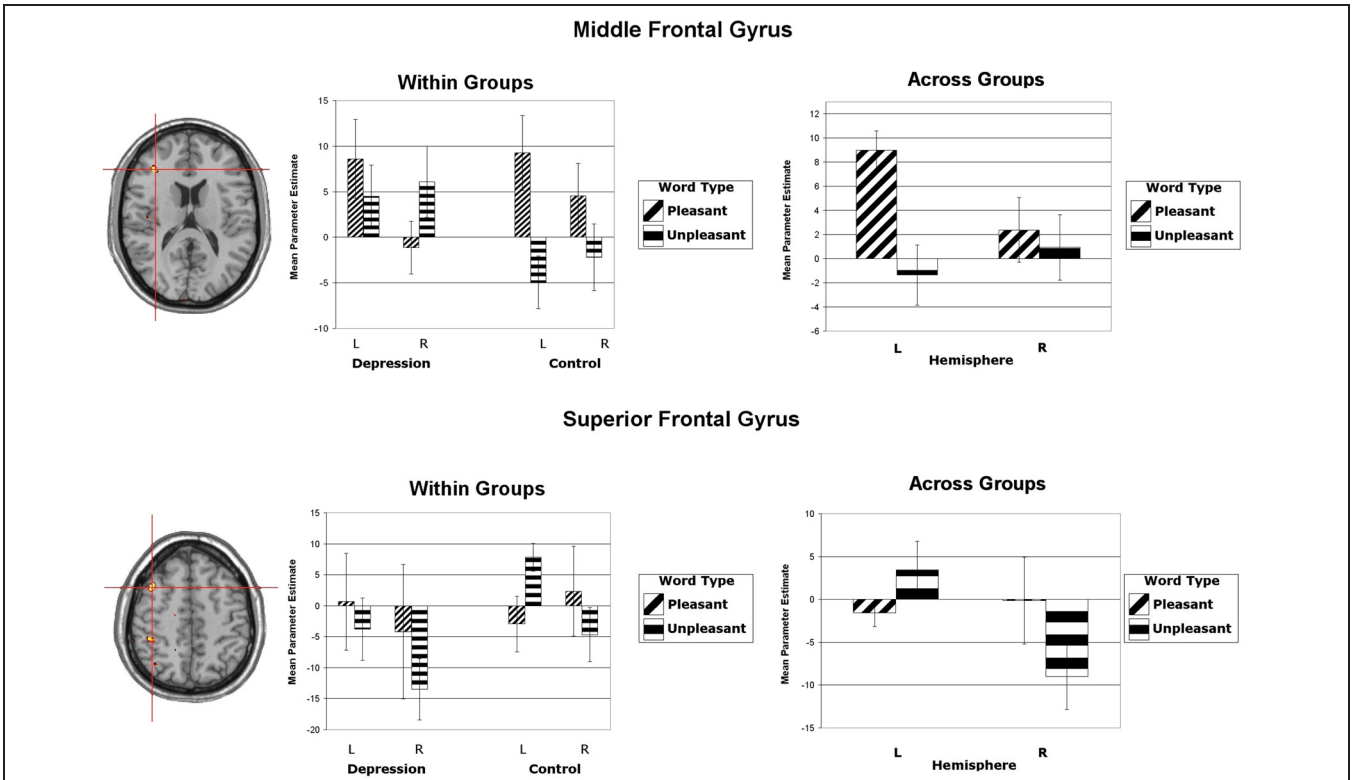

FIGURE 2 | Upper panels: Region yielding a Valence × Hemisphere interaction in middle frontal gyrus of dorsolateral prefrontal cortex. The left panel shows the significant cluster in an axial slice at Talairach $z = 16$. (Although the center of this cluster was inferior to that illustrated in **Figure 1**, the means showed the same pattern.) **Lower panels:** Region yielding a Valence × Hemisphere interaction in superior frontal gyrus of dorsolateral prefrontal cortex. The left panel shows the significant cluster in an axial slice at Talairach $z = 49$. **All panels**: Activation is arbitrarily overlaid on left-hemisphere anatomy, as hemisphere was included as a factor in the analysis. The red crosshairs are placed over the center of effect size. Bar graphs are mean parameter estimates for each level as a function of Valence and Hemisphere by group and averaged across groups. Error bars represent 1 standard error above and below the mean. From Herrington et al. (2010). Copyright the Society for Psychophysiological Research.

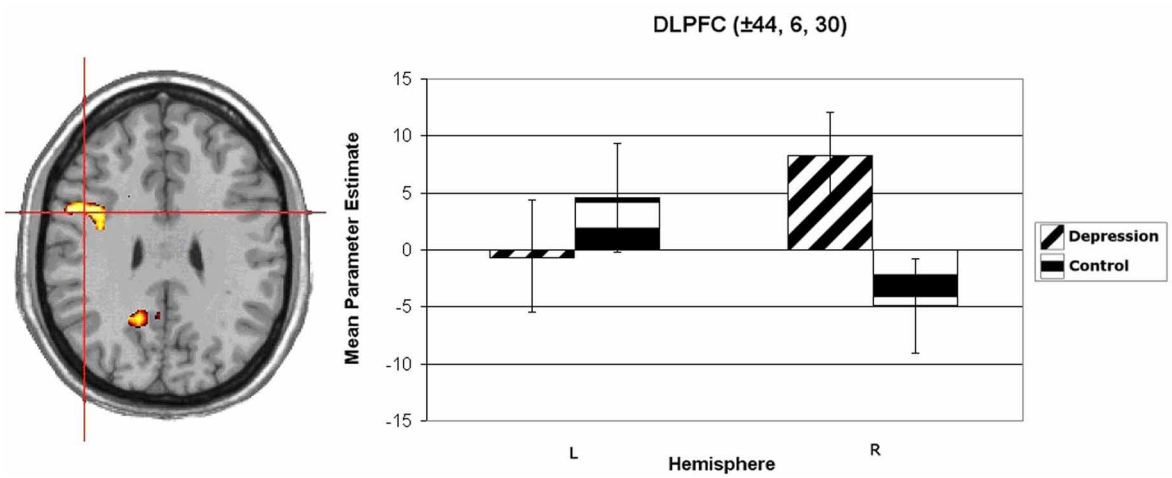

FIGURE 3 | Group × Hemisphere interaction for unpleasant vs. neutral word activation in dorsolateral prefrontal cortex (DLPFC). Activation is arbitrarily overlaid on left-hemisphere anatomy, as hemisphere was included as a factor in the analysis. The red crosshairs are placed over the center of effect size for the cluster. Panel on right plots average parameter estimates as a function of Group (Depression, Control) and Hemisphere. Coordinates are the center of effect size at $z = 30$ in Talairach space. Error bars represent 1 standard error above and below the mean. From Herrington et al. (2010). Copyright the Society for Psychophysiological Research.

to be localized to the same brain quadrant as a positive emotion: frontal cortex is functionally differentiated with respect to emotion processing.

Engels et al. (2010) replicated the rightward lateralization of DLPFC activity in depression, showing it to depend on a particular pattern of comorbid anxiety (high anxious arousal). In contrast, Engels et al. (2010) found reduced rightward lateralization in a separate region, in IFG, again moderated by comorbid anxiety (high anxious arousal, low anxious apprehension). Thus, even within a hemisphere, frontal areas can show contrasting relationships with psychological variables, some of which are consistent with the traditional valence interpretation of frontal lateralization, and some of which are not. Furthermore, when anxious arousal is high and anxious apprehension is low, depression is associated with a decrement in left DLPFC (Engels et al., 2010). High anxious apprehension appears to counteract this pattern, possibly by boosting brain activity in compensatory regions of left PFC. The findings indicate that, if both types of anxiety are not taken into account, activation asymmetries for depression may not be reliably detected, yet another contribution to the lack of consistency in the literature. It is easy to imagine that a literature employing various tasks, and involving a variety of psychological functions differentially engaging various brain regions, could produce diverse findings.

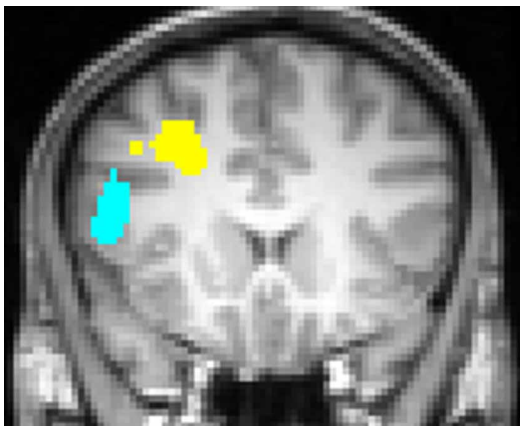

FIGURE 4 | Left inferior frontal gyrus (blue) region more active for negative words than for neutral words, significantly moreso for subjects scoring high in anxious apprehension, and left dorsolateral prefrontal cortex (yellow) region more active for positive words than for neutral words, with no differentiation by level of anxious apprehension or anxious arousal, displayed at Talairach $y = 18$. Neurological convention (left-hemisphere on left of panel). From Engels et al. (2007). Copyright the Society for Psychophysiological Research.

This line of fMRI studies finding evidence of frontal lateralization related to valence also examined activation associated with approach and avoidance concepts. As illustrated in **Figure 5**, Spielberg et al. (2011) described two left-hemisphere DLPFC areas in which incongruent color-words prompted more activity than did congruent words in subjects with high scores on self-report measures of approach temperament. However, a left medial-posterior orbital frontal cortex region showed the opposite effect. This contrary lateralization, in line with other studies of orbitofrontal cortex and emotional valence (for reviews,

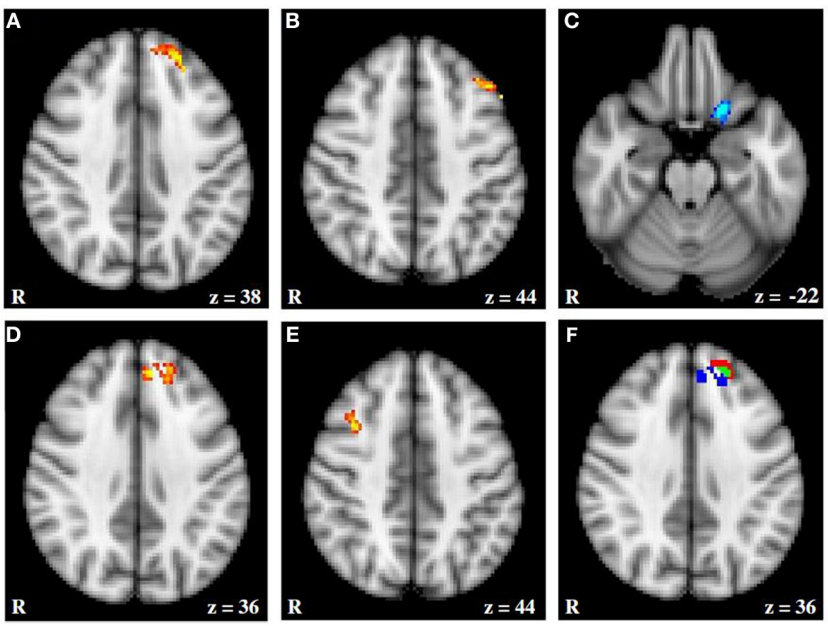

FIGURE 5 | fMRI activation moderated by approach and avoidance temperament. (**A** and **B**) Activation for Incongruent–Congruent contrast (IvC) correlating positively with approach temperament. **(C)** Activation for IvC correlating negatively with approach temperament. (**D** and **E**) Activation for IvC correlating positively with avoidance temperament. **(F)** Overlap between activation correlating with approach and avoidance temperament; red = activation associated with approach; blue = activation associated with avoidance; green = overlap in activation. Axial slices are at MNI 152 *z* coordinates noted. From Spielberg et al. (2011). Copyright Elsevier Inc.

see O'Doherty, 2004; Wager et al., 2008), could also contribute to inconsistencies in the traditional EEG alpha literature. Dolcos et al. (2011) reviewed studies showing diverse functional connectivity between various regions of frontal cortex and limbic regions. These could contribute to different regions of frontal cortex having different roles in emotion processing and showing different functional lateralization.

Figure 6 (Spielberg et al., 2011) illustrates that, close to a left-hemisphere frontal region showing the predicted positive relationship with approach temperament, a left-hemisphere region showed a positive relationship with avoidance temperament, contrary to traditional prediction. (The approach-related cluster was significantly lateralized, whereas the avoidance-related cluster was not.) Indeed, there was some overlap, such that activation in an 18-voxel subregion correlated positively with both approach and avoidance temperament. Spielberg et al. (2012b) replicated the association between approach motivation and left-hemisphere activation in lateralized regions of DLPFC and also of avoidance and right DLPFC. However, these effects were not moderated by the valence of the stimuli, further evidence that processes serving motivation and emotional valence can be implemented in different regions of PFC. Furthermore, the left-frontal regions sensitive to approach motivation, positive valence, and anxious apprehension were mutually distinct. These findings again indicate that frontal cortex is functionally differentiated in a way that belies gross regional generalizations.

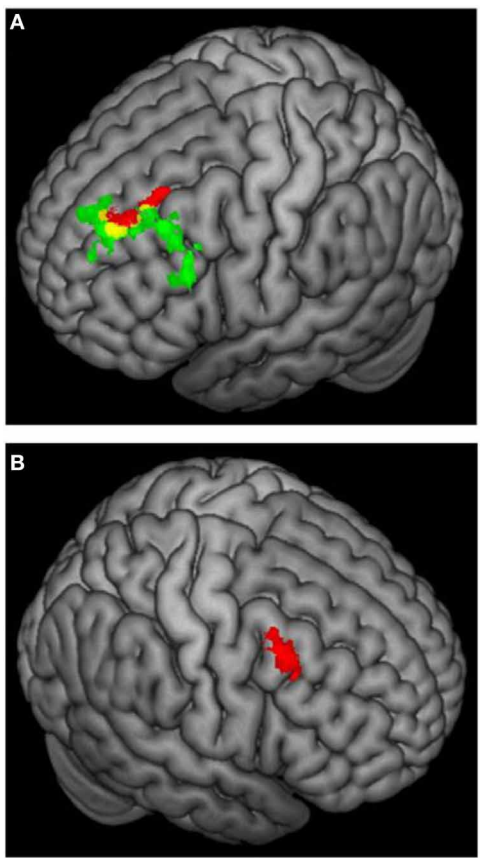

FIGURE 6 | 3D rendering of fMRI activation moderated by approach and avoidance temperament. (A) Activation for incongruent vs. congruent contrast correlating positively with approach temperament (green) or positively with avoidance temperament (red); yellow = overlap in activation. **(B)** Activation for incongruent vs. congruent contrast correlating positively with avoidance temperament. From Spielberg et al. (2011). Copyright Elsevier Inc.

Studies of psychopathology in this line of research further underscore the diversity of frontal-lobe specialization. Recent work (e.g., **Figure 3**) has identified a brain region in left PFC that points to a mechanism by which depression may interfere with the ability to modulate top–down attentional processing, degrading concentration and task performance (Levin et al., 2007; Engels et al., 2010; Herrington et al., 2010). Furthermore, different types of anxiety (Nitschke et al., 1999, 2001) modulate PFC activity in distinct ways. As noted above, a left PFC brain region more active when anxious apprehension is high, distinct from a left PFC region active in a positive valence context (differentiated in **Figure 4**), contrasts with a right-hemisphere region more active when anxious arousal is high (Engels et al., 2007). Thus, "anxiety" is not a monolithic phenomenon whose cortical instantiation can be assigned to a single brain region, and accordingly it does not show a single, consistent pattern of lateralization.

ANGER: A DECISIVE TESTING GROUND?

A potentially informative manipulation in the literature on emotion and frontal lateralization has involved anger. Harmon-Jones (2003) and others have noted that anger is typically classified as involving both approach and negative valence, so it seems uniquely useful in comparing valence/arousal and approach/avoidance interpretations, which otherwise tend to face methodological confounds (see Carver and Harmon-Jones, 2009a,b, for review and response to commentaries). In commentaries on that review, Watson (2009) raised concerns about this strategy, arguing that anger shows both approach and avoidance properties (see also Stewart et al., 2010), and Tomarken and Zald (2009) suggested that hemodynamic neuroimaging results then available generally did not support the approach interpretation of frontal laterality (though see Herrington et al., 2009; Berkman and Lieberman, 2010).

Harmon-Jones (2004) developed a self-report questionnaire to assess subjects' attitude toward anger, documenting that anger can be judged to be a positive feeling but that this did not account for EEG alpha results indicating leftward frontal laterality associated with trait anger. Stewart et al. (2008) went further, noting that anger may sometimes have important positive valence or appetitive qualities rather than being exclusively negative in valence, so anger manipulations may not unambiguously distinguish valence and approach views. Focusing on resting alpha asymmetry, Stewart et al. (2008) demonstrated that the anger/asymmetry story for EEG alpha is complex, with different anger styles (anger-out vs. anger-in) showing distinct lateralization patterns. Furthermore, anxious apprehension moderated anger-related lateralization. In addition, subjects high in trait anger who differed in approach- and avoidance-related motivational tendencies displayed greater

left-frontal lateralization than did control participants regardless of motivational direction. These results are not well explained by either valence or motivation views. Partly because anger is multifaceted, it has not proved to be the decisive context for resolving the valence/motivation dispute that was hoped for.

TWO MODELS OF FRONTAL LATERALIZATION: CURRENT STATUS

The present selective review has emphasized a single line of research from a single lab. Although this limits generalizability, it has the value of holding constant a host of variables that normally confound comparisons of findings across studies. The body of work reviewed here shows that, even holding many things constant, in a single lab, most of it on a single MRI scanner, considerable, systematic, and replicable regional differentiation of lateralized frontal function is apparent, associated with a variety of psychological constructs.

On the debate between the valence/arousal interpretation and the approach/avoidance interpretation of frontal lateralization of emotion, the literature provides numerous examples of support for each, recently replicated in the fMRI studies discussed above. But contrary findings and caveats also abound. The frontal cortex is a large landscape with enormous potential regional specialization that need not follow a simple theme (e.g., Brodmann Area 10 alone may have numerous, differentially specialized subregions; Burgess et al., 2011). Attempts to choose between a general valence/arousal account and a general approach/avoidance account of lateralized activity associated with emotion, motivation, or psychopathology no longer seem viable. The present contention is that the literature now makes clear that neither account is of much help in providing a comprehensive account of frontal function, lateralized or otherwise.

It may be tempting to retain longstanding approaches as long as no equally comprehensive replacement is available, and it can be noted that individual differences may have complicated interpretation of particular findings that challenge those approaches. It can also be argued that neither model has been thoroughly tested. But enough conceptual, practical, and experimental challenges have accrued that neither traditional approach seems viable. The present review suggests that the debate between those two positions, while historically generative, should be over. Both may be still useful in specific contexts, but both now appear too coarse, and neither is comprehensive.

On the issue of EEG as a means of addressing such questions, a focus on large brain regions was useful across decades of low-density scalp EEG recording. In modern-day EEG research, low density often still suffices for some purposes. For example, some components of the event-related brain potential with sufficiently distinctive and well established topography, with well-known sensitivity to parameters such as age, stimulus modality, and task, may be measured effectively with just a few recording sites. When distinctions are less established, or when spatial localization is important in identifying phenomena, higher-density recording can be invaluable, especially if augmented with MEG or MRI (e.g., Silton et al., 2010, 2011; White et al., 2010; Hanlon et al., 2011; Williams et al., 2011).

More is often better, but even with high-density recording (generally considered to be 64+ channels) one faces choices. One cannot surround the head with sites. There are times when local electrode density may be more important, such as distinguishing finger locations in motor cortex, and times when spatial extent may be more important, such as localizing deeper sources (e.g., Hanlon et al., 2011; Williams et al., 2011). In the design of an electrode montage for general-purpose use, a critical choice, other than number of channels, is how inferior to place the most inferior electrodes. Reaching to or beyond the cheekbone and below the eyes can substantially enhance representation of more inferior frontal brain activity, at some cost of increased artifact. Depending on what one is trying to study, where one positions the electrodes, and a host of other trade-offs, EEG may achieve sub-centimeter source localization accuracy, better than routine fMRI and better than needed for many purposes (Miller et al., 2007; Aine et al., 2012). Dense-array MEG can often do somewhat better still. fMRI optimized for such localization can do even better, at some cost to temporal resolution, though trade-offs can provide improved temporal resolution as well. Rather than cast various neuroimaging methods as competing, it is their complementarity and integration that will benefit the field.

It has become clear that traditional hemisphere and quadrant models of regional brain function in emotion and psychopathology are generally too coarse. Network accounts of brain function are growing in prominence, though challenging to operationalize and test. For example, Spielberg et al. (2012a) offered a proposal for a network in frontal cortex and other areas subserving motivation that accommodates many of the findings reviewed above. Sheline et al. (2010) proposed that a region of dorsal medial PFC serves as a critical junction for three resting-state networks reaching beyond frontal cortex and found that this region shows exaggerated connectivity to those networks in depression. The optimal level of granularity will surely vary widely, as a function of research context. Regional specialization may even be adaptive and thus beneficially unstable (Duncan, 2001) on a variety of temporal and spatial scales. Much good work lies ahead, with the proviso that localization is of brain activity, not psychological function, and that the psychological and biological phenomena we pursue need to be understood across multiple scales in parallel.

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What shall I be, what must I be: neural correlates of personal goal activation

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How is the brain engaged when people are thinking about their hopes, dreams, and obligations? Regulatory focus theory postulates two classes of personal goals and motivational systems for pursuing them. Ideal goals, such as hopes and aspirations, are pursued via the *promotion* system through "making good things happen." Ought goals, such as obligations or responsibilities, are pursued via the *prevention* system through "keeping bad things from happening." This study investigated the neural correlates of ideal and ought goal priming using an event-related fMRI design with rapid masked stimulus presentations. We exposed participants to their self-identified ideal and ought goals, yoked-control words and non-words. We also examined correlations between goal-related activation and measures of regulatory focus, behavioral activation/inhibition, and negative affect. Ideal priming led to activation in frontal and occipital regions as well as caudate and thalamus, whereas prevention goal priming was associated with activation in precuneus and posterior cingulate cortex. Individual differences in dysphoric/anxious affect and regulatory focus, but not differences in BAS/BIS strength, were predictive of differential activation in response to goal priming. The regions activated in response to ideal and ought goal priming broadly map onto the cortical midline network that has been shown to index processing of self-referential stimuli. Individual differences in regulatory focus and negative affect impact this network and appeared to influence the strength and accessibility of the promotion and prevention systems. The results support a fundamental distinction between promotion and prevention and extend our understanding of how personal goals influence behavior.

Keywords: regulatory focus, promotion, prevention, personal goals, fMRI, behavioral activation system, behavioral inhibition system

INTRODUCTION

A person's hopes, dreams, and wishes, whether attained or unattained, have always been seen as central to an individual's identity—as the essence of who a person is because they represent that which a person strives to be (James, 1890/1948). The kind of individual we wish to be, and the kind of person we believe we must be, are powerful influences on behavior and affect whether we see ourselves as succeeding or failing to attain those wishes and obligations (Kelly, 1955). Classic (Allport, 1955) as well as contemporary (Morf and Mischel, 2012) personality theorists, for example, have used the concept of *becoming* as a rubric for understanding individual differences in motivational orientation along with the affective consequences of failing to be that which we want to be or must be. Personal goals are real in a profoundly psychological sense—dreams and obligations are "truth" for individuals whether or not they "come true."

The *goal* construct in psychology captures much of how hopes, dreams, and wishes guide behavior and experience. Behavioral scientists have conceptualized personality as reflecting differences among people in terms of the higher-order goals they pursue and their characteristic ways of pursuing them (Cantor and Zirkel, 1990). Indeed, goals are a central construct in theories of behavior because they provide a unified conceptual framework linking internal states (needs, motives, beliefs) and the social world. When people believe they have attained an important goal, they may feel joyful, satisfied, fulfilled, or worthy; when people believe they have failed to attain a goal, they may feel inadequate, hopeless, worthless, guilty, or ashamed (Sullivan, 1953; Rogers, 1961). Yet, to date there has been little research examining how neural systems are engaged when people think about their personal goals, both when the goals are attained as well as when they are not.

In an influential review, Austin and Vancouver (1996) defined goals as *internal representations of desired states* and identified approach and avoidance goals as among the most important classes of goals. The vast behavioral science and neuroscience literatures on approach and avoidance attest to the centrality of these dimensions for understanding goal-directed behavior. Those literatures are dominated by the behavioral activation and inhibition systems model, postulating brain/behavior systems that underlie temperament-based approach and avoidance as well as dispositional positive and negative affectivity (Watson et al., 1999). Both the behavioral activation system (BAS) and behavioral inhibition system (BIS) are hypothesized to regulate

proximal goal-directed behaviors in response to cues for reward, in the case of BAS, or threat, in the case of BIS (Carver and Scheier, 1998). The two systems each represent a locus for the interaction of cognitive and affective processes, and each is associated with neural circuitry identified originally on the basis of animal research and shown to have analogs in the human brain (Gray, 1990, 1994).

Many personality and social theorists take a complementary perspective on the regulation of approach and avoidance, emphasizing abstract, higher-order goals that are cross-situational and integrated within the individual's sense of self. Higgins (1997) proposed a theory of *regulatory focus* that postulated two motivational systems for attainment of desired outcomes. Each is activated by contextual cues but also manifests trait-like properties across situations. Individual differences in regulatory focus are stable over time and predict which goals will be more likely to be used to guide behavior, as well as the strategies and means for pursuing them (Strauman, 1996). The behavioral and affective consequences of individual differences in regulatory focus are well-established (Higgins, 2012).

RFT draws on prior studies of self-evaluation and discrepancy monitoring and describes two regulatory systems that serve critical but distinct survival needs. The *promotion system*, which develops in response to children's need for nurturance (Bowlby, 1988), supports the attainment of positive outcomes by strategic approach, i.e., by "making good things happen." The promotion system is particularly active in the pursuit of ideals (aspirations, advancement, and accomplishment)—that is, the kind of person an individual can be or might be. The *prevention system*, which develops in response to children's need for security (Bowlby, 1988), also supports the attainment of positive outcomes, but instead by strategic avoidance, i.e., by "keeping bad things from happening." The prevention system is particularly active in pursuit of oughts (fulfillment of responsibilities, duties, and obligations)—that is, the kind of person an individual believes she/he must be or is supposed to be.

Individuals vary both in the characteristic ways they construe their goals and their chosen strategies to pursue them. As a consequence of variation in life experiences, a person might acquire increased value or personal relevance for one type of goal. For example, a strong value placed on prevention goals will result in goal pursuit strategies that involve keeping bad things from happening—for example, by avoiding pitfalls and negative outcomes in the service of ultimate goal attainment. In addition, the same desired end-state can be represented in different ways by prevention-oriented vs. promotion-oriented individuals. The same goal—such as being honest—could be represented as an ideal or aspiration (a promotion goal) or as an obligation or responsibility (a prevention goal).

In this article, we examine the neural correlates of priming personal goals using ideals and oughts as exemplars of the two types of goal representations postulated within RFT. We consider three largely unexplored questions about how the brain is engaged in pursuit of ideals and oughts. First, does priming of an individual's ideal vs. ought goals, already shown to result in distinct cognitive, motivational, and affective responses, also lead to discriminable patterns of neural activation? Second, do activation patterns associated with ideal vs. ought goals vary as a function of individual differences relevant to self-regulation? And third, since self-regulatory cognition is inherently connected with affect and with vulnerability to disorders such as depression and anxiety, do activation patterns observed following ideal and/or ought goal priming vary depending on an individual's current level of negative affect?

Based on existing findings in social cognitive neuroscience, there are several different patterns of neural activation that might characterize responses to priming of promotion and prevention goals (and, in turn, contribute to the construct validity of regulatory focus). One set of regions are those structures known to be activated by reward or threat cues, consistent with the role of BAS and BIS as mechanisms for individual differences in sensitivity to such cues (Amodio et al., 2007). There are conceptual links between the BAS system and the promotion system, since promotion goal pursuit requires responsiveness to opportunities for rewards in the environment and the use of strategic approach behaviors to achieve desired ends. There are similar links between the BIS system and the prevention system, because of the relevance of the strategic avoidance of negative outcomes in prevention goal pursuit. BAS-related regions implicated in response to incentives include the ventral striatum and ventromedial prefrontal cortex, with the former a locus for the coding of predictions regarding positive outcomes and the latter important for the processing of the hedonic significance of stimuli (Bjork et al., 2004; McClure et al., 2004; Kringelbach, 2005; Clithero et al., 2011). Individual differences in BIS strength have been associated with circuits linking the hippocampus, subiculum, and related structures (sometimes also including the basolateral and centromedial nuclei of the amygdala) (e.g., Reuter et al., 2004). Thus, the neural correlates of promotion vs. prevention could reflect the neuroanatomical distinctions between the substrates of BAS and BIS.

Another potential set of neural correlates of promotion/prevention goal activation is the group of regions referred to collectively as cortical midline structures (Northoff and Bermpohl, 2004; Lou et al., 2010; Qin and Northoff, 2011). These structures, which typically include the orbital and adjacent medial prefrontal cortex, the anterior cingulate cortex, the dorsomedial prefrontal cortex, and the posterior cingulate cortex, are regarded as an anatomical unit because of strong reciprocal projections among the individual structures and similar patterns of connectivity with other brain regions. They also are characterized as a network that subserves the representation and processing of self-referential stimuli (Beer and Ochsner, 2006). This set of regions may underlie the activation of promotion and prevention goals that are functionally linked to aspects of one's identity, including higher-order goals representing one's ideal self or ought self.

A third possibility is that the promotion and prevention goal representations overlap with the Self-Memory System postulated by Conway (SMS; Conway and Pleydell-Pierce, 2000). The SMS is a conceptual framework linking self and memory that consists of two main components: the working self and the autobiographical memory knowledge base. Drawing in part on studies of self-discrepancy and autobiographical memory (e.g., Strauman, 1990), Conway (2001) proposed that frontotemporal networks

mediate the connection between anterior regions associated with the working self (e.g., one's currently active goals and beliefs) and the autobiographical knowledge base, accessed through temporal lobe regions, needed to effectively pursue such goals within a dynamic interpersonal context.

Several studies have examined associations between regulatory focus and brain activity, with the evidence to date suggesting a link between promotion/prevention and midline cortical structures as well as a pattern of prefrontal cortex asymmetry akin to that observed in the BAS/BIS literature (Davidson and Irwin, 1999). Amodio et al. (2004) examined the associations between an implicit assessment of individual differences in regulatory focus and an EEG index of resting frontal cortical asymmetry. They observed that chronic promotion focus was associated with greater left frontal activity, whereas chronic prevention focus was associated with greater right frontal activity. Cunningham et al. (2005) found that neural activation when making good/bad judgments differed by individuals' regulatory focus: chronic promotion focus was associated with greater activation in the amygdala, anterior cingulate, and extrastriate cortex following positive stimuli, and chronic prevention focus was associated with activity in the same regions for negative stimuli. Touryan et al. (2007) also used fMRI to study the impact of individual differences in regulatory focus on memory for emotional words. They observed that activity in posterior cingulate cortex, associated with self-referential processing, was greater for correctly remembered stimulus words when they were consistent with an individual's regulatory focus. Packer and Cunningham (2009) investigated how regulatory focus interacted with reflection on personal goals and observed differential activation patterns according to goal domain (promotion vs. prevention) and temporal distance (short-term vs. longer-term).

Two studies have used idiographically selected promotion and prevention goals as stimuli within fMRI designs. Eddington et al. (2007) used incidental semantic priming via a "depth of processing" judgment task to examine patterns of cortical activation associated with promotion and prevention goals. An area of left PFC was activated during promotion goal priming across all four judgment tasks, and the magnitude of activation in this region was correlated significantly with individual differences in strength of orientation to promotion goals. In contrast, activation at this site did not correlate significantly with orientation to prevention goals or with individual differences in BAS/BIS strength. Eddington et al. (2009) examined the neural correlates of promotion and prevention goal priming in a sample of unmedicated adult patients meeting Diagnostic and Statistical Manual-IV-R criteria for major depressive disorder (MDD) as well as an age- and gender-matched control sample of adults with no psychiatric history, using the same judgment task. They hypothesized that MDD patients would show an attenuated left PFC response to promotion priming compared to the non-depressed controls. There was a significant difference in activation between the depressed and non-depressed groups following promotion goal priming, with controls showing greater left medial orbital PFC activation following promotion priming than the depressed patients. In addition, a region in right PFC was activated following prevention priming among MDD patients with comorbid anxiety.

The findings to date suggest that promotion and prevention may be associated with distinct patterns of neural activation, but none of the prior studies was designed specifically to address that question. In the present study, we adapted an fMRI paradigm developed by Diaz and McCarthy (2007) for rapid masked presentation of semantic stimuli. Masking provides a method for identifying cognitive processes that are preattentive, routinized, and automatic (Dehaene et al., 2001). The use of rapid masked idiographic goal priming offers several significant advantages. First, promotion and prevention goals can be activated automatically like other highly accessible social constructs (i.e., without intentional selection of a goal upon which to focus one's efforts); therefore, a paradigm that would allow detection of implicit priming effects was highly desirable. Second, the two studies by Eddington and colleagues were restricted in the number of goal priming trials included because individuals typically describe a small number of motivationally significant personal goals, thereby limiting the number of goal words available for use as explicit priming stimuli. The use of rapid masked stimulus presentation allows for a greater number of trials within an event-related design (in part because stimuli can be repeated more frequently). Third, because the participant's task in the Diaz and McCarthy paradigm is simply to make a response whenever she/he sees a non-word stimulus in color (e.g., ampersands in red font), a task that was non-self-referential, there is less potential for overlap or interference between the experimental task and priming-based activation of idiographically selected promotion and prevention goals.

Using this paradigm, we explored three aspects of the neural correlates of promotion and prevention goal representations. First, we examined whether BOLD activation patterns would differ for idiographic priming of promotion goals vs. prevention goals. Second, we examined whether activation in regions associated with promotion/prevention goal priming would be correlated with ratings of perceived success pursuing goals and/or BAS/BIS strength. Third, we examined whether the activation patterns observed following promotion and/or prevention goal priming would be modulated by the individual's current level of negative affect, specifically dysphoric and anxious symptoms.

MATERIALS AND METHODS

OVERVIEW

Based on an event-related fMRI paradigm developed by Diaz and McCarthy (2007), participants were exposed to a continuing series of rapidly presented masked visual stimuli including (1) a subset of each participant's ideal and ought goals assessed in a prior session, (2) ideal and ought goals of a different participant (as a yoked-control condition), and (3) non-word letter strings. Participants were told that the task was to respond as quickly as possible whenever they detected a string of letters or symbols presented in a colored font. The detection task was actually a means to keep participants attending to the continuous stimulus presentation. BOLD signal responses to ideal and ought goals were contrasted with responses to control words to test hypotheses about neural correlates of personal goal activation.

PARTICIPANTS

Participants were recruited through the introductory psychology research pool at Duke University and were part of a larger sample ($N = 75$) who had completed a study earlier in the semester. The initial study session, described as an investigation of personality, included several self-report measures relevant to the present research. Approximately two months after the personality study, potential subjects were contacted by phone and invited to participate in what was described as an investigation of visual attention. Thirty-three students (16 male) agreed to participate; one withdrew from the study prior to the MRI session for medical reasons, and a second student's imaging data were unusable due to technical problems; thus, data from 31 participants were included in analyses. All participants were between the ages of 18 and 22 and were right-handed as indicated by self-report. Participants reported normal neurological history and had normal or corrected-to-normal visual acuity. All participants gave informed consent in accordance with Duke University Institutional Review Board guidelines and received cash payment as compensation for their time.

PROCEDURE

Individual difference measures

During the personality study session, participants completed a measure of chronic regulatory focus, a measure of temperament-based approach and avoidance tendencies, and two measures of distress. The *Regulatory Focus Questionnaire* (RFQ; Higgins et al., 2001) is a 22-item Likert-style instrument designed to measure individual differences in orientation toward promotion and prevention goals. The RFQ contains four scales (two each for promotion and prevention): two *history* scales measuring the extent to which the individual's socialization history was characterized by an emphasis on promotion or prevention goals, and two *success* scales measuring the extent to which the individual believes she/he has been successful in attaining promotion or prevention goals. Because the psychometric properties of the history scales have yet to be determined, only the success scales were used in the present study. Sample items include: "I feel like I have made progress toward being successful in my life" (promotion success); and "Not being careful enough has gotten me into trouble at times" (prevention success—reverse-scored). Higgins et al. (2001) reported that the success scales had internal consistency reliability (coefficient alpha) of 0.75 or higher, and a 2-month test-retest reliability (Pearson correlation) of 0.79 or higher.

The *BIS/BAS Scale* (BIS/BAS; Carver and White, 1994) is a well-validated instrument containing four scales to measure individual differences in BAS and BIS sensitivity: BIS subscale (coefficient alpha = 0.74), BAS reward responsiveness subscale (coefficient alpha = 0.73), BAS drive subscale (coefficient alpha = 0.76), and BAS fun-seeking subscale (coefficient alpha = 0.66). We report results for a general BAS principal component score combining all three BAS subscales.

The *Beck Depression Inventory* (BDI; Beck et al., 1961) is a widely used 21-item measure of depressive and dysphoric symptoms. Respondents are asked to endorse items varying in severity from (0) to (3) in a number of life areas. For example, "I do not feel sad" scored (0); and "I am so sad or unhappy that I can't stand it" scored (3). The highest rating for each item was summed across all 21 items to create a continuous measure of depressive symptoms.

The *State Trait Anxiety Inventory* (STAI; Spielberger et al., 1970) is a self-report assessment which includes separate measures of state anxiety and the more general quality of trait anxiety. Participants completed only the trait version for the current investigation. The essential qualities evaluated by the 20-item STAI-T scale are feelings of apprehension, tension, nervousness, and worry (e.g., "I am jittery"). Items are rated on a 4-point scale ranging from 1 (*not at all*) to 4 (*very much so*) and summed to create a scale score. Given the high correlations for the BDI and STAI in this sample ($r = 0.75$), and our anticipation that we would not find distinct patterns of dysphoric vs. anxious affect in this unselected sample of healthy college students (Nitschke et al., 2001), the two scales were combined by summing individual scale z-scores into a single dysphoric/anxious index representing current level of negative affect.

Promotion and prevention goal generation and selection

During the personality study session, participants also completed a computerized version of the *Selves Questionnaire* (SQ; Higgins et al., 1986). The SQ is a semi-structured measure that was used to sample participants' own promotion and prevention goals. Participants listed traits or attributes for two different self-state representations: the attributes of the kind of person they ideally would like to be (ideal self-guides, which function as promotion goals) and the attributes of the kind of person they believe it is their obligation or responsibility to be (ought self-guides, which function as prevention goals). Personal goal stimuli for the priming task were obtained from each participant's responses to the computerized SQ. Following the procedures used by Strauman (1996), four promotion goals ("ideal self" responses) and four prevention goals ("ought self" responses) that were semantically unrelated were identified for each participant from among that participant's total set of SQ responses. All of the goals selected from participants' SQ responses were positively valenced. Then the promotion and prevention goals were pooled across subjects, and for each participant a set of eight yoked-control words was selected from that pool so that each yoked-control word was semantically unrelated to all of the participant's promotion and prevention goals. The yoked-control priming condition was included to rule out the alternative hypothesis that the semantic content of an ideal or ought word, rather than its status as a personal goal, might account for the activation observed following a priming trial.

Goal priming task

The fMRI task was adapted from Diaz and McCarthy (2007). Participants viewed a continuous stream of masked words and non-words while performing a detection task in which they were asked to make a response to a visible colored non-word stimulus (e.g., percent signs in red font). The detection task ensured participant engagement, while the non-word priming controlled for perceptual and orthographic processing. The masked word stimuli were of three types: a subset of the participant's promotion

(ideal) goals, a subset of the participant's prevention (ought) goals, and yoked-control words (ideal and ought goals of other participants which had no self-regulatory significance for the participant her/himself). Three runs, each 600 s in length, were conducted. The stimuli for each run consisted of words (ideal goals, ought goals, or a yoked-control word) and non-word letter strings that were masked and displayed in a fixed width font. All goal words (ideal, ought, and yoked-control) were positively valenced trait attributes. The non-words were random consonant strings, each 4–10 characters in length. Each letter string was padded with pound signs so that letters were centered and each stimulus was 12 characters in length, in order to ensure that the same amount of the visual field was occupied on any given priming trial.

Figure 1 presents an example sequence of priming trials within the overall experimental design as viewed by each participant. Participants viewed a constantly changing visual display in which a stimulus was presented every 1500 ms for a duration of 33 ms. The majority of the trials were masked non-words; a masked word from one of the three remaining stimulus conditions was presented approximately every 12 s. In each run, 16 ideal priming trials, 16 ought priming trials, and 16 yoked-control priming trials were included. All word and non-word letter strings were preceded and followed by pound sign strings for 155 ms, which served as pattern masks. In turn, the pound sign strings alternated with percent sign strings such that the subject was exposed to a continuously changing visual stream. The masked non-word trials ensured that brain regions responsive to physical features and orthography would be continuously active. Any brain region that was responsive to one of the three word priming conditions therefore reflected a higher level of cognitive processing. Participants were instructed to press a button when they detected a letter or symbol string presented in a color font. Those target events occurred infrequently (mean interval = 25 s) and were not in close temporal proximity to word priming trials. All stimuli were displayed on MRI-compatible LCD goggles.

Manipulation check

The participants were not informed that words or non-words would be presented. In order to evaluate subjects' perceptions of the masked stimuli, both subjective and objective assessments were conducted. Prior to imaging, participants were shown individual masked trials and were asked to report "anything and everything that you see." No participant reported seeing words, and most simply reported that they saw rapidly flashing strings of pound signs or percent signs. After the three runs were completed, subjects again were questioned about what they experienced and then completed a brief questionnaire in which both words that had been presented in each of the three word priming conditions and an equal number of words that had not been presented were listed. Participants were told that during the task they had been exposed periodically to words and were asked to indicate whether they believed each word had been presented or not.

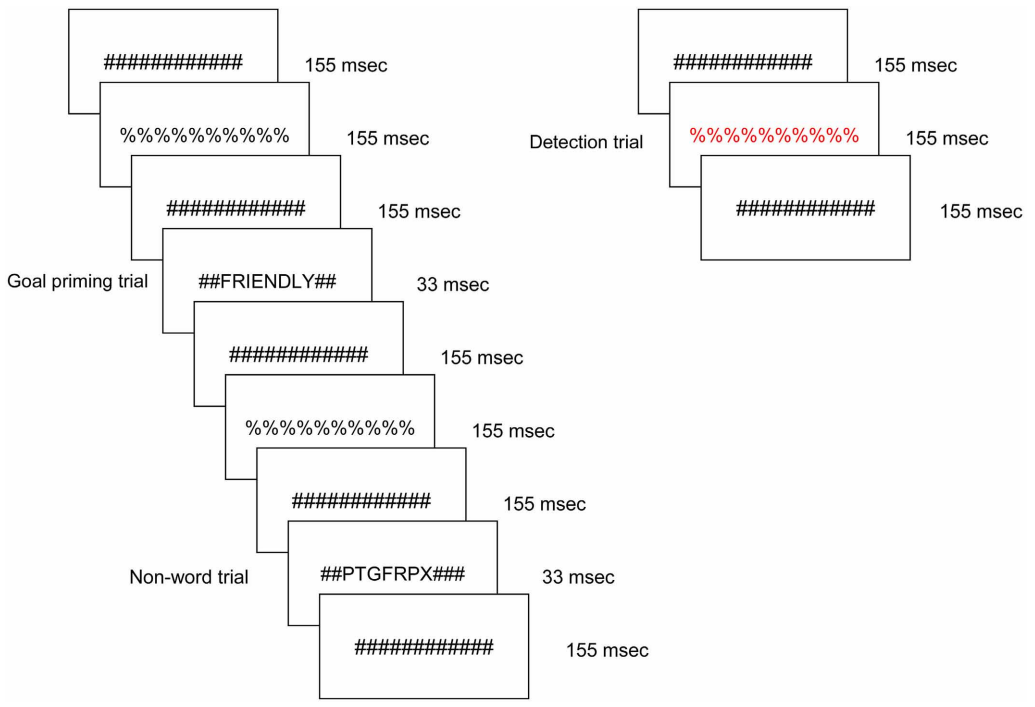

FIGURE 1 | Schematic of the experimental task, displaying a typical sequence of priming trials. The sequence for an individual trial consisted of alternating pound signs and percent signs, in between which a word or non-word was inserted. Promotion goal, prevention goal, and yoked-control priming stimuli were inserted throughout the run. Incidental to those stimuli visible colored symbol stimuli were displayed to which participants were instructed to respond with a button press as quickly as possible.

No participant performed significantly beyond chance levels in identifying presented vs. not-presented words.

fMRI parameters and data processing

Functional images sensitive to blood oxygenation level-dependent (BOLD) contrast were acquired using an inverse spiral pulse sequence (TR, 1.5 s; TE, 35 ms; FOV, 24 cm; image matrix, 64^2; 34 contiguous axial slices; voxel size $3.75 \times 3.75 \times 3.8$ mm) on the research-dedicated 3.0 Tesla GE Signa EXCITE HD system at Duke's Brain Imaging and Analysis Center (BIAC: www.biac.duke.edu). The 3.0 T has an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz, in addition to its volume birdcage head coil. Each of the three runs consisted of the acquisition of a time series of 242 brain volumes (TR = 1.5 s, run length = 363 s). Four initial RF excitations were performed (and discarded) to achieve steady state equilibrium. High-resolution structural images were acquired using a 3D fast SPGR pulse sequence (TR, 12.2 ms; TE, 5.3 ms; FOV, 24 cm; image matrix, 256^2; voxel size $0.9375 \times 0.9375 \times 1.9$ mm). A semi-automated high-order shimming program was used to ensure global field homogeneity.

Analyses of the BOLD signal were conducted using FEAT (FMRI Expert Analysis Tool; Smith et al., 2004; Woolrich et al., 2009), part of FSL (FMRIB's Software Library, Oxford University; www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing steps were applied: motion correction using MCFLIRT, slice-timing correction, removal of non-brain voxels using BET, spatial smoothing with a Gaussian kernel of FWHM 8 mm, and high-pass temporal filtering with a cutoff of 100 s. Registration to high resolution and standard images was carried out using FLIRT.

Statistical analyses

Analyses were conducted to identify regions reliably activated by ideal and ought goal priming respectively, and each proceeded in three stages. First, preprocessed functional data were analyzed using a general linear model with local autocorrelation correction (Woolrich et al., 2001). For each run, we set up separate regressors for promotion (ideal), prevention (ought), yoked-control, and non-word primes. A nuisance regressor modeled the target detection component of the task. All regressors consisted of unit impulses convolved with a canonical hemodynamic response function. The contrast of interests were comparing ideal vs. control and ought vs. control priming. We then combined data across runs for each subject using a fixed-effects model, and combined data across subjects using a mixed-effects model (Beckmann et al., 2003; Woolrich et al., 2004). We also used the mixed-effects models to obtain statistical tests for whether the two individual differences measures of interest (promotion/prevention success and BAS/BIS strength) and the dysphoric/anxious symptom index significantly modulated activation following goal priming. All z-statistic (Gaussianised t) images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster-significance threshold of $p < 0.05$ (Worsley, 2001). As Brodmann labels can be somewhat misleading (Zilles and Amunts, 2010), we report probabilistic anatomical labels for local maxima within statistically significant clusters derived from the Harvard-Oxford Cortical and Subcortical Structural Atlases along with approximate Brodmann areas.

RESULTS

BOLD ACTIVATION: PROMOTION > CONTROL PRIMING

We analyzed the fMRI data for promotion goal priming by contrasting responses to ideal priming with responses to yoked-control priming. As shown in **Table 1**; **Figure 2**, we found two brain regions that responded significantly more in response to ideal primes than to yoked-control primes, constituting main effects for promotion priming. The first cluster included occipital pole and lingual gyrus (both bilateral, approximately BA 18). The second cluster, predominantly left-sided, included subcallosal cortex (approximately BA 11/25), caudate, and thalamus.

We then repeated the analysis including covariates representing individual differences in self-regulation, BAS/BIS, and current level of dysphoric/anxious symptoms (see below) to determine whether responses to ideal priming were modulated by any of these variables. There were no significant findings for BAS or BIS strength, but we found two areas in which activation for ideal primes compared to yoked-control primes increased as individuals reported *higher* levels of success attaining *promotion* goals (**Table 2**; **Figure 3**). The first cluster included bilateral precuneus cortex (approximately BA 7) and bilateral posterior and anterior cingulate cortex (approximately BA 23 and 31). The second cluster included bilateral caudate and thalamus.

BOLD ACTIVATION: PREVENTION > CONTROL PRIMING

We analyzed the fMRI data for prevention goal priming by contrasting responses to ought priming with responses to yoked-control priming. As shown in **Table 2**; **Figure 2**, we found a cluster comprised of two subregions constituting main effects of prevention priming that responded significantly more to ought primes than to yoked-control primes: left and right precuneus cortex (approximately BA 7) and left and right posterior cingulate gyrus (approximately BA 31).

We then repeated the analysis including the covariates described above. Again there were no significant findings for BAS or BIS strength, but we found a cluster in which response to ought primes relative to yoked-control primes increased as individuals reported *higher* levels of success attaining *prevention* goals (**Table 2**; **Figure 4**). That cluster, which was entirely right-sided, included lateral occipital cortex (approximately BA 7), angular gyrus (approximately BA 40), precuneus cortex (approximately BA 31), and superior parietal lobule (also approximately BA 7). We also found a cluster in which response to ought primes relative to yoked-control primes increased as individuals reported *lower* levels of success attaining *promotion* goals. That cluster, which was entirely left-sided, included superior frontal gyrus (approximately BA 8) and middle frontal gyrus (approximately BA 6).

GOAL PRIMING BOLD RESPONSES MODULATION BY NEGATIVE AFFECT

In order to determine whether responses to ideal priming were modulated by current distress level, we also included the dysphoric/anxious index within the ideal vs. control contrast analysis as a covariate. As shown in **Table 3**, we found a cluster that

Table 1 | Regions showing significantly greater activation following promotion (ideal) priming trials compared to control priming trials.

Probabilistic anatomical label	*x*	*y*	*z*	*Z* statistic	Cluster volume (*p*)
MAIN EFFECT FOR CONTRAST					
Occipital pole (57%), supercalcarine cortex (6%)	4	−94	18	3.89	2451 mm^3 ($p < 0.01$)
Lingual gyrus (70%)	2	−80	−6	3.41	
Lingual gyrus (50%)	−8	−66	−8	3.29	
Lingual gyrus (17%)	−6	−70	−12	3.10	
Lingual gyrus (69%), intracalcarine cortex (16%)	2	−74	2	3.08	
Lingual gyrus (5%)	0	−68	−8	3.00	
Paracingulate gyrus (10%)	−14	44	−4	3.90	1677 mm^3 ($p < 0.05$)
Subcallosal cortex (14%)	−12	26	−4	3.78	
Subcallosal cortex (60%)	0	12	−4	3.70	
Thalamus (98%)	4	−18	8	3.68	
Subcallosal cortex (54%)	−10	26	−10	3.53	
Subcallosal cortex (45%)	−6	24	−4	3.48	
POSITIVELY CORRELATED WITH PROMOTION SUCCESS SCORE					
Precuneus cortex (41%), cuneal cortex (9%)	−8	−74	36	4.02	2878 mm^3 ($p < 0.01$)
Posterior cingulate gyrus (37%)	−10	−34	38	3.95	
Precuneus cortex (42%), posterior cingulate gyrus (42%)	−2	−54	18	3.35	
Posterior cingulate gyrus (72%), anterior cingulate gyrus (21%)	0	−18	40	3.16	
Precuneus cortex (51%), posterior cingulate gyrus (6%)	6	−56	16	3.14	
Superior parietal lobule (8%), angular gyrus (6%)	−30	−52	34	3.09	
Right caudate (93%)	10	16	6	3.71	2138 mm^3 ($p < 0.01$)
Left caudate (45%)	−24	−28	12	3.45	
Left thalamus (38%)	−2	−26	6	3.34	
Right thalamus (100%)	6	−16	10	3.27	
Left thalamus (88%)	−4	−24	2	3.10	

Coordinates of local maxima within each cluster of activation are in MNI space. Probabilistic labels reflect the likelihood that a coordinate belongs to a given region; for clarity, only labels whose likelihood exceeds 5% are shown.

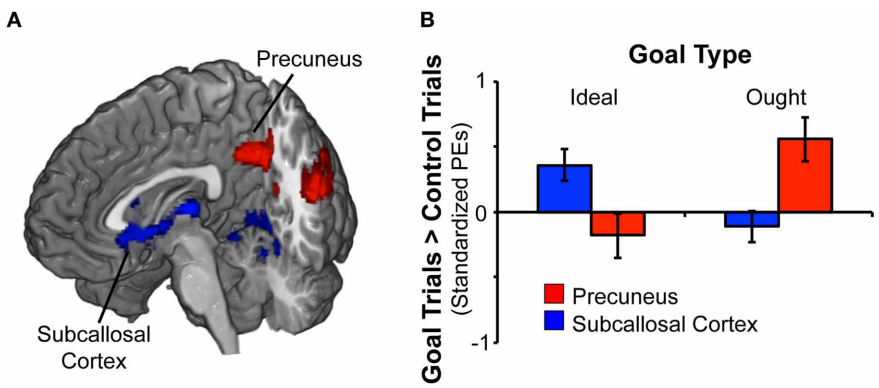

FIGURE 2 | Rapid masked promotion and prevention goal priming induced distinct patterns of activation. (A) To identify brain regions associated with activation of a promotion goal, we contrasted ideal goal priming vs. control priming. There was a significant effect for promotion goal priming in both subcallosal cortex and lingual gyrus (shown in blue). Likewise, to identify brain regions associated with activation of a prevention goal, we contrasted ought goal priming vs. control priming. There was a significant effect for prevention goal priming in precuneus and posterior cingulate gyrus (shown in red). **(B)** The chart displays mean standardized parameter estimates (PEs) at selected sites for the ideal vs. control contrast as well as the ought vs. control contrast. Within the subcallosal cortex ($x - 10$, $y26$, $z - 10$), activation was significant greater in response to ideal priming (vs. control priming). Within the precuneus ($x - 32$, $y14$, $z46$), activation was significantly greater in response to ought priming (vs. control priming).

showed a significantly greater response to ideal primes than to yoked-control primes as individuals reported higher levels of negative affect. This bilateral cluster included the frontal pole (approximately BA 8) and paracingulate gyrus (approximately BA 9 and 10). There were no regions identified in this analysis where activation was negatively correlated with the symptom index. We also had included the dysphoric/anxious index as a covariate within the ought vs. control contrast. However, we

Table 2 | Regions showing significantly greater activation following prevention (ought) priming trials compared to control priming trials.

Probabilistic anatomical label	*x*	*y*	*z*	*Z* statistic	Cluster volume (*p*)
MAIN EFFECT FOR CONTRAST					
Precuneus cortex (62%), posterior cingulate gyrus (13%)	–6	–54	38	3.77	1815 mm^3 ($p < 0.05$)
Precuneus cortex (90%)	4	–58	36	3.65	
Precuneus cortex (44%)	8	–60	36	3.64	
Posterior cingulate gyrus (24%)	20	–36	26	3.42	
Posterior cingulate gyrus (14%)	–24	–36	30	3.08	
POSITIVELY CORRELATED WITH PREVENTION SUCCESS SCORE					
Lateral occipital cortex (68%)	36	–70	54	3.72	1579 mm^3 ($p < 0.05$)
Angular gyrus (26%), superior parietal lobule (10%)	36	–54	38	3.59	
Lateral occipital cortex (12%)	36	–76	56	3.55	
Precuneus cortex (16%)	20	–44	40	3.34	
Superior parietal lobule (15%)	26	–48	42	3.27	
Precuneus cortex (17%)	16	–56	34	3.19	
NEGATIVELY CORRELATED WITH PROMOTION SUCCESS SCORE					
Middle frontal gyrus (17%)	–32	14	46	3.75	1614 mm^3 ($p < 0.05$)
Superior frontal gyrus (43%)	–20	36	48	3.45	
Superior frontal gyrus (48%)	–14	26	62	3.37	
Superior frontal gyrus (20%), Middle frontal gyrus (7%)	–26	18	64	3.33	
Superior frontal gyrus (20%)	–16	24	50	3.30	
Frontal pole (63%), superior frontal gyrus (8%)	–12	44	44	3.29	

Coordinates of local maxima within each cluster of activation are in MNI space. Probabilistic labels reflect the likelihood that a coordinate belongs to a given region; for clarity, only labels whose likelihood exceeds 5% are shown.

found no regions where there was significantly greater activation in response to ought vs. yoked-control priming as a function of negative affect.

DISCUSSION

Despite their centrality for behavior, motivation, mood, and identity, only recently have personal goals such as hopes, dreams, and obligations been examined from a cognitive neuroscience perspective. Personal goals are similar to more concrete, situation-specific goals in that they frequently entail either approach or avoidance, but they are distinct with regard to their abstractness, their motivational significance, and their centrality to the self. In this study, we explored the neural correlates of two classes of personal goals: promotion goals, which represent desired outcomes that an individual would attain by "making good things happen," and prevention goals, which also represent desired outcomes but which are attained by "keeping bad things from happening." Using rapid masked priming with idiographically selected ideal and ought goals (both of which are desired personal attributes), we observed distinct neural activation patterns for the two goal types. In addition, we found that activation following goal priming is modulated by individual differences in perceived success of promotion and prevention goal attainment (but not BAS/BIS strength) as well as by current level of negative affect. Promotion and prevention goals have distinct neural correlates, in keeping with the behavioral distinctions between the two hypothesized motivational systems.

The activation patterns from the ideal > control and ought > control contrasts were reliably distinguishable and were most closely associated with the cortical midline structures model of the self (Northoff and Bermpohl, 2004). Nonetheless, it may be more accurate to say that priming of ideal and ought goals activated regions known to be associated with a key psychological process that RFT would predict is relevant: namely, the representation of desired outcomes for the self. We did not observe activation of regions most frequently associated with responses to spatiotemporal cues for either reward (e.g., ventral striatum) or threat (e.g., amygdala). Thus, the data are more consistent with a model organized primarily around personal goals as aspects of identity than a model of approach/avoidance or positive/negative affectivity. Of course, this could reflect the paradigm itself, particularly since our intent was to examine goal priming *per se* rather than a more extended cycle of ongoing self-evaluation triggered by the presence of a discrete cue for reward or threat.

We observed that promotion goal priming led to activation in frontal and occipital regions as well as caudate and thalamus, whereas prevention goal priming was associated with activation in precuneus and posterior cingulate cortex. Furthermore, individual differences in self-perceived success vs. failure to attain promotion and prevention goals were correlated with activation in specific regions that were differentially responsive to promotion vs. prevention goal priming. For those individuals with higher scores on the promotion success scale, the ideal > control contrast was associated with activation in additional regions including bilateral precuneus and both anterior and posterior cingulate cortex (proximal to, but not identical to, the loci observed for the main effect of the ought > control contrast). For participants scoring higher on the prevention success scale, ought

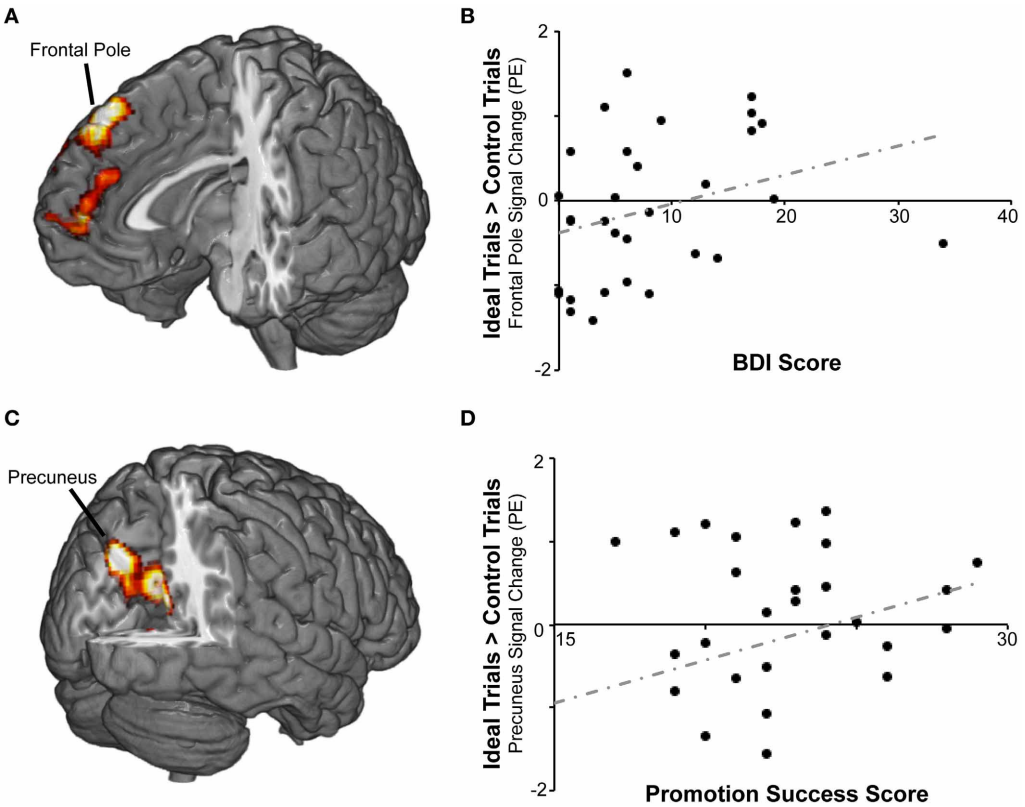

FIGURE 3 | BOLD responses to promotion goal priming were modulated by individual differences in self-reported success pursuing promotion goals and by scores on the symptom index. **(A)** For the ideal > control contrast, symptom index scores were positively correlated with activation in frontal pole and paracingulate gyrus. **(B)** The scatterplot displays mean standardized PEs at the right frontal pole ($x8$, $y40$, $z52$) as a function of symptom index scores. **(C)** For the ideal > control contrast, promotion success scores were positively correlated with activation in precuneus, posterior cingulate, and other regions. **(D)** The scatterplot displays mean standardized PEs at the left precuneus ($x-8$, $y-74$, $z36$) as a function of promotion success scores.

goal priming was associated with activation in right occipital and parietal regions. Additionally, a correlation was observed between lower scores on the promotion success scale and left prefrontal activation following priming with ought goals.

The differences in activation observed for the two classes of personal goals were striking given that both sets of stimuli were self-generated by participants, both were self-descriptive, both were positively valenced, and both represented the kind of person the individual wanted to become. The only difference between the two stimulus sets was the kind of personal goal they represented—in one case (ideal), the individual's hopes, aspirations, and desired accomplishments, and in the other (ought), the individual's sense of duties, obligations, and responsibilities. In fact the same personal goal—for instance, to be successful—could be a promotion goal for one person and a prevention goal for another. RFT would predict that in such an instance, although the goal itself is identical, the motivational impetus, cognitive strategies, behavioral means, and affective responses to goal pursuit would differ radically. For the former individual, being successful would be attained by a strategic emphasis on accomplishment or being the best one could be, whereas for the latter, being successful would be attained by meeting one's responsibilities and obligations. Our findings provide evidence that the distinction between promotion and prevention goals is evident in terms of neural correlates from the moment such a goal is activated by a contextual cue.

The activation patterns associated with each type of personal goal involved regions within the cortical midline structures associated with self-referential processing as well as regions linked to other aspects of self-regulation (Amodio and Frith, 2006; Beer et al., 2009; Heatherton, 2011). For example, promotion goal priming-activated areas within orbital and medial PFC, both of which have been reliably demonstrated to be linked to a range of self-referential mental processes, including representation and monitoring of self-referential knowledge (Northoff and Bermpohl, 2004). Promotion priming also was associated with activation in the caudate and thalamus, which have been identified as components of both intuition and implicit learning as well as broader networks underlying reward sensitivity, preparatory motor functions, social judgment, and goal pursuit behavior (e.g., Lieberman, 2000; Rameson et al., 2010). The greater caudate activation associated with ideal priming among high-success individuals also may reflect the role of the caudate in reward learning and appetitive goal pursuit. Thus, ideals

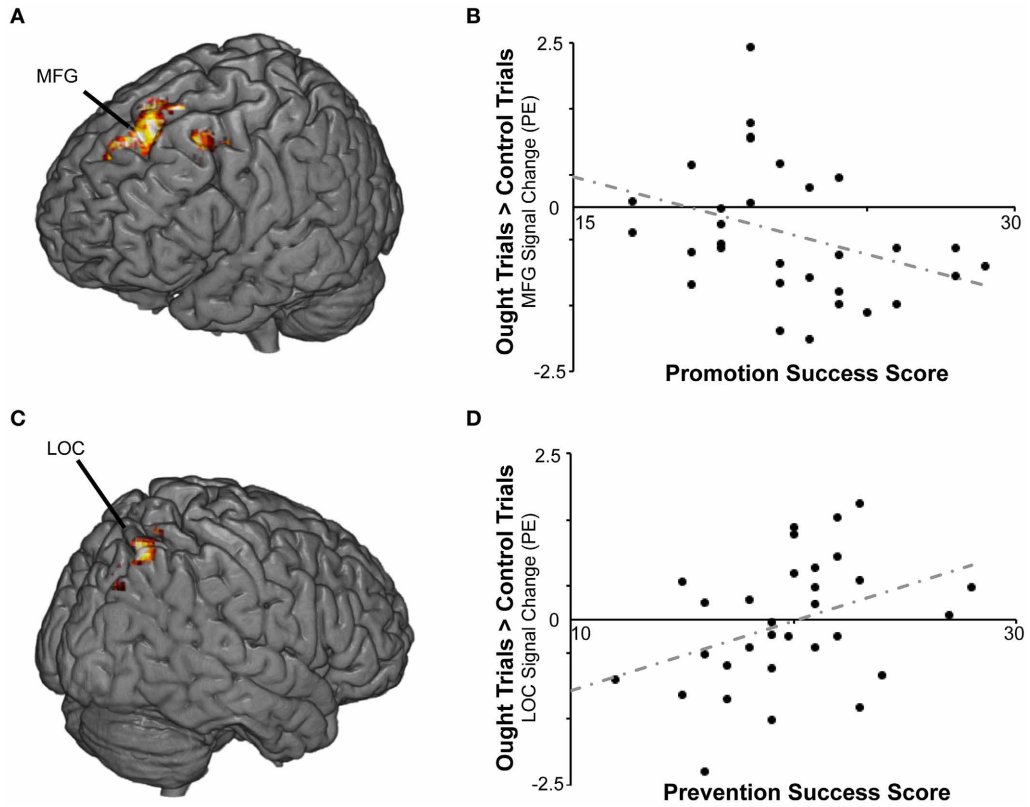

FIGURE 4 | BOLD responses to prevention goal priming were modulated by individual differences in self-reported success pursuing both types of personal goals. (A) For the ought > control contrast, promotion success scores were negatively correlated with activation in middle (MFG) and superior frontal gyrus. **(B)** The scatterplot displays mean standardized PEs at the left middle frontal gyrus ($x - 32$, $y14$, $z46$) as a function of promotion success scores. **(C)** For the ought > control contrast, prevention success scores were positively correlated with activation in lateral occipital cortex (LOC) and other regions. **(D)** The scatterplot displays mean standardized PEs at the right LOC ($x36$, $y - 70$, $z54$) as a function of prevention success scores.

Table 3 | Regions showing significantly activation positively correlated with symptom index scores following promotion (ideal) priming trials compared to control priming trials.

Probabilistic anatomical label	*x*	*y*	*z*	*Z* statistic	Cluster volume (*p*)
Frontal pole (36%), superior frontal gyrus (32%)	8	40	52	4.59	2295 mm^3 ($p < 0.01$)
Paracingulate gyrus (57%), frontal pole (24%)	8	54	4	3.95	
Paracingulate gyrus (40%), anterior cingulate gyrus (13%)	–12	44	16	3.84	
Frontal pole (24%)	–12	56	42	3.74	
Frontal pole (21%)	26	56	36	3.71	
Frontal pole (14%)	–20	58	36	3.31	

Coordinates of local maxima within each cluster of activation are in MNI space. Probabilistic labels reflect the likelihood that a coordinate belongs to a given region; for clarity, only labels whose likelihood exceeds 5% are shown.

may engage regions that subserve representation and pursuit of abstract positive outcomes via direct, task-focused activity. In contrast, prevention goal priming was associated with activation in precuneus and posterior cingulate gyrus, which are implicated in the default mode network (e.g., Buckner et al., 2008) but also in phenomena such as self-reflection, self-awareness, and social adaptation (Pearson et al., 2011). As such, oughts may engage regions that support third-person perspective and moral reasoning.

Do the observed findings correspond to our knowledge of how individuals represent and pursue their goals? Given the likelihood that human psychological capabilities evolved in response to an increasingly complex social environment (Leary, 2004), activities such as the pursuit of personal goals would of necessity incorporate cognitive processes involving representations of self and significant others (Derryberry and Reed, 1996). In order for humans to survive and thrive, they must be not only capable of effective responses to survival-relevant stimuli. They

also must be capable of representing and pursuing higher-order, cross-situational, socially embedded goals, and the representational, monitoring, and evaluative functions required must be integrated into coherent brain/behavior systems (Mischel, 2004). For the higher-order personal goals that people pursue, there is no necessarily spatiotemporal "moving toward or away from"; rather, the strategies people use involve "bringing about" or "making happen" (Carver and Scheier, 1998). This phenomenological distinction raises the possibility that brain/behavior systems for *strategic* approach and avoidance, such as are postulated in RFT, would be functionally discriminable from those for spatiotemporal approach and avoidance. For example, personal goals such as being successful, or intelligent, or trustworthy require a top-down coordination that brings relevant concrete goal representations into working memory across a range of situations (Carver and Scheier, 1990). The present data could be interpreted as reflecting how such top-down coordination is manifested differentially within the brain when promotion or prevention self-regulation is engaged.

Our findings were somewhat different from those reported by Eddington et al. (2007, 2009), especially in the case of promotion priming, where left orbital prefrontal activation was found to be discriminantly associated with promotion goal cues which had been presented in the context of a self-reference judgment task. We see the distinctions between the two sets of findings as primarily reflecting differences in the experimental paradigm used. Eddington et al. (2007, 2009) used a task that had been designed to identify neural signatures of explicit self-referential processing; they simply included a set of idiographically selected ideal and ought attributes within the stimuli used for the judgment task. Their findings, in essence, revealed a promotion-goal-specific activation pattern which was embedded within an instructional set emphasizing self-descriptiveness and requiring a specific judgment. In contrast, the rapid masked priming paradigm in the present study was selected so that goal-related activation patterns could be observed without the potentially complicating factor of an explicit self-evaluation in reference to the goal being primed. The distinction between the activation patterns found by Eddington and colleagues and those observed in the present study warrants additional study.

Based on these findings, does RFT help to refine our knowledge of the brain regions involved in the representation of personal goals? We suggest that in terms of the postulated distinctions between promotion and prevention, the answer is a qualified yes. The psychological dynamics of the promotion system can be viewed in signal detection terms (Tanner and Swets, 1954; Trope and Liberman, 1996), particularly as involving eagerness, which increases with greater proximity (in this case, conceptually or symbolically rather than spatiotemporally) to the target (Higgins, 1998). As such, we postulate that self-reflection may be less central to promotion-based goal pursuit, since promotion goals "loom larger" as the individual gets closer to attaining them (Higgins, 1998), and indeed we did not observe main effects of promotion-triggered activation in posterior midline structures associated with self-reflective thought.

Prevention system dynamics also can be viewed in signal detection terms, with the system organized to avoid errors of commission (albeit still in the service of ultimately attaining a positive end-state). As such, the prevention system relies upon vigilance as the dominant motivational state and self-evaluation as a recursive cognitive process. Consistent with this characterization, prevention goal priming was associated with activation in areas engaged by tasks that require self-reflection and even self-awareness, as well as by decisions involving judgments of morality and principle (e.g., Greene and Haidt, 2002). Such processes are of primary relevance to the pursuit of personal goals that are construed in terms of obligation, responsibility, or a sense of "should" (Higgins, 1997).

Of course, the findings do not represent a self-contained set of brain/behavior systems associated with personal goal pursuit. Self-regulation is too complex and multifaceted to be modeled adequately by a single experimental task. It would have been unlikely to find activation in areas associated with psychological processes that are substantially "downstream" from goal activation, such as consummatory behavior, goal disengagement, or affect regulation. Nonetheless, the activation patterns immediately following promotion and prevention goal priming were discriminable, and the rapid masked priming technique provided sufficient sensitivity to detect those patterns—which appeared to be broadly consistent with RFT's conceptualizations for each system.

We also observed that individual differences in self-reported success pursuing a particular kind of goal predicted activation following priming with idiographic exemplars of such goals, whereas individual differences in temperament-based approach and avoidance tendencies (operationalized using the Carver and White BIS/BAS Scales) did not. The behavioral activation and inhibition systems are hypothesized to represent inborn, presumably genetically determined variation in sensitivity to cues for spatiotemporal approach/avoidance behavior and/or the intensity and duration of behavioral responses to such cues. In contrast, individual differences in the strength of the promotion and prevention systems have been linked to socialization (Manian et al., 2006), and in particular to variability in the messages parents convey to their children about the relative importance of making good things happen vs. keeping bad things from happening. Strauman and Wilson (2010) postulated that the two sets of systems have different phylogenetic and developmental origins as well as distinguishable functions. Whereas BAS and BIS appear to operate in response to immediate, concrete cues for reward and danger respectively, promotion and prevention operate as "world views" or cognitive styles and provide a functional link between pursuit of higher-order personal goals and the social world. Eddington et al. (2007) reported that the Carver and White scales did not predict neural responses to promotion or prevention goal priming, and the present data are in concordance with their findings. Together, the two studies provide evidence that the neurobiological bases of BAS/BIS and promotion/prevention are likely to be distinct—and offer the possibility that the two sets of systems interact in complex ways to influence goal-directed behavior in any specific situation.

Both RFT and its precursor, self-discrepancy theory (Higgins, 1987), predict that perceived lack of progress toward a motivationally significant personal goal would be associated with

negative affect. Both theories also postulate that chronic distress, as well as emotional disorders such as depression and anxiety, can interfere with effective goal pursuit (Strauman, 2002). To explore the impact of negative affect on personal goal activation, we examined whether individual variability in negative affect (assessed by creating a dysphoric/anxious index from the BDI and STAI) would predict neural responses to promotion or prevention goal priming. For individuals reporting greater levels of distress, promotion priming was associated with additional activation in the bilateral frontal pole and paracingulate gyrus. Prevention goal priming did not reveal any regions where activation was modulated by self-reported distress.

What might this pattern of results signify about the influence of chronic distress on self-regulation? Level of negative affect was associated with greater recruitment of bilateral frontal regions in response to cues for "making good things happen," suggesting that higher levels of distress could introduce a greater degree of recruitment of prefrontal regions in the goal pursuit process. More speculatively, such increased frontal activity could signify activation of negative cognitive schemas, as hypothesized in cognitive models of depression (e.g., Beck et al., 1979), which would be likely to interfere with effective strategic pursuit of promotion goals. The nature of the promotion system dictates that the individual's optimal strategy is to ignore errors or unsuccessful trials and continue with goal pursuit efforts. Too much engagement of self-evaluation would complicate goal pursuit efforts by diverting processing resources away from the eager motivational state that characterizes successful promotion goal pursuit. The study was not intended to explore clinically relevant emotional states and symptom patterns, and it may be premature to extrapolate these findings to depression and related internalizing disorders. Still, the modulation of neural response to ideal priming by negative affect was robust enough to emerge from an analysis that included other statistically significant covariates.

In summary, the rapid masked stimulus presentation technique that we used to prime participants' promotion and prevention goals led to interpretable and reliably distinguishable patterns of neural activation. The findings are broadly consistent with established findings from the social neuroscience literature, and the discriminability of the activation patterns associated with the two types of personal goals provides support for the critical distinction in RFT between promotion and prevention as modes of self-regulation. To the extent that those modes become automatic and systematized over time, then perhaps it will be of value to speak of promotion and prevention "systems" assuming that present data are replicated using other goal-relevant tasks. Furthermore, to the extent that individual differences relevant to self-regulation of personal goal pursuit might be expected to influence the strength and accessibility of the two systems, our findings also were consistent with the view that the neural correlates of the systems may differ as a function of individuals' beliefs about their success vs. failure in attaining such goals.

We close with several comments about the limitations of the present research and its potential implications for future studies. As noted previously, the priming paradigm may be a reasonable operationalization of one phase of a self-regulatory cycle—automatic activation of goal pursuit via exposure to a goal-relevant cue—but it would not be likely to identify neural responses to other phases of that cycle, such as regulation of affect in response to goal pursuit feedback or other conscious processes. Likewise, we did not systematically choose the participants on the basis of potentially relevant individual differences, and the priming task did not explicitly target such individual variability. Our analyses of those individual differences (in regulatory focus, in BAS/BIS strength, and in chronic distress) are correlational and represent first steps in an ongoing process of investigation. It should be emphasized that the promotion and prevention systems are constructs, in the same way as more familiar brain/behavior systems. We are using those constructs to guide prediction and interpretation but not making claims about neural structure or neuroanatomical connectivity. Nonetheless, we offer these findings as, to our knowledge, the first neuroimaging evidence for the construct validity of the promotion and prevention systems and the critical roles that individual differences and chronic affective states play in the day-to-day function of those systems.

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Emotion and deliberative reasoning in moral judgment

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According to an influential dual-process model, a moral judgment is the outcome of a rapid, affect-laden process and a slower, deliberative process. If these outputs conflict, decision time is increased in order to resolve the conflict. Violations of deontological principles proscribing the use of personal force to inflict intentional harm are presumed to elicit negative affect which biases judgments early in the decision-making process. This model was tested in three experiments. Moral dilemmas were classified using (a) decision time and consensus as measures of system conflict and (b) the aforementioned deontological criteria. In Experiment 1, decision time was either unlimited or reduced. The dilemmas asked whether it was appropriate to take a morally questionable action to produce a "greater good" outcome. Limiting decision time reduced the proportion of utilitarian ("yes") decisions, but contrary to the model's predictions, (a) vignettes that involved more deontological violations logged faster decision times, and (b) violation of deontological principles was not predictive of decisional conflict profiles. Experiment 2 ruled out the possibility that time pressure simply makes people more like to say "no." Participants made a first decision under time constraints and a second decision under no time constraints. One group was asked whether it was appropriate to take the morally questionable action while a second group was asked whether it was appropriate to refuse to take the action. The results replicated that of Experiment 1 regardless of whether "yes" or "no" constituted a utilitarian decision. In Experiment 3, participants rated the pleasantness of positive visual stimuli prior to making a decision. Contrary to the model's predictions, the number of deontological decisions increased in the positive affect rating group compared to a group that engaged in a cognitive task or a control group that engaged in neither task. These results are consistent with the view that early moral judgments are influenced by affect. But they are inconsistent with the view that (a) violation of deontological principles are predictive of differences in early, affect-based judgment or that (b) engaging in tasks that are inconsistent with the negative emotional responses elicited by such violations diminishes their impact.

Keywords: moral decision-making, moral judgment, dual process, emotion

INTRODUCTION

A belief dating back to ancient times is that emotions cloud good judgment. This adage implies a common sense belief that we have two competing systems for making decisions, one based on emotion and one based on reason. Recently, Greene (2007) proposed a dual-process model which explains moral judgment as the outcome of neurologically separable affective and deliberative processes. According to this model, strong affective responses are the domain of the ventromedial prefrontal cortex (VMPC). Deliberative decision-making is subserved by the dorsolateral prefrontal cortex. When there is no prepotent affective response, deliberative reasoning prevails. When a conflict between the outputs of these areas occurs, it is detected by the anterior cingulate cortex, which signals the need for cognitive control. This need is answered by the anterior dorsolateral prefrontal cortex; if the latter prevails, the output of the deliberative system is selected. If not, the prepotent affective response constitutes the judgment.

This dual-process explanation of moral judgment is consistent with several decades of cognitive science research on decision-making in other domains. Numerous researchers have partitioned decisional processes into two competing systems, a "System 1" that is quick and reflexive and a "System 2" that is slow and deliberative (e.g., Gilbert, 1989; Sloman, 1996; Chaiken and Trope, 1999; Hammond et al., 1999; Evans, 2003; Kahneman, 2003). According to these researchers, however, System 1 is not solely the domain of emotion. Instead, intuition, heuristics, and experience-based biases are also considered vital parts of the rapid, reflexive System 1.

The singling out of emotion as the primary factor in early moral judgment is based on two lines of evidence. The first line depends on a theoretical commitment regarding the nature of utilitarian and deontological decision-making. Utilitarian reasoning judges the moral acceptability of an action based on its consequences, seeking to maximize the "greatest good for the greatest

number." In contrast, consequences are irrelevant to deontological concerns; instead the moral permissibility of an action depends on its adherence to purportedly universal moral rules (categorical imperatives). Greene et al. (2009) identified two particular deontological principles which, when violated, elicit a high proportion of deontological judgments. The first is whether the agent harms the victim in a manner that involves *personal force* (use of an agent's muscles), and the second is whether the harmful outcome is intended or an unavoidable side effect of the action taken. An example of personal force would be pushing an individual onto the path of an oncoming trolley. Pushing a switch instead which diverts a trolley onto the individual's path is impersonal. If diverting the trolley was done in order to deliberately kill the person, it is intentional harm. If instead, it was done to prevent the trolley from killing five people in its path, it is a forsee but unavoidable and unintended side effect. According to Greene et al. (2009), these two factors, when combined, yield the highest level of moral condemnation. As the authors put it ". . .personal force was found to interact with intention such that the personal force factor only affects moral judgments of intended harms, while the intention factor is enhanced in cases involving personal force."

The second line of evidence consists of studies reporting activation of VMPC that is specific to moral judgments as compared to semantic judgments or other non-moral judgments (Greene et al., 2001; Moll et al., 2001; Heekeren et al., 2003). Importantly, when reasoning about moral dilemmas that pit deontological principles against utilitarian outcomes, individuals with damage to ventromedial frontal cortex (and hence impaired socio-emotional processing systems) are more likely to make utilitarian judgments than intact individuals or patients with damage to other areas of the brain. This outcome has been interpreted to mean that moral judgment becomes more deliberation-driven when affect-elicitation is impaired (Koenigs et al., 2007). Consistent with this interpretation, Greene et al. (2008) found that requiring participants to perform a concurrent digit-search task while making moral judgments selectively increased decision time for utilitarian judgments. They interpreted this to mean that it takes time and cognitive resources to be a utilitarian.

One implication of this dual-process analysis is that early moral judgments should be more affect-based while later ones should be more reasoning-based, a crucial prediction tested by Suter and Hertwig (2011) using dilemmas that pitted the welfare of a few against the welfare of many. Participants were required to make such moral decisions under unlimited-time or reduced-time conditions, and three types of deontological violations were employed: (a) high-conflict dilemmas, in which personal force was used to intentionally inflict harm, (b) low-conflict dilemmas, in which personal force was used to inflict harm that was an unintended side effect of the action taken, and (c) impersonal dilemmas, in which a harm was a side effect and no personal force was used. They found that restricting decision time reduced the number of utilitarian decisions for high-conflict vignettes, but not for low conflict or impersonal vignettes. These results are consistent with Greene's dual-process model because truncating decision time deprived participants of the additional time needed to engage in deliberative (utilitarian) reasoning and/or to resolve decisional conflicts.

While consistent with Greene's dual-process model, several factors hamper interpretation of Suter and Herwig's (2011) results. First, the materials used were chosen because they differed in deontological criteria yet all yielded low inter-subject consensus in pilot work – each vignette elicited an equivalent number of "yes" and "no" judgments. These selection criteria ignored the most important factor in the fast vs. slow dual-process framework: decision time. If a vignette elicits a high degree of conflict between the two systems, then it should yield long decision times because it takes time to resolve conflicting system outputs. Because people differ in terms of how they choose to resolve the conflict, low inter-subject consensus results. Yet consensus and decision times reported by Greene et al., 2008, Supplementary Materials) did not necessarily show this pattern. For example, "Crying Baby," which involves both personal force and intentional harm, yielded low inter-subject consensus (60% utilitarian judgments) and long mean decision time (5.7 s). But "Sophie's Choice," a dilemma that involves neither personal force nor intentional harm, also yielded low inter-subject consensus (62%) and long mean decision time (6.1 s). In contrast, "Donation," a dilemma that also involves neither violation, yielded nearly identical low-inter-subject consensus (63%) but rapid mean decision time (4.8 s). For this reason, decision consensus may constitute an insufficient or misleading measure of hypothesized inter-system conflict.

Second, reading time was not controlled by Suter and Hertwig (2011) in a manner that ruled out the possibility that participants were devoting reading time to decision time. Participants were given a maximum of 35 s to read each vignette before the screen advanced to the decision question, yet no mention is made of vignette word count. For this reason, it is not clear whether decision time was held constant across vignettes.

These confounds were addressed in Experiment 1. Reading time was controlled in a scrolling format, and two methods were used to categorize vignettes as high or low decisional conflict. The first method categorized vignettes based on the *a priori* deontological factors proposed by Greene et al. (2009) and used by Suter and Hertwig (2011). The second was entirely empirically based. The dual-process model predicts that conflict between the two systems lengthens decision time because the conflict must be resolved. It also decreases inter-subject consensus because some people may resolve in favor of System 1 outputs while others may resolve in favor of System 2. Accordingly, *high decisional conflict vignettes* were defined as dilemmas that elicit long decision times and low inter-subject consensus. Conversely, *low decisional conflict vignettes* were defined as those that elicit fast decision times and high inter-subject decision consensus. *Moderate decisional conflict vignettes* were defined as those that elicit moderate decision times and moderate consensus. Decision time was manipulated, and the impact of restricting decision time on moral judgment was assessed. The model predicts that truncating decision time should preclude adequate deliberative processing, thereby shifting the balance of the judgments in favor of emotional outcomes. Because violations of deontological principles are predicted to elicit rapid negative affective responses, this means that early judgments should be more deontologically based than later ones. Moreover, vignettes that show long decision times and low inter-subject consensus

should be exactly those that pit deontological outcomes against utilitarian ones.

A third confounding factor was the conflation of content with decisional processes, that is, the identification of deontology with System 1 and utilitarianism with System 2. Because no direct measure of the two systems was employed, this confound is a particularly serious one. In the materials employed by Suter and Hertwig (2011), all "yes" responses constituted utilitarian judgments and all "no" response constituted deontological ones. Matthews (2001) has argued that stressors, such as restricting decision time, may change the total quantity of decision-making resources available due to changes in (a) biological or neural functioning, (b) processing load (i.e., multiple tasks may overload the processing of information), or (c) strategic reallocation of processing resources (i.e., emotion-focused coping). An alternative interpretation of Suter and Herwig's (2011) results, therefore, is that reducing decision time simply made people more likely to say "no" in order to cope with emotional or processing overload, not because they were resolving in favor of deontological concerns. To test this alternative explanation, decision queries in Experiment 2 were worded such that a "yes" or "no" response could be either a deontological decision or a utilitarian decision. If Greene's dual-process model is correct, then the same results should obtain regardless of whether "yes" or "no" constitutes a utilitarian response.

Finally, the impact of emotion was specifically investigated in Experiment 3. A crucial aspect of the dual-process model proposed by Greene and colleagues is the role of emotion in moral judgment, not simply fast decisional processes. Emotion has been found to impact moral judgments when people are given ample time to make decisions, and the nature of the emotion elicited matters. The elicitation of disgust has been found to create harsher attitudes toward immoral behavior in general (Schnall et al., 2008), elicitation of joviality or mirth makes deontological violations seem more permissible (Valdesolo and DeSteno, 2006; Strohminger et al., 2011), and inducing feelings of "elevation" or benevolence makes such violations appear less permissible (Strohminger et al., 2011). Particularly relevant is the impact of stress on moral judgment. Youssef et al. (2012) used the Trier Social Stress Test (TSST) to induce stress (assessed by salivary cortisol levels). They found that activation of the stress response yielded a reduction in utilitarian responses that was specific to personal moral dilemmas that described deontological violations. The reduction in utilitarian judgments under conditions of time constraints (Suter and Hertwig, 2011) or concurrent task demands (Greene et al., 2008) may be simply due to the stress involved in conflict resolution.

To test this alternative explanation, participants in Experiment 3 read moral dilemmas and rated the pleasantness of esthetically pleasing photographs prior to rendering a decision. Reflecting on pleasant emotional stimuli is inconsistent with the hypothesized negative affect elicited by deontological violations. Performance of this group was compared to that of a control group who simply made decisions, and to a second control group who engaged in a cognitive distraction task based on the same stimuli. If deontological decisions are indeed strongly determined by rapid, negative affective responses, then inducing a pleasant emotional state during decision-making should decrease the frequency of deontological judgments in favor of utilitarian ones.

EXPERIMENT 1

Greene's dual-process model predicts that (a) early decisions should be emotion based while later decisions should be reason-based, and that (b) vignettes that describe deontological violations should elicit more emotion-based judgments. The purpose of Experiment 1 was to test these predictions. As in Suter and Hertwig (2011), the utilitarian structure of all dilemmas was the same: choose to sacrifice few to save many. They differed, however, in terms of decisional conflict profiles and in terms of deontological violations. Decision time was truncated for some subjects while others were given unlimited time to make their decisions. It was predicted that (a) vignettes whose decisional profiles are most strongly consistent with a conflict between the fast and slow systems should also be those that are most strongly impacted by a reduction in decision time, and (b) these same vignettes should also be those that describe deontological violations, thereby yielding strong emotional responses that are contrary to reasoned utilitarian aggregate benefit analyses.

METHODS AND MATERIALS

PARTICIPANTS

Participants were 189 undergraduate students at the University of Illinois at Urbana-Champaign who participated in order to receive class credit. Sixty-four percent were female, and all ranged in age from 18 to 24. The median age for both females and males was 19.

MATERIALS AND PROCEDURE

A total of 20 moral vignettes were used in the initial pool. Eighteen were selected from the battery of vignettes used in Greene et al., 2008, see the Supplementary Materials from that paper for decision times and consensus). These were "Crying Baby," "Footbridge," "Hard Times," "Lawrence of Arabia," "Sacrifice," "Safari," "Smother for Dollars," "Sophie's Choice," Standard Fumes," "Standard Trolley," "Submarine," "Transplant," "Vaccine Policy," "Vaccine Test," "Vitamins," "Modified LifeBoat," "Modified Bomb," and "Donation." In all of these moral dilemmas, an action that benefits "the greater good" also has negative consequences for a minority of individuals. The percent utilitarian judgments for these vignettes ranged from 3 to 91%, and decision times ranged from 3 s to a little over 7 s. Two additional vignettes were used which were designed to elicit strong affect. "Cancer Toddler" was based on a dilemma used by Hauser et al. (2006). It describes a situation where five railway workers will die unless the participant redirects a runaway train toward their own terminally ill child. "Fumes with Friends" was a modification of the "Standard Fumes" vignette from Greene et al. (2008). Here, participants must choose between allowing toxic fumes to kill three hospital patients, or redirecting the fumes to another room where they will kill their best friend. This brought the total number of vignettes used to 20.

A custom E-Prime program was employed for the presentation of instructions and vignettes, and for the collection of participants' responses. A session began with instructions in which participants were told they would be reading a series of stories and making decisions about them. They were then given a practice vignette. The order of the 20 experimental vignettes was randomized.

At the beginning of each trial, the computer displayed a white screen with gray letterboxes at the top and bottom of the screen.

A black plus sign was located in the center of the screen to serve as a mask and to separate each trial. A counter indicating the trial number was located in the top letterbox, and instructions appeared in the bottom letterbox. Participants were instructed simply to press a key when they were ready to begin reading the first vignette.

Vignettes were presented as vertically scrolling text on the computer screen. The gray letterboxing remained at the top and bottom of the screen, creating a window in which the vignette text appeared. Only 2.5 lines of text were visible at a time. This controlled for reading speed by preventing participants from reading too far ahead in the vignette. After the entire vignette had been presented, participants were prompted to respond by the appearance of text on screen asking, "Is it appropriate to [take the action] in order to [produce the outcome]?" Participants indicated "yes" by pressing the 1 key on the number pad, and "no" by pressing the 3 key on the number pad.

Participants were randomly assigned to one of two conditions. In the *unlimited-time* condition, participants were allowed as much time as they wanted to respond. In the *restricted-time* condition, decision time was abbreviated to 200 ms for each word in the decision question, which resulted in an average of 4,400 ms. If no response was given with this time period, the gray letterboxes turned red, the words "Respond Immediately" appeared within both letterboxes, and two additional seconds were given for participants to respond. After these additional 2 s expired, or a response was recorded, a brief mask (a plus sign in the center of the screen) marked the end of the trial. Decision times were recorded at millisecond accuracy.

RESULTS AND DISCUSSION

Table 1 presents percent utilitarian decisions (decision consensus) and mean decision times for each vignette reported by Greene et al., 2008, Supplementary Materials) and obtained under conditions of unlimited decision time in Experiment 1, along with the vignettes' deontological features. In the present study, percent utilitarian decisions ranged from 3 to 85%. There was nearly identical agreement between our subjects and those of Greene et al. (2008) on vignette decisions, $r = 0.95$, $t(16) = 11.55$, $p < 0.001$. Mean decision times ranged from 2,830 to 7,605 ms. The correlation between mean decision times in both studies for these vignettes was lower but still statistically significant, $r = 0.47$, $t(16) = 2.15$, $p < 0.05$.

VIGNETTE CLASSIFICATIONS

Given the moderate decision time correlation, we relied on decision times and consensus from our own subject population to classify vignettes into decisional conflict categories.

The vignettes were divided into five categories based on decisional conflict profiles as shown in **Table 1**. Starting from the top of **Table 1**, these were the category divisions. *Low Decisional Conflict-No vignettes* were those that elicited high "No" decision consensus and fast decision times; this category included "Hard Times," "Transplant," "Smother for Dollars," and "Footbridge." *Moderate Conflict-No vignettes* were those that elicited moderate "no" decisional consensus and moderately fast decision times; these were "Sacrifice," "Fumes with Friends," and "Vitamins." *High Decisional Conflict vignettes* were defined as those that elicited low decision consensus and long decision times; this category included

Table 1 | Vignettes used in Experiments 1 and 2 ranked by % utilitarian responses.

Vignette	Personal	Intention	% Util[a]	Dec. time (ms)[a]	% Util[b]	Dec. time (ms)[b]
Hard times	No	Intend	3	4,089	9	5,262
Transplant	Yes	Intend	5	2,830	12	3,047
Smother for dollars	Yes	Intend	8	3,766	7	4,242
Footbridge	Yes	Intend	15	3,107	21	4,288
Modified safari	No	Intend	28	6,455	22	5,442
Sacrifice	No	Intend	28	6,588	51	6,139
Fumes w/friends	No	Side effect	36	7,706	n/a	n/a
Vitamins	Yes	Side effect	38	5,602	35	6,352
Crying baby	Yes	Intend	40	6,366	60	5,651
Sophie's choice	No	Intend	41	7,139	62	6,133
Cancer toddler	No	Side effect	52	7,366	n/a	n/a
Standard fumes	No	Side effect	62	4,935	76	4,417
Donation	No	Side effect	67	7,606	63	4,830
Modified lifeboat	Yes	Intend	67	3,742	71	4,526
Lawrence of Arabia	No	Intend	68	4,904	82	6,881
Vaccine test	No	Side effect	68	4,941	79	7,125
Vaccine policy	No	Side effect	75	5,694	85	6,164
Standard trolley	No	Side effect	80	4,176	82	4,335
Submarine	No	Intend	80	4,709	91	5,983
Modified bomb	Yes	Intend	85	4,690	90	7,073

[a] *Results from current study;* [b] *Results from Greene et al. (2008).*

"Crying Baby," "Sophie's Choice," and "Cancer Toddler." *Moderate Conflict-Yes vignettes* were those that elicited moderate "Yes" decision consensus and faster decision times; these included "Standard Fumes," "Modified Lifeboat," "Lawrence of Arabia," and "Vaccine Test." *Low Decisional Conflict-Yes vignettes* were those that elicited fast decision times and high "yes" decision consensus; these were "Standard Trolley," "Modified Bomb," and "Submarine." Three vignettes that could not be classified according to these criteria were excluded. They were "Modified Safari, "Vaccine Policy," and "Donation."

DECISION CONFLICT ANALYSIS

Seven participants in the reduced-decision time condition were eliminated because they did not enter a decision for two or more vignettes. The remaining participants in this condition were able to reach a decision in 99.3% of the remaining trials. Participants therefore had ample time to reach a decision in the time allotted, and presumably only extended deliberation was interrupted. This strongly suggests that restricting decision time to 6 s did not impose an onerous cognitive load. The relevant means were substituted for the 0.7% ($n = 10$ trials) that had missing data. The resulting mean proportion utilitarian decisions are illustrated in **Figure 1**.

These mean proportions were analyzed via mixed ANOVA with decision time (Unlimited or Reduced) as a between subject variable and conflict (Low-No, Moderate-No, High, and Moderate-Yes, Low-Yes) as repeated measures. The main effects of decision time and conflict category were both significant, $F(1,182) = 9.37$, MSe = 0.16, $p < 0.005$, $\eta^2 = 0.05$, and $F(4, 728) = 277.42$, MSe = 0.05, $p < 0.00001$, $\eta^2 = 0.60$, respectively. These main effects were modified by a higher order interaction, $F(4, 728) = 3.91$, MSe = 0.05, $p < 0.005$, $\eta^2 = 0.02$.

Planned comparisons indicated a pattern of results that differed from Suter and Hertwig (2011). As predicted by the dual-process model and as reported by Suter and Hertwig (2011), limiting decision time significantly reduced the number of utilitarian decisions in the High-Conflict condition, $t(1,182) = 3.98$, $p < 0.0001$ (two-tailed test), but had no impact on Moderate Conflict-No and Low Conflict-No categories, t's(182) = 0.07 and 1.44, respectively, p's > 0.05 (two-tailed test). But unlike Suter and Hertwig (2011), we found a significant reduction in "Yes" decisions in both the Moderate Conflict-Yes and Low Conflict-Yes categories, t's(182) = 2.03 and 1.95, respectively, p's < 0.05 (two-tailed tests). This suggests an across-the-board shift in strategy toward saying "no" under time pressure.

Decision times were analyzed in order to ensure that time restriction did in fact result in shorter decision times relative to the unlimited-time condition. If it had no effect, this would invalidate the intent of the manipulation, which was to reduce opportunity for deliberation and/or conflict resolution. Decision times were trimmed to eliminate times that equaled or exceeded 3 SD from the mean within the appropriate Conflict × Decision Time cell. This resulted in the elimination of 1.22% of the data. Remaining mean decision times were calculated for each subject within each decisional conflict category. These are presented in **Figure 2**.

Mean decision times were analyzed via mixed ANOVA with condition (Unlimited or Reduced Time) as a between subject variable and conflict (Low Conflict-Yes, Moderate Conflict-Yes, High Conflict, Moderate Conflict-No, and Low Conflict-No) as repeated measures. The main effect of decision time was significant, as was the main effect of conflict, $F(1,182) = 107.67$, MSe = 12,578, $p < 0.0001$, $\eta^2 = 0.37$, and $F(2,728) = 68.76$, MSe = 2,188, $p < 0.0001$, $\eta^2 = 0.27$. The interaction of these variables was also significant, $F(2, 728) = 22.96$, MSe = 2,188, $\eta^2 = 0.11$, $p < 0.00001$.

Planned comparisons indicated that people made quicker decision times in the reduced-time condition than in the unlimited-time condition regardless of conflict category, t's(182) = 7.83, 8.57, 9.75, 7.07, and 7.60 for the Low Conflict-No, Moderate Conflict-No, High Conflict, and Moderate Conflict Conflict-Yes and Low Conflict-Yes categories, respectively, p's < 0.0001. Hence, people did indeed take longer to reach decisions in each conflict condition – not just the High-Conflict category – when allowed to take as much time as they wanted.

As is apparent from **Figure 2**, the pattern of decision times is not entirely consistent with dual-process model predictions.

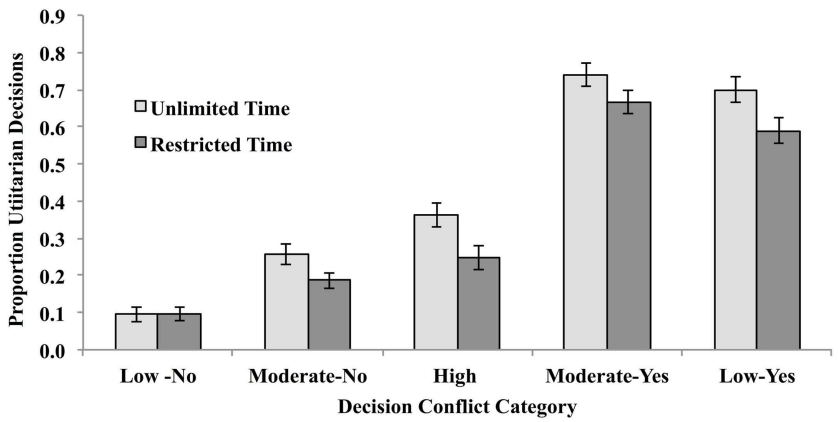

FIGURE 1 | Proportion utilitarian decisions made under unlimited- and reduced-decision time for high-conflict vignettes (long decision times and low inter-subject decision consensus), moderate conflict vignettes (moderate decision times and moderate inter-subject decision consensus), and low-conflict vignettes (fast decision times and high inter-subject decision consensus) in Experiment 1.

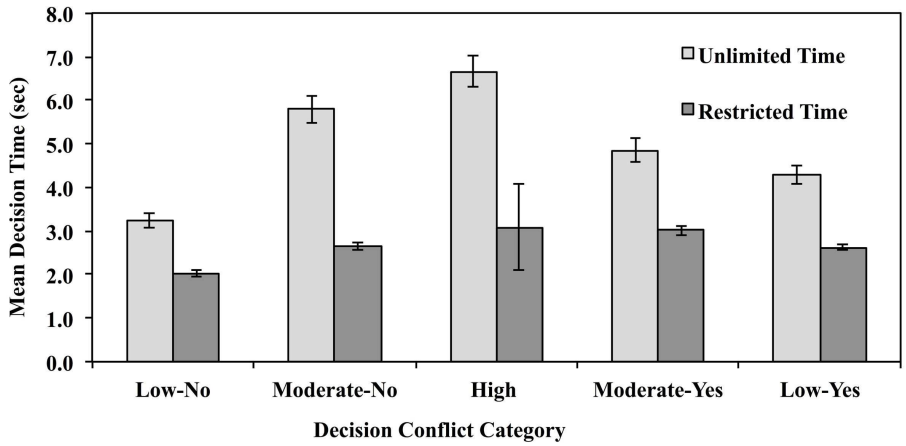

FIGURE 2 | Mean decision time for decisions made under unlimited- and reduced-decision time for high-conflict vignettes (long decision times and low decision consensus), moderate conflict vignettes (moderate decision times and moderate inter-subject decision consensus), and low-conflict vignettes (fast decision times and high inter-subject decision consensus) in Experiment 1.

If utilitarian judgments require more deliberative thought, then "yes" decisions should take longer than "no" decisions, and high decisional conflict judgments should take the longest time of all conflict categories. Looking first at the unlimited-time condition, planned comparisons showed that Low Conflict-Yes decisions did in fact take longer than Low Conflict-No decisions, $t(91) = 7.45$, $p < 0.0001$, but the opposite was true for Moderate Conflict decisions, $t(91) = -5.61$, $p < 0.0001$. Moderate Conflict-No decisions took as long as High-Conflict decisions, $t < 1$. The same pattern is apparent in the data published by Greene et al. (2008). Mean decision time for vignettes that elicited the fewest utilitarian decisions ("Hard Times," "Transplant," and "Smother") was 4.18 s; for vignettes that elicited the greatest number ("Modified Bomb," "Submarine," "Standard Trolley," and "Lawrence of Arabia"), mean decision time was 6.07 s. But for personal dilemmas that elicited moderate decisional conflict, the opposite was true; "no" responses required an average of 5.36 s ("Footbridge," "Modified Safari," and "Vitamins") "yes" responses required an average of 4.47 s ("Standard Fumes" and "Modified Lifeboat").

Turning now to the reduced-time condition, Low Conflict-Yes decisions required more time ($M = 2.96$) than Low Conflict-No decisions ($M = 2.10$) $t(91) = 10.71$, $p < 0.0001$. Moderate-Yes decisions ($M = 2.85$) took no longer than Moderate-No decisions ($M = 2.88$), $t < 1$. High-Conflict decisions ($M = 6.78$) took longer than any other decision [High vs. Low-Yes $t(91) = 4.36$, $p < 0.0001$, High vs. Low-No $t(91) = 12.89$, $p < 0.0001$, High vs. Moderate-Yes $t(91) = 5.01$, $p < 0.0001$, High vs. Moderate-No $t(91) = 5.08$, $p < 0.0001$]. Thus, when decision time was truncated – and deliberation thereby cut short – utilitarian decisions tended to take longer than deontological decisions, and resolving decisional conflicts took longest of all.

Summary of decisional conflict analyses

Reducing decision time lowered the proportion of "yes" decisions for vignettes that usually elicit "yes" responses. It also lowered the proportion of "yes" decisions for vignettes that normally elicit nearly equivalent numbers of "yes" and "no" responses and hence implicate high decisional conflict. Vignettes that typically elicit "no" responses were unaffected by reductions in decision time. This pattern of results is predicted by the dual-process model in that saying "yes" is described as a utilitarian judgment that requires deliberative reasoning. But decision time for "no" responses took longer than "yes" responses when the vignette profiles indicated moderate conflict. This is inconsistent with dual-process predictions.

DEONTOLOGICAL PRINCIPLES

The results of the decision conflict analysis would be consistent with the dual-process model proposed by Greene (2007) if two conditions were true. First, deontological decisions must be rapid ones, that is, they must be the domain of System 1. Second, a shift in strategy from saying "yes" to saying "no" must reflect a strategic change from taking time to resolve deontological and utilitarian concerns to relying solely on fast deontological outputs.

A deontological analysis was conducted in order to test these predictions. According to the dual-process model, vignettes that described deontological violations (using personal force to inflict intentional harm) should induce long decision times and low decision consensus. This is because the fast, deontological system outputs a "no" response while the slower, utilitarian system outputs a "yes" response, and resolving the conflict takes time and cognitive resources. In contrast, those that describe no such violations yield no such conflict, hence there is little need for time- and resource-demanding conflict resolution. This was the reasoning used by Suter and Hertwig (2011) when classifying vignettes as "high" or "low" conflict.

As is apparent from the data presented in **Table 1**, participants' decision times and decision consensus did NOT reflect differences in deontological violations. "Crying Baby," "Cancer Toddler," and "Sophie's Choice" all showed low inter-subject consensus and long decision times, yet only the first of these ("Crying Baby") involves personal force and intentional harm. Of the four vignettes that

elicited the fastest "no" decisions, one involves neither type of violation ("Hard Times"); conversely, of the four that elicited the fastest "yes" decisions, one described both types of violations ("Modified Bomb"), one involved no personal force ("Submarine"), and two described neither type of violation ("Vaccine Policy" and "Standard Trolley"). This means that the deontological criteria of personal force and intention were not entirely predictive of decision time or inter-subject decision consensus. Other unidentified factors apparently contribute to making decisions slow or fast, difficult or easy.

To better assess the relationship between deontic violations and decision profiles, two regression analyses were conducted. Vignettes were assigned a score of 2 if both principles were violated ($n = 6$ vignettes), a score of 1 if only one principle was violated ($n = 6$ vignettes), and a score of 0 if none were violated ($n = 6$ vignettes). (Impersonal vignettes "Donation," and "Vaccine Policy" were excluded.) The proportion utilitarian decisions in the unlimited-time condition was then regressed onto deontological score. The regression was not significant, $F < 1$, adjusted $R^2 = -0.02$. Mean decision times were also regressed onto deontological score, and this regression was also not significant, $F(1,16) = 3.31$, $p = 0.09$, adjusted $R^2 = 0.12$. Thus, factors other than personal force and intention contribute to decision consensus and decision times.

To test this more precisely, vignettes were re-classified into two categories. The first included five vignettes that described the use of personal force to inflict intended harm (PF-I): "Footbridge," "Lifeboat," "Smother for Dollars," "Modified Bomb," and "Crying Baby." ("Transplant" was excluded as surgery did not seem to us to involve personal force to the same degree as the others, even though it is "up close and personal.") Using Suter and Hertwig's classification scheme, these would constitute "High-Conflict Personal" vignettes. The second category included five vignettes that clearly describe actions in which the harm involved no personal force and was a side effect rather than an intended outcome (NPF-SE): "Standard Fumes," "Fumes with Friends," "Cancer Toddler," "Standard Trolley," and "Sophie's Choice." ("Donation" and "Vaccine Policy" were excluded because they were not "personal," "Hard Times" was excluded because no death was involved, unlike all the others, and "Vaccine Test" was excluded because it involves the use of a syringe.) Using the classification scheme of Hertwig and Suter, these would constitute "Low-Conflict Personal" vignettes. The proportion utilitarian ("yes") decisions were calculated for each subject for these two sets of vignettes, and they are depicted in **Figure 3**.

The dual-process model and the results of Suter and Hertwig (2011) predict that these two categories should yield the most divergence in decision consensus. Four planned comparisons were conducted to test these predictions. As predicted, when participants were allowed to take as much decision time as they wanted, more "yes"/utilitarian decisions obtained when no deontological violations were described, mean NPF-SE = 0.54 vs. mean PF-I = 0.43, $t(91) = 3.64$, $p < 0.0001$. When decision time was reduced, however, no difference obtained, mean PF-I = 0.36 vs. mean NPF-SE = 0.39, $t(91) = 1.21$, $p = 23$. This was because time truncation had less impact on vignettes that involved violations (0.43–0.46) than on vignettes that did not involve violations (0.54–0.39), $t(182) = 1.88$, $p = 0.03$ (one-tailed test).

The same analysis was done on mean decision times, which are depicted in **Figure 4**.

Contrary to dual-process predictions, when given as much decision time as they wanted, participants took significantly less time to render decisions for vignettes involving personal force and intentional harm ($M = 4.33$ s) than for vignettes that did not involve such violations ($M = 6.19$ s), $t(91) = 7.29$, $p < 0.001$. When decision time was truncated, they still took less time when deontological violations were involved ($M = 2.45$ s) than when they were not involved ($M = 3.17$), $t(91) = 9.23$, $p < 0.0001$. Yet these deontological violations should have put these vignettes in greatest decisional conflict with their utilitarian properties.

Summary of deontological analyses

People quickly reject courses of action that require intentionally harming someone through the use of personal force. When neither

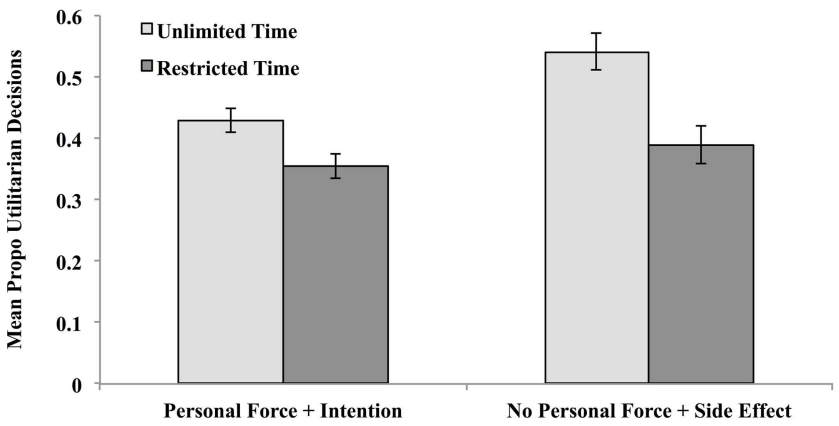

FIGURE 3 | Proportion utilitarian ("Yes") decisions made as a function of decision time (unlimited or reduced) for vignettes that involve the use of personal force to intentionally produce harm and for vignettes that do no involve the use of personal force but yield harm as an unintended side effect in Experiment 1.

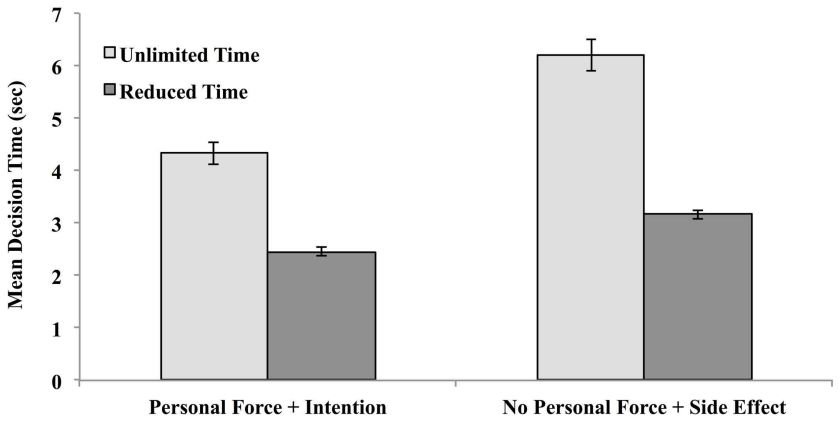

FIGURE 4 | Mean decision time for utilitarian ("Yes") decisions as a function of decision condition (unlimited or reduced-decision time) for vignettes that involve the use of personal force to intentionally produce harm and for vignettes that do no involve the use of personal force but yield harm as an unintended side effect in Experiment 1.

principle is violated, they require more time to make a moral judgment. As a result, truncating decision time had a stronger impact on vignettes that, according to Greene's (2007) model, require more deliberation and/or conflict resolution between conflicting deontological and utilitarian outputs. Decisional conflict, however, could not be predicted solely on the basis of personal force and intentional harm. Other vignette features appear to contribute to decisional conflict as measured by decision time and consensus. Moreover, conflicts between deontological and utilitarian outcomes yielded faster rather than slower decision times. This pattern of results is consistent with two alternative decision-making strategies: (a) saying "no" under time pressure or (b) using deontological principles as heuristics.

EXPERIMENT 2

The results of Experiment 1 are inconsistent with Greene's (2007) claim that time is needed to overcome a prepotent emotional response, but they are also consistent with two other explanations. The first is that under time pressure, people are more likely to say "no" to difficult dilemmas than they are to say "yes." In the studies cited in our introduction and in Experiment 1 above, saying "no" was not only equivalent to doing nothing, it also constituted a deontological response. The apparent rise in deontological judgments may have in fact have reflected nothing more than people saying "with so little time to decide, I choose to do nothing." Hence, it was imperative to decouple "no" and "deontological judgment" to see if people really were making more deontological judgments; Experiment 2 addressed that confound, and ruled out that alternative explanation. The second is that deontological principles constitute heuristic rules, allowing rapid decisions to be made, and have little to do with emotion.

Experiment 2 addressed the first of these alternate explanations – that decision time pressure yields a strategy shift toward simply saying "no." Participants again made moral judgments under both unlimited-time and restricted-time conditions. They were required to make a rapid response (within 6 s), and then were given the opportunity to deliberate as long as they wanted. Half of the participants were queried in a way that "no" responses were consistent with deontological principles while "yes" responses were consistent with utilitarian principles. The remaining participants were queried in such a way that the reverse was true.

METHODS AND MATERIALS

PARTICIPANTS

Sixty-five students at the University of Illinois served as participants in the study. They were recruited via advertisement on the Psychology Department website, and were paid $5 for their participation. Sixty-two percent were female, and ages ranged from 18 to 21.

MATERIALS

The same vignettes were used as in Experiment 1. The trial driver consisted of a Qualtrics survey run on dedicated iMac computers. The instruction screen stated the following: "Before each story, you will see a prompt that says "READY?" and an arrow. When you are ready to begin, click on the arrow, then place your cursor on the X on the next screen. The story will begin 2 s after the X appears. You will have 6 s to make your first decision about each story. IT IS VERY IMPORTANT THAT YOU ENTER A DECISION WITHIN THIS TIME FRAME. A timer will be displayed in the upper left corner of the screen so you know how much time you have left. You will then be given as much time as you need to enter a second decision. The two decisions may end up being the same, or you may decide you would like to change your mind." The first decision prompt displayed the label "First Decision," a count-down timer, the question, and the choices "Yes" and "No." Participants entered their decision by clicking on one of the choices. If a decision was not made within the allotted time, the screen advanced to the next screen. This screen showed the label "Second Decision," the question and the same choices.

The questions in the "Take Action" condition all took the following form: "Is it appropriate to <take the described action> under the circumstances." A "yes" response is consistent with a utilitarian judgment, and a "no" response is consistent with a

deontological judgment. The questions in the "Refuse to Take Action" condition all took the following form: "Is it appropriate to REFUSE to <take described action> under the circumstances?" Here, a "no" response is consistent with a utilitarian judgment, and a "yes" response is consistent with a deontological judgment.

RESULTS AND DISCUSSION

DECISIONAL CONFLICT ANALYSES

Vignettes were classified as in Experiment 1, and mean proportion utilitarian decisions for each category were calculated. They are depicted in **Figure 5**. Decision times were analyzed as in Experiment 1. They were trimmed to eliminate times that equaled or exceeded 3 SD from the mean within the appropriate Conflict × Decision Time cell. This resulted in the elimination of 1.85% of the data. Remaining mean decision times were calculated for each subject within each conflict condition. These are presented in **Figure 5**.

These means were analyzed via mixed ANOVA with question type (Take Action or Refuse to Take Action) as a between subject variable; decisional conflict category (Low-No, Moderate-No, High, and Moderate-Yes, Low-Yes), and decision trial (First and Second) served as repeated measures. The main effect of conflict category was significant, $F(4, 252) = 98.30$, MSe = 0.10, $p < 0.0001$, $\eta^2 = 0.61$, and, as predicted, it was modified by a significant interaction with trial, $F(4,252) = 3.65$, MSe = 0.02, $p < 0.006$, $\eta^2 = 0.06$. Importantly, this interaction was *not* modified by question type, $F < 1$. This means that it did not matter whether "yes" or "no" constituted a utilitarian judgment.

Planned comparisons indicated that, as predicted by the dual-process model, limiting decision time significantly reduced the number of utilitarian decisions in the High-Conflict condition, $t(1,64) = 2.72$, $p < 0.01$ (two-tailed test). No other comparison was significant. Given our within-subject design, this means that, when given the opportunity to deliberate further, participants changed their deontological responses to utilitarian responses ONLY for high decisional conflict dilemmas.

The interaction of question type and trial was significant, $F(1, 63) = 5.11$, MSe = 0.03, $p < 0.03$, $\eta^2 = 0.08$. This interaction was due to the "refuse to take" query form imposing a decisional load separate from other factors. When asked whether to refuse to take the stated action, participants increased their utilitarian decisions from the first trial ($M = 0.42$) to the second ($M = 0.47$), simple

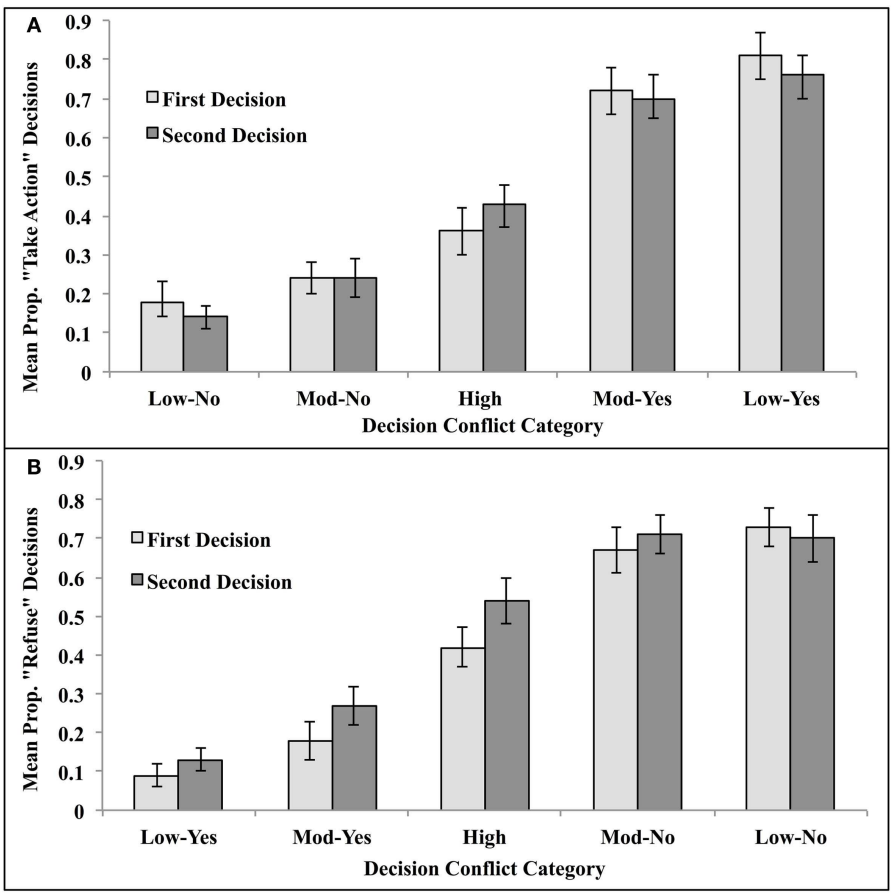

FIGURE 5 | Proportion utilitarian decisions made under unlimited- and reduced-decision time for high decisional conflict vignettes, moderate conflict vignettes, and low-conflict vignettes when the moral judgment was queried as (A) "Is it appropriate to <take the described action>?" or (B) "Is it appropriate to refuse to <take the described action>?" in Experiment 2. A "yes" response constituted a utilitarian decision for the former query, while a "no" response constituted a utilitarian decision for the latter.

effects $F(1, 32) = 5.19$, MSe $= 0.01$, $p < 0.05$. No increase obtained when they were asked whether to take the action, M first $= 0.46$, M second $= 0.45$, simple effects $F < 1$. This interaction was not modified by conflict category, $F < 1$, indicating that the effect held regardless of decisional conflict profiles.

Decision times were trimmed as in Experiment 2. Mean times are presented in **Figure 6**.

Mean decision times were analyzed via mixed ANOVA with question type (Take Action or Refuse to Take Action) as a between subject variable, and trial (First or Second Decision) and conflict category (Low Conflict-Yes, Moderate Conflict-Yes, High Conflict, Moderate Conflict-No, and Low Conflict-No) as repeated measures. The main effects of conflict category and trial were both significant, as was their interaction $F(4, 252) = 10.07$, MSe $= 0.85$, $p < 0.0001$, $\eta^2 = 0.15$, $F(1, 63) = 16.61$, MSe $= 3.13$, $p < 0.001$, $\eta^2 = 0.21$, $F(4, 252) = 4.13$, MSe $= 0.63$, $p < 0.003$, $\eta^2 = 0.06$, respectively. The main effect of question type was NOT significant, $F < 1$. This means that the results of Experiment 1 were not due to a conflation of "yes" with utilitarian decisions and "no" with deontological decisions.

Planned comparisons indicated that when decision time was restricted on the first trial, people took longer to make decisions about High-Conflict vignettes than for any other type of vignette: High Conflict vs. Moderate Conflict-Yes vignettes, $t(64) = 6.23$, $p < 0.001$, Moderate Conflict-No vignettes, $t(64) = 5.52$, $p < 0.001$, Low Conflict-Yes vignettes, $t(64) = 5.14$, $p < 0.0001$, and Low Conflict-No vignettes, $t(64) = 9.57$, $p < 0.001$. When given the opportunity to reflect and deliberate on the second trial, they spent more time thinking about High-Conflict vignettes than they did Low-Conflict vignettes regardless of final decision: Conflict-Yes vignettes, $t(64) = 2.39$, $p < 0.05$; for Low Conflict-No vignettes, $t(64) = 1.98$, $p < 0.05$. (There were no differences between the additional time taken for High Conflict and Moderate Conflict-Yes or Moderate Conflict-No vignettes, t's < 1.)

Summary of decisional conflict analyses

As in Experiment 1, people rendered fewer utilitarian judgments for dilemmas that induce high decisional conflict when decision time was truncated. When given more time, they were more likely

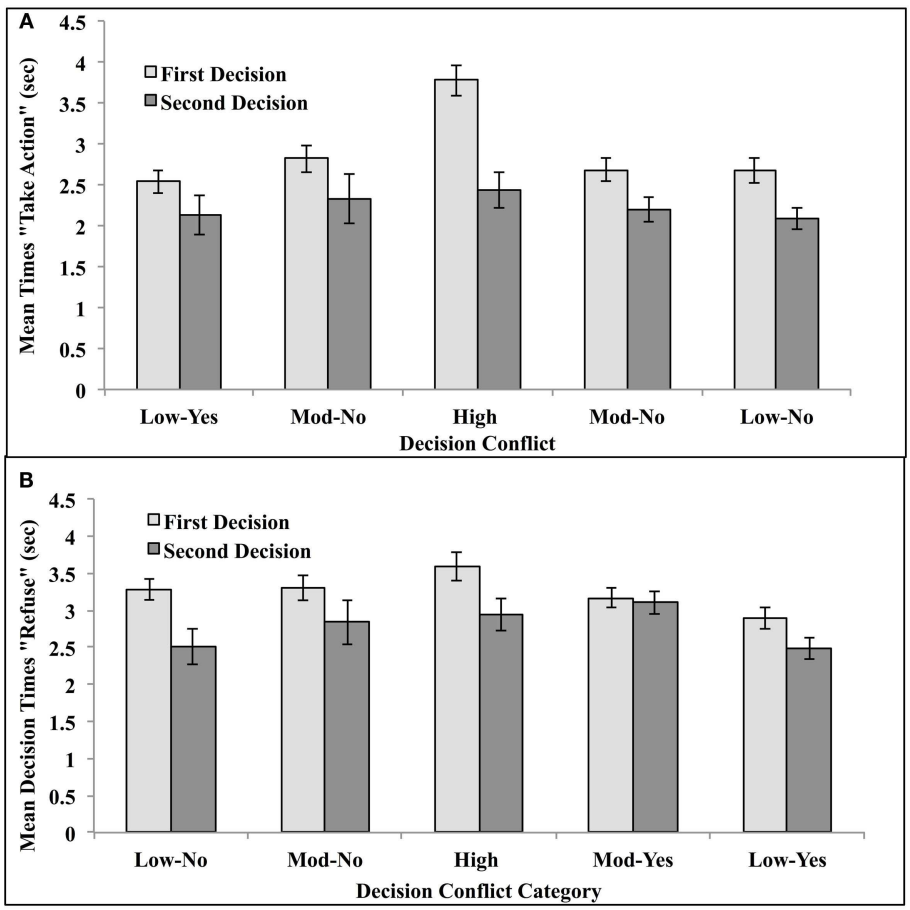

FIGURE 6 | Mean decision time for decisions made under unlimited- and reduced-decision time for high-conflict vignettes, moderate conflict vignettes, and low-conflict vignettes in Experiment 2. First decisions were made within a time constraint of 6 s. Second decisions were made without time constraints. Moral judgments were queried as **(A)** "Is it appropriate to <take the described action>?" or **(B)** "Is it appropriate to refuse to <take the described action>?" A "yes" response constituted a utilitarian decision for the former query, while a "no" response constituted a utilitarian decision for the latter.

to change their deontological judgments into utilitarian ones. They also required more time to make utilitarian judgments when decision time was truncated and when they were given unlimited time to decide. These results held regardless of whether a "yes" or "no" decision constituted a utilitarian judgment.

DEONTOLOGICAL ANALYSES

As in Experiment 1, vignettes were re-classified using personal force and intention as discriminating features. A mixed ANOVA was conducted on proportion utilitarian decisions using question type (Take Action or Refuse to Take Action) as a between subject variable, and decision time (Restricted and Unlimited) and deontic classification (Personal Force + Intention and No Personal Force + Side Effect) as repeated measures. The analysis returned a significant interaction of trial and deontic classification, $F(1,63) = 8.18$, MSe $= 0.01$, $p < 0.01$, $\eta^2 = 0.12$. When people were given the opportunity to further deliberate about dilemmas that did not violate deontological principles, they reliably increased the number of utilitarian decisions they made from 0.48 to 0.54, $t(64) = 2.41$, $p < 0.025$. Having a second chance to think about their decisions had no reliable effect, however, when the dilemmas violated deontological principles, 0.51 vs. 0.49, $t(64) = 1.35$, $p = 0.18$. This result would seem to suggest that deontological judgments are either driven solely by application of heuristic rules or influenced strongly by prepotent emotional responses, while utilitarian decisions constitute outcomes of deliberative conflict resolution processes.

The interaction of trial and question type was significant, $F(1,63) = 8.12$, MSe $= 0.02$, $p < 0.01$, $\eta^2 = 0.11$. When asked whether it was appropriate to refuse to take the stated action, the proportion of utilitarian decisions increased with additional decision time from 0.47 to 0.53, $t(32) = 2.53$, $p < 0.025$. When asked whether it was appropriate to take the stated action, allowing additional decision time had no reliable effect [0.51 for the first decision and 0.49 for the second, $t(31) = 1.46$, $p = 0.15$].

Turning now to decision times, **Figure 7** illustrates mean decision times for first and second decisions as a function of question type.

An ANOVA based on the same factors returned three significant effects: the main effect of deontic classification $F(1,63) = 5.92$, MSe $= 0.38$, $p < 0.02$, $\eta^2 = 0.09$, the main effect of trial, $F(1,63) = 28.20$, MSe $= 1.19$, $p < 0.0001$, $\eta^2 = 0.31$, and the main effect of question type, $F(1,63) = 4.87$, MSe $= 2.12$, $p < 0.03$, $\eta^2 = 0.07$. These results meant that people took longer to make decisions when the question asked whether to refuse to take action ($M = 3.02$ s) than whether to take action ($M = 2.62$ s), they took more time to make their first decision ($M = 3.18$ s) than to make their second decision ($M = 2.46$), and to make judgments when no deontological principles were violated ($M = 2.91$) than when they were violated ($M = 2.72$). This last effect, again, is contrary to dual-process predictions.

Summary of deontological analyses

The overall pattern of results indicate that (a) it is easier to think about whether to take action than whether to refuse to take action, and (b) dilemmas that violate deontological principles yield faster decisions than dilemmas that do not. They also show that reducing decision time has greater impact on dilemmas that comprise a conflict between fast and slow decisional processes such that fewer utilitarian judgments obtain.

EXPERIMENT 3

The results of Experiments 1 and 2 clearly show dilemmas that induce decisional conflict between deontological and utilitarian principles impact decision time as well as decision consensus. Limiting decision time shifts the decisional balance in favor of deontological judgments, but these results do not necessarily implicate the role of emotion in the deontological reasoning process. The fast System 1 identified by Kahneman (2003) and others also includes rule-based heuristic decision-making and intuition. The fast deontological decisions our participants displayed may have been due to the invocation of heuristic deontological rules, such

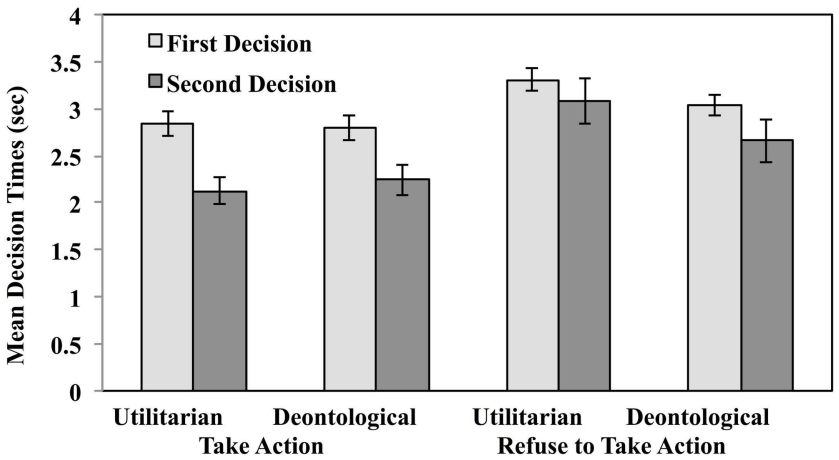

FIGURE 7 | Mean decision times for utilitarian and deontological judgments as a function of question type in Experiment 2. First decisions were made within a time constraint of 6 s. Second decisions were made without time constraints.

as never using a person as an object (as is done when using personal force) or never intentionally causing another being harm. This is supported by the fact that deontological violations were associated with faster decision times. As mentioned previously, Youssef et al. (2012) found that activation of the stress response yielded a reduction in utilitarian responses that was specific to personal moral dilemmas that described deontological violations. The reduction in utilitarian judgments under conditions of time constraints (Suter and Hertwig, 2011) or concurrent task demands (Greene et al., 2008) may be simply due to the stress involved in conflict resolution.

The purpose of Experiment 3 was to investigate the separate impact of emotion and cognition on rapid decisional outputs. Participants made decisions under time constraints for a subset of moral dilemmas that normally elicit distress. Midway through the allotted decision-making time, one group of participants rated photographs selected to elicit pleasant emotional states while a second performed a cognitive task on the same photographs. They then delivered their judgments. We predicted that shifting attention to pleasant emotional stimuli would ameliorate emotional stress thereby freeing up vital decision-making resources and hence decrease the number of deontological decisions in favor of utilitarian ones.

METHODS AND MATERIALS

PARTICIPANTS

One-hundred thirty-five undergraduate students at the University of Illinois at Urbana-Champaign served as participants in the study. Fifty-eight percent were female, and ages ranged from 18 to 21. An equal number ($n = 45$) participated in the control, emotion rating, and cognitive task groups. Participants were paid $5 for their participation.

MATERIALS

Vignettes from the previous studies were selected for use based on the following criteria: High and moderate decisional conflict as evidenced by decision times and decision consensus, violations of personal force and intentional harm (PF-I), and no personal force and harm as a side effect (NPF-SE). These criteria yielded the following vignettes which served as materials: Crying Baby (High Decisional Conflict, PF-I), Sophie's Choice (High Decisional Conflict, NPF-SE), Vitamins (Moderate Decisional Conflict-No, PF-I), Fumes with Friends (Moderate Decisional Conflict-No, NPF-SE), Lifeboat (Moderate Decisional Conflict-Yes, PF-I), and Vaccine Test (Moderate Decisional Conflict-Yes, NPF-SE). In addition, "Modified Safari" served as an initial practice problem, and "Cancer Toddler" served as the last (unscored) problem.

Distractor materials consisted of photographs of pleasant houses in attractive landscaping. The houses differed in terms of number of windows, ranging from 6 to 12.

PROCEDURE

The trial driver was a Qualtrics survey run on dedicated iMac computers. A control group simply read each vignette and entered a decision within a restricted-time period. The instruction screen contained the following information: "You will read eight stories. Before each story, you will see a prompt that says "READY?" and an arrow. When you are ready to begin, click on the arrow, then place your cursor on the X on the next screen. The story will begin 2 s after the X appears. It will scroll up through the window at a comfortable reading rate."

"When the story ends, you will have 4 s to think about it. A timer will be displayed in the upper left corner of the screen so you know how much time you have left. Lastly, you will be have 20 s to enter a decision about the story you read. The timer will also be displayed." Safari and Lawrence of Arabia served as practice dilemmas, and were always the first second dilemmas displayed. The remaining six dilemmas were presented in random order. The questions asked were the same as the positive format questions in Experiment 2. Participants entered their decisions by clicking on either "yes" or "no" radio buttons.

The emotion group was given the following instructions: "You will read eight stories. Before each story, you will see a prompt that says "READY?" and an arrow. When you are ready to begin, click on the arrow, then place your cursor on the X on the next screen. The story will begin 2 s after the X appears. It will scroll up through the window at a comfortable reading rate."

"When the story ends, you will have 4 s to think about it. A timer will be displayed in the upper left corner of the screen so you know how much time you have left. Then you will see a picture of a house. You will be asked to rate the house in terms of how pleasing you find it to be. You will have 10 s to give your rating, and a timer will be displayed. Lastly, you will have 10 s to enter a decision about the story you read and a timer will be displayed." The house rating trials consisted of a color photograph of a house with a rating scale beneath it. The scale consisted of radio buttons that were labeled Very Unpleasant, Unpleasant, Somewhat Unpleasant, Neutral, Somewhat Pleasant, Pleasant, and Very Pleasant. Participants entered their decisions by clicking on a radio button that reflected their judgment.

The cognitive group was given the following instructions: "You will read eight stories. Before each story, you will see a prompt that says "READY?" and an arrow. When you are ready to begin, click on the arrow, then place your cursor on the X on the next screen. The story will begin 2 s after the X appears. It will scroll up through the window at a comfortable reading rate."

"When the story ends, you will have 4 s to think about it. A timer will be displayed in the upper left corner of the screen so you know how much time you have left. Then you will see a picture of a house. You will be asked to count the number of windows in the house and multiply the total by three. You will have 10 s to record your answer and a timer will be displayed. Count WHOLE windows, not window panes. Count only windows that can be opened as a unit." This was followed by three photographs of multi-paned windows captioned "This is counts as <> windows." This was done to ensure that no confusion would result in participants counting window panes rather than windows. The instructions then continued. "Lastly, you will be have 10 s to enter a decision about the story you read and a timer will be displayed." Participants entered their window answers by selecting from among four multiple choice options.

RESULTS AND DISCUSSION

DECISIONS

The proportion utilitarian judgments for each condition is depicted in **Figure 8**.

The proportion observed for the control condition was used as the expected probability of a utilitarian response. If rapid, negative affective responses are primarily responsible for deontological judgments, then disruption of negative emotional processing through exposure to pleasant stimuli should reduce their number relative to utilitarian judgments. This should be particularly true for high decisional conflict dilemmas that pit deontic violations against utilitarian concerns. In fact, the opposite obtained: For the high-conflict dilemma that involved personal force and intentional harm (Crying Baby), 40% of the control group (18 out of 45) gave utilitarian judgments. In the emotion rating condition, 20% (9 out of 45) gave a utilitarian decision, which constituted a significant *reduction* in utilitarian judgments, $Z = -2.59$, $p < 0.01$. In the cognitive condition, 45% (20 out of 51) gave a utilitarian judgment, which did not differ from the baseline control, $Z = +0.45$, $p = 0.64$. This pattern suggests that rapid judgments for this type of dilemma are primarily driven by System 1, non-deliberative processing, and that reducing or disrupting negative affect processing make people *more likely* to render a deontological judgment.

The same pattern of results obtained for the dilemma that did not involve personal force or intentional harm (Sophie's Choice). Here, 58% (26 out of 45) gave a utilitarian response in the control condition. In the emotion condition, only 27% (12 out of 45) gave a utilitarian judgment, which also constituted a significant reduction in such judgments $Z = -4.11$, $p < 0.0001$. Among participants who engaged in the cognitive task, 49% (22 out of 45) gave a utilitarian judgment, which did not differ from the expected proportion $Z = -1.09$, $p = 0.27$. Thus, inducing a pleasant emotional state again shifted the decisional balance in favor of deontological judgments.

Turning now to Moderate Conflict-Yes dilemmas, we found the following. For the dilemma that violated the two deontological principles (Lifeboat), 76% of the control group (34 out of 45) gave utilitarian judgments, and neither the emotion (73%) nor the cognitive manipulation (82%) yielded significant changes from baseline, both Z's $= -0.24$ and $+0.80$, p's $= 0.42$ and 0.78, respectively. The same was true for the dilemma that did not involve deontological violations (Vaccine Test); here 78% of the control group (33 out of 45) gave utilitarian judgments. The percentages for the emotion and cognitive task groups were 82% (37 out of 45) and 84% (38 out of 45), Z's $= +1.23$ and $+1.56$, p's $= 0.21$ and 0.11, respectively.

Turning lastly to Moderate Conflict-No dilemmas, we found the following. For the dilemma that violated the two deontological principles (Vitamins), 49% of the control group (22 out of 45) gave utilitarian judgments, and neither the emotion (51%, 23 out of 45) nor the cognitive manipulation (56%, 25 out of 45) yielded significant changes from baseline, Z's $= +0.13$ and $+0.73$, p's $= 0.89$ and 0.46, respectively. For the dilemma that did not involve deontological violations (Fumes with Friends), 40% of the control group (18 out of 45) gave utilitarian judgments. Here, again, neither the emotion nor the cognitive task impact judgment values (emotion 49%, $n = 22$ out of 45, $Z = +1.07$, $p = 0.28$; cognitive 40%, $n = 18$ out of 45, $Z = 0$, $p = 1$).

While the results of the decision analysis indicates the emotion distractor task impacted high-conflict judgments, an alternative explanation is that the groups differed in terms of the amount of time they spent making decisions after they completed their tasks. To rule out this possible explanation, decision times were analyzed, and specific comparisons were made.

Decision times were analyzed via mixed ANOVA using distractor condition (Emotion, Cognitive, or Control) as a between subject variable, and vignette decisional conflict (High, Moderate-Yes, and Moderate-No) and deontology (Personal Force + Intention and No Personal Force + Side Effect) as repeated measures. The main effects of distractor condition, decisional conflict, and deontology were all significant, $F(2, 132) = 81.49$, MSe $= 11.86$, $p < 0.0001$, $\eta^2 = 0.56$; $F(2, 264) = 13.28$ MSe $= 7.08$, $p < 0.0001$, $\eta^2 = 0.09$; $F(1, 132) = 7.62$, $p < 0.0001$, $\eta^2 = 0.17$. These main effects were modified by higher order interactions, Distractor Condition × Conflict $F(4, 264) = 4.70$, $p < 0.001$,

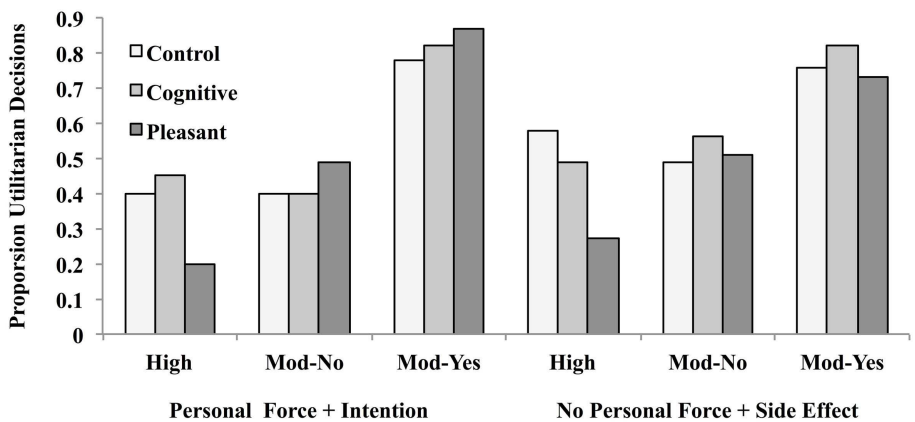

FIGURE 8 | Proportion utilitarian judgments following an emotion rating task involving pleasant stimuli, a cognitive task requiring mental arithmetic, and a control group that involved neither in Experiment 3. Dilemmas either involved the use of personal force to inflict intentional harm, or no personal force where harm was an unintended side effect, and were pre-classified as involving high or moderate decisional conflict.

$\eta^2 = 0.07$; Distractor Condition × Deontology $F(2, 132) = 14.51$, $p < 0.0001$, $\eta^2 = 0.18$.

Planned comparisons were conducted contrasting decision times between the two distractor task groups for each vignette category. (All tests two-tailed.) When deontological principles were violated, participants took equally long to make decisions following the emotion rating task and the cognitive task; the same was true when deontological principles were not violated, all t's < 1. Similarly, the type of distractor task did not differentially impact decision times for High Conflict, Moderate Conflict-No, and Moderate Conflict-Yes vignettes, t's < 1. This rules out the possibility that differences in decision outcomes between the emotion and cognitive groups were due to differences in the amount of time spent on deliberation following completion of their respective tasks.

Collapsing across distractor task, planned comparisons replicated the results of Experiments 1 and 2: Participants once again took longer to make decisions about vignettes that did not violate deontological principles ($M = 3.56$) than vignettes that did ($M = 3.30$) $t(189) = 2.07$, $p < 0.05$.

Participants took longer to render judgments for high decisional conflict dilemmas ($M = 3.98$) than for moderate decisional conflict dilemmas, Mod-No $= 3.13$, $t(89) = 5.11$, $p < 0.0001$; Mod-Yes $= 3.18$, $t(89) = 4.57$, $p < 0.0001$. The moderate conflict dilemmas did not differ from each other, $t < 1$.

Summary of decisional conflict and deontological analyses

This pattern of results indicates that (a) dilemmas whose consensus and decision time profiles are consistent with high decisional conflict were strongly influenced by emotional state, (b) exposure to pleasant emotional stimuli decreased utilitarian judgments, (c) the impact of emotion did not depend on whether deontological violations occurred, and (d) the impact of emotion was not due to changes in the amount of time spent in decisional processing. These results suggest that reducing the stress involved in resolving decisional conflicts between early deontological and later utilitarian outcomes is responsible for shifting the balance in favor of deontological judgments. This pattern of results is inconsistent with the claim that prepotent negative emotional responses elicited by deontological violations must be overcome in order to render utilitarian judgments.

DISCUSSION

In these experiments, decisional conflict was defined in two ways, (a) as a conflict between utilitarian and deontological principles, and (b) as long decision times coupled with low inter-subject consensus. The results of Experiment 1 showed that when decision time was truncated, people rendered fewer utilitarian judgments for dilemmas that induce high decisional conflict when defined in either way. Experiment 2 replicated this effect and showed that when given more time, they were more likely to change their deontological judgments into utilitarian ones than vice versa. These results held regardless of whether a "yes" or "no" decision constituted a utilitarian judgment. This overall pattern of results is consistent with Greene's (2007) dual-process model of moral judgment in which deontological judgments are the domain of a fast System 1 process while utilitarian judgments are handled by a slower, deliberative System 2. They also confirm the validity of personal force and intentional harm as important deontological principles in moral judgment.

Two findings were inconsistent with the predictions of the model. First, the longest decision times should obtain when rapid deontological judgments conflict with slower utilitarian judgments. Yet such conflicts were associated with rapid decision times. All dilemmas described the same utilitarian structure of harming few to save or help many. Yet people were found to quickly reject these actions if they also required intentionally harming someone through the use of personal force. When neither personal force nor intentional harm is involved, they took more time to reach a decision.

Second, the results of Experiment 3 were not consistent with the involvement of emotion in deontological judgments. According to the model, deontological violations elicit strong negative affect which biases the judgment outcome toward rejecting the proposed course of action described in the dilemma – contrary to utilitarian concerns. Reducing negative affect therefore should have increased the frequency of utilitarian judgments. Instead, the opposite obtained: Exposure to pleasant emotional stimuli was found to *decrease* utilitarian judgments for high decisional conflict dilemmas, regardless of whether the dilemmas involved deontological violations. This result suggests that the stress of decisional conflict is the crucial factor that interferes with deliberative reasoning, not the negative affect that is induced by deontological violations. This leaves open the possibility that deontological judgments may be described more as a rapid, heuristic process than an emotion-driven one.

Our results also show that, decisional conflict cannot be predicted on the basis of deontological violations as was done by Suter and Hertwig (2011) and others. Dilemmas whose decisional profiles reflected long decision times and low inter-subject consensus were not necessarily the same ones that involved deontological violations, nor were dilemmas that boast rapid times and high utilitarian consensus necessarily the same ones that were free of deontological violations. Other factors seem to be responsible for at least some of these decisional conflict profiles. For this reason, caution should be observed when defining dilemmas as "high" or "low" entirely theoretically, without taking empirical decisional profiles into account.

It should be noted that our results are not inconsistent with dual-process explanations of moral judgment in general. Our experiments were designed to test a specific dual-process model – the model proposed by Greene et al. (2001) and Greene (2007). According to that model, when deontological principles are violated, fast negative affect is evoked which must be overcome by slower deliberation. Our results are inconsistent with this aspect of the model: The presence or absence of violations of deontological principles was not predictive of differences in early, affect-based judgment (Experiments 1 and 2), and diminishing negative emotional affect led to more deontological judgments, not fewer (Experiment 3).

Most importantly, these results are relevant to teasing apart the separate contributions of intuition, emotion, and heuristic processes in moral judgment. Each of these typically yield rapid decisional outputs. Previous research suggested that utilitarian

judgments may be decreased by inducing disgust (Schnall et al., 2008), stress (Youssef et al., 2012), or "elevation" (benevolence; Strohminger et al., 2011). Conversely, making light of deontological violations by making them seem funny increases utilitarian judgments (Valdesolo and DeSteno, 2006; Strohminger et al., 2011). Our results add to this literature by showing that exposure to pleasant emotional stimuli dramatically reduces utilitarian judgments, while inclusion of a cognitive task did not impact moral judgments. This suggests that the impact of the emotion task was not due to simple stress reduction. Instead, the type or quality of the emotion elicited appears crucial to moral judgment outcomes.

Our results are also inconsistent with the predictions of theories which treat emotions as epiphenomena which play no substantive role in moral judgment (Rawls, 1971; Cushman et al., 2006; Hauser et al., 2006). Haidt (2001, 2007) has proposed that moral judgments are primarily fast, intuition-based judgments, and reasoning occurs only later to justify a judgment already made. Our results show that moral judgments do indeed occur quite rapidly, but the results of Experiment 2 show that these rapid judgments are frequently reversed upon more reflection. The most accurate interpretation of our results appears to be the moral judgment involves both fast and slow decisional processes, and that early emotional responses play an important role that is not yet well understood.

Our results seem to indicate that person-based considerations often weigh more heavily in moral judgment than principle-based considerations. What seems to be most influential is victim characteristics, as seen in **Table 2**. Of the vignettes logging fewer than 65% utilitarian decisions, almost all of the victims belonged to a vulnerable class (i.e., child, patient, injured innocent) or had other characteristics that would elicit a compassion response (i.e., fat man, fellow hostage). Of the eight vignettes that logged greater than 65% utilitarian decisions, five had characteristics that would lessen compassion because danger or risk is part of their position (i.e., terrorist's son, combatants, workmen, soldier, and fellow passenger) and two did not involve fatal harm. (The primary difference between "fellow hostage" and "fellow passenger" is that the former had no choice in becoming a hostage while the latter chose to enter the lifeboat.) This interpretation is consistent with other studies that have reported victim characteristics to weigh in moral judgment. For example, Cikara et al. (2010) found that intergroup biases and stereotypes weigh heavily on neural systems implicated in moral decision-making.

From this viewpoint, factors that elicit greater compassion for the victim or put the decision-maker in an emotional state that is conducive to compassion will decrease their willingness to impose harmful consequences on the victim, hence decreasing the likelihood of a utilitarian response. Our data indicate that this person-assessment process takes place rapidly in System 1, and results in affective responses that are primarily expressed in terms of degree of compassion for the victim. Harms to a vulnerable person are seen as a greater harm than harms to those less vulnerable. This is a utilitarian concern. If correct, then the identification of deontological judgments with a rapid, affective response and utilitarian judgments with a slower, deliberative response is not warranted. Instead, both deontological and utilitarian heuristics may be part of the System 1 process. Fast responses to these vignettes can obtain simply by applying a extremely simple "greater good" heuristic (i.e., always choose that action that maximizes the number of lives saved, regardless of victim characteristics), or by applying a deontological heuristic (e.g., never use a person as a means to an end). The deliberative aspect of a dual-process account involves the careful weighing of the outcomes of these heuristics, particularly when a conflict among the outputs occurs.

Table 2 | Victim characteristics of vignettes ranked according to % utilitarian decisions.

Vignette	% Utilitarian	Victim
Hard times	3	Child
Transplant	5	Patient
Smother for dollars	8	Patient
Footbridge	15	Fat man
Modified safari	28	Fellow hostage
Sacrifice	28	Child
Fumes w/friends	36	Injured friend
Vitamins	38	Patient
Crying baby	40	Child
Sophie's choice	41	Child
Cancer toddler	52	Child
Standard fumes	62	Injured innocent
Donation	67	n/a
Modified lifeboat	67	Fellow passenger
Lawrence of Arabia	68	Combatants
Vaccine test	68	Patients
Vaccine policy	75	n/a
Standard trolley	80	Workman
Submarine	80	Soldier
Modified bomb	85	Terrorist's son

We tested an influential theory that explains moral judgment as the outcome of parallel rapid affective and slower deliberative processes. People were required to make decisions about moral dilemmas that involved harming some in order to save many. These dilemmas were selected on the basis of previous research to vary in terms of the gravity of the harm and hence the degree of affective response elicited. We found that restricting decision time (in order to limit time available for deliberation and increase task stress) had little impact on judgments that induced little decisional conflict, but significantly decreased the proportion of decisions that were consistent with deliberative aggregate benefit analyses for dilemmas that induced high conflict. We also found that requiring people to rate the emotional pleasantness of visual stimuli in a distractor task similarly decreased the proportion of utilitarian-type moral judgments. These results are consistent with the prediction that truncating decision time shifts decision profiles in favor of weighting affective features of the dilemma more heavily than their utilitarian structures.

Our findings are directly relevant to three other papers published in this volume. The work reported by Henderson et al. (2012) indicates that exposure to moderate, controllable stress benefits performance, but exposure to uncontrollable stress or having a more extreme response to stress tends to harm performance. The analysis provided by Kanske (2012) suggested

that stress can be leveraged in order to benefit performance. But we found induction of even moderate stress through restricting decision time had a pronounced affect on moral judgments. Finally, Trübutschek and Egner (2012) demonstrate that previous reports of emotion-modulated trial–transition effects are likely attributable to the effects of emotion on cognitive control processes. Similarly, our results indicate that affective processes can strongly impact decisional profiles in predictable ways.

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Time-dependent effects of cortisol on selective attention and emotional interference: a functional MRI study

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Acute stress is known to induce a state of hypervigilance, allowing optimal detection of threats. Although one may benefit from sensitive sensory processing, it comes at the cost of unselective attention and increased distraction by irrelevant information. Corticosteroids, released in response to stress, have been shown to profoundly influence brain function in a time-dependent manner, causing rapid non-genomic and slow genomic effects. Here, we investigated how these time-dependent effects influence the neural mechanisms underlying selective attention and the inhibition of emotional distracters in humans. Implementing a randomized, double-blind, placebo-controlled design, 65 young healthy men received 10 mg hydrocortisone either 60 min (rapid effects) or 270 min (slow effects), or placebo prior to an emotional distraction task, consisting of color-naming of either neutral or aversive words. Overall, participants responded slower to aversive compared to neutral words, indicating emotional interference with selective attention. Importantly, the rapid effects of corticosteroids increased emotional interference, which was associated with reduced amygdala inhibition to aversive words. Moreover, they induced enhanced amygdala connectivity with frontoparietal brain regions, which may reflect increased influence of the amygdala on an executive network. The slow effects of corticosteroids acted on the neural correlates of *sustained* attention. They decreased overall activity in the cuneus, possibly indicating reduced bottom-up attentional processing, and disrupted amygdala connectivity to the insula, potentially reducing emotional interference. Altogether, these data suggest a time-specific corticosteroid modulation of attentive processing. Whereas high circulating corticosteroid levels acutely increase emotional interference, possibly facilitating the detection of threats, a history of elevation might promote sustained attention and thereby contribute to stress-recovery of cognitive function.

Keywords: corticosteroids, emotional interference, attention, functional MRI, amygdala, prefrontal cortex, cuneus, insula

INTRODUCTION

Stress has profound influence on the brain's attentional resources. When exposed to an acutely stressful situation, the brain shifts into a mode of hypervigilant processing in which the detection and assessment of potential threats is optimized by prioritized sensory processing (de Kloet et al., 2005; van Marle et al., 2009), and the amygdala, key modulator of vigilance and emotional processing in the brain (Phelps and Ledoux, 2005), is activated (van Marle et al., 2009). This surge in vigilance in immediate response to stress is thought to be mediated by the central release of norepinephrine (NE) by tonic activation of the locus coeruleus (LC) (Aston-Jones and Cohen, 2005; Valentino and Van Bockstaele, 2008; Cousijn et al., 2010). This state of hypervigilance is highly adaptive and enhances chances of survival during stressful situations, but it comes at the cost of specificity (van Marle et al., 2009), impaired selective attention (Tanji and Hoshi, 2008; Henderson et al., 2012) and increased susceptibility to distraction (Skosnik et al., 2000; Braunstein-Bercovitz et al., 2001; Aston-Jones and Cohen, 2005), resulting from impaired prefrontal cortex (PFC) processing underlying executive functioning (Arnsten, 2009; Qin et al., 2009) and exhaustion of attentional resources (Sato et al., 2012). It might cumulate in stress-related disorders such as depression and post-traumatic stress disorder (PTSD), which are characterized by an attentional bias toward negative emotional information (Williams et al., 1996). Therefore, normalization of attentional processing some time after the stressful event is very important for well-being. Notably, these disorders are characterized by aberrant corticosteroid signaling (Yehuda et al., 2001).

Corticosteroids, released in response to stress as the end-product of the hypothalamic-pituitary-adrenal (HPA) axis, are well-known modulators of human cognition. The hormones exert their actions upon binding of the mineralocorticoid (MR) and glucocorticoid receptor (GR), which are abundantly

expressed in the brain (Sapolsky et al., 1983; Reul and de Kloet, 1985; de Kloet, 1991). Recent research in rodents has indicated that corticosteroid-binding can induce both rapid non-genomic and slow genomic effects by acting on receptors that are respectively located in the plasma membrane and in the nucleus (Di et al., 2003; Karst et al., 2005; Wiegert et al., 2005). These distinct temporal pathways are thought to serve different functions (Joels et al., 2006, 2011). The rapid actions of corticosteroids on the one hand, have been suggested to work in concert with (and amplify) the effects of catecholamines (Roozendaal et al., 2006; Joels and Baram, 2009) to optimize rapid adaptive behavior by relocating neural resources away from higher-order cognitive processing regions in the PFC to the limbic structures (Diamond et al., 2007). Therefore, they might boost the effects of catecholamines on attentional processing, increasing emotional interference. The slow corticosteroid-induced genomic cascade is on the other hand thought to be responsible for the regulation of the stress response and the restoration of homeostasis in the aftermath of stress (de Kloet et al., 2005; Henckens et al., 2010, 2011c).Thereby, the slow corticosteroid effects might contribute to the normalization of attentional processing in the aftermath of stress. However, these time-dependent effects of corticosteroids on the neural substrates of selective attention have never been tested.

Here, we set out to investigate the time-dependent effects of corticosteroids on the neural correlates of selective attentional processing. In a randomized, double-blind, placebo-controlled design, 65 young healthy men received 10 mg hydrocortisone either 60 min (to target the rapid corticosteroid effects) or 270 min (slow corticosteroid effects), or placebo prior to functional MRI scanning. Selective attention was assessed by means of an emotional distraction task, in which participants were asked to identify the font color of neutral and highly aversive words as fast and accurate as they could (Mathews and MacLeod, 1985; McKenna, 1986). Proper selective attention is critical for task-execution, since it requires participants to focus on just one source of information for processing (i.e., font color) while ignoring competing information, including word meaning (e.g., emotion). It is well-known that under such competitive conditions, the presence of emotionally salient information disrupts the ability to attend selectively to the task-relevant information (Arnsten and Goldman-Rakic, 1998; Dolcos and McCarthy, 2006; Dolcos et al., 2011). Typically, this results in slower reaction times and lower accuracy for color naming of emotional words relative to neutral words, which serves as a measure of emotional interference. By measuring the corticosteroid effect on emotional interference induced by the emotional, attention-grabbing distracters (Bishop, 2008; Wingenfeld et al., 2009), this task enabled us to assess corticosteroid effects on selective attention. Moreover, this task enabled us to assess corticosteroid effects on sustained attention, i.e., one's ability to maintain a consistent response during continuous (i.e., repetitive) task performance. In other words, it measures the ability to keep the selective attention maintained over time (McDowd, 2007). Since sustained attention is required to complete any cognitively planned activity, here task execution, it could be assessed by analyzing overall task performance, regardless of the emotional valence of the words.

MATERIALS AND METHODS

PARTICIPANTS

Seventy-two young (age range 18–29, median 21), right-handed, Dutch speaking, healthy male volunteers gave written informed consent to participate in the study. Women were excluded from participation, since previous research has indicated that women respond differently to hydrocortisone than men, both in behavior (Andreano and Cahill, 2006; Bohnke et al., 2010) and brain activation (Stark et al., 2006; Merz et al., 2010). Moreover, their response to hydrocortisone is modulated by oral contraceptive use and varies over the menstrual cycle (Merz et al., 2011). Therefore, in order to reduce variance we here recruited the group with the most stable response to hydrocortisone. Furthermore, individuals who met any of the following criteria were excluded from participation: history of head injury, autonomic failure, history of or current psychiatric, neurological, or endocrine disorders, current periodontitis, acute inflammatory disease, acute peptic or duodenal ulcers, regular use of corticosteroids, treatment with psychotropic medications, narcotics, beta-blockers, steroids, or any other medication that affects central nervous system or endocrine systems, medical illness within the three weeks prior to testing, self reported mental or substance use disorder, daily tobacco or alcohol use (or experienced inconvenience in refraining from these activities for three days), exercising at the professional level, regular night shift work, or current stressful episode or major life event. Four participants were excluded from analyses because of unreliable cortisol manipulation [abnormal basal cortisol levels (1 × placebo) or no elevation in salivary cortisol level in response to CORT intake (2 × rapid CORT, 1 × slow CORT)], and another three participants because of insufficient task performance (based on outlier analyses (>3 SD below average performance; 2 × placebo, 1 × slow CORT). Thus, the results comprise data of 21 men in the placebo group, and 22 men in the rapid CORT and 22 men in the slow CORT group. The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands) and executed in accordance with the declaration of Helsinki.

STUDY DESIGN

Prior to arrival

To minimize differences in baseline cortisol levels we instructed participants not to use any recreational drugs for three days and to refrain from drinking alcohol, exercising, and smoking for 24 h prior to the appointment. Furthermore, participants were requested not to brush their teeth, floss, or eat and drink anything but water for 1 h prior to the session enabling adequate saliva sampling for cortisol assessment. They were asked to take a light lunch and do so no later than 1 h before arrival; their lunch could not contain any citrus products, coffee, tea, milk, or sweets (Maheu et al., 2005). Throughout the entire study period, participants were only given water to drink, except for a scheduled lunch at $t = -180$ min.

Arrival

To reduce the impact of diurnal variation in cortisol levels, all testing was performed in the afternoon, between 12 pm (±30 min)

and 6:00 pm (±30 min), when hormone levels are relatively stable. Upon arrival participants received an information brochure about the procedure, they gave informed consent, and completed an intake questionnaire to ensure that in- and exclusion criteria were met. Thirty minutes after arrival, a first saliva sample was taken, followed by another one 15 min later, in order to measure a reliable baseline level. Participants were asked to complete a first Profile of Mood States (POMS) questionnaire (Reddon et al., 1985; Wald and Mellenbergh, 1990; de Groot, 1992), after which they briefly trained the emotional distraction task to ensure proper performance during scanning. Immediately after the second saliva sample (at $t = -270$ min) participants received the first capsule. During the entire period (∼4 h) prior to scanning, participants waited in a quiet room where they were free to conduct any activities except for anything potentially arousing (e.g., video games). At 60 min prior to the emotional distraction task participants were asked to complete another POMS questionnaire, and received the second capsule. Both drug capsules, containing either 10 mg CORT or placebo (cellulose), were administered orally. This dose is known to elevate salivary cortisol levels to moderate to high stress levels (Kirschbaum et al., 1996; Morgan et al., 2000; Tops et al., 2003), and has been shown to be successful in the induction of corticosteroid effects on declarative memory (Kirschbaum et al., 1996; Tops et al., 2003). Depending on the group to which the participant was (randomly) assigned he received either; the 1st capsule containing placebo, the 2nd containing placebo (placebo group); the 1st capsule CORT, the 2nd placebo (slow CORT group); or the 1st capsule placebo, the 2nd CORT (rapid CORT group). The experiment described here was part of a larger study into the time-dependent effects of corticosteroids on emotional and cognitive brain function. Results on the other tasks have been reported elsewhere (Henckens et al., 2010, 2011a,b,c).

Emotional interference task

The emotional interference task started 60 min after administration of the second capsule (at $t = 0$ min) (**Figure 1A**). In brief, series of colored words were presented to the participants, and they were asked to press one of four buttons as fast as possible for the color in which the word was displayed. Words were presented either in blue, magenta, yellow, or gray, which was counterbalanced across subjects, and colors were matched in luminosity. Colors were chosen for their distinctiveness, while any associations with go- or stop-signals (i.e., green and red) were excluded to prevent their confounding effects on reaction times, inducing increased variability between colors. Participants used both their index- and middle fingers to respond, ensuring proper fast responding.

Words belonged to one of two categories, neutral or aversive, and were selected for the emotional valence and arousal ratings of their translation in English in the Affective Norms for English Words (ANEW) database (Bradley and Lang, 1999). Aversive words were selected for their high arousal and low valence, as rated on a 1–9 scale using the Self-Assessment Manikin (SAM) scales (Bradley and Lang, 1994), while neutral words were selected for their low arousal and neutral valence ratings. Subsequently, words were translated in Dutch and categories were matched on average word length [mean ± SEM; 6.63 ± 1.62 (neutral), 6.84 ± 1.85 (aversive)] and word form frequency [1006.56 ± 103.77 (neutral), 920.60 ± 88.97 (aversive)], and lemma frequency [1528.63 ± 154.16 (neutral), 1307.12 ± 135.11 (aversive)] based on the Dutch lexical database CELEX (Baayen et al., 1995). In total, 128 words of each category were selected. To confirm proper valence and arousal levels of these Dutch words, all participants were asked to rate the words one day after the experiment, using the SAM scales (Bradley and Lang, 1994). These ratings confirmed word categorization. The sets of aversive and neutral words differed on arousal [mean ± SEM; 3.79 ± 0.07 (aversive), 1.70 ± 0.04 (neutral), $t_{(254)} = 24.29$, $p < 0.001$] and valence [3.13 ± 0.06 (aversive), (5.31 ± 0.04 neutral), $t_{(254)} = -32.37$, $p < 0.001$].

The total task lasted 12 min and consisted of eight blocks of each category (containing 16 words presented for 1.5 s, 0.15 s ISI, 3.6 s inter-block fixation), supplemented with eight fixation blocks. Words were presented in a pseudo-random color (immediate color repetition was not allowed). Blocks were presented in a

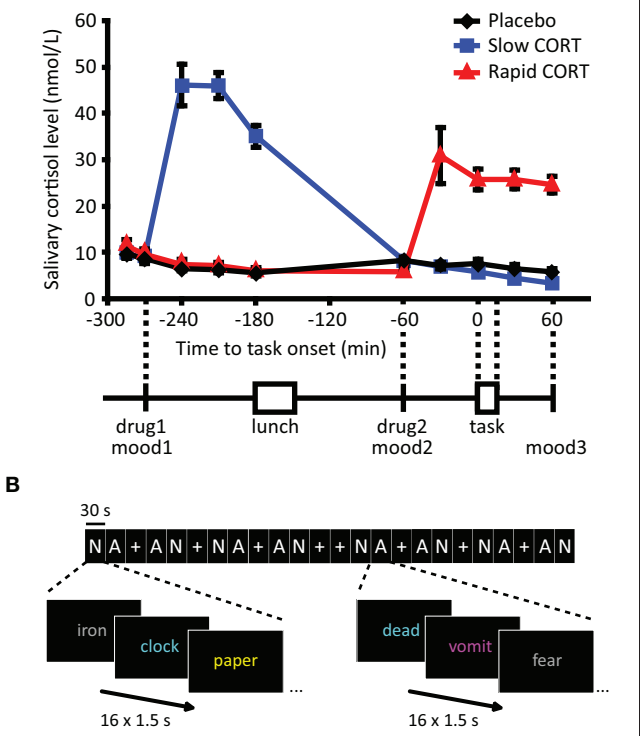

FIGURE 1 | Salivary cortisol data and experimental design. **(A)** Participants received two capsules (drug1 and drug2) containing either 10 mg of hydrocortisone (CORT) or placebo at different time points before the emotional distraction task. Hydrocortisone intake significantly elevated salivary cortisol levels in both hydrocortisone administration groups to levels observed during moderate-to-severe stress (Morgan et al., 2000). **(B)** The emotional distraction task consisted of 30 s-blocks of neutral (N) or aversive (A) words or fixation (+). Participants were requested to button press as fast as possible for the color in which the presented words were displayed. Mood: POMS questionnaire (Reddon et al., 1985; Wald and Mellenbergh, 1990; de Groot, 1992). Error bars represent S.E.M. N.B. In reality Dutch words were used, the words in **Figure 1B** only serve an illustrative purpose.

mirrored design avoiding covariation with linear drift, and adjacent blocks of the same emotion were avoided (**Figure 1B**). To ensure proper understanding and sufficient performance, participants had twice a short two-block practice of nonsense words (random letters); once earlier that day outside the MRI scanner (at $t = -270$ min), and once inside the scanner immediately prior to the actual task ($t = 0$ min). Since participants were instructed to respond as fast and as accurately as possible, task performance was assessed both in terms of reaction times and error rates (Swick and Jovanovic, 2002; Wagner et al., 2006; Weiss et al., 2007; Kertzman et al., 2010). Sustained attentional performance was defined by overall performance on the task combining both neutral and aversive trials, whereas selective attention (i.e., emotional interference) was assessed by contrasting performance between these trials (aversive vs. neutral). The session ended with a high resolution anatomical scan.

PHYSIOLOGICAL AND PSYCHOLOGICAL MEASURES

Saliva collection and analysis

Cortisol levels were measured from saliva at ten time points: two baseline measurements at the beginning of the experimental day ($t = -285$, –270 min), and eight samples thereafter ($t = -240$, -210, -180, -60, -30, 0, 30, and 60 min) to assess cortisol changes throughout the experiment. Saliva was collected using a commercially available collection device (Salivette®, Sarstedt, Germany). For each sample, the participant first placed the cotton swab provided in each Salivette tube in his mouth and chewed gently on it for 1 min to produce saliva. The swab was then placed back in the Salivette tube, and the samples were stored in a freezer at −25°C until assayed. Laboratory analyses were performed at the Department of Biopsychology, TU Dresden, Germany. After thawing, Salivettes were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary free cortisol concentrations were subsequently measured using a commercially available chemiluminescence-immuno-assay (CLIA) with high sensitivity of 0.16 ng/ml (IBL, Hamburg, Germany).

Mood state

To determine whether hydrocortisone administration led to psychological side-effects, mood state was assessed using the POMS questionnaire (Reddon et al., 1985; Wald and Mellenbergh, 1990; de Groot, 1992) at three time points: at the beginning of the experiment ($t = -285$ min), just prior to the intake of the second capsule ($t = -60$ min), and at the end of the experiment ($t = 60$ min).

PHYSIOLOGICAL AND PSYCHOLOGICAL STATISTICAL ANALYSIS

Behavioral and physiological data were analyzed in SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) using repeated measured ANOVAs with drug condition (placebo vs. rapid CORT vs. slow CORT) as between subject factor. Due to the high levels of skewness and kurtosis of the POMS questionnaire (Reddon et al., 1985; Wald and Mellenbergh, 1990; de Groot, 1992), mood data were analyzed using non-parametric tests. Changes over time in mood state were assessed by Friedman tests, and Mann–Whitney U tests were used to assess potential drug effects on mood. Alpha was set at 0.05 throughout.

MRI ACQUISITION

At approximately 4.5 h after arrival, participants were taken to the scanner room and the procedures were explained. Participants lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. They were asked to lie as still as possible, keep their eyes open, and look directly and continuously at the center of the screen in front of them.

Participants were scanned by a Siemens (Erlangen, Germany) MAGNETOM Avanto 1.5 Tesla MRI scanner equipped with an 8-channel head coil. A series of blood oxygenation level dependent (BOLD) T2*-weighted gradient echo EPI images was acquired with the following parameters: TR = 2340 ms, TE = 35 ms, FA = 90°, 32 axial slices approximately aligned with AC-PC plane, slice matrix size = 64 × 64, slice thickness = 3.5 mm, slice gap = 0.35 mm, FOV = 212 × 212 mm^2. Owing to its relatively short TE, this sequence yields optimal contrast-to-noise ratio in the medial temporal lobes. High resolution anatomical images were acquired for individuals by a T1-weighted 3D Magnetization-Prepared RApid Gradient Echo (MP-RAGE) sequence, which employed the following parameters: TR = 2250 ms, TE = 2.95 ms, FA = 15°, orientation: sagittal, FOV = 256 × 256 mm^2, voxel size = 1.0 mm isotropic.

fMRI DATA ANALYSIS

Data were analyzed using Statistical Parametric Mapping software (SPM5; UCL). The first five EPI volumes were discarded to allow for T1 equilibration. Before analysis, the images were motion corrected using rigid body transformations and least sum of squares minimization. Subsequently, they were temporally adjusted to account for differences in sampling times across different slices. All functional images were then coregistered with the high-resolution T1-weighted structural image using normalized mutual information maximization. The anatomical image was subsequently used to normalize all scans into Montreal Neurological Institute (MNI) 152 space. All functional images were resampled to a voxel size of 2 mm isotropic. Finally, all images were smoothed with an isotropic 8 mm full-width-at-half-maximum Gaussian kernel to accommodate residual functional/anatomical variance between subjects. Data were analyzed using a general linear model, in which blocks were modeled based on emotion type. Regressors were temporally convolved with the canonical hemodynamic response function of SPM5. The six covariates corresponding to the movement parameters obtained from the realignment procedure were also included in the model. To reduce unspecific differences between scan sessions, and to correct for any unspecific, global effects of drug intake on hemodynamic response instead of neuronal activation (Desjardins et al., 2001; Peeters and Van Der Linden, 2002), global normalization using proportional scaling was applied. The single subject parameter estimates from each session and condition obtained from the first-level analysis were included in subsequent random-effects analyses. For the second-level analysis, a factorial ANOVA was used, with emotion (neutral vs. aversive) as the within-subject factor, and drug condition (placebo vs. rapid CORT vs. slow CORT) as the between-subject factor.

Statistical tests were family-wise error (FWE) rate corrected ($p < 0.05$) for multiple comparisons at the voxel level for the

main effects, and on the cluster-level using a height threshold of $p < 0.01$ for the drug × emotion interaction, depending on the robustness of the effects. Correction for multiple comparisons was done across the entire brain or for regions of interest (ROI) using a small volume correction. Given the abundance of GRs and MRs in the amygdala (de Kloet, 1991) and its involvement in emotional processing (Phan et al., 2002; Ochsner and Gross, 2005), this region was considered ROI. Data concerning the amygdala was corrected for a reduced search volume, defined as a sphere with 4 mm radius, centered on the locus of previously observed stress effects on amygdala responsivity (Ossewaarde et al., 2010).

FUNCTIONAL CONNECTIVITY ANALYSIS

For connectivity analyses, the time-course of amygdala activity was obtained by extracting the first eigenvariate of the anatomically defined bilateral amygdala [WFU PickAtlas Tool (version 2.4)]. To obtain time-course correlation images irrespective of the experimental conditions, a new statistical model was constructed with the time-course of the amygdala as covariate of interest and the convolved regressors for the experimental conditions and realignment parameters as covariates of no interest, as well as a constant. Time course correlation images were obtained for the amygdala and entered into subsequent random-effects analyses, using a factorial ANOVA with drug condition (placebo vs. rapid CORT vs. slow CORT) as the between-subject factor. Similar to the conventional fMRI analyses, statistical tests were FWE rate corrected ($p < 0.05$) for multiple comparisons at the voxel level for the main effects of amygdala coupling across drug conditions, and on the cluster-level using a height threshold of $p < 0.01$ to assess cortisol effects. Visualizations of activations were created in SPM5 by superimposing statistical parametric maps thresholded at $p < 0.01$ uncorrected (unless specified otherwise) onto a canonical T1-weighted image in a standard MNI 152 space.

RESULTS

PHYSIOLOGICAL AND PSYCHOLOGICAL MEASURES

As expected, oral administration of 10 mg hydrocortisone increased salivary cortisol levels to those observed during moderate-to-severe stress (Morgan et al., 2000) (**Figure 1A**), which was evidenced by a significant main effect of group [$F_{(2,\ 62)} = 41.63$, $p < 0.001$] and a time × group interaction [$F_{(18,\ 110)} = 29.04$, $p < 0.001$). Increased levels were observed from 30 min post-administration onwards in both hydrocortisone administration conditions, and the levels remained elevated for at least 90 min. As intended, treatment resulted in elevated cortisol levels during fMRI scanning in the rapid hydrocortisone condition, whereas the levels in the slow condition had already returned to baseline.

Post-experiment debriefing showed that participants were unable to identify the substance received. As expected, hydrocortisone administration did not affect mood as assessed three times during the experiment using the POMS questionnaire (Reddon et al., 1985; Wald and Mellenbergh, 1990; de Groot, 1992) (**Table 1**). Although significant reductions in levels of depression scores [Friedman's ANOVA; $\chi^2_{(2)} = 9.16$, $p = 0.01$], anger scores [$\chi^2_{(2)} = 7.93$, $p = 0.02$], vigor scores [$\chi^2_{(2)} = 73.17$, $p < 0.001$], and tension scores [$\chi^2_{(2)} = 22.41$, $p < 0.001$] were observed over the course of the experiment, and levels of fatigue [$\chi^2_{(2)} = 48.41$, $p < 0.001$] increased, none of these factors were affected by drug administration. Groups did not differ on any aspect of mood state at baseline, nor at any other time point during the experiment (all $p > 0.1$). Changes in mood over time were also not affected by drug administration (all $p > 0.05$). Hence, differences in brain activity found between drug conditions cannot readily be explained by any psychological effects of drug administration.

EMOTIONAL INTERFERENCE TASK

Overall task performance, assessing sustained attention by combining results on the neutral and aversive trials, was not significantly affected by hydrocortisone intake. No effects of group were found on reaction times [$F_{(2,\ 62)} = 1.49$, $p = 0.233$]. Analysis of the error rates, however, seemed to indicate better performance due to the slow effects of corticosteroids. The slow corticosteroid group seemed to make fewer errors than the other groups, but significance just reached trend level [main effect of group: $F_{(2,\ 62)} = 2.33$, $p = 0.106$, slow CORT vs. placebo: $F_{(1,\ 41)} = 2.26$, $p = 0.141$, slow CORT vs. rapid CORT: $F_{(1,\ 42)} = 6.27$, $p = 0.016$]. Processes of sustained attention might thus benefit from the slow effects of corticosteroids.

Next, we tested for the effects of emotion on task performance. As expected, emotion interfered with selective attention. Participants responded significantly slower to aversive words compared to neutral ones [Main effect of emotion (emotional interference): $F_{(1,\ 62)} = 9.42$, $p = 0.003$]. Emotion did however not significantly affect error rates [$F_{(1,\ 62)} < 1$] (**Table 1**).

Table 1 | Behavioral performance on the emotional interference task.

	Placebo	Rapid CORT	Slow CORT
Reaction times neutral, in ms	674 (17)	702 (23)	650 (20)
Reaction times aversive, in ms	687 (17)	709 (23)	664 (20)
Emotional interference on reaction times, in Δms	12 (7)	7 (7)	14 (6)
Correct responses neutral, in %	95.03 (1.03)	95.29 (0.64)	96.63 (0.64)
Correct responses aversive, in %	95.24 (0.90)	93.96 (0.77)	96.80 (0.63)
Emotional interference on correct responses, in Δ%	0.21 (0.44)	−1.33 (0.50)*	0.17 (0.77)
–	–	–	–

Mean values (SEM). All groups were similarly affected in their reaction times by emotional interference, displaying slower responses to aversive compared to neutral words. However, the rapid corticosteroid (CORT) group specifically was impaired in its accuracy of responding due to emotional interference. The rapid CORT group made fewer correct responses to the aversive compared to the neutral words than placebo ($p < 0.05$), and this comparison reached a trend for the difference with corticosteroids' slow effects.*

Hydrocortisone intake had no significant influence on the emotion effect on reaction times [Emotion × group interaction: $F_{(2, 62)} < 1$], but did show a trend for the influence of corticosteroids on the emotion effect on correct response rate [$F_{(2, 62)} = 2.20$, $p = 0.12$]. This trend appeared to be caused by the rapid corticosteroid (CORT) group, which was significantly affected [$T_{(21)} = -2.65, p = 0.015$] in its accuracy of responding by emotional interference, whereas both other groups were not (both p's> 0.6). The rapid effects of corticosteroids induced fewer correct responses for the aversive relative to the neutral words than placebo [Emotion group interaction (rapid CORT vs. placebo): $F_{(1, 41)} = 5.23$, $p = 0.03$], and this comparison reached a trend for the difference with corticosteroids' slow effects [Emotion × group interaction (rapid CORT vs. slow CORT): $F_{(1, 42)} = 2.65$, $p = 0.11$)] No such differences were observed between the slow effects of corticosteroids and placebo [Emotion × group interaction (slow CORT vs. placebo): $F_{(1, 41)} < 1$]. Thus, the rapid effects of corticosteroids appeared to increase the susceptibility to emotional interference.

BRAIN ACTIVATION DATA

We first identified brain regions involved in task execution in comparison to rest (fixation). As expected, task execution recruited a large cluster of brain regions involved in visual processing, including the bilateral middle and inferior occipital lobe, calcarine, cuneus, cerebellum, lingual gyrus, and fusiform gyrus (**Table 2**). Moreover, brain regions involved in motor and executive function were activated, including the angular, parietal and precentral cortex, and the superior and middle frontal gyrus. Regions deactivated by task execution included regions of the default mode network; the medial PFC (superior, middle, and orbitofrontal cortex), the temporal lobe (covering the hippocampus and amygdala), cingulate gyrus (posterior, middle, and anterior), precuneus and cuneus, and regions within the cerebellum (**Table 2**).

Subsequently, we tested for the effect of emotion during task execution. Regions that were more active during the processing of aversive compared to neutral words were mainly language-related areas in the left inferior frontal cortex (BA45), left inferior orbitofrontal cortex, superior temporal pole, and the middle temporal lobe (BA38). No regions were more active during the processing of neutral compared to aversive words (**Table 2**).

Next, we examined how corticosteroids affected sustained attentional processing. Looking into the main effect of drug (contrasting all three drug conditions) revealed a main effect in the cuneus [$(-18, -72, 36)$, $F_{(2, 124)} = 16.36, p = 0.022$], which was driven by reduced activity due to the *slow* effects of corticosteroids [placebo > slow CORT: $(-18, -72, 36)$, $T_{(124)} = 5.51$, $p = 0.004$]. Under basal (i.e., placebo) conditions this part of the cuneus was activated during task-execution, suggesting its involvement in visual processing (Hahn et al., 2006), but the slow effects of corticosteroids reduced its activation. In contrast, we did not find any main effect on brain processing in the rapid corticosteroid condition.

To test how corticosteroids influenced selective attention, or emotional interference, we next checked for a drug × emotion interaction in the brain. Indeed, we found a trend toward such interaction in the amygdala specifically [$(20, -4, -16)$, $F_{(2, 124)} = 5.02$, $p_{SVC} = 0.077$] (**Figure 2A**). This interaction appeared to be driven by an increased effect of emotional interference due to the *rapid* effects of corticosteroids [Emo(rapid CORT) > Emo(placebo): $(20, -4, -16)$, $T_{(124)} = 3.15$, $p_{SVC} = 0.037$; Emo(rapid CORT) > Emo(slow CORT): $(22, -4, -18)$, $T_{(124)} = 2.49$, $p_{SVC} = 0.071$]. Whereas amygdala responsivity with placebo or under the influence of slow effects of corticosteroids did not distinguish between neutral and aversive words, suggesting sufficient suppression of emotional interference, the rapid effects of corticosteroids-induced significantly higher amygdala responses while color-naming aversive compared to neutral words [$(22, -2, -16)$, $T_{(124)} = 3.96, p_{SVC} = 0.036$] (**Figure 2B**). Thus, the increase in emotional interference observed in behavioral performance due to the rapid corticosteroid effects, was reflected in the brain as an enhanced emotion effect in the amygdala, indicating failed suppression of emotional processing.

BRAIN CONNECTIVITY DATA

Next, we assessed whether the corticosteroid-induced alterations in amygdala responses were related to any changes in functional connectivity of this region to the rest of the brain. First, brain regions were identified that were functionally coupled, i.e., displaying significantly correlated time courses of activity, to the amygdala across all drug conditions. Activity in the amygdala was positively associated to activity in a large cluster covering the bilateral amygdala itself, thalamus, pallidum, putamen, hippocampus, parahippocampal gyrus, fusiform, middle and superior temporal lobe, insula, and inferior, middle, and superior orbitofrontal cortex. Other regions positively associated with amygdala activity included the brain stem (including the LC), regions within the anterior and middle ACC, superior frontal cortex, and regions within the cerebellum (**Table 3**). Conversely, amygdala activity was negatively associated with activity in frontal regions such as the medial superior frontal gyrus, superior, middle, and inferior frontal gyrus, and regions within the anterior and middle ACC, and with the insula, brain stem, and cerebellum. Overall, these patterns of functional connectivity are in line with previous studies (Roy et al., 2009; van Marle et al., 2010; Henckens et al., 2011b) and support models of emotion processing that suggest reciprocal ventral and dorsal systems (Phillips et al., 2003). However, one remarkable difference is the negative coupling of the amygdala to the insula observed in this study. This might suggest that the insula, during task execution, is functioning as part of an executive network (Binder et al., 2004; Nee et al., 2007) instead of the salience network (Seeley et al., 2007).

Second, when contrasting connectivity patterns between drug conditions, the *rapid* effects of corticosteroids influenced amygdala connectivity to regions involved in task execution including the middle frontal and precentral gyrus [$(42, 26, 40)$, $T_{(62)} = 4.79$, $p < 0.001$], and the postcentral gyrus [$(-52, -20, 34)$, $T_{(62)} = 4.39$, $p = 0.005$] (**Figure 3A**). Whereas these structures displayed *negative* connectivity with the amygdala under basal (i.e., placebo) conditions, the rapid corticosteroid effects induced

Table 2 | Peak voxels and corresponding *T* values of significantly activated clusters in main effects of task, emotion, and drug.

	MNI-coordinates			Peak *T*-value
	x	*y*	*z*	
POSITIVE EFFECT OF TASK				
Extended cluster covering visual processing areas: inferior, middle, and superior occipital gyrus, calcarine, lingual gyrus, fusiform gyrus, cerebellum	16	−92	−4	8.90***
	−16	−92	−8	23.28***
Supplemental motor area Middle cingulate cortex	−4	8	50	20.12***
Precentral cortex, R Superior frontal cortex, R Inferior parietal cortex, R Angular cortex, R	32	−56	52	14.15***
Inferior parietal cortex, L Angular cortex, L	−30	−52	48	19.06***
Precentral cortex, L Superior frontal cortex, L	−28	−4	54	15.50***
Middle frontal cortex, R	48	38	30	6.95***
Middle frontal cortex, L	−34	52	30	5.10*
Inferior frontal cortex, L	−40	28	24	5.93***
Insula, R	34	24	2	4.91*
Insula, L	−32	20	6	7.21***
Thalamus, R	12	−16	10	8.37***
Thalamus, L Putamen, L	−10	−18	10	10.65***
Putamen, R	26	4	−6	7.48***
Brain stem	−6	−28	−4	5.39**
Cerebellum, L	−20	−62	−50	5.66**
NEGATIVE EFFECT OF TASK				
Activation cluster covering the bilateral angular cortex, middle occipital cortex, cuneus, precuneus, posterior and middle cingulate cortex, middle temporal gyrus, lingual gyrus, parahippocampus gyrus, hippocampus, amygdala	−44	−76	32	17.86***
	46	−76	28	
Activation cluster covering the middle frontal cortex, superior frontal cortex, superior medial cortex, anterior cingulate cortex, rectus and middle orbitofrontal cortex	28	26	40	14.05***
	−24	30	44	
Inferior frontal cortex, L	−46	42	6	5.02*
	−58	32	2	4.96*
Middle orbitofrontal cortex, L	−48	50	0	4.91*
Insula, R	36	6	12	5.91***
Lingual gyrus, L	−14	−60	−4	5.57**
Cerebellum, R (Crus2)	44	−66	−40	6.84***
Cerebellum, L (Crus2)	−42	−70	−40	5.10*
Cerebellum, R (9)	6	−50	−42	5.97***
POSITIVE EFFECT OF EMOTION				
Inferior frontal cortex and inferior orbitofrontal cortex, L	−44	32	0	5.95***
Superior temporal pole, L	−58	6	−10	5.57**
Middle temporal pole, L	−52	14	−24	5.21*
MAIN EFFECT OF DRUG				
Placebo > slow CORT				
Cuneus, L	−18	−72	36	5.51**

*The peak x, y, z coordinates are given in MNI152 standard space coordinates. L and R denote left and right. Main effects of task are all thersholded at $p < 0.05$ FWE corrected at the voxel-level. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.*

positive connectivity between the amygdala and this executive network. In addition, the slow effects of corticosteroids altered amygdala connectivity to the left insula [(−38, 10, −8), $T_{(62)} = 3.85$, $p = 0.001$]. The negative amygdala-insula coupling observed under placebo conditions was weakened by the slow effects of corticosteroids (**Figure 3B**).

DISCUSSION

In this study we investigated the time-dependent effects of corticosteroids on selective attention and emotional interference. The results suggest that the rapid effects of corticosteroids specifically increased emotional interference in terms of error rate, which was associated with reduced amygdala inhibition to aversive words. Moreover, they induced enhanced amygdala connectivity with frontoparietal brain regions, possibly reflecting increased influence of the amygdala on an executive control network. In contrast, the slow corticosteroid effects seemed to modulate the neural correlates of sustained attention by decreasing cuneus' activity, potentially indicating reduced stimulus-driven (bottom-up) attentional processing. Furthermore, they altered the coupling of the amygdala to the insula, which might affect emotional interference. Thus, corticosteroids seemed to modulate different aspects of attentive processing in a time-specific manner.

Previous animal work has indicated that corticosteroids, next to their well-established slow genomic effects, also exert rapid non-genomic effects on brain function (Joels et al., 2006). In the amygdala, the hormones have been shown to rapidly affect neuronal plasticity by binding to MR, leading to an increase

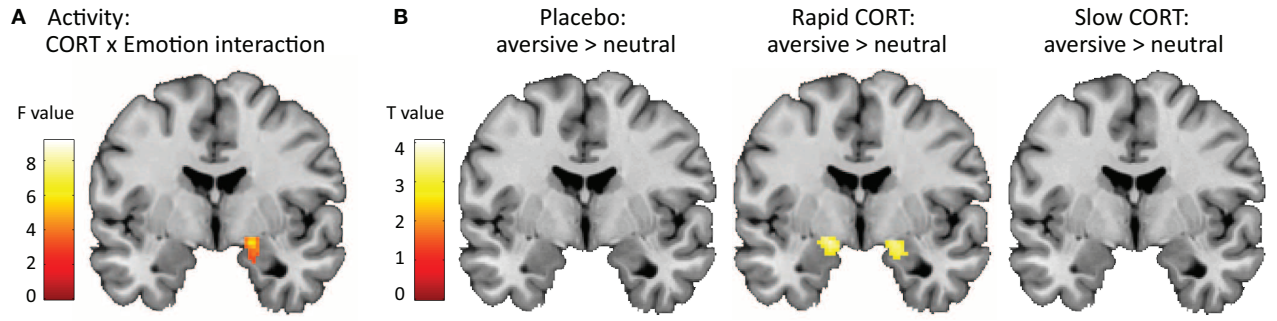

FIGURE 2 | Effects of corticosteroids on amygdala activity. **(A)** Hydrocortisone administration induced trend of a corticosteroid *x* emotion interaction in the amygdala ($y = -4$). For visualization purposes the statistical parametric map is thresholded at $p < 0.05$ uncorrected with a minimal cluster-size of 250 voxels. **(B)** This interaction appeared to be driven by a significant effect of emotion in the amygdala due to the rapid effects of corticosteroids, suggesting insufficient suppression of emotional interference in this group. The amygdala in the placebo and slow corticosteroid group did not distinguish between the processing of aversive vs. neutral words. For visualization purposes the statistical parametric maps are thresholded at $p < 0.005$ uncorrected with a minimal cluster-size of 25 voxels.

in glutamate release (Karst et al., 2010). At the same time, the binding of primarily intracellular GRs initiates a corticosteroid-induced genomic cascade that modulates the expression of over 200 genes (Datson et al., 2001). Here, we aimed to dissociate these two effects experimentally by administering 10 mg of hydrocortisone at either 60 or 270 min prior to the emotional distraction task. The timing of the rapid corticosteroid condition was based (A) on a previous study in our lab revealing an elevation in human salivary cortisol levels from 30 min after hydrocortisone intake onwards (Henckens et al., 2011a), (B) previous rodent studies revealing a ∼20 min delay between elevations in corticosteroid levels in plasma and brain (Droste et al., 2008), and (C) rapid effects of corticosteroids administered directly to amygdala slices in rodents from ∼10 min post administration onwards (Karst et al., 2005). The genomic effects of corticosteroids on the other hand generally do not start earlier than at least 3 h after exposure to high corticosteroid levels *in vivo* (Joels et al., 2003; Morsink et al., 2006) and these effects last for hours (Joels and de Kloet, 1992; Joels et al., 2003). Thus, administration of hydrocortisone at 60 min prior to scanning probably caused sufficiently high levels of the hormone in the brain to evoke rapid non-genomic effects whereas this delay was too short to allow development of gene-mediated events. Conversely, when hydrocortisone was applied at 270 min prior to testing, hormone levels were back to baseline levels again during the behavioral task, making non-genomic actions not likely to happen, yet allowed enough time for the gene-mediated actions to occur. For these reasons, the rapid corticosteroid effects observed here most likely reflect corticosteroid's non-genomic effects, whereas the slow corticosteroid effect most likely involve a gene-mediated mechanism, although obviously this cannot be proven in the human brain.

Here we showed that the rapid corticosteroid effects increase emotional interference. Participants had difficulty ignoring emotional input; they made more mistakes for the aversive words and failed to down-regulate their amygdala response to this input. These findings are in line with the hypothesis that the rapid effects of corticosteroids act in concert with catecholamines in response to stress to optimize rapid adaptive behavior (Roozendaal et al., 2006; Diamond et al., 2007). Previous studies have already shown that during acute stress, the brain switches into a hypervigilant stimulus-driven reflex-like mode of processing, characterized by heightened overall attention, but also by increased susceptibility to (emotional) distraction (Skosnik et al., 2000; Braunstein-Bercovitz et al., 2001; Henderson et al., 2012) and impaired flexibility (Plessow et al., 2012). Performance on relatively easy (e.g., perceptual) tasks seems to benefit by this state of increased arousal, but performance on more difficult tasks requiring executive control seems to deteriorate (Jasinska et al., 2012; Lee et al., 2012). Recent neuroimaging studies have indicated that this hypervigilant brain state is associated with enhanced sensory processing (Henckens et al., 2009), increased amygdala responsivity to emotional input (van Marle et al., 2009) and tightened amygdala connectivity to the salience network (van Marle et al., 2010). Moreover, PFC function gets deteriorated (Qin et al., 2009). This state-change of brain processing has previously been attributed to the actions of catecholamines on brain function (Arnsten and Li, 2005; Hermans et al., 2011; Qin et al., 2012). Our findings of increased emotional interference indicate that, next to the effects of catecholamines, the rapid effects of corticosteroids also contribute to this state of hypervigilance.

Earlier animal work already indicated that corticosteroids' rapid non-genomic effects, mediated by membrane-bound steroid receptors, boost amygdala activity (Kavushansky and Richter-Levin, 2006; Karst et al., 2010), while impairing PFC function (Barsegyan et al., 2010). Next to that, evidence for corticosteroid-modulation of noradrenergic function is abundant, both in animal (Roozendaal et al., 2006; McReynolds et al., 2010; Zhou et al., 2012) and human research (van Stegeren et al., 2007, 2010). Recent drug administration studies in humans for example showed that corticosteroid administration in combination with the administration of reboxetine (a noradrenaline-reuptake inhibitor) induced a negative response bias in the amygdala (Kukolja et al., 2008), and boosted emotion-induced retrograde amnesia (Hurlemann et al., 2007), in line with our findings of increased distraction by aversive input and increased susceptibility to the effects of emotion, respectively.

Table 3 | Peak voxels and corresponding *T* values of significantly activated clusters that show functional coupling with the bilateral amygdala.

	MNI-coordinates			Peak *T*-value
	x	*y*	*z*	
POSITIVE OVERALL AMYGDALA COUPLING				
Extended cluster covering the bilateral amygdala, brainstem (LC), thalamus, pallidum, putamen, hippocampus, parahippocampal gyrus, fusiform gyrus, middle and superior temporal lobe, inferior,middle and superior orbitofrontal cortex, anterior cingulate cortex and cerebellum	22	−2	−16	43.38***
Superior frontal cortex, R	20	70	8	5.45*
Middle cingulate cortex	0	0	46	5.50*
Caudate, L	−8	16	22	6.83***
Thalamus, R	16	−20	16	5.66*
Midbrain	14	−28	−26	7.99***
Cerebellum Crus2, L	−36	−80	−36	6.45***
NEGATIVE OVERALL AMYGDALA COUPLING				
Anterior and middle cingulate cortex, superior medial cortex, R	2	28	10	9.85***
Middle cingulate cortex, R	22	−16	32	9.08***
Middle cingulate cortex, L	−24	−4	36	9.80***
Inferior frontal gyrus, R	64	18	18	5.81**
Inferior frontal gyrus, L	−52	28	22	9.19***
Inferior frontal gyrus, L	−42	14	32	5.40*
Inferior and middle frontal gyrus, L	46	40	26	6.57***
Middle frontal gyrus, L	−26	48	30	5.59*
Middle and superior frontal gyrus, L	−20	54	30	5.56*
Superior frontal gyrus, R	20	54	32	7.37***
Superior frontal gyrus, R	20	18	56	5.81**
Insula, R	−44	−2	6	8.70***
Insula, L	44	−4	4	8.86***
Thalamus, R	0	−18	6	9.42***
Middle temporal gyrus, R	58	−42	4	7.60***
Parahippocampal gyrus, R	16	−28	−16	8.20***
Inferior occipital and lingual gyrus, R	36	−86	−6	7.02***
Inferior occipital and lingual gyrus, middle temporal gyrus, L	−26	−90	−4	7.16***
Inferior parietal cortex, L	−50	−50	36	5.53*
Cerebellum, L	−18	−30	−18	5.85**
Cerebellum and brain stem, L	−16	−44	−28	13.39***
Brain stem	0	−8	−16	5.72*

*The peak x, y, z coordinates are given in MNI152 standard space coordinates. L and R denote left and right. Overall amygdala coupling is thresholded at $p < 0.05$ FWE corrected at the voxel-level, *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ whole-brain corrected.*

However, administration of hydrocortisone on brain function has produced quite conflicting results. One potential confounding factor is the type of brain function investigated in these studies. A widely accepted phenomenon from memory research for example is that corticosteroids influence processes of memory encoding and consolidation in an opposite manner than memory retrieval (Roozendaal, 2002), although both processes heavily depend on hippocampal function. Nevertheless, corticosteroids boost memory encoding and associated hippocampal activation (van Stegeren et al., 2010), whereas they impair hippocampal activation during memory retrieval (de Quervain et al., 2003). Similarly, differential effects of corticosteroids have been observed depending on the function studied of the PFC (Henckens et al., 2011a,c) and amygdala (Henckens et al., 2010; Lovallo et al., 2010; Tabbert et al., 2010; van Stegeren et al., 2010). Another crucial factor possibly explaining the discrepancies between studies is the dose in which hydrocortisone was administered (Lupien et al., 2007). Previous research has indicated that corticosteroids influence memory processing in an inverted U-shaped relationship (Lupien et al., 1997), with both low and high doses impairing memory consolidation, while moderate levels improve consolidation (Roozendaal, 2000). Also the effects of corticosteroids on working memory (Lupien et al., 1999) and startle response (Buchanan et al., 2001) have been shown to be dose-dependent. This non-monotonic relationship between corticosteroids and their effects on cognitive function is hypothesized to be related to the differential activation of the MRs and GRs, which show distinct affinity for the hormone (de Kloet, 2003). The doses used in previous research range from 10–100 mg of hydrocortisone, and obviously produce different results. A recent review on the immediate effects of corticosteroids on selective attention concluded that corticosteroids actually facilitate stress-coping via the inhibition of autonomic processing of goal-irrelevant threatening information, when administered in a dose of >35 mg (Putman and Roelofs, 2011). The authors admit that lower doses might lead to different results. Here, we used a dose of 10 mg of hydrocortisone to mimic cortisol elevations in response to a moderate-to-severe stressor, and show that the rapid effects of corticosteroids increase emotional interference during executive function.

Moreover, the rapid effects of corticosteroids also affected amygdala connectivity. Connectivity to the middle frontal gyrus and precentral and postcentral gyrus was increased 60 min after hydrocortisone administration. Being part of an executive and

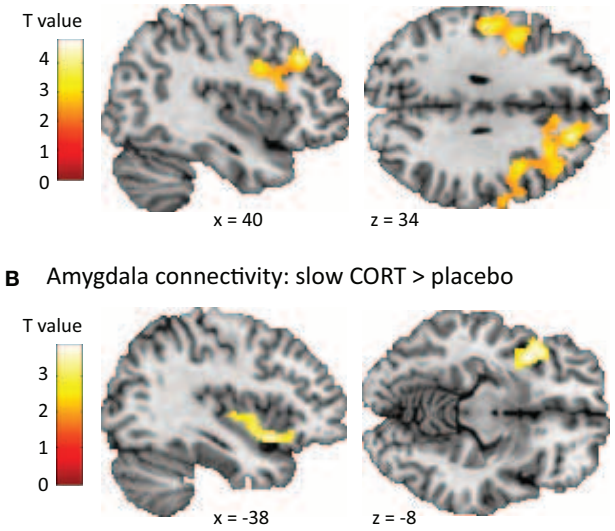

FIGURE 3 | Effects of corticosteroids on amygdala connectivity. (A) The rapid effects of corticosteroids increased the functional connectivity of the amygdala to regions involved in task execution (middle frontal gyrus, precentral gyrus, and postcentral gyrus), potentiating its influence on task execution. **(B)** The slow effects of corticosteroids disrupted the negative connectivity between the amygdala and insula, attenuating the effects the amygdala can exert on task execution. For visualization purposes the statistical parametric maps are thresholded at $p < 0.01$ uncorrected with a minimal cluster-size of 250 voxels.

motor network, these regions were recruited during task execution (**Table 2**). Whereas the pre- and postcentral gyrus are involved in more basic motor functions, the middle frontal gyrus is known for its role in response selection and suppression of automatic response tendencies (Forstmann et al., 2008), as well as in resolving interference (Nee et al., 2007). Under basal (i.e., placebo) conditions, all of these regions were negatively coupled to the amygdala, underlining their opposing roles in task execution. In contrast, the rapid effects of corticosteroids led to positive coupling between the amygdala and the executive network. Although one cannot infer any directionality from such correlative evidence, this might be suggestive for increased influence of the amygdala on brain regions crucially involved in task execution. This interpretation of the data would fit with the increase in emotional interference, but future research is needed to test this assumption.

Besides these rapid effects of corticosteroids on emotional interference we showed that the slow effects of corticosteroids modulated the neural correlates of sustained attention by reducing activity of the cuneus. This brain region is involved in basic visual processing, and has been shown to be engaged by stimulus-driven, bottom-up attentional processing (Hahn et al., 2006). Previous research has indicated that acute stress boosts visual processing (Henckens et al., 2009; van Marle et al., 2009), and more specifically, the rapid effects of corticosteroids have been shown to increase cuneus' regional cerebral activity during rest (Ganguli et al., 2002; Strelzyk et al., 2012). These data suggest that stress, or the rapid effects of corticosteroids, boost early visual processing and thereby shift the brain into a rather automated visually guided response-mode, which serves the fight-or-flight response. The slow effects of corticosteroids might in turn counteract these effects by reducing cuneus' activity, and shifting the brain back from a stimulus-driven response mode to a more controlled mode. This rationale fits with the general idea about the restorative role the slow corticosteroid effects serve in the aftermath of stress in order to return to homeostasis (de Kloet et al., 2005). The slow effects of corticosteroids have been shown to divert energy supply to challenged tissues and control the excitability of neuronal networks (de Kloet et al., 2008). Evidence from recent human neuroimaging studies also supports this hypothesis by showing that corticosteroids' slow effects are the exact opposite of those of acute stress. Whereas acute stress impairs PFC function (Qin et al., 2009) and boosts amygdala activity (van Marle et al., 2009), the slow effects of corticosteroids' enhanced PFC function (Henckens et al., 2011c) and suppressed amygdala responsivity to faces (Henckens et al., 2010). Here, we showed that the slow effects of corticosteroids reduced cuneus' activity, which might be another means to restore proper brain function in the aftermath of stress.

The slow effects of corticosteroids also reduced the negative connectivity between the amygdala and left anterior insula, seen under placebo conditions. The amygdala and anterior insula share widespread reciprocal connections (Mufson et al., 1981), and are known for their role in mediating autonomic arousal as part of the so-called salience network (Seeley et al., 2007). Connectivity in this network is known to be increased by acute stress (van Marle et al., 2010; Hermans et al., 2011) and serve the fight-or-flight response by promoting the information exchange between regions involved in autonomic-neuroendocrine control and vigilant attentional reorienting. However, next to the typical link to cortical control of autonomic function, the insula is consistently reported to be activated during experiments in which task conditions are challenging, and decisions have to be made (Binder et al., 2004). Therefore, it was recently suggested (Eckert et al., 2009) that the anterior insula engages brain regions selectively responsive to task demands and attention systems critical for coordinating task performance. In line with this hypothesis, a recent meta-analysis on neuroimaging studies into the resolution of interference pointed toward the involvement of the anterior insula in resolving interference (Nee et al., 2007). Although one cannot infer directionality from the correlative analysis performed, one could speculate that the negative connectivity between the amygdala and insula observed in our experiment reflects the interference of the amygdala with proper task performance. By reducing this connectivity, the slow effects of corticosteroids might attenuate the effect the amygdala can exert on task execution. Therefore, also the reduced amygdala-insula connectivity could entail a mechanism by which the slow effects of corticosteroids restore brain function in the aftermath of stress. However, this interpretation should be tested in future research.

Some limitations to the study should also be mentioned. First of all, this study involved a pharmacological manipulation to model the effects of corticosteroids, which does obviously not

capture all aspects of the complex stress response. Real-life cortisol release in response to stress is accompanied by the release of many other neuromodulators, such as NE, corticotrophin-releasing hormone, dopamine, and serotonin (Joels and Baram, 2009), with which corticosteroids could potentially interact. Because we did not induce stress, the generalization from our results to stressful situations remains speculative. Nevertheless, mere administration of hydrocortisone reveals a cleaner mechanistic account for the corticosteroid effect, which was the aim of this study.

Secondly, we investigated men only, thus the obtained results cannot be readily generalized to women. Hydrocortisone administration has been shown to induce distinct effects in men and women, both in behavior (Andreano and Cahill, 2006; Bohnke et al., 2010) and brain activation (Stark et al., 2006; Merz et al., 2010). Although important, sex-differences were beyond the scope of this initial study, which is why we opted to recruit male subjects only, allowing easier comparison with an earlier study in stressed individuals (Henckens et al., 2009).

Furthermore, the increase in emotional interference by the rapid effects of corticosteroids was only observed in terms of error rate (i.e., lower correct response rate) and not in terms of reaction times (i.e., slower responding). On the other hand, the overall effect of emotion was only observed for reaction times. One could suggest that these findings reflect a shift in response strategy induced by the rapid effects of corticosteroids rather than an increase in emotional interference (Chen and Johnson, 1991). This would mean that the rapid CORT group shifted from an accuracy-driven strategy, affecting reaction times while optimizing accuracy, toward a speed-driven strategy, affecting error rates but optimizing speed. However, besides the observed differences (i.e., increase in emotional interference) in error rate one would then also expect differences (i.e., reduced emotional interference effect) in reaction times. This does not seem to be the case. No differences between groups in overall reaction times [$F_{(2,\ 62)} = 1.49$, $p = 0.23$], nor emotional interference in reaction times [$F_{(2,\ 62)} < 1$] were observed, indicating that the rapid CORT group is not different from the other groups in terms of reaction times. In terms of error rate, the rapid CORT group was significantly affected, indicating increased emotional interference in this group. Moreover, if it would be the case that the rapid CORT group shifted away from an accuracy-driven toward a speed-driven strategy, one would expect faster responding in this group, which is also not observed. All in all, it is difficult to speculate about the reason why we did find interference effects in one measure and not the other. However, small behavioral effects are not unprecedented in previous studies (Haas et al., 2006; Mincic, 2010). Importantly, behavioral emotional interference effects are most consistently observed in psychopathological groups in response to words that are specific to their disorder (Dalgleish, 1995; Williams et al., 1996), and in normal subjects when the words are related to current concerns endorsed by them (Gilboa-Schechtman et al., 2000), reflecting their attentional bias. Overall, in normal subjects, behavioral interference by emotional distracters is either not detected at all (Williams et al., 1996), is depending on specifc personality traits such as trait anxiety (Richards et al., 1992; Krug and Carter, 2010) or extraversion (Haas et al., 2006) or habituates rapidly (McKenna, 1986; Compton, 2003). We used rather general aversive words, non-specific to the participants, which might explain why we only find overall effects in terms of reaction times and not error rate. Nevertheless, emotional interference can express itself in both reaction times and number of errors (Swick and Jovanovic, 2002; Wagner et al., 2006; Weiss et al., 2007; Kertzman et al., 2010; Crocker et al., 2012).

Furthermore, the slow effects of corticosteroids manifested themselves only as altered brain activity, without translating to behavioral differences. The most likely explanation for the absence of a (clear) behavioral effect might be a lack of power of our neuroimaging study. Compared to behavioral studies, which tend to test large groups of subjects, our sample size is relatively small. Brain activity is supposed to be a more sensitive measure than behavioral output, which is the consequence of many parallel neural operations. Therefore, regional differences in brain activity are more easily detected with smaller samples, but these samples offer little power to observe behavioral effects. However, a trend toward a better overall performance due to the slow effects of corticosteroids was observed in the behavioral data, since the slow corticosteroid group tended to make fewer errors than the other groups. These data therefore seem to support the enhanced sustained attention due to the slow effects of corticosteroids, but future studies using larger sample sizes are needed to confirm these effects.

Lastly, we interpreted the effects of emotional interference as a measure of selective attention, because this condition requires the attentional selection of relevant features while ignoring competing information. However, these findings cannot be readily generalized to other selective attention tasks. The emotional component might be critical in interfering with attentional processing, as corticosteroids have been shown to exert more prominent effects on the processing of emotional compared to neutral information (Roozendaal et al., 2006). Therefore, future studies are necessary to determine whether the rapid effects of corticosteroids can be regarded as generally or emotion-specifically interfering with the neural processing of selective attention.

In conclusion, these results suggest that the rapid effects of corticosteroids increase emotional interference and selective attention. Although increased susceptibility to interference, and thus impaired selective attention, is often seen as a maladaptive response of attenuating higher-cognitive function, it is first and foremost a highly adaptive response in threatening situations. Wide-spread, unfocussed attention might contribute to the detection of potential threats in the environment (Aston-Jones and Cohen, 2005), enhancing an organism's chances of survival. Moreover, it might have beneficial effects on memory processing (Henckens et al., 2009), since additional environmental cues can also be encoded during a salient event. Normalization some time after the stressful event is equally important. When not properly regulated, the increased processing of irrelevant emotional input due to combined corticosteroid and noradrenergic actions as well as the lack of normalization can be detrimental. Patients with stress-related disorders such as depression and PTSD are known to be compromised in their capability to suppress emotional

irrelevant information (Paunovi et al., 2002; Mitterschiffthaler et al., 2008), which is thought to reflect their attentional bias toward negative emotional information (Williams et al., 1996). Notably, these illnesses are characterized by aberrant corticosteroid signaling (Yehuda et al., 2001). Our results provide thus a mechanistic account for these problems with attention and emotional interference, by showing that the rapid effects of corticosteroids interfere with amygdala function, and the slow effects modulate the neural correlates of sustained attention.

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Neural mechanisms of attentional control differentiate trait and state negative affect

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The present research examined the hypothesis that cognitive processes are modulated differentially by trait and state negative affect (NA). Brain activation associated with trait and state NA was measured by fMRI during an attentional control task, the emotion-word Stroop. Performance on the task was disrupted only by state NA. Trait NA was associated with reduced activity in several regions, including a prefrontal area that has been shown to be involved in top-down, goal-directed attentional control. In contrast, state NA was associated with increased activity in several regions, including a prefrontal region that has been shown to be involved in stimulus-driven aspects of attentional control. Results suggest that NA has a significant impact on cognition, and that state and trait NA disrupt attentional control in distinct ways.

Keywords: negative affect, attentional control, prefrontal cortex, emotion, fMRI

INTRODUCTION

Research in psychology and psychiatry is moving toward an emphasis on examining and integrating psychological and biological factors that cut across categories of psychopathology in order to identify "intermediate phenotypes" that advance our understanding of the nature and causes of psychopathology (Cuthbert and Insel, 2010; Sanislow et al., 2010). The NIMH Research Domain Criteria (RDoC) project has identified Negative Valence Systems as fundamental to the development and maintenance of psychopathology. Negative affect (NA) appears to be a dimension common to some if not all of the constructs identified thus far as key to Negative Valence Systems (e.g., fear, anxiety, loss). Efforts to isolate unique vs. overlapping factors in anxiety and depression initially targeted state NA as common to both (Clark and Watson, 1991a). Further research found that the stable personality dimension of negative temperament or neuroticism was not only common to both anxiety and depression but predictive of their onset and course (Clark et al., 1994; Ormel et al., 2004). Converging evidence has since provided an abundance of empirical support that state NA is present in most disorders and that trait NA is a risk factor for psychopathology in general (for a review, see Clark, 2005).

Although trait NA (accepted by many as essentially synonymous with negative temperament and neuroticism, see Gray and Watson, 2001) is associated with a disposition to experience negative mood states (e.g., worry, anger, fear, guilt, sadness; Costa and McCrae, 1980; Watson and Clark, 1984), it has other important correlates that persist even outside of negative mood states. Trait NA is linked to poor self-esteem, pessimism, and a negative attributional style (Clark et al., 1994; Luten et al., 1997). Further, individuals high in trait NA often dwell on failures, mistakes, and disappointments (Watson and Clark, 1984) and have deficient mood-regulation skills (Costa et al., 1986; Kokkonen and Pulkkinen, 2001). Trait NA is also associated with a greater impact of life stress on the development of affective disorders (for a review, see Ormel et al., 2004).

Cognitive dysfunction has been highlighted as another important factor in affective disorders, which are characterized by deficits in executive functions and biased cognitive processing (Mathews and MacLeod, 2005; Levin et al., 2007; Clark and Beck, 2010; Gotlib and Joormann, 2010). Trait NA is associated with biases in perception, memory, and interpretation, such that individuals with high trait NA recognize and recall negative information more readily than those with low trait NA (Martin, 1985; Larsen, 1992), interpret ambiguous information in a more negative manner (Haney, 1973), and appraise situations as more stressful and threatening (Gallagher, 1990; Hemenover and Dienstbier, 1996; Oliver and Brough, 2002). Negative mood states also influence various cognitive processes, including restricting the range of thoughts and actions that come to mind and biasing perception and memory toward negatively valenced words (Fredrickson and Branigan, 2005; Chepenik et al., 2007). In addition, both state and trait NA appear to influence judgments and beliefs (Clark and Watson, 1991b; Clore and Huntsinger, 2007).

Negative moods are associated with a bias toward a systematic processing strategy that relies more on attention to situational details than on pre-existing knowledge (for reviews, see Schwarz and Clore, 1996; Heller and Nitschke, 1997). Further, emotional states evoke emotion knowledge that is experiential and context-dependent, whereas emotional traits are associated with emotion

knowledge that appears to be somewhat context-independent and based on stable beliefs about emotions in general (Robinson and Clore, 2002). Therefore, it seems likely that, in emotional contexts, certain cognitive processes are modulated differentially by transient emotional states vs. enduring traits. The present study aimed to distinguish correlates of trait and state NA, given that many studies confound their effects and preclude an understanding of potentially unique cognitive mechanisms through which they differentially contribute to symptoms of psychological disorders.

One mechanism through which trait and state NA contribute to serious psychological symptoms may be via attentional control deficits, manifested in both anxiety and depression (Derryberry and Reed, 1994; Compton, 2000; Bredemeier et al., 2011). Neuroimaging work has revealed several brain areas that appear to function abnormally in anxiety and depression during tasks involving attentional control in the context of emotional distracters, including dorsolateral prefrontal cortex (DLPFC), both dorsal and rostral portions of anterior cingulate cortex (ACC), amygdala, and parietal regions (e.g., Bruder et al., 1997; Heller et al., 2003; Engels et al., 2007, 2010; Bishop, 2008; Herrington et al., 2010). Given that anxiety and depression are both associated with dysfunction in these brain regions, it seems likely that trait and state NA are linked to disruption in some or all of these areas as well, leading to attentional control problems that may put individuals at risk for the development and maintenance of psychological disorders.

We propose that trait and state NA are associated with differential attentional control impairments, linked to dysfunction in distinct attentional networks, a top-down control system and a stimulus-driven control system (Corbetta and Shulman, 2002; Corbetta et al., 2008). Given that trait NA is associated with a somewhat context-independent reliance on beliefs and knowledge, we propose that it is associated with dysfunction in more goal-directed, top-down attentional processing, implemented by a dorsal frontoparietal network. This network is influenced by current goals, expectations, and pre-existing information. In contrast, we expect that state NA will be associated with an increase in stimulus-driven attention, implemented by a ventral frontoparietal network, given that negative moods are related to a systematic processing strategy involving attention to contextual details. The present study also integrates the theoretical and empirical foundation of these distinct attentional networks with the cascade-of-control model (Banich, 2009).

The cascade-of-control model proposes that distinct areas of DLPFC implement different functions necessary for attentional control. It posits that posterior DLPFC is involved in imposing a top-down attentional set that maintains overall task goals and biases parietal regions toward processing task-relevant information, whereas mid-DLPFC is involved in selecting and maintaining the most relevant aspects of stimuli that have been received (Banich, 2009). In support of this distinction for emotion-modulated attentional processing, Herrington et al. (2010) showed that individuals high in anhedonic depression exhibited reduced posterior DLPFC activity in response to negative stimuli. In contrast, mid-DLPFC was more active for positive stimuli, regardless of anhedonic depression levels. Herrington et al. (2010) proposed that posterior DLPFC imposes more static, persistent, context-insensitive aspects of an affective set and is associated with trait affect, whereas mid-DLPFC modulates aspects of emotion processing that are more transient, stimulus-driven, context-dependent, and related to state affect. The model also proposes a temporal cascade of processing such that DLPFC comes online first and influences later ACC activity (Banich, 2009; Silton et al., 2010). When incorrect responses are made, ACC signals back to posterior DLPFC to assert stronger top-down control on future trials (Banich, 2009).

The present study examined hypotheses based on the cascade-of-control model in the context of an emotion-word Stroop task, which requires attentional control in order to ignore distracting emotional information. Trait NA was hypothesized to be associated with decreased activation in posterior DLPFC, as well as other areas involved in top-down attentional control, in the context of emotionally arousing, distracting information. In contrast, state NA was expected to facilitate the processing of emotionally arousing, salient stimuli and thus linked to increased activation in mid-DLPFC, as well as other areas involved in the processing of contextual information. Additionally, exploratory analyses examined neural correlates of the interactive effects of trait and state NA, given that behavioral research has found that the interaction between traits and states has important implications for understanding their impact on cognition and behavior (e.g., MacLeod and Mathews, 1988; MacLeod and Rutherford, 1992; Tamir and Robinson, 2004).

Most work in the psychopathology literature investigating cognitive control deficits in emotional contexts has focused on negative stimuli. When positive stimuli are excluded, it is unclear whether the observed attentional problems are valence-specific or are driven by high levels of emotional arousal (which tend to be associated with highly valenced stimuli). There is accumulating evidence that anxious individuals selectively attend to both positive and negative stimuli (Martin et al., 1991; Becker et al., 2001; Sass et al., 2010) and that depressed individuals exhibit reduced emotional reactivity to negative and positive stimuli (Rottenberg et al., 2002, 2005). In addition, trait and state NA appear to be associated with difficulties disengaging attention from salient, distracting information (Compton, 2000; Bredemeier et al., 2011). The present study therefore included both positive and negative stimuli matched on arousal.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited from the local community via advertisements, gave written informed consent, and participated in the study, which was approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign. All participants were right-handed, native speakers of English with self-reported normal color vision and no reported neurological disorders or impairments. Participants were excluded if they exhibited current substance abuse or dependence, mania, or psychosis, as assessed by the Structured Clinical Interview for the DSM-IV. Participants were given a laboratory tour, informed of the procedures of the study, and screened for claustrophobia and other contraindications for MRI participation. Thirty participants were excluded from analyses for a variety of reasons, including excessive motion

in the scanner, technical errors during fMRI acquisition, loss of questionnaire or RT data, outliers on the questionnaires or in RT (outliers were defined as greater than 3 standard deviations from the mean), or error rates exceeding 15%. The final sample included 101 paid participants (62 females, age $M = 34.57$, SD $= 9.27$).

QUESTIONNAIRES

During the laboratory tour, participants completed the 28-item Negative Temperament scale of the General Temperament Survey (GTS-NT) to assess trait NA (Watson and Clark, 1993). Participants were instructed to decide whether each statement mostly described them and to rate each item as true or false. Sample items include "I often have strong feelings such as anxiety or anger without really knowing why," "I sometimes get all worked up as I think about things that happened during the day," and "Often life feels like a big struggle." State NA was measured using the NA scale from the Positive and NA Schedule (PANAS-NA; Watson et al., 1988), which was administered immediately before participants performed the emotion-word Stroop task during fMRI. Participants indicated the extent to which they were feeling each of 10 negative emotions (e.g., afraid, nervous, irritable, upset) that day on a scale from 1 ("*very slightly or not at all*") to 5 ("*extremely*").

Participants also completed measures of anxiety and depression during the laboratory tour. These measures were used in analyses to determine whether results depended on anxiety and depression. The 16-item Penn State Worry Questionnaire (PSWQ) was used to assess anxious apprehension or worry (Meyer et al., 1990; Molina and Borkovec, 1994). Participants responded to questions such as "Many situations make me worry," by rating how characteristic each statement was of them on a scale from 1 ("*not at all typical*") to 5 ("*very typical*"). Participants also completed the Anxious Arousal and Anhedonic Depression subscales of the Mood and Anxiety Symptom Questionnaire (MASQ), rating how much they experienced each item during the previous week on a scale from 1 ("*not at all*") to 5 ("*extremely*"; Watson et al., 1995a,b). The MASQ Anxious Arousal subscale (MASQAA) consists of 17 items in which participants responded to statements such as "Heart was racing or pounding." The eight-item MASQ Anhedonic Depression subscale (MASQAD8) was used as it has been shown to reflect depressed mood (Nitschke et al., 2001) and to predict current and lifetime depressive disorders (Bredemeier et al., 2010). The MASQAD8 scale consists of items such as "Felt like nothing was very enjoyable."

STIMULI AND EXPERIMENTAL DESIGN

Participants performed two tasks, a color-word Stroop and an emotion-word Stroop, during the fMRI session and also in a similar EEG session. Only fMRI data from the emotion-word Stroop task are reported here. The order of the Stroop tasks within session and the order of fMRI and EEG sessions were counterbalanced. The emotion-word Stroop task employed a block design consisting of blocks of positive or negative emotion words alternating with blocks of neutral words. Each participant received one of eight orders designed to ensure that the blocks of emotional and neutral words preceded each other equally often. There was a brief rest period after every fourth block. Additionally, there were four fixation blocks (one at the beginning, one at the end, and two in the middle) in which a brighter fixation cross was presented for 1500 ms, followed by a dimmer fixation cross for an average of 500 ms.

Participants received 256 trials in 16 blocks (four positive, eight neutral, four negative) of 16 trials, with a variable ITI averaging 2000 ms (±225 ms) between trial onsets. A trial began with the presentation of a word for 1500 ms, followed by a fixation cross for an average of 500 ms. Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue). Participants were instructed to press one of four buttons to indicate the color of the ink in which the word appeared on the screen, while ignoring the word meaning (thus making word meaning irrelevant to the task). Each color occurred equally often with each word type (positive, neutral, negative), and trials were pseudorandomized such that no more than two trials featuring the same color appeared in a row. Participants completed 32 practice trials before starting the main task.

The 256 emotion-word stimuli were selected from the Affective Norms for English Words (ANEW) set (Bradley and Lang, 1999). Sixty-four positive (e.g., birthday, laughter), 64 negative (e.g., suicide, war), and two sets of 64 neutral (e.g., hydrant, moment) words were carefully selected on the basis of established norms for valence, arousal, word length, and frequency of use in the English language (Bradley and Lang, 1999). Both positive and negative words were selected to be highly arousing, whereas the neutral words were selected to be low in arousal (see Herrington et al., 2010, for detailed stimulus characteristics). Stimuli were displayed using back projection, and word presentation and reaction time (RT) measurement were controlled by STIM software (James Long Company, Caroga Lake, NY, USA).

IMAGE ACQUISITION

MR data were collected using a 3-T Siemens Allegra scanner. Gradient field maps were collected to correct for geometric distortions in the functional data caused by magnetic field inhomogeneity (Jezzard and Balaban, 1995). Three hundred and seventy functional images were acquired using a Siemens gradient-echo echo-planar imaging sequence (TR 2000 ms, TE 25 ms, flip angle 80°, FOV 22 cm). Thirty-eight oblique axial slices (slick thickness 3 mm, in-plane resolution 3.4375 mm × 3.4375 mm, 0.3 mm gap between slices) were acquired parallel to the anterior and posterior commissures. After the functional acquisition, an MPRAGE structural sequence was also acquired (160 axial slices, slice thickness 1 mm, in-plane resolution 1 mm × 1 mm) for registering each participant's functional data to standard space.

fMRI DATA REDUCTION AND ANALYSES

Image processing and statistical analyses were implemented primarily using the FSL analysis package[1]. Functional data for each participant were motion-corrected using rigid-body registration via FMRIB's linear registration tool MCFLIRT (Jenkinson et al., 2002). Spikes or sudden intensity shifts were corrected using AFNI's 3dDespike program[2]. The time series of one

[1] http://www.fmrib.ox.ac.uk/fsl
[2] http://afni.nimh.nih.gov/

participant was truncated due to excessive motion only at the end of the scan. All other participants demonstrated less than 3.3 mm absolute motion or 2 mm relative motion (participants with motion exceeding this threshold were excluded from analysis, leaving $N = 101$). After motion correction and despiking, each time series was corrected for geometric distortions caused by magnetic field inhomogeneity. Remaining preprocessing steps, single-subject statistics, and higher-level regression analyses were done with FEAT (FMRI Expert Analysis Tool, FMRIB's Software Library[3]). The first three fMRI volumes of each time series were discarded in order to allow the MR signal to reach a steady state. The data were then intensity-normalized, temporally filtered with a high-pass filter, and spatially smoothed using a 3D Gaussian kernel (FWHM = 5 mm).

Regression analyses were then performed on each participant's time series using FILM, FMRIB's Improved Linear Model with autocorrelation correction (Woolrich et al., 2001). Statistical maps were generated via multiple regression computed for each intracerebral voxel. Four explanatory variables were created for each condition (positive, neutral, negative, and rest) and included in the regression model, with fixation left as the unmodeled baseline. Each explanatory variable was convolved with a gamma function to approximate the temporal course of the blood-oxygen-level-dependent (BOLD) hemodynamic response function. Each explanatory variable yielded a per-voxel effect-size parameter estimate (β) map representing the magnitude of activation associated with that explanatory variable. In order to create comparisons of interest, β values for the relevant parameters were contrasted. As is customary in our laboratory research (for further discussion, see Herrington et al., 2010), data were analyzed with respect to positive affect (positive vs. neutral words), NA (negative vs. neutral words), arousal (positive and negative words vs. neutral words), and valence (negative vs. positive words). Because preliminary analyses indicated that the effects of interest were similar for both positive and negative words, this report will focus on the arousal contrast. However, the orthogonal valence contrast (negative vs. positive words) is also reported to indicate that the effects in brain regions of interest (e.g., posterior vs. mid-DLPFC) were similar for both positive and negative stimuli.

For each participant, the functional activation maps were warped into a common stereotaxic space [the 2009 Montreal Neurological Institute (MNI) 152 symmetrical 1 mm × 1 mm × 1 mm template; Fonov et al., 2009] using FMRIB's Non-Linear Image Registration Tool, FNIRT (Andersson et al., 2007). First, the middle volume of the functional scan was registered to the structural scan using rigid-body registration (only allowing *xyz* translation and rotation). Next, the structural scan was registered to the MNI template using a two-step process. First, a linear registration was carried out, allowing xyz translation, rotation, zoom, and shear. Finally, a non-linear registration using cubic b-spline basis functions was carried out, with the results of the linear registration as a starting point. The three registration steps (rigid-body function to structural, affine structural to MNI, and non-linear structural to MNI) were concatenated to create a warp that mapped functional to MNI space and was then applied to the β maps.

Cross-subject inferential statistical analyses of brain activation were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). The arousal contrast was entered as a dependent variable (DV) in a multiple regression analysis with questionnaire scores (GTS-NT scale for trait NA and PANAS-NA scale for state NA) entered as continuous predictors to predict activation voxel-by-voxel. Two different higher-level analysis approaches served to identify (1) brain areas associated with both trait and state NA and (2) brain areas showing distinct relationships with them. First, separate regressions were performed for each questionnaire (without the shared variance from the other questionnaire removed). These essentially provided zero-order correlations between trait or state NA and activation in each brain voxel. These were followed by a conjunction analysis to reveal areas in common for trait and state NA (Nichols et al., 2005). A conjunction *z* map was created by comparing the *z* value of each voxel in the trait NA map with the *z* value in the state NA map. If the *z* scores were of opposite signs, the value for the voxel in the conjunction *z* map was set to zero. If the *z* scores were in the same direction, the value for the voxel in the conjunction *z* map was assigned to the *z* value with the weaker significance. The conjunction *z* map was then thresholded to identify significant clusters, using the thresholding method described below. Second, the GTS-NT and PANAS-NA scores were entered simultaneously as predictors into a higher-level regression analysis. The resulting β map for each predictor reflected the unique variance associated with that predictor. Because the conjunction analyses identified no shared brain regions, and results for the zero-order correlations in the first set of analyses generally resembled results from the second set of analyses, the latter are reported below. The interaction between trait and state NA was added as a third independent variable (IV) to this latter analysis to examine regions where the relationship between trait NA and brain activation depended on the level of state NA.

Significantly activated voxels were identified via thresholding of per-voxel *t*-tests conducted on contrast βs maps that were converted to *z* scores. All hypotheses regarding the main effects of trait and state NA were directional, justifying one-tailed tests for these analyses. Monte Carlo simulations via AFNI's AlphaSim program were used to estimate the overall significance level (probability of a false detection) for thresholding the 3D functional *z* map image (Ward, 2000). The simulations provided the appropriate cluster size to give an overall family wise error rate of $p \leq 0.05$ (although all clusters reported here survived a more stringent family wise error rate of $p = 0.01$).

To limit the number of voxels under consideration, *a priori* regions of interest were examined using masks of the frontal cortex, ACC, amygdala, and parietal cortex that were created using the Harvard-Oxford probabilistic atlas available with FSL. For each of these masks, a cluster size threshold was computed and used only for voxels within the mask. An individual voxel level threshold *z* value of 2.0537 was used for all masks. The minimum cluster sizes for the masks were: frontal cortex = 702 mm^3, ACC = 351 mm^3, amygdala = 234 mm^3, and parietal cortex = 780 mm^3. A whole-brain gray-matter mask was used to examine areas not involved in *a priori* hypotheses (cluster size threshold = 1170 mm^3). All

[3]http://www.fmrib.ox.ac.uk/analysis/research/feat/

analyses were also conducted using two-tailed tests, with results largely in line with the planned one-tailed tests. In no case did a two-tailed test result in significant clusters in the direction opposite to hypotheses. Two-tailed results for these analyses are thus not reported here. Because the analysis examining the interaction between trait and state NA was exploratory, two-tailed tests using the whole-brain gray-matter mask were conducted (cluster size threshold = 2340 mm^3).

LATERALIZATION ANALYSES

Research supports important distinctions in functional specialization of the two hemispheres, particularly the frontal cortex (e.g., Herrington et al., 2005, 2010; Engels et al., 2007, 2010; Spielberg et al., 2011; for reviews, see Heller et al., 1998; Herrington et al., 2009). Therefore, analyses were conducted for the clusters that emerged in the frontal cortex to determine whether they were significantly lateralized. Lateralization was tested using a locally written Matlab program (Spielberg et al., 2011). This program implemented a repeated measures homogeneity of slopes General Linear Model, with hemisphere as the repeated measure, trait and state NA scores as continuous predictors, and fMRI activation for the arousal contrast as the DV. This ANCOVA was conducted on a per-voxel basis, and the resultant β maps were thresholded as described above, with the exception that *F*-tests were used. Because testing laterality determines whether the β in a voxel in the right hemisphere differs significantly from the β in the homologous voxel in the left hemisphere, half as many tests are conducted as in a full-brain analysis. Therefore, a mask containing only the right frontal hemisphere was created.

BEHAVIORAL DATA

Average RT and number of errors were computed for each condition (positive, neutral, and negative). An ANOVA examined RT differences across conditions, and a Friedman test determined whether the number of errors differed across conditions. An arousal interference score was calculated by subtracting each participant's average neutral-word RT from the mean of their positive-word and negative-word RT averages. Higher interference scores indicate that participants took longer to respond to emotionally arousing words than neutral words. To examine the relationship between arousal interference and trait and state NA, arousal RT interference was entered as a DV in regression analyses first with each questionnaire entered separately and second with the questionnaires entered simultaneously as predictors. The interaction between trait and state NA then was added to this latter analysis to examine whether the relationship between trait NA and arousal interference depended on the level of state NA. Although RT interference was the primary behavioral measure of interest, Poisson regression analyses were also conducted using number of task errors as the DV.

ANALYSIS OF BRAIN ACTIVATION AND BEHAVIOR RELATIONSHIPS

In order to explore the relationship between behavioral performance and neural activation in the clusters associated with trait and state NA, β values were averaged across all voxels in each cluster to create a single score for each cluster for each participant. Correlations between arousal RT interference and cluster scores, as well as number of task errors and cluster scores, were calculated using PASW Statistics (SPSS) 18.

MEDIATION ANALYSES

A multiple mediation analysis was conducted *post hoc* to follow-up results from primary analyses in order to better understand relationships between brain activation and behavior. The multiple mediation model involves an IV, a DV, and *j* possible mediators (M). In the present model, the IV was left posterior DLPFC, the DV was arousal RT interference, and the possible mediators were the rostral anterior cingulate cortex (rACC), precuneus, and caudate clusters that emerged from the trait NA analysis (see below). The multiple mediation model allows for the testing of several potential mediators simultaneously and has several advantages over testing separate simple mediation models. It can be used to determine (1) whether an overall mediation effect exists (analogous to conducting a regression analysis with multiple predictors and evaluating total R^2) and (2) whether specific variables uniquely mediate the direct effect (conditional on other mediators being included in the model). It also reduces the likelihood of parameter bias due to omitted variables (see Preacher and Hayes, 2008, for discussion).

Following the recommendation of Preacher and Hayes (2008), mediation (examined via significance of the indirect effect $a_j \times b_j$) was determined by using bootstrapped confidence intervals rather than the Sobel (1982) test. The bootstrap method is preferred over the Sobel test because the former does not require the assumption of a normal distribution, and simulations have shown that bootstrapping methods have higher power while still performing well regarding Type I error rates (MacKinnon et al., 2002, 2004). The SPSS macro script of Preacher and Hayes (2008) was used to conduct multiple mediation analyses by calculating 95% bias-corrected and accelerated bootstrap confidence intervals for the indirect effect involving 5,000 repetitions.

RESULTS

BEHAVIORAL PERFORMANCE

A repeated measures ANOVA [$F(2, 98) = 12.38$, $p < 0.001$, with Huynh–Feldt correction] and *post hoc* paired *t*-tests indicated that RT for negative words ($M = 721$ ms, SD = 100 ms) was longer than RT for both neutral ($M = 704$ ms, SD = 99 ms) and positive words ($M = 703$ ms, SD = 96 ms). A Friedman non-parametric test [$\chi^2(2) = 10.50$, $p < 0.01$] and *post hoc* analyses with Wilcoxon Signed Ranks Tests showed that individuals made more errors in the neutral-word condition (Md = 4, 2–6) than both the positive-word (Md = 3, 2–4) and negative-word conditions (Md = 3, 2–5).

Table 1 lists the results of the regression analyses for the behavioral data. State NA was associated with arousal-related RT interference and total number of task errors. Higher levels of state NA were associated with (1) responding more slowly to emotionally arousing words than to neutral words and (2) committing more errors. Trait NA was not associated with arousal RT interference or errors. The interaction between trait and state NA predicted task errors, such that increased trait NA was associated with increased task errors at high levels of state NA, but with decreased errors at low levels of state NA.

Table 1 | Regression analyses for behavioral data.

Variable	DV = Arousal RT interference		
	Beta[t]	*p*	R^2
ENTERED SEPARATELY			
GTS NT (trait NA)	−0.04	0.70	0.00
PANAS-NA (state NA)	0.20	0.04	0.04
ENTERED SIMULTANEOUSLY			
Step 1			
GTS NT	−0.10	0.32	0.05
PANAS-NA	0.23	0.03	
Step 2			
GTS NT × PANAS-NA	−0.28	0.62	0.05
Variable	**DV = Total task errors**		
	Beta	**Wald χ^2**	***p***
ENTERED SEPARATELY			
GTS NT	0.01	4.26	0.04
PANAS-NA	0.04	16.08	0.00
ENTERED SIMULTANEOUSLY			
Step 1			
GTS NT	0.01	1.04	0.31
PANAS-NA	0.04	12.66	0.00
Step 2			
GTS NT × PANAS-NA	0.01	11.67	0.00

[t] *Standardized betas for RT interference analyses; GTS NT, general temperament survey negative temperament scale; PANAS-NA, positive and negative affect schedule negative affect scale.*

Table 2 | Brain areas moderated by trait and state negative affect and correlations with behavior.

Region	Cluster size (mm^3)	Mean *z* value	Location			r_{RT}
			X	*Y*	*Z*	
TRAIT NEGATIVE AFFECT						
L middle frontal gyrus/precentral gyrus (posterior DLPFC)[a]	3,200	−2.35	−34	16	39	0.38**
Rostral anterior cingulate cortex[b]	1,430	−2.41	−3	40	0	0.27**
Precuneus[c]	3,902	−2.36	−3	−60	22	0.45**
L caudate[d]	2,678	−2.29	−10	5	3	0.43**
STATE NEGATIVE AFFECT						
L middle frontal gyrus/inferior frontal gyrus (mid-DLPFC)[a]	1,182	2.35	−26	29	40	0.37**
L medial frontal cortex[a]	1,124	2.31	−6	52	−10	0.42**
Rostral anterior cingulate cortex[b]	547	2.28	0	39	2	0.26**
Dorsal anterior cingulate cortex[b]	390	2.30	−9	33	21	0.36**
Posterior dorsal anterior cingulate cortex[b]	586	2.33	−2	−3	36	0.26**
Precuneus[c]	5,471	2.48	−4	−62	21	0.46**
L parahippocampal gyrus[d]	1,636	2.42	−21	−14	−25	0.24*
L&R nucleus accumbens/caudate[d]	3,230	2.45	−1	14	−2	0.46**

*L, left; R, right; Location, Coordinates are for the center-of-mass in MNI152 2009a symmetrical space; r_{RT}, correlation between reaction time interference and activation in each ROI; [a] Correction for only frontal cortex voxels; [b] Correction for only anterior cingulate cortex voxels; [c] Correction for only parietal cortex voxels; [d] Correction for all gray-matter voxels. *$p < 0.05$; **$p < 0.01$.*

BRAIN REGIONS UNIQUELY ASSOCIATED WITH TRAIT NEGATIVE AFFECT

Table 2 lists the four brain regions that were negatively correlated with trait NA. In line with hypotheses, higher levels of trait NA were associated with less brain activation in left posterior DFPFC [middle frontal gyrus (MFG) extending into precentral gyrus], rACC, and precuneus (see **Figure 1**). In addition, a cluster emerged in left caudate when using the whole-brain gray-matter mask. There were no significant amygdala clusters. Further, there were no significant clusters positively correlated with trait NA. An examination of the valence contrast (negative vs. positive words) confirmed that there were no significant activations overlapping with any of these four areas, indicating that these results were not driven by negative or positive words alone.

Follow-up analyses were conducted to determine whether these effects depended on anxiety and depression. PSWQ, MASQAA, and MASQAD8 scores were included in a multiple regression analysis along with trait and state NA scores ($N = 99$ due to missing PSWQ data for two individuals). All of the results remained significant for trait NA, with the exception of the caudate.

BRAIN REGIONS UNIQUELY ASSOCIATED WITH STATE NEGATIVE AFFECT

Table 2 lists the regions that were positively correlated with state NA. In line with hypotheses, higher levels of state NA were associated with more activation in mid-DLPFC [MFG, extending into inferior frontal gyrus (IFG)], ACC, and precuneus (see **Figure 1**). Three separate clusters emerged in the ACC: rACC, an anterior region of dorsal ACC (dACC), and posterior dACC. In addition to mid-DLPFC, a second cluster emerged using the frontal cortex mask, in left medial frontal cortex. Finally, when using the whole-brain gray-matter mask, two additional clusters emerged: one in left parahippocampal gyrus and one spanning left and right nucleus accumbens/caudate. There were no significant amygdala clusters. Further, there were no significant clusters negatively correlated with state NA. An examination of the valence contrast (negative vs. positive words) confirmed that there were no significant activations overlapping with any of these eight areas.

Follow-up analyses were conducted to determine whether these effects depended on anxiety and depression. All of the results remained significant for state NA when PSWQ, MASQAA, and MASQAD8 were added to the regression analysis.

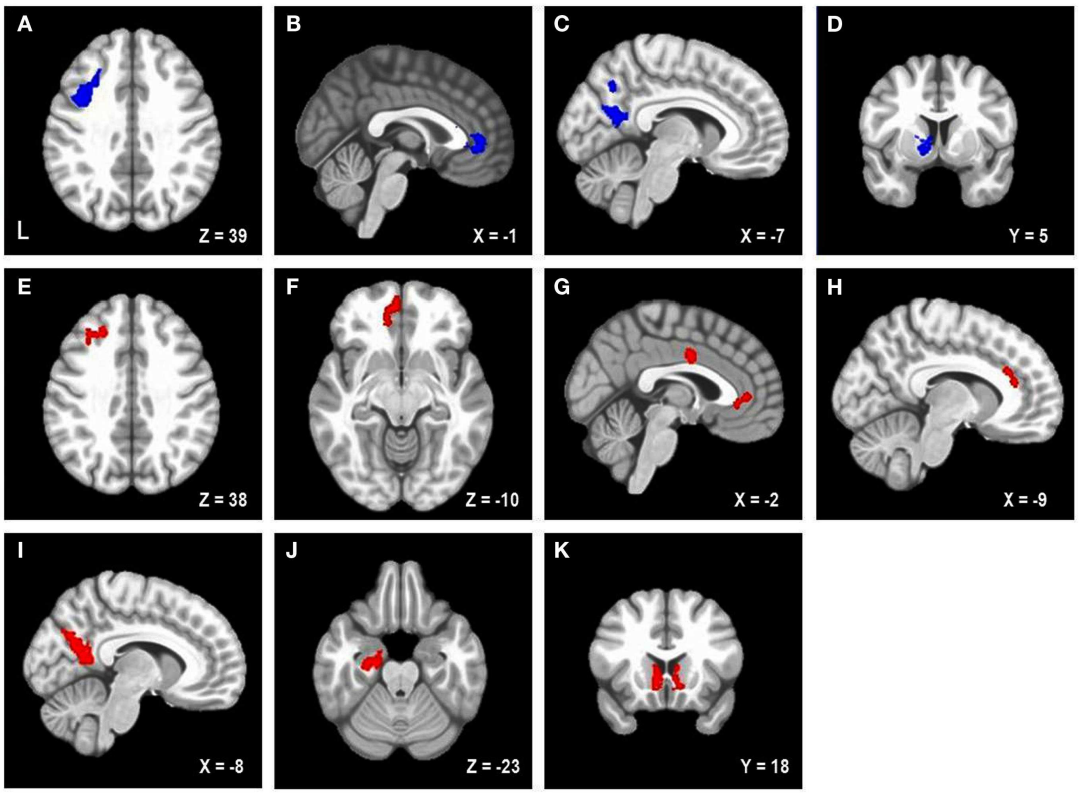

FIGURE 1 | Areas uniquely associated with either trait or state negative affect (NA). Blue = decreased brain activation associated with trait NA **(A–D)**. Red = increased brain activation associated with state NA **(E–K)**. L, left. Clusters of activation in **(A)** Left posterior DLPFC, **(B)** Rostral anterior cingulate cortex (rACC), **(C)** Precuneus, **(D)** Left caudate, **(E)** Left mid-DLPFC, **(F)** Left medial frontal cortex, **(G)** rACC and posterior dorsal ACC (dACC), **(H)** dACC, **(I)** Precuneus, **(J)** Parahippocampal gyrus, **(K)** Bilateral nucleus accumbens/caudate.

THE INTERACTIVE EFFECTS OF TRAIT AND STATE NEGATIVE AFFECT

Table 3 lists the seven regions negatively associated with the interaction between trait and state NA. These regions include left DLPFC (lateral MFG), medial superior frontal gyrus (SFG), bilateral superior parietal cortex (extending into occipital cortex), bilateral middle temporal gyrus (MTG), and occipital cortex (spanning intracalcarine cortex/lingual gyrus/occipital fusiform gyrus; see **Figure 2**). Graphing the interactions for all brain areas showed that increased trait NA was associated with decreased activation in these areas at high levels of state NA but with increased activation at low levels of state NA (see **Figure 2**). No regions were positively correlated with the interaction between trait and state NA. An examination of the valence contrast (negative vs. positive words) indicated that there were no significant activations overlapping with any of these areas.

LATERALIZATION ANALYSES

Lateralization analyses were conducted to explore whether the three left frontal clusters (posterior DLPFC associated with trait NA, mid-DLPFC/IFG associated with state NA, and lateral MFG associated with their interaction) were significantly lateralized. Only the lateral MFG cluster associated with the interaction between trait and state NA was significantly left-lateralized.

CORRELATIONS BETWEEN BRAIN ACTIVATION AND BEHAVIORAL PERFORMANCE

As presented in **Table 2**, all clusters associated with trait and state NA were positively correlated with RT to high-arousing vs. neutral stimuli. These positive correlations indicate that, as activation in these areas increased, participants were more distracted by the emotional nature of the words. Furthermore, as seen in **Table 3**, five of the seven clusters associated with the interaction between trait and state NA were also positively correlated with RT interference from arousing words, including left DLPFC (MFG), medial SFG, left superior parietal cortex, and left and right MTG. Only the cluster located in mid-DLPFC (positively associated with state NA) was marginally correlated with error rate ($r = 0.17$, $p = 0.08$). As activation in this area increased, participants made more errors.

MEDIATION ANALYSES

Less activation in posterior DLPFC for higher levels of trait NA was consistent with hypotheses. It was also expected that less activation in this region would be associated with decrements in performance, such that individuals with high levels of trait NA would have more difficulty ignoring the arousing nature of the stimuli given their difficulty recruiting posterior DLPFC to implement top-down attentional control. However, the positive correlation

Table 3 | Brain areas with interactive effects for trait and state negative affect and correlations with behavior.

Region	Cluster size (mm^3)	Mean *z* value	Location			r_{RT}
			X	*Y*	*Z*	
L lateral middle frontal gyrus[a]	2,828	−2.52	−44	16	37	0.32**
Medial superior frontal gyrus[a]	2,750	−2.37	−1	44	38	0.37**
L superior parietal cortex/occipital cortex[a]	2,594	−2.42	−26	−72	39	0.12*
R superior parietal cortex/occipital cortex[a]	2,424	−2.38	33	−69	45	0.14
L middle temporal gyrus[a]	7,422	−2.60	−61	−37	−4	0.43**
R middle temporal gyrus[a]	6,990	−2.43	58	−46	−3	0.22*
Occipital cortex (intracalcarine cortex/ lingual gyrus/occipital fusiform gyrus)[a]	24,198	−2.43	−4	−74	−5	−0.04

*L, left; R, right; Location, Coordinates are for the center-of-mass in MNI152 2009a symmetrical space; r_{RT}, correlation between reaction time interference and activation in each ROI; [a], Correction for all gray-matter voxels 2-tailed test. *$p < 0.05$; **$p < 0.01$.*

between brain activation in this area and RT interference indicated that less activation in posterior DLPFC was associated with better performance (less distraction by the emotional words). A multiple mediation analysis (see **Figure 3**) was conducted to investigate the possibility that the impact of posterior DLPFC activation on behavioral performance was actually mediated by other brain areas. This hypothesis is in line with the cascade-of-control model, which posits that the ACC comes online after the DLPFC in order to implement response-related attentional processes, such as evaluating responses.

The results of the mediation analysis are presented in **Table 4**. The total indirect effect was significant, as was each of the specific indirect effects, indicating that the rACC, precuneus, and caudate clusters each mediated the relationship between posterior DLPFC activation and RT interference. As shown in the table, the effect of posterior DLPFC on RT interference was reduced from 0.67 to 0.06 by the three mediators, going from a significant ($p = 0.0001$) to a non-significant ($p = 0.84$) relationship, indicating full mediation. Consistent with the cascade-of-control model, rACC mediated the relationship between DLPFC and RT interference. Importantly, the effect of rACC on RT interference (path b) was negative, indicating that less activation in rACC was associated with more interference from arousing stimuli (when partialing out the effect of the posterior DLPFC). Thus, less activation in posterior DLPFC is associated with less activation in rACC, which is in turn associated with difficulty ignoring emotionally arousing stimuli.

DISCUSSION

Overall, results of the present study indicate that trait NA, state NA, and their interaction have unique correlates in a selective attention task involving emotional distraction. The pattern of brain activation associated with trait NA suggests that individuals high in trait NA have difficulty engaging top-down aspects of attentional control to maintain task goals in the presence of irrelevant information (Banich, 2009; Herrington et al., 2010). As hypothesized, trait NA was associated with less activation to emotionally arousing stimuli in posterior DLPFC, which plays a key role in implementing top-down attentional control in order to ignore distracting information and focus on the task at hand (Banich et al., 2000a,b, 2009; Compton et al., 2003; Milham et al., 2003). This finding is consistent with studies that found less activity in this area in individuals high in anhedonic depression in the context of negative vs. neutral words (Engels et al., 2010; Herrington et al., 2010). The present finding suggests that abnormal activation in this area is not specific to depression but is associated with trait NA, a more general risk factor for developing and maintaining anxiety and depression (Ormel et al., 2004). Further, individuals high in trait NA had difficulty ignoring salient, arousing information, both positively and negatively valenced, suggesting that their attentional deficit was not limited to negative stimuli. Consistent with this finding, neuroticism has been associated with difficulty ignoring salient distracters during a non-emotional task (Bredemeier et al., 2011).

Corbetta et al. (2008) proposed that posterior portions of the frontal cortex are part of a dorsal frontoparietal network involved in the top-down selection of stimuli congruent with goals and expectations based on previous experiences. Further, posterior DLPFC feeds signals to a separate ventral attentional network that detects salient stimuli in order to bias processing of the appropriate stimulus features (Corbetta et al., 2008). Given that individuals high in trait NA are theorized to rely excessively on pre-existing knowledge and ignore meaningful contextual details (Robinson and Clore, 2002), dysfunction in a key node of the dorsal attentional network may help explain their difficulty integrating pre-existing information with immediate environmental information most relevant for current goals. Functional impairments in posterior DLPFC also perturb activity in parietal regions that it modulates. In the present study, less activation in a parietal region associated with trait NA, the precuneus, suggests that this area failed to receive signals from posterior DLPFC to bias processing toward task-relevant aspects of stimulus representations (color information) and away from irrelevant features (word meaning; Banich et al., 2000b). Further, the precuneus is a central hub linking the frontal cortex with other parietal regions (Bullmore and Sporns, 2009). Thus, dysfunction in the precuneus may prevent successful modulation of other key parietal areas.

The cascade-of-control model (Banich, 2009) asserts that attentionally demanding tasks first recruit DLPFC, which in turn influences later ACC activity. Silton et al. (2010) confirmed this hypothesized within-trial sequence using fMRI-guided event-related potential (ERP) source localization. In the present study, high trait NA was associated with hypoactivity in rACC, a region involved in evaluating interference from emotionally salient distracters (Whalen et al., 1998; Vuilleumier et al., 2001; Mohanty

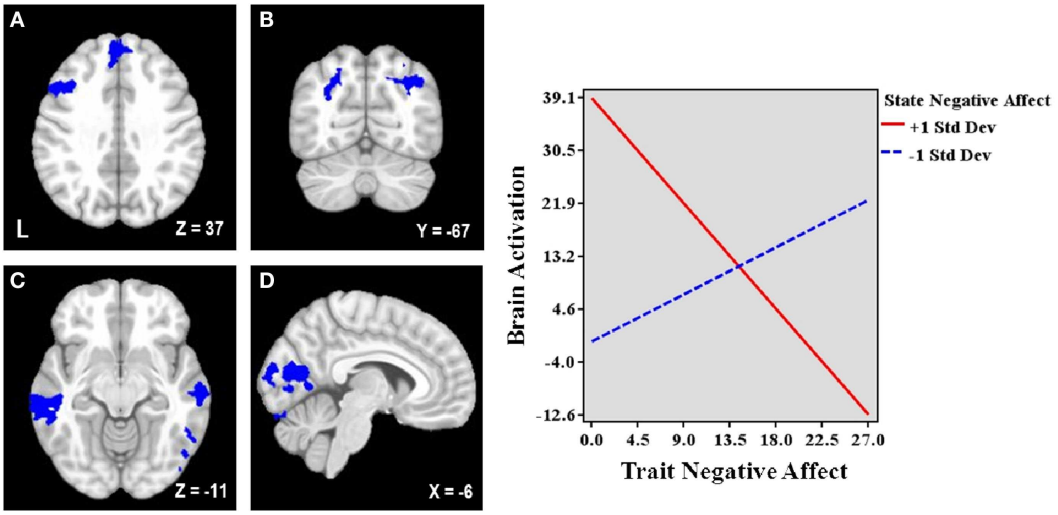

FIGURE 2 | Brain areas associated with the interaction between trait and state negative affect (NA). Blue = Less activation when both dimensions are high than when one dimension is high. L, left. Clusters of activation in **(A)** Left lateral middle frontal gyrus (MFG) and medial superior frontal gyrus, **(B)** Bilateral parietal cortex/occipital cortex, **(C)** Bilateral middle temporal gyrus, **(D)** Occipital cortex. Graphing the two-way interaction for each region shows that trait NA's relationship with these brain areas depends on the level of co-occurring state NA, such that increased trait NA is associated with decreased activation in all of these areas at high levels of state NA but with increased activation at low levels of state NA. Depicted is a representative graph from left MFG.

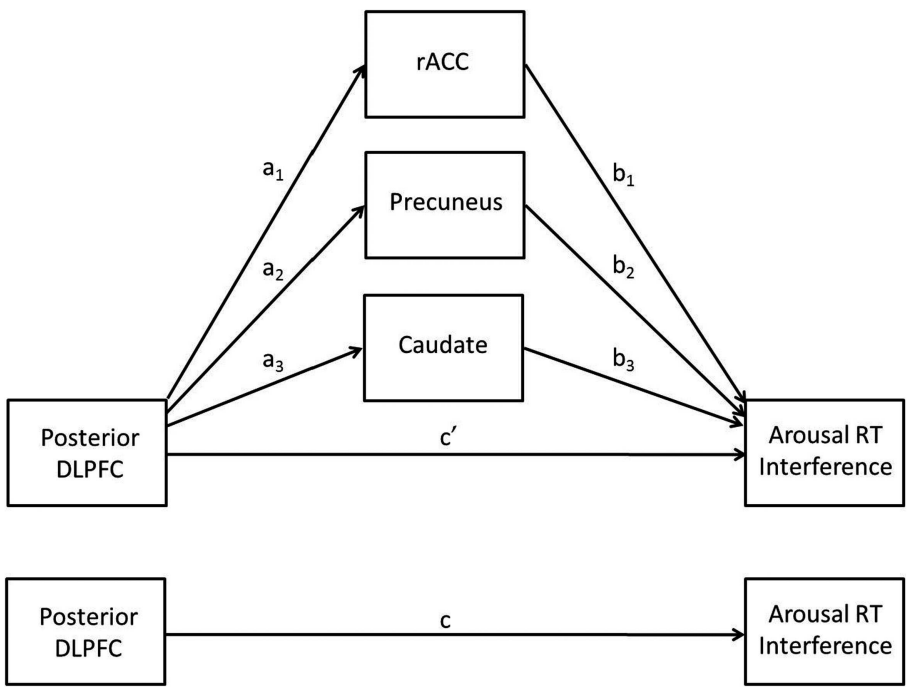

FIGURE 3 | The multiple mediation model.

et al., 2007). The combination of hypoactivity in both posterior DLPFC and rACC regions in individuals high in trait NA suggests a mechanism by which they have difficulty exerting top-down control to handle conflict from emotional distracters. Further, the finding that rACC activation mediated the relationship between posterior DLPFC activation and RT interference suggests that DLPFC failed to recruit rACC to compensate for poor attentional control, thus leading to increased distraction from emotionally arousing stimuli. Similar deficits in the fronto-cingulate network have been observed in anxious individuals (Bishop et al., 2004;

Table 4 | Summary of multiple mediation analysis.

IV = L posterior DLPFC	DV = Arousal RT interference				
Mediators (M)	**Path a (IV to M)**	**Path b (M to DV)[a]**	**Path c (IV to DV total)**	**Path c′ (IV to DV direct)**	**a × b (Indirect effect)**
rACC	1.29**	−0.29*			−0.37*
Precuneus	1.06**	0.51**			0.54**
Caudate	1.34**	0.33*			0.45*
			0.67**	0.06	
					Total indirect effect: 0.61*

[a] *Partialing out effects of IV; *p ≤ 0.05; **p < 0.01.*

Engels et al., 2007) and may be related to high levels of trait NA rather than anxiety-specific symptoms.

In contrast to trait NA, the pattern of brain activity associated with state NA suggests that, when individuals are in negative moods, they engage in excessive processing of salient stimuli. This is problematic when their performance is penalized due to constant interruption of top-down processing to focus on stimuli features that are not task-relevant. State NA was associated with increased activation in mid-DLPFC, an area involved in stimulus-driven attentional control. Previous studies support the role of mid-DLPFC in selecting and processing the most pertinent aspects of stimuli in the environment and ignoring irrelevant features (for review, see Herrington et al., 2005, 2010; Engels et al., 2007; Banich, 2009). Further, this anterior portion of MFG has been proposed to be part of a stimulus-driven ventral attentional network (Corbetta et al., 2008). In the present study, the cluster in mid-DLPFC extended ventrally into IFG, another key node in this network. This network detects salient stimuli in the surroundings and determines their behavioral relevance, as well as interrupts top-down processing in order to reorient attention to stimuli that have been determined to be "important" (Corbetta et al., 2008). Hyperactivity in mid-DLPFC may indicate that individuals high in state NA were over-attending to the emotional aspects of the words, which impeded their ability to focus on the ink color (Engels et al., 2010). This explanation is supported by the significant relationship between increased activity in mid-DLPFC and increased behavioral (RT) interference for emotionally arousing than for neutral words. Mid-DLPFC activation was also marginally positively correlated with overall task errors.

State NA was also associated with three clusters in ACC: one in anterior dACC, one in posterior dACC, and one in rACC. The anterior portion of dACC appears to be involved in response evaluation (Milham and Banich, 2005; Banich, 2009), whereas the posterior portion plays a critical role in response selection (Milham et al., 2001, 2003; Banich, 2009). Further, if DLPFC function earlier in the processing stream is problematic, posterior dACC must deal with unresolved selection issues (e.g., Milham et al., 2002; Silton et al., 2010). In the present study, increased activation in both portions of dACC was associated with increased interference from emotional stimuli. Increased dACC activity may reflect (1) unsuccessful attempts to compensate for dysfunctional DLPFC control and (2) attempts to signal the DLPFC to engage stronger top-down control in the future, in order to override stimulus-driven processing of irrelevant information (Milham et al., 2003; Banich, 2009). A third cluster located in rACC overlapped with the cluster that emerged in the trait NA analysis. However, the relationship between state NA and rACC was in the opposite direction of trait NA and rACC, such that increased levels of state NA were associated with increased activation in rACC. In addition to being involved in attentional control during emotional tasks, rACC has been implicated in regulating responses to emotional material (Bush et al., 2000).

A cluster in medial frontal cortex also emerged in the state NA analysis. This region has been implicated in various functions related to affective states, including responding to emotional pictures and making attributions about emotional states (Lane and McRae, 2004; Ochsner et al., 2004, 2009). Increased activation in both rACC and medial frontal cortex in the present study for individuals high in state NA suggests that they were involved in attending to the emotional content of the stimuli and/or their own mood states. State NA was also associated with activation in precuneus and parahippocampal gyrus. Given that precuneus activation was associated with difficulty ignoring the emotional content of the words, it is likely that individuals high in state NA were biased toward the processing of word meaning instead of word color. Previous studies of the Stroop task found decreased parahippocampal activity was associated with successful implementation of attentional control and proposed that it reflected inhibited binding of ink color and word meaning (Compton et al., 2003). Increased activation in the hippocampal gyrus in the present study may indicate that individuals high in state NA were not inhibiting word meaning optimally, which contributed to detriments in their performance.

The results of the present study indicate that co-occurring high levels of trait and state NA are associated with a distinct pattern of brain activation, beyond the additive effects of trait and state NA. The clusters that emerged for the interaction analysis of trait and state NA did not overlap with any of the clusters associated with the main effects, highlighting the importance of considering the interactive effects of these constructs. Relative to being high in only one dimension, being high or low in both trait and state NA was associated with less activation in lateral MFG and medial SFG, indicating difficulty maintaining a top-down, goal-congruent task set while dealing with distracting emotional information (Ferstl et al., 2005; Spielberg et al., 2011). The combination of high trait and state NA was also associated with decreased activation in several areas early in the dorsal processing stream, including occipital cortex, bilateral MTG, and bilateral superior parietal areas. Hypoactivation

in frontal areas as well as in visual and temporal areas suggests that these latter regions were not appropriately modulated by the prefrontal cortex to bias processing of the relevant sensory representations (Banich et al., 2000b). Decreased activation in superior parietal cortex suggests that combined trait and state NA will lead to more difficulty allocating attentional resources in a top-down manner than high trait or state NA alone (Husain and Nachev, 2007; Corbetta et al., 2008).

In summary, state and trait NA appear to disrupt attentional control in distinct ways. Individuals with high trait NA appear to have difficulty sustaining attention and persisting in goal achievement in environments involving salient distractions, as well as trouble anticipating and preparing for upcoming tasks (Corbetta et al., 2008). Present results are consistent with research indicating that high trait anxious individuals exhibit problems engaging proactive control, or "sustaining representation of task requirements or goals throughout periods of high control demand" (Fales et al., 2008, p. 240), though such deficits may not be specific to anxiety. Difficulty implementing top-down attentional control in the face of distracting emotional information likely contributes to the biased expectations, interpretations, and attributions of environmental information associated with high levels of trait NA. Individuals high in trait NA appear to rely excessively on (potentially inappropriate) knowledge based on previous experiences, failing to integrate it with pertinent information in the current context in order to respond adaptively.

In contrast, high levels of state NA are associated with an over-reliance on more transient aspects of attentional control and excessive processing of salient information. Hyperactivity of a key node in a stimulus-driven attentional network likely leads to repeated interruption of top-down processing to focus on task-irrelevant contextual details. Whereas individuals with high trait NA appear to be ineffective at incorporating information from their immediate environment, those high in state NA appear to have the opposite problem, such that they have difficulty appropriately attending to ongoing goals. The present findings support the assertion that trait NA is not simply the tendency to experience negative states; rather, it has correlates dissociable from state NA. Further, present results contribute to the understanding of the psychological and biological mechanisms through which trait and state NA trigger and maintain symptoms of anxiety and depression.

The present study benefited from a sample size that is unusually large for the fMRI literature, as well as an analysis strategy that allowed for the examination of the distinct correlates of trait and state NA, rather than confounding their effects. Given that trait and state NA are moderately correlated, measuring just one dimension may reflect effects that are not specific to that dimension and can be misleading. Further, the study extends the literature by examining attentional control in the context of distracting emotional stimuli that are both positively and negatively valenced, equated for arousal levels.

Limitations include a correlational design, which cannot determine whether trait and state NA lead to the development of attentional control difficulties or vice versa. In addition, due to the nature of the task and methods used, distinct stages of attention (e.g., orientating vs. disengaging) could not be examined to determine whether trait and state NA are associated with difficulties at different stages. Future research could employ other attentional tasks and utilize ERP methods to address this question. Another empirical question that remains to be tested is the extent to which these results generalize to other types of emotional stimuli (e.g., faces, emotional scenes), as it is likely that there would be some differences (e.g., Isaac et al., 2012). Finally, future work should also examine tasks that involve salient, non-emotional distracters in order to determine whether these attentional control deficits are specific to emotional information.

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Loss of sustained activity in the ventromedial prefrontal cortex in response to repeated stress in individuals with early-life emotional abuse: implications for depression vulnerability

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Repeated psychosocial stress in early-life has significant impact on both behavior and neural function which, together, increase vulnerability to depression. However, neural mechanisms related to repeated stress remain unclear. We hypothesize that early-life stress may result in a reduced capacity for cognitive control in response to a repeated stressor, particularly in individuals who developed maladaptive emotional processing strategies, namely trait rumination. Individuals who encountered early-life stress but have adaptive emotional processing, namely trait mindfulness, may demonstrate an opposite pattern. Using a mental arithmetic task to induce mild stress and a mindful breathing task to induce a mindful state, we tested this hypothesis by examining blood perfusion changes over time in healthy young men. We found that subjects with early-life stress, particularly emotional abuse, failed to sustain neural activation in the orbitofrontal and ventromedial prefrontal cortex (vmPFC) over time. Given that the vmPFC is known to regulate amygdala activity during emotional processing, we subsequently compared the perfusion in the vmPFC and the amygdala in depression-vulnerable (having early-life stress and high in rumination) and resilient (having early-life stress and high in mindfulness) subjects. We found that depression-vulnerable subjects had increased amygdala perfusion and reduced vmPFC perfusion during the later runs than that during the earlier stressful task runs. In contrast, depression-resilient individuals showed the reverse pattern. Our results indicate that the vmPFC of depression-vulnerable subjects may have a limited capacity to inhibit amygdala activation to repeated stress over time, whereas the vmPFC in resilient individuals may adapt to stress quickly. This pilot study warrants future investigation to clarify the stress-related neural activity pattern dynamically to identify depression vulnerability at an individual level.

Keywords: early-life stress, repeated stress, depression vulnerability, depression resilience, fMRI, ventromedial prefrontal cortex

INTRODUCTION

Stress is a significant risk factor for depression and anxiety. Chronic stress can produce significant detrimental effects psychologically and physiologically (McEwen and Stellar, 1993). In response to chronic stress, some individuals develop neural habituation and adapt to the stress, but others may become sensitized to the stressor and may have prolonged or amplified neural responses over time (McEwen and Stellar, 1993). Studying neural response to a repeated stressor over time enables us to characterize neural signatures to identify depression vulnerability. The pattern of individual differences in response to a repeated stressor over time may become an important feature in differentiating vulnerability to depression and anxiety from resilience at an individual level. However, neuroimaging studies on repeated stress are rare, and the impact of repeated stress on neural circuits related to depression vulnerability remains unclear.

McEwen and Stellar (1993) proposed four types of maladaptive responses to repeated stress: (1) lack of habituation, (2) prolonged response, (3) inability to reduce reactivity, (4) inability to respond. For the first three types of responses, stronger neural, or physiological responses may be found in response to a repeated stressor compared to a single-time stressor. Studies in peripheral reactivity such as blood pressure have demonstrated this reactivity pattern (Schneider et al., 2003). However, brain regions that reflect this response pattern to repeated stress are still under investigation.

By contrast, a number of brain regions such as the ventromedial prefrontal cortex (vmPFC), ventrolateral prefrontal cortex (vlPFC), amygdala, and hippocampus can reveal maladaptive response patterns in individuals vulnerable to stress in response to repeatedly presented stressors (McEwen, 1999; Taylor et al., 2004, 2011). Dysfunction of these regions while processing emotional events are frequently reported in individuals with depression (Siegle et al., 2007; Fitzgerald et al., 2008; Wang et al., 2008), anxiety, post-traumatic stress disorder (PTSD) (Shin et al., 2004a,b), and in individuals vulnerable to depression such as those with an early-life stress history (Matsumoto et al., 2009; Pechtel and Pizzagalli, 2011). Early-life stress history refers to exposure to emotional or physical abuse, such as neglect and harsh and chaotic parenting in childhood (Bernstein et al., 2003). Both the vmPFC and vlPFC have direct projections to the amygdala (Sah et al., 2003; Holland and Gallagher, 2004) and have been found to exert a top-down, inhibitory effect on the amygdala. Typically, while regulating negative affect, healthy individuals have demonstrated higher vmPFC (Urry et al., 2006) or vlPFC (Taylor et al., 2006) activation and lower amygdala activation. A study on early-life stress (Taylor et al., 2006) found that in response to threatening cues, healthy controls showed a *negative* correlation between activation of the right vlPFC and amygdala activity, whereas participants with an early-life stress history showed a *positive* correlation between the two regions. These results suggest a possible failure to recruit the prefrontal cortex effectively for regulating emotional responses to threatening cues, and thus no reduction in amygdala activity was found in individuals with early-life stress. Therefore, it is important to further clarify the neural response pattern between the prefrontal cortex and the amygdala to repeated stressors in individuals with early-life stress.

We hypothesized that individuals with early-life stress would show an activation pattern in response to a repeated stressor that reflects long-term stress exposure, characterized by sustained amygdala hyperactivation and attenuated activation in the vmPFC or vlPFC over time due to failed recruitment of sustained activity from the prefrontal cortex to regulate amygdala response continuously.

While history of early-life stress undoubtedly is a risk factor for future depression (Wals and Verhulst, 2005), not everyone with early-life stress eventually develops depression (Charney and Manji, 2004). Individual differences in the ability to regulate stress and emotional reactions to stressful situations can modulate brain activity and peripheral physiology, with implications for vulnerability vs. resilience to depression. For example, individuals who tend to ruminate about chronic stress and negative emotions develop depression more easily in response to acute life stress (Nolen-Hoeksema, 1991). Rumination is defined as "repetitively focusing on the fact that one is depressed; on one's symptoms of depression; and on the causes, meanings, and consequences of depressive symptoms" (Nolen-Hoeksema, 1991). It has been consistently found that rumination increases negative mood (Ward et al., 2003) and predicts the onset and relapse of depression (Nolen-Hoeksema, 1991; Nolen-Hoeksema et al., 1993; Just and Alloy, 1997). Therefore, rumination is a key cognitive trait underlying vulnerability to depression.

Some individuals with early-life stress may develop traits that enable them to be resilient (Marks et al., 2010; Binder et al., 2011; Carli et al., 2011). One such trait is mindfulness. Trait mindfulness, also known as dispositional mindfulness, refers to the self-regulation of attention as well as an orientation of openness, curiosity, and acceptance to all experiences (Bishop et al., 2004). Individuals who are high in trait mindfulness in daily life demonstrate better psychological health and lower incidence of depression (Keng et al., 2011). Therefore, it is conceivable that those who have developed trait mindfulness in spite of having an early-life stress history have a different neural activity pattern in response to a repeated stressor compared to individuals with early-life stress who have developed trait rumination.

We hypothesized that individuals with early-life stress, will show increasingly or consistently high activation in the amygdala and low or quickly reduced cognitive regulatory responses of the vmPFC following a repeatedly presented mild stressor during later relative to early trials. We predicted this activation pattern to repeated stress over time will be found particularly in individuals with early-life stress and high trait rumination, whereas an opposite pattern will be found in individuals with early-life stress and high trait mindfulness.

MATERIALS AND METHODS

PARTICIPANTS

To avoid the confounding influence of menstrual cycle on stress sensitivity (Ossewaarde et al., 2010), only male participants [$n = 19$, mean (SD) age = 27.05 (7.21)] were recruited in the study. Participants were recruited from the subject registry at the Duke-UNC Brain Imaging and Analysis Center. The exclusion criteria were: (1) MRI contradictions, (2) current or history of neurological and psychiatric disorders, (3) drug abuse, and (4) current medication use. The study was approved by the Duke University Health System Institutional Review Board. All participants have signed written consent.

PROCEDURES

A stress induction task and a mindful breathing task were administered over two different days separated by 7–10 days. The order of the stress and mindfulness tasks was counterbalanced among the participants. Each day was composed of a pre-scan stress/mindfulness task training session and an imaging scan session. Detailed procedures can be found in our previous report (Paul et al., 2013). A number of questionnaires were administered during pre-scan session to quantify affective state [*Positive Affect and Negative Affect Scale*, PANAS (Watson et al., 1988)], state anxiety level [*Spielberger State and Trait Anxiety Inventory*, STAI-State (Spielberger et al., 1983)], self-reported stress level [*Perceived Stress Scale*, PSS (Cohen et al., 1983)], trait rumination [*Ruminative Response Scale*, RRS (Nolen-Hoeksema, 1991)], and trait mindfulness [*Five Facet Mindfulness Questionnaire*, FFMQ (Baer et al., 2006)]. Early-life stress was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998), which contains five subscales: three assessing abuse (emotional, physical, and sexual) and two assessing neglect (emotional and physical). Early-life stress experiences were defined as either having at least three out the five subscales with a score >6 or meeting any of the

following cut-off scores (Bernstein and Fink, 1998): emotion abuse ≥9; emotion neglect ≥10; physical abuse ≥10; physical neglect ≥10; or sexual abuse ≥8.

The imaging session was composed of an anatomical scan, a resting state scan, and four pairs of stress (or mindful breathing) task and an emotional go/no-go (EGNG) task runs. Using this design, we previously investigated the effect of stress and mindfulness inductions on successful inhibition to negative vs. to neutral pictures during the EGNG task (Paul et al., 2013). In this report, we focus on the blood perfusion changes during while subjects performed the stress task and the mindful breathing task. Changes in heart rate, respiration rate, and cortisol level were measured during the stress and mindful breathing tasks to objectively evaluate stress level. After completing each stress or mindful breathing task run, self-ratings of stress were also obtained immediately using a likert scale (ranged from 0 to 4, from not stressful at all to very stressful). Salivary cortisol levels were measured at the beginning, middle, and end of the scan session. All imaging scans were completed in the late afternoon to obtain low and stable cortisol levels, when individuals are more responsive to stimulation (Jansen et al., 1998) during these hours. Caffeine, smoking, and exercise were prohibited 2 h prior to scanning.

EXPERIMENTAL DESIGN

Stress induction task

We used a mental arithmetic paradigm (Soufer et al., 1998; Wang et al., 2005) to induce stress similar to the Trier Social Stress Test (Kirschbaum et al., 1993). Participants were given a four-digit starting number and a two-digit integer (presented for 5 s) at the beginning of a run. Participants had to subtract a two-digit integer from the starting number and subtract continuously. The subtraction was temporarily paused every 45 s when a fixation cross was presented, and continued when the fixation cross disappeared. Participants reported the final subtraction value at the completion of a run. Each run started with a different number and participants subtracted a different integer from the starting number during each run. Each run lasted 5 min. At the end of each run, subjects rated their stress level using a 1–4 analog bar (with 1 being not stressful at all and 4 being very stressful) (**Figure 1**).

Mindful breathing task

During the pre-scan session of the mindful breathing task day, participants were trained to: (1) focus their attention on the bodily sensations of breathing and count breaths from 1 to 10, (2) notice their mind wander and return to counting when mind wandering happens, and (3) simply return attention to breathing without getting frustrated when their mind wanders. These instructions mirror a commonly used mindfulness meditation practice (Hanh, 1976). Participants were instructed to follow these instructions during the mindful breathing task. For both stress and mindful tasks, participants paused when a fixation cross was displayed on the screen (**Figure 1**).

We validated the stress and mindful breathing task in our previous study. Subjects rated the stress induction task as more stressful, had higher cortisol level, faster heat beat, and respiratory rate during the stress task across all runs than during the mindful breathing task (Paul et al., 2013). In this study, we investigated whether modulated moderated the effect of repeated mental stress.

BIOCHEMICAL AND PHYSIOLOGICAL MEASURES

To validate the stress and mindful tasks, peripheral biochemical and physical measures were collected including salivary cortisol level, heart rate, and respiration rate. Participants were given a Salivette (Sarstedt AG & Co., Germany) to collect salivary right before, in the middle, and right after the whole scan session. Salivary cortisol levels were assessed with solid-phase Coat-A-Count ^{125}I radioimmunoassays for Cortisol (TKCO) provided by Siemens Healthcare Diagnostics (Los Angeles, CA, USA) following our previous work (Schultheiss and Stanton, 2009; Stanton et al., 2009). Heart rate and respiration rate were continuously monitored during scanning using a pulse oximeter and a chest belt, respectively (Biopac Systems, Goleta, CA, USA).

IMAGE ACQUISITION AND ANALYSIS

A 3.0 T GE MR750 scanner was used to acquire images at the Duke-UNC Brain Imaging and Analysis Center. After acquiring a T1-weighted SPGR anatomical image (matrix = 256 × 256 × 180, 1 mm^3) axially parallel to the anterior and posterior commissures (AC-PC) line, we acquired perfusion images during a 5-min resting state and stress/mindful breathing tasks using an

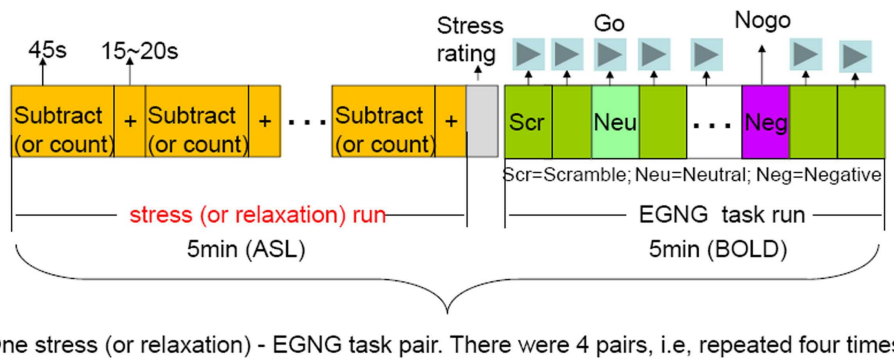

FIGURE 1 | Overview of the study design. There were four pairs of the stressful-EGNG tasks (also the same for the mindful-EGNG tasks). In this report, we focused our analysis on the stress (and mindful) task period and compared the repetition effect of stressful (and mindful) condition on perfusion changes over time (Run 1 vs. Run 4).

arterial spin labeling (ASL) sequence. A modified FAIR with spiral out sequence using a spatially selective inversion pulse and the QUIPSSII saturation pulses sequence (Wong et al., 1998) was used to allow quantitative determination of perfusion. A delay of 1 s was inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters were: repetition time (TR) = 4 s, echo time (TE) = 3.2 ms, TI1 = 600 ms, TI2 = 1600 ms, and flip angle = 90 °. Thirty-four slices ($64 \times 64 \times 34$ matrix; $\sim 3.5\,mm^3$ voxel size) were acquired from inferior to superior in a sequential order. BOLD images were acquired during the emotional go/no-go task.

The analysis was carried out using FEAT-perfusion fMRI analysis (MRI Expert Analysis Tool Version 5.98), part of the FSL analysis package (FMRIB Software Library)[1]. We conducted full perfusion signal modeling[2], where three explanatory variables (EVs) were modeled: the BOLD signal, the (constant-height) tag-control difference, and the activation component of the tag-control signal (formed by multiplying the first two EVs together). Thus, the activation component of the tag-control signal is our study interest. The following standard preprocessing steps were taken: removal of non-brain signal outside the head using the Brain Extraction Tool (BET), slice-time correction, coregistration, motion correction, normalization, spatial smoothing (5 mm FWHM), and high-pass filtering (1/60 Hz).

Given that the primary goal of the study is to investigate the repetition effect of stress on perfusion changes over time and the modification effect of early-life stress, we focused our data analysis on between-run differences within subjects (i.e., the first run vs. the last run). Calculating the perfusion change from Run 1 to Run 4 is the way we modeled change over time, and in particular, response patterns to repeated stress. An increase in perfusion from Run 1 to Run 4 (i.e., Run 4–Run 1) demonstrates either neural sensitization in regions related to affective processing or more effective recruitment of resources in a brain region related to cognitive control, and a decrease from Run 1 to Run 4 demonstrates neural habituation or less effective recruitment of resources in a brain region related to cognitive control. The results were also confirmed by using the early two runs (Run 1 and Run 2) vs. the later two runs (Run 3 and Run 4). The between-run differences were computed using a fixed effect model for each subject under both stressful task condition and mindful breathing task condition. For the group level analysis, we first examined significant perfusion between-run difference in the group during the stress and mindful tasks separately using random effect model (FLAME1) to investigate which regions demonstrated a habituation effect over the course of the stress task and the mindfulness task across all participants. Then, to understand whether the habituation effect was stress or mindfulness specific, we examined differences in neural adaptation patterns between the two tasks. We compared the difference in perfusion of Run 1 vs. Run 4 between the stressful and mindful task condition using paired t-test with a random effects analysis.

To investigate the modification effect of early-life stress on habituation in response to repeated stress over time, we then conducted regression analyses to examine the association between perfusion changes from Run 1 to Run 4 with the measurements of early-life stress. Given the theory that early-life stress is associated with depression in adulthood, we first investigated the relationship between the total CTQ score and CTQ subcomponent scores with trait rumination (RRS) and trait mindfulness (FFMQ) as well as each facet of FFMQ using simple linear (total score of measurement) and multiple linear regression analysis (subcomponents). The total or subscores of CTQ which showed significant correlation ($p < 0.05$) with RRS or FFMQ were used to do the whole-brain voxel-wise analysis with perfusion changes from Run 1 to Run 4. For all imaging-related analyses, significance was determined using a voxel significance level of $z > 2.3$, with a whole-brain-corrected cluster significance threshold of $p < 0.05$.

Finally, to further understand the perfusion pattern in response to the repeated stressor across time related to depression vulnerability and resilience, we also subsequently identified individuals with early-life stress who possibly were vulnerable or resilient to depression using the following criteria: (1) vulnerable ($n = 5$), having early-life stress experiences, RRS ≥ 40, FFMQ < 150, and (2) Resilient ($n = 5$), having early-life stress experiences, RRS < 40, FFMQ ≥ 150. Individuals who did not have early-life stress experience were defined as Neutral ($n = 6$). The psychological measures for each of the groups were shown in **Table 1**. There were three participants who had missing RRS and FFMQ data. Because of the small sample size of the Vulnerable, Resilient, and Neutral groups, we investigated the perfusion changes using Region-of-Interest (ROI) analysis. The ROIs were identified by extracting the significant clusters from the regression analyses in the third level analysis. The mean signal strength with each ROI for each run in each subject was calculated.

RESULTS

BEHAVIORAL RESULTS

The negative association of early-life stress with trait mindfulness

There was not a significant correlation between RRS and either the CTQ total score or the score of subcomponents. However, multiple

Table 1 | The Neuropsychological measures for the three groups, group resilient to depression, the group vulnerable to depression, and the group neutral to depression that were defined based on the RRS and FFMQ scores.

No. of subjects	Resilient	Vulnerable	Neutral
	5	5	6
RRS	26.4 (3.2)	43.6 (3.0)	28.5 (4.0)
FFMQ	152.2 (3.5)	125.2 (11.9)	115.3 (16.5)
Total CTQ	28.6 (3.3)	32.2 (3.3)	29.8 (6.5)
Emotional abuse	5.2 (0.4)	8 (1.4)	7 (2.8)
Physical abuse	5.8 (1.3)	5.6 (0.9)	5.5 (0.8)
Sexual abuse	5 (0)	5.4 (0.9)	5 (0)
Emotional neglect	7 (1.6)	7.8 (2.9)	6.8 (2.6)
Physical neglect	5.6 (0.9)	5.4 (0.5)	5.5 (0.8)

Italics are used when referring to the subscales of the CTQ (Childhood Trauma Questionnaire).

[1] www.fmrib.ox.ac.uk/fsl

[2] http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/perfusion.html

regression analysis showed that, among the CTQ subcomponents, emotional abuse was inversely associated with non-reactivity, one of the five facets of the mindfulness on the FFMQ ($t = 2.23$, $p = 0.05$), meaning that individuals with more severe emotional abuse during childhood had lower trait non-reactivity. Trait non-reactivity is the ability to step back from one's experiences without becoming overly engrossed in them (Baer et al., 2006), which we previously found having protective effect from depression vulnerability (Paul et al., 2013). Therefore, emotional abuse seemed to be an important risk factor for depression vulnerability, and the score of emotion abuse was used to our following neuroimaging data analysis.

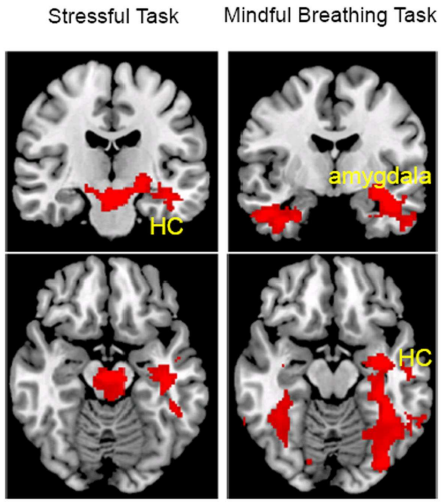

FIGURE 2 | The main effect of task repetition (Run 1–Run 4) on perfusion during the stress (left) and mindful breathing (right) tasks (voxel-wise analysis, $Z > 2.3$, $p < 0.05$ cluster correction). HC, hippocampus cortex.

NEUROIMAGING RESULTS

The habituation to the repeated stressor and repeated mindful task

First, we investigated regions that showed a habituation effect, i.e., regions that showed perfusion decrease from Run 1 to Run 4 (Run 1–Run 4) under the stress and mindful breathing conditions separately across all participants. The voxel-wise analyses revealed that when a stressor was presented repeatedly (**Figure 2**; **Table 2**), the perfusion was significantly decreased in the left middle and superior temporal cortex from the first to the last run (i.e., Run 1–Run 4) suggesting there was a habituation effect in these regions under the stressful condition. During the repeated mindful breathing task (**Figure 2**; **Table 2**), the perfusion was significantly decreased in the left amygdala, hippocampus, fusiform gyrus, and bilateral thalamus, therefore, there was a habituation effect in these regions during the mindfulness induction. In a direct comparison of the stress task and mindful breathing task, however, we did not find significant differences in perfusion comparing the Run 1–Run 4 contrast between the 2 days.

The association of early-life stress with less habituation to the repeated stressor

Given that only the emotional abuse subscore of the child trauma score was significantly correlated with mindfulness (negatively), we used the emotional abuse subscore to compute the regression analyses with the perfusion change from Run 1 to Run 4. The whole-brain voxel-wise analysis revealed that the emotional abuse subscore was significantly correlated with a reduction in perfusion level from Run 1 to Run 4 in the right orbitofrontal cortex and the vmPFC (**Figure 3**; **Table 3**) during the stress task. Taking the significant cluster of vmPFC as a ROI, we confirmed that the significant correlation between the reduction of perfusion from Run 1 to Run 4 and emotional abuse in childhood ($r_{14} = 0.59$, $p = 0.016$, for double confirm purpose) was not due to outliers (see the lower plot in **Figure 3**). The *post hoc* ROI analysis showed that the perfusion reduction from Run 1 to Run 4 during the

Table 2 | Regions that revealed habituation effect (Run 1–Run 4) of the stressful task and the mindful breathing task (those in italic are subclusters).

Region	Hemisphere	Cluster size	Peak voxel (*x*)	Peak voxel (*y*)	Peak voxel (*z*)	Maximum *Z*-value
HABITUATION EFFECT OF THE STRESSFUL TASK						
Cerebellum crus I	R	13957	28	−80	−22	4.36
amygdala	L		*−28*	*−6*	*−14*	*3.74*
hippocampus	L		*−32*	*−26*	*−11*	*3.01*
temporal pole	L		*−42*	*−12*	*−30*	*4*
	R		*40*	*0*	*−36*	*3.92*
cerebellum vermis	L		*−6*	*−49*	*−23*	*3.28*
fusiform gyrus	L		*−28*	*−56*	*−6*	*3.52*
	R		*36*	*−36*	*19*	*2.87*
Lateral parietal cortex	R	1801	32	−70	54	3.47
HABITUATION EFFECT OF THE MINDFUL BREATHING TASK						
Midbrain	L	1862	−6	−16	−16	4.7
midbrain	*R*		*6*	*−10*	*−12*	*3.7*
pons	*R*		*2*	*−20*	*−24*	*4.25*
thalamus	*L*		*−20*	*−20*	*−10*	*3.71*
hippocampus	*L*		*−40*	*−20*	*−16*	*3.73*

stressful condition was also significantly correlated with the CTQ total score ($r_{14} = 0.56$, $p = 0.024$, **Figure 3**). A similar association was not found in response to the repeated mindful breathing task, indicating that reported early-life stress was uniquely associated with a habituation response in the vmPFC perfusion under acute stress conditions in the laboratory.

Habituation effect in depression-vulnerable vs. resilient individuals – subsequent ROI analyses

We further performed an exploratory investigation on the perfusion pattern in the vmPFC and in the amygdala in response to the repeated stressor in depression-vulnerable and resilient individuals. The vmPFC ROI was defined using voxels that revealed significant correlation between emotional abuse and the reduction of Run 1–Run 4 perfusion, and the amygdala ROI was defined using voxels showing significant habituation effect during the mindful breathing task. Only ROI analyses were conducted due to the small number of subjects who met the vulnerable or resilient criteria. We focused on the vmPFC and amygdala regions because of the well-known association of these two regions with early trauma (Taylor et al., 2006; Hart and Rubia, 2012) and the inverse relationship between the two regions in emotion regulation.

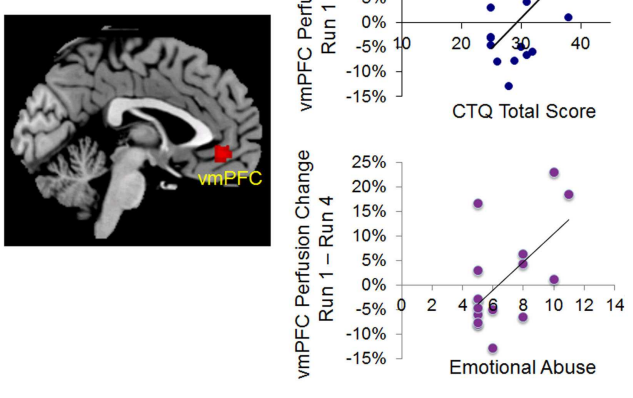

FIGURE 3 | Left, voxel-wise analysis on the correlation between emotional abuse score and the perfusion changes from Run 1 to Run 4 during repeated stress (voxel-wise analysis, $z > 2.3$, $p < 0.05$ cluster correction). Right, correlation plots based on ROI analyses confirming the significant correlation between the perfusion changes from Run 1 to Run 4 during repeated stress and emotional abuse score (lower plot) and Childhood Trauma Questionnaire (CTQ) Total Score (upper plot).

As the bar graph shown in **Figure 4**, ROI analyses on the vmPFC and amygdala revealed an inverse relationship. For individuals vulnerable to depression, the perfusion level in the amygdala increased from Run 2 to Run 4 relative to Run 1, whereas the perfusion level in the vmPFC was decreased from Run 3 to Run 4 relative to Run 1. Interestingly, depression-resilient individuals showed a linear decrease in perfusion level from Run 1 to Run 4 in the amygdala, whereas the perfusion level of the vmPFC did not change significantly across the four runs. By contrast, individuals who did not experience childhood trauma (*N* in **Figure 4**) revealed a sustained activity perfusion level in the vmPFC when they were repeatedly exposure to stress and sustained activation in the amygdala.

DISCUSSION

The current study investigated the impact of early-life stress on blood flow over time during a repeated stress induction task and during a repeated mindful breathing task. We found a inverse correlation between emotional abuse and non-reactivity (a subcomponent of mindfulness) which is consistent with previous finding that childhood emotional abuse and neglect proved more predictive of adult depression than childhood sexual or physical abuse (Powers et al., 2009). Our voxel-wise regression analysis revealed a clear association between childhood emotional abuse and reduced orbitofrontal and vmPFC perfusion over time when participants were exposed to stress repeatedly. The orbitofrontal and vmPFC sends projections to the amygdala, and is known to regulate amygdala activity (Price, 2005; Urry et al., 2006). Therefore, we speculate that a lack of sustained orbitofrontal and vmPFC activity, coupled with amygdala hyperactivity, in response to a repeated stressor, might be an important neural signature of depression vulnerability.

Our interpretation was supported by our subsequent ROI analyses which confirmed that individuals who experienced early-life stress and were high in trait rumination had reduced vmPFC activity in the later compared to earlier stressful trials, individuals who experienced early-life stress but were high in trait mindfulness had sustained vmPFC activity, and individuals who did not have early-life stress had an increased vmPFC perfusion over time. The inverse relationship between the vmPFC and the amygdala has been consistently reported in the literature (Phelps et al., 2004; Harenski and Hamann, 2006; Ohira et al., 2006; Urry et al., 2006). Our results suggest that healthy adults exert effortful control over emotion via increasing the vmPFC activity when they are repeatedly exposed to a stressor. For individuals who develop stress resilience, they may regulate amygdala activity more efficiently than healthy adults without this trait resilience by sustaining the vmPFC activity without further increasing the effortful vmPFC activity. Whereas when individuals are vulnerable to stress, the vmPFC has a limited capacity for cognitive control to regulate

Table 3 | Regions that revealed significant correlation between perfusion reduction during repeated stress and emotional abuse (those in italic are subclusters).

Region	Hemisphere	Cluster size	Peak voxel (*x*)	Peak voxel (*y*)	Peak voxel (*z*)	Maximum *Z*-value
Orbital frontal cortex	R	1909	36	54	−10	4.68
Orbital frontal cortex	*R*		*34*	*60*	*−4*	*3.84*
Ventromedial prefrontal cortex	*M*		*−1*	*45*	*−6*	*3.25*

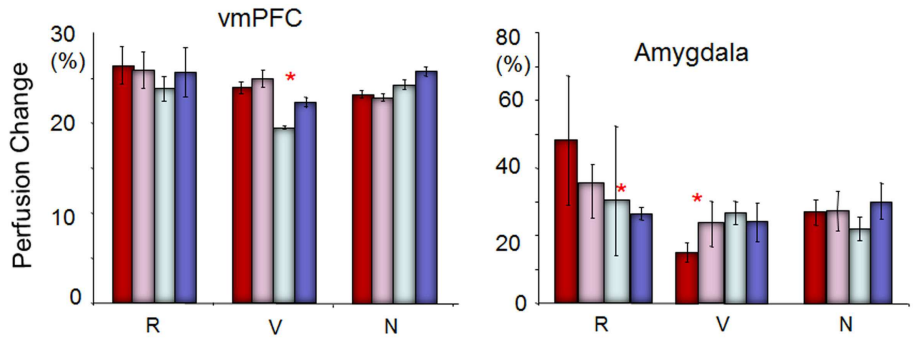

FIGURE 4 | The perfusion changing pattern in the vmPFC and amygdala to repeated stress across runs among individuals resilient to depression (*R*), vulnerable to depression (*V*), and neutral (*N*, not resilient and not vulnerable). Red = Run 1; pink = Run 2; silver = Run 3; blue = Run 4. The perfusion level in the amygdala was increased from Run 2 to Run 4 relative to Run 1, whereas the perfusion level in the vmPFC was decreased from Run 3 to Run 4 relative to Run 1 for individuals vulnerable to depression. On the other hand, depression-resilient individuals showed a linear decrease in perfusion level from Run 1 to Run 4, whereas the perfusion level of the vmPFC did not change significantly across the four runs. *Indicates significant difference between the first two runs with the last two runs in ROI analyses (paired *t*-tests, $p < 0.05$).

emotional responding, and could not effectively regulate amygdala activity in the later runs. Therefore, our study suggests that a lack of sustained vmPFC activity when repeatedly exposed to stress might be an important neuroimaging marker that distinguishes stress vulnerability vs. resilience in individuals with early-life stress.

However, the interpretation is preliminary due to the small sample size for the stress vulnerable and resilient groups. Another caveat of the study is the fact that we only recruited males in the study. The literature on sex differences in stress response is mixed (Kudielka and Kirschbaum, 2005; Wang et al., 2007; Ossewaarde et al., 2010). According to Ossewaarde et al. (2010), women have different responses to stress and facial expressions during different menstrual phases. Their results also indicated general stress sensitivity during the late luteal phase, as indicated by stress-induced heart rate changes and reported negative affect. Indeed, a study by Kirschbaum et al. (1993) found that the salivary cortisol response of women in the luteal phase was similar to men, but women taking oral contraceptives or in the follicular phase demonstrated lower free cortisol responses. Wang et al. (2007) further showed that stress in men was associated with cerebral blood flow (CBF) increase in the right prefrontal cortex and CBF reduction in the left orbitofrontal cortex, whereas stress in women activated the ventral striatum, putamen, insula, and cingulate cortex. There, future studies with larger sample sizes of both males and females are needed to verify our findings. Studies include women, and either collect menstrual-cycle phase data or only examine women in the luteal phases are recommended, to minimize the effect of menstrual-cycle phase on stress reactivity and further clarify the literature on sex-related differences in stress reactivity. In addition, future studies using causal modeling are necessary to further understand whether a lack of regulatory control by the vmPFC over the amygdala is the most important regulatory pathway in depression vulnerability.

Of note, although the hippocampus is often regarded as the most vulnerable region to stress and has consistently been found damaged in patients with PTSD (Astur et al., 2006; Werner et al., 2009; Dickie et al., 2011; Thomaes et al., 2013), we did not find an association of perfusion change over time in the hippocampus with early-life stress. Instead, we found reduced perfusion in the hippocampus when repeatedly practicing mindful task suggesting a task learning effect. The reason that we did not find a significant association between the perfusion change in the hippocampus and early-life stress might be due to the fact that some individuals with early-life stress in our sample have developed resilience to stress. Our subsequent analysis with the amygdala demonstrated the pattern we would have expected with the hippocampus, and future studies in a larger sample size would clarify this hypothesis about stress and the hippocampus.

We also found decreased blood flow over time in the amygdala, fusiform gyrus, and bilateral thalamus specifically during the mindful breathing task. The reduced blood perfusion from Run 1 to Run 4 under the mindfulness condition fits well with previous knowledge in that repeated mindful breathing can result in habitation and less excitation over time in the regions related to emotional salience (amygdala, thalamus) and imagery memory (hippocampus and fusiform gyrus) (Byrne et al., 2007; Bird et al., 2012). Nevertheless, we did not find any significant difference in the perfusion pattern in the vmPFC or any other regions when comparing perfusion patterns over time between stress and mindful conditions. One explanation for this result might be that the stress task did not evoke a sufficiently strong stress response to see a statistical difference in our small sample size. Therefore, only individuals who had experienced early-life stress revealed stronger change in neural response to the repetition of such a mild stressor, suggesting that early-life stress might have a sensitized effect in these individuals. In this sense, a mild stressor might be more useful in detecting stress vulnerability. On one hand, our mental arithmetic task only involved mental effort but not negative feedback or psychological pressure, which are two important elements of mental stress (Dickerson and Kemeny, 2004). It will be informative in future studies to compare neural responses to different elements and different types of stressors.

In summary, we found an association between early-life stress and reduced perfusion level in the vmPFC in response to repetition

of a mild stressor. The effect was particularly strong in individuals who had early-life stress and also developed trait rumination, but not in those who had strong trait mindfulness. Our results open an opportunity of assessing stress vulnerability and resilience by continuously monitoring the vmPFC and amygdala perfusion or activation change over time. Functional MRI typically has large variation across subjects and difficult to establish a norm range, which has limited its application clinically for individualized diagnosis. The dynamic changing pattern in brain perfusion over time found in this study is important because it relies on the changing pattern within subject across time rather than a norm value. If confirmed by future studies using larger samples of males and females, changing patterns of perfusion to repeated exposures of stress over time, could be a novel way to identify depression vulnerability at an individual level.

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The effect of moderate acute psychological stress on working memory-related neural activity is modulated by a genetic variation in catecholaminergic function in humans

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Acute stress has an important impact on higher-order cognitive functions supported by the prefrontal cortex (PFC) such as working memory (WM). In rodents, such effects are mediated by stress-induced alterations in catecholaminergic signaling, but human data in support of this notion is lacking. A common variation in the gene encoding Catechol-O-methyltransferase (COMT) is known to affect basal catecholaminergic availability and PFC functions. Here, we investigated whether this genetic variation (Val158Met) modulates effects of stress on WM-related neural activity in humans. In a counterbalanced crossover design, 41 healthy young men underwent functional magnetic resonance imaging (fMRI) while performing a numerical N-back WM task embedded in a stressful or neutral context. Moderate psychological stress was induced by a well-controlled procedure involving viewing strongly aversive (versus emotionally neutral) movie material in combination with a self-referencing instruction. Acute stress resulted in genotype-dependent effects on WM performance and WM-related activation in the dorsolateral PFC, with a relatively negative impact of stress in *COMT* Met-homozygotes as opposed to a relatively positive effect in Val-carriers. A parallel interaction was found for WM-related deactivation in the anterior medial temporal lobe (MTL). Our findings suggest that individuals with higher baseline catecholaminergic availability (*COMT* Met-homozygotes) appear to reach a supraoptimal state under moderate levels of stress. In contrast, individuals with lower baselines (Val-carriers) may reach an optimal state. Thus, our data show that effects of acute stress on higher-order cognitive functions vary depending on catecholaminergic availability at baseline, and thereby corroborate animal models of catecholaminergic signaling that propose a non-linear relationship between catecholaminergic activity and prefrontal functions.

Keywords: stress, working memory, Catechol-O-methyltransferase, catecholamine, prefrontal cortex, fMRI

INTRODUCTION

Acute stress has an important impact on higher-order cognitive function such as working memory (WM). These effects are believed to result from stress-induced alterations of large-scale brain network functioning including the prefrontal cortex (PFC), through stress-sensitive neuromodulatory systems (Goldman-Rakic, 1995; Aston-Jones and Cohen, 2005; Arnsten, 2007, 2009; McEwen, 2007; Sara, 2009; Hermans et al., 2011). In particular, stress-induced changes in catecholaminergic signaling play a central role in modulating prefrontal functions in rodents (Arnsten and Goldman-Rakic, 1998; Arnsten, 2009). Yet, direct human data in support of this notion is lacking. A variation (Val158Met) in the gene encoding Catechol-O-methyltransferase (*COMT*) is associated with individual differences in basal catecholaminergic availability (Lotta et al., 1995; Mannisto and Kaakkola, 1999) and prefrontal functions (Chen et al., 2004). We, therefore, conjecture that effects of acute stress may interact with *COMT* genotype to alter WM-related PFC function in humans.

Exposure to acute stress leads to rapid activation of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis, and is accompanied by a tonical increase of central release of catecholamine levels (de Kloet et al., 2005; Arnsten,

2009; Joels and Baram, 2009). Through ascending projections from brainstem nuclei where the locus coeruleus norepinephrine and midbrain dopaminergic systems locate, these stress-sensitive catecholamines alter neuronal functioning of widely distributed brain regions, particularly including the PFC (Arnsten and Li, 2005; Aston-Jones and Cohen, 2005; Arnsten, 2009; Sara, 2009). Converging evidence from human behavioral and neuroimaging studies have confirmed that acute stress indeed alters WM performance with both detrimental (Elzinga and Roelofs, 2005; Oei et al., 2006; Luethi et al., 2008; Schoofs et al., 2008) and enhancing (Lewis et al., 2008; Weerda et al., 2010; Hidalgo et al., 2011) effects, likely through altered efficiency of WM-related processing in dorsolateral PFC (Porcelli et al., 2008; Qin et al., 2009; Weerda et al., 2010). Interestingly, animal studies suggest that stress-sensitive catecholamines exert an inverted U-shaped influence on prefrontal functions (Aston-Jones and Cohen, 2005; Vijayraghavan et al., 2007), in which prefrontal functioning reaches an optimum at an intermediate level of catecholaminergic activity (Arnsten and Li, 2005; Aston-Jones and Cohen, 2005; Vijayraghavan et al., 2007). These implicate that acute stress may have variable (i.e., either detrimental or enhancing) effects on PFC functions depending on levels of stress-induced catecholaminergic activity.

The intracellular enzyme COMT plays a key role in regulating catecholaminergic availability. A single nucleotide polymorphism (SNP) in the gene coding *COMT*, which causes a Valine-to-Methionine substitution at codon 158 (Val158Met), leads to a 3–4 fold decrease in the ability of this enzyme to catabolize catecholamines (Lotta et al., 1995; Mannisto and Kaakkola, 1999). As a consequence, basal levels of catecholaminergic availability in Met-homozygotes are presumed to be increased throughout the cortex, particularly for the PFC (Chen et al., 2004). Associations have been found in humans between *COMT* genotype and higher-order PFC functions and emotional processing in both health and disease (Drabant et al., 2006; Meyer-Lindenberg et al., 2006; Bishop et al., 2008). Interestingly, recent evidence from human and rodent studies suggests that *COMT* genotype may interact with catecholaminergic manipulations altering PFC function (Mattay et al., 2003; Bertolino et al., 2004; Papaleo et al., 2008). Specifically, one study demonstrated that *COMT* knockout mice (Met-like genotype) is associated with better WM functioning at baseline, but also with a higher sensitivity to stress. In contrast, the *COMT-Val* transgenic mice (Val-like genotype) are associated with inferior WM performance at baseline, but are less sensitive to stress (Papaleo et al., 2008). Based on these findings and the aforementioned inverted U-shaped relationship between catecholaminergic signaling and neurocognitive functioning, one may hypothesize that effects of experimentally induced moderate stress on WM-related prefrontal activity in humans would exhibit a similar genotype-dependency, with stronger detrimental effects of stress in *COMT* Met-homozygotes.

To test this hypothesis, 41 healthy young men underwent functional magnetic resonance imaging (fMRI) while performing a numerical N-back WM task (including 2- and 0-back conditions). In counterbalanced order, one session involved stress induction while the other session served as control. Moderate psychological stress was induced experimentally by a standardized cinematographic procedure in which participants saw strongly aversive (vs. neutral control) movie material combined with a self-referencing instruction, which has been shown previously to elicit physiological and psychological stress responses (Henckens et al., 2009; Qin et al., 2009; Hermans et al., 2011). To validate our stress manipulation, measures of heart rate (HR), α-amylase, salivary cortisol, and subjective negative affect were acquired prior to, during and after fMRI scanning. Given the relatively low frequency of Val-homozygotes in our sample, Val-carriers were treated as a single group in all analyses. We predicted that moderate psychological stress would have an interactive effect on the differential neural activity reflecting WM load (2- vs. 0-back) in Met-homozygotes and Val-carriers, with a stronger stress-induced reduction of differential dorsolateral PFC activity in Met-homozygotes. Because WM-related activation of the dorsolateral PFC is normally accompanied by deactivation in the medial temporal lobe (MTL), and adaptive changes in reciprocal organization of dorsal executive and ventral affective brain areas under arousal and stressful circumstance (Dolcos and McCarthy, 2006; Oei et al., 2011; Cousijn et al., 2012), we also conjectured a corresponding genotype-dependent effect in the MTL.

MATERIALS AND METHODS

PARTICIPANTS

Forty-one young, healthy, right-handed males (Caucasian ethnicity, aged 18–35 years) with normal or corrected-to-normal vision participated in this study. There are 16 Met-homozygotes (Met/Met), 7 Val-homozygotes (Val/Val) and 18 heterozygotes (Val/Met). Participants reported no history of neurological, psychiatric, or endocrine disease, and no current use of psychoactive drugs or corticosteroids. None of them had experienced severe physical or emotional trauma. Only men were included to avoid confounds related to gender differences and menstrual cycle-dependent variance in stress responsiveness (Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2005). All had participated before in MRI experiments to minimize stress responses evoked by unfamiliarity with the environment and procedures. The study was in accordance with the Declaration of Helsinki and institutional guidelines of the local ethics committee (CMO Region Arnhem-Nijmegen, Netherlands). All participants gave written informed consent. Data from two participants (1 Met-homozygote and 1 heterozygote) were excluded from further analysis completely, either due to technical failure or excessive head movement during scanning.

Participants were tested in a mixed factorial design with stress induction as within-subject factor and genotype as between-subject factor. The groups (*COMT* Met-homozygotes and Val-carriers) did not differ significantly regarding age ($p > 0.1$) and trait anxiety ($p > 0.4$) (see **Table 1**).

GENERAL PROCEDURE

The experiment was carried out in the afternoon (after 1 pm) to ensure relatively stable and low levels of endogenous cortisol. After arrival, 1 h before scanning, participants trained on the WM task extensively and completed various questionnaires. To determine whether baseline cortisol levels differed between COMT

Table 1 | Participant demographics.

	Met-homozygotes ($n = 15$)	Val-carriers ($n = 24$)	Total ($n = 39$)
Age (mean ± SE)	23.51 ± 1.13	23.82 ± 5.57	23.67 ± 5.55
Anxiety (mean ± SE)	28.52 ± 5.57	31.00 ± 5.33	30.49 ± 5.50

Note: Due to either technical failure or excessive head movement during scanning, data from two participants were excluded from further analyses. SE, standard of error of mean; anxiety, trait anxiety scores.

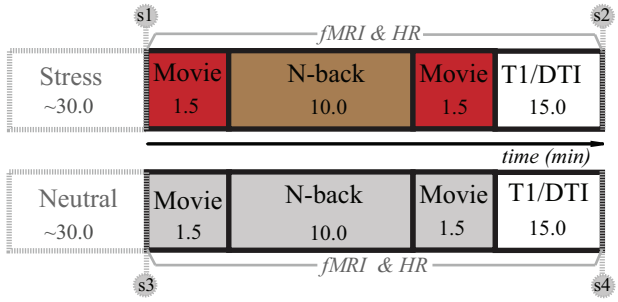

FIGURE 1 | Overview of experimental design. The experiment consisted of stress and control conditions (or sessions), and the order was counterbalanced across participants. After preparation outside the scanner, a numeric N-back WM task was administered twice: in one session it was embedded in a stressful context and the other one in a neutral control condition (see Stress induction for details). Note: The numbers in the squares indicate the time in minutes. S1–S4 represents four saliva samples coinciding with subjective mood ratings (PANAS). T1 and DTI stand for a high-resolution anatomical scan and a diffusion tensor imaging scan.

genotypes, all participants were asked to take one saliva sample as baseline in the late afternoon on the day before the experiment at home. Other saliva samples and subjective affect positive and negative affect scales (PANAS) were obtained before and after both experimental conditions. The actual fMRI experiment consisted of four short movie clips to ensure that tasks of interest were fully embedded in a continuously stressful (or neutral control) context. Between the first and second movie clips, participants performed the numeric N-back task (**Figure 1**). Before and after the stress and control condition, saliva samples and subjective affect ratings were collected and HR was measured throughout the experiment. The two conditions were separated by approximately 20 min, consisting of a structural MRI scan and a perfusion fMRI scan.

STRESS INDUCTION

In the stress induction condition, moderate acute psychological stress was induced by showing short movie clips within the MRI scanner containing scenes with strongly aversive content (extreme violence) selected from a commercially available movie (*Irreversible*, 2002, by Gaspar Noé). The N-back task was fully embedded in short movie clips (**Figure 1**) containing scenes with extremely aversive content. In the control condition, participants watched equally long movie clips from another movie (*Comment j'ai tué mon père*, 2001, by Anne Fontaine) which were equal in luminance and similar in language but contained only non-arousing scenes. Matching for audiovisual characteristics was performed by the authors by selecting aversive and neutral clips out of a set of candidate clips which best matched on the measures described in Hermans et al., 2011. After short introductory texts, participants were asked to watch the movies attentively and take an eyewitness perspective as to involve them maximally in the action taking place in the movie clips. The WM task was closely surrounded by two movie clips in time in order to boost stress induction and create a continuously stressful context.

We chose to use a stress induction procedure involving exposure to aversive cinematographic material in combination with self-referencing instruction, because of the following considerations (also see Hermans et al., 2011). First, this procedure allows us to create an ecologically valid model for examining stress-induced adaptive alterations (i.e., hypersensitivity at the cost of higher-order cognitive functions) when exposing to acutely stressful experiences in the real world that may ultimately trigger emotional trauma with detrimental effects on various higher-order prefrontal cognitive functions. Second, exposure to highly aversive films in combination with self-referencing instruction meets the requirements for the physiological stress response in humans, particularly with activation of the sympatho-adrenomedullary system (SAM) and substantial elevation of epinephrine and norepinephrine levels, as described by Mason (Mason, 1968). Finally, unlike stressors based on public speaking, and cognitive performance in combination with negative social evaluation (Kirschbaum et al., 1993; Wang et al., 2005; Pruessner et al., 2008), our stress induction is likely to yield emotion focused rather than social or problem-focused coping strategies and plausibly triggers a state of fearful arousal. From a more general and broader standpoint of view, such a state of fearful arousal has been long believed to be an important feature of psychological stress in both animals and humans (Mason, 1968; Arnsten and Goldman-Rakic, 1998; Mobbs et al., 2007; Arnsten, 2009; Shackman et al., 2011). Moreover, previous studies have shown that this method elicits a measurable psychological, physiological, and neuroendocrine stress response (Henckens et al., 2009; Qin et al., 2009; van Marle et al., 2009), although it has relatively lower cortisol elevations than other social and/or cognitive challenging stressors. Notably, our stress induction procedure has been validated by one recent pharmacological study in humans, demonstrating that stress-sensitive noradrenergic (probably dopaminergic as well) activity plays a central role in regulating acute psychological stress (Hermans et al., 2011). This nicely fits the primary goal of our present study addressing how a genetic variation in catecholaminergic function modulates the effect of acute psychological stress on WM processing in humans.

N-BACK TASK

Using a blocked-design, participants completed six cycles of alternating 0- and 2-back conditions interleaved by a jittered

resting-fixation baseline ranging from 8 to 12 s. Within each block, a random digit sequence consisting of 15 single digits was shown to participants. Each digit was presented for 400 ms, followed by an inter-stimulus interval of 1400 ms. Each block lasted 27 s. During the 0-back condition, participants were asked to detect whether the current item on the screen was a "1" or not. During the 2-back condition, participants were asked to detect whether the current item had appeared two positions back in the sequence. Participants were instructed to make a button press with their index finger when detecting a target. Before fMRI scanning, they were extensively trained in performing the task to minimize interindividual variability and reduce practice effects. During this pretraining session, we trained every participant to perform 10 cycles of alternating 0- and 2-back conditions as used in our previous study (Qin et al., 2009). We did not set up specific performance criteria during pretraining, because we intended to minimize potential anticipatory and psychological stress induction when performing challenging WM task conjoint with performance evaluation (Dickerson and Kemeny, 2004; Pruessner et al., 2008).

PHYSIOLOGICAL AND PSYCHOLOGICAL MEASUREMENTS OF STRESS

To assess the SNS and HPA axis responses to the stress manipulation, saliva was sampled with salivette collection devices to determine the levels of α-amylase and cortisol. Samples were taken on the day before the experiment and before and after both conditions (five in total) and were stored at −20°C until analysis. The analysis (Cousijn et al., 2010; Strahler et al., 2010) was carried out at the Biopsychology Department in Dresden, where samples were prepared for biochemical analysis by centrifuging at $1500 \times g$ for 5 min, which resulted in a clear supernatant of low viscosity. Salivary-free cortisol concentrations were determined with a chemiluminescence assay with high sensitivity of 0.16 ng/mL (IBL). Concentration of α-amylase in saliva was measured by an enzyme kinetic method: saliva was processed on a Genesis RSP8/150 liquid handling system (Tecan). First, saliva was diluted 1:625 with double-distilled water by the liquid handling system. Twenty microliters of diluted saliva and standard were then transferred into standard transparent 96-well microplates (Roth). Standard was prepared from "Calibrator f.a.s." solution (Roche Diagnostics) with concentrations of 326, 163, 81.5, 40.75, 20.38, 10.19, and 5.01 U/L α-amylase, respectively, and double-distilled water as zero standard. After that, 80 mL of substrate reagent (α-amylase EPS Sys; Roche Diagnostics) were pipetted into each well using a multichannel pipette. The microplate containing sample and substrate was then warmed to 37°C by incubation in a water bath for 90 s. Immediately afterwards a first interference measurement was obtained at a wavelength of 405 nm with a standard ELISA reader (Anthos Labtech Instruments HT2). The plate was then incubated for another 5 min at 37°C in the water bath, before a second measurement at 405 nm was taken. Increases in absorbance were calculated for unknowns and standards. Increases of absorbance of diluted samples were transformed to α-amylase concentrations using a linear regression calculated for each microplate (Graphpad Prism 4.0 c for MacOSX; Graphpad Software). For one subject no data were acquired and for one subject the analysis did not succeed, whereas data of a third subject were not taken into account because he consumed caffeine shortly before the experiment. Behavioral and fMRI data quality of these three subjects were good, thus they were included in further analysis.

To assess autonomic activity throughout the experiment, we continuously recorded HR with an infrared pulse oximeter (MR-compatible) placed on the index finger of the left hand. Offline artifact correction and analysis of the HR frequency was done with in-house software. The HR frequency was averaged for the duration of each movie clip and the task. HR data from one participant were excluded due to excessive artifacts, while corresponding behavioral and fMRI data were included into further analysis.

Mood state was assessed using the positive and negative affect scale (PANAS) questionnaire (Watson et al., 1988) at four time points coinciding with the collection of salivary samples.

GENOTYPING

Genetic analyses were performed at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre, in a laboratory which has a quality certification according to CCKL criteria. High molecular weight DNA was isolated from saliva using Oragene containers (DNA Genotek, Ottawa, ON, Canada) according to the protocol supplied by the manufacturer. All participants were genotyped for the *COMT* SNP rs4680 (G > A; Val1 58 Met) using Taqman® analysis (Applied Biosystems, Nieuwerkerk a/d IJssel, Netherlands). Genotyping was carried out in a volume of 10 μl containing 10 ng of genomic DNA, 5 μl of Taqman Mastermix (2×; Applied Biosytems), 0.375 μl of the Taqman assay, and 3.625 μl of Milli-Q. The amplification protocol consisted of an initial denaturation step at 95°C for 10 min followed by 40 cycles of denaturation at 92°C for 15 s and annealing and extension at 60°C for 60 s. Allele-specific fluorescence was subsequently measured on an ABI 7500 FAST (Applied Biosystems). Taqman genotyping assays were validated before use and 5% duplicates and blanks were taken along as quality controls during genotyping. Genotyping results were only considered valid if duplicates and blanks were called correctly and genotypes could be called for at least 95% of the sample tested. All genotype frequencies were tested for Hardy-Weinberg Equilibrium.

fMRI DATA ACQUISITION

During MRI scanning, whole brain T2*-weighted echo planar imaging based on blood oxygenation level-dependent contrast (EPI-BOLD) fMRI data were acquired with a Siemens Trio 3.0 T MR-scanner (Erlangen, Germany) using an ascending slice acquisition sequence. Parameters of the sequence are following: 37 axial slices; volume repetition time, TR 2.18 s; echo time, TE 25 ms; 80° flip angle; slice matrix size, 64 × 64; slice-thickness, 3.0 mm; slice gap, 0.3 mm, field of view, FOV 212 × 212 mm. Two hundred six volumes were acquired during the N-back task. High-resolution structural images (1 × 1 × 1 mm) were acquired using a T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR, 2.3 s, TE, 3.03 ms, 8° flip angle, 192 contiguous sagittal slices, slice matrix size, 256 × 256, FOV, 256 × 256 mm).

Table 2 | Physiological and psychological measurements of stress ($n = 39$).

	Cortisol (nmol/l)		α-amylase (U/l)		HR (beats per minute)			Negative affect	
	Pre-	Post-	Pre-	Post-	M1	*N*-back	M2	Pre-	Post-
Stress (mean ± SE)	7.68 ± 0.80	7.97 ± 0.93	47.77 ± 6.09	58.06 ± 7.55	68.10 ± 1.85	64.71 ± 1.55	65.80 ± 1.72	12.80 ± 0.47	16.28 ± 0.89
Control (mean ± SE)	8.32 ± 0.73	6.39 ± 0.46	55.30 ± 7.14	49.36 ± 6.71	59.92 ± 1.32	63.24 ± 1.42	60.29 ± 1.34	13.13 ± 0.61	12.54 ± 0.46

Note: HR, heart rate; Pre-, saliva sampling prior to stressor or control session; Post-, saliva sampling posterior to stressor or control session; M1 and M2, movie clips prior and posterior to N-back task; Negative affect, negative affect scale; SE, standard error of mean.

Table 3 | Averaged (mean ± SE) accuracy and reaction times for 0- and 2-back working memory ($n = 39$).

		Met-homozygotes ($n = 15$)		Val-carriers ($n = 24$)		Total ($n = 39$)	
		Control	Stress	Control	Stress	Control	Stress
Accuracy	0-back	0.992 ± 0.005	1.000 ± 0.000	0.956 ± 0.029	0.961 ± 0.024	0.955 ± 0.019	0.976 ± 0.015
	2-back	0.849 ± 0.063	0.795 ± 0.046	0.862 ± 0.044	0.889 ± 0.025	0.857 ± 0.026	0.855 ± 0.023
RTs	0-back	845.3 ± 24.1	824.2 ± 14.1	863.4 ± 28.8	841.1 ± 19.4	856.8 ± 16.3	834.8 ± 13.9
	2-back	960.3 ± 42.9	945.8 ± 24.6	977.3 ± 37.6	964.8 ± 25.9	971.0 ± 23.8	957.8 ± 19.9

Note: RT, reaction times; SE, standard error of mean.

fMRI DATA ANALYSIS

Image preprocessing and statistical analysis was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The first five EPI volumes were discarded to allow for T1-equilibration. Remaining functional images were rigid-body motion corrected and the mean image was coregistered to each participant's T1-weighted MR-image. Subsequently, images were transformed into a common stereotactic space, and resampled into 2 mm isotropic voxels. Finally, images were spatially smoothed by convolving with an isotropic 3D-Gaussian kernel (8 mm full width at half maximum). The data were statistically analyzed using general linear models and statistical parametric mapping (Friston et al., 1995).

To assess neural activity associated with 0- and 2-back conditions, the two conditions were modeled separately as boxcar regressors and convolved with the canonical hemodynamic response function in SPM5. Additionally, realignment parameters were included to account for movement-related variability. The analysis furthermore included high-pass filtering using a cutoff of 1/128 Hz, global intensity normalization, and serial correlations correction using a first-order autoregressive [or AR(1)] model.

The contrast parameter images for the 2- vs. the 0-back condition, generated at the single-subject level, were submitted to a second-level analysis within a stress-by-genotype group mixed factorial analysis of variance (ANOVA). The analysis of WM-related deactivations was conducted based on the opposite contrast of 0- vs. 2-back condition. We used an alpha of 0.05 corrected for multiple comparisons based on suprathreshold cluster size statistics (Worsley et al., 1996). The initial threshold for this analysis was set at $p < 0.001$, uncorrected. Given our clear hypotheses regarding the PFC, this region was additionally investigated with a reduced search region consisting of an unbiased, anatomically defined, gray matter mask of the PFC covering the entire prefrontal areas, by using non-stationary suprathreshold cluster-size approach based on Monte-Carlo simulations (Forman et al., 1995; Ward, 2000; Nichols and Hayasaka, 2003; Hayasaka et al., 2004). This approach allows us to determine the minimum cluster size that controls for false positive

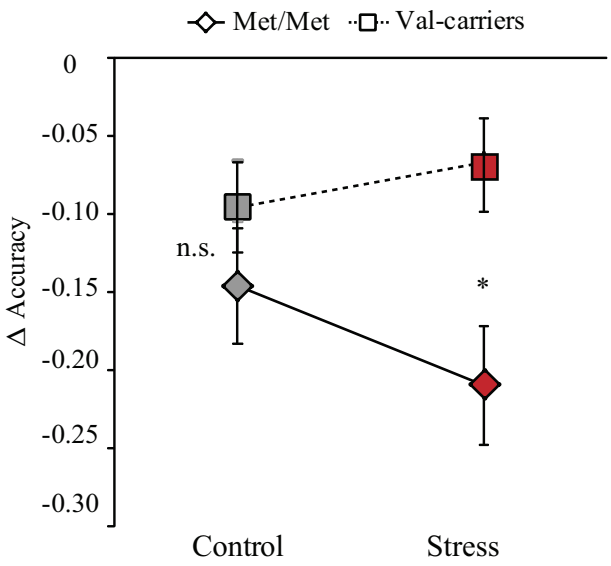

FIGURE 2 | Stress-by-*COMT* genotype interaction effect on WM performance. Difference of accuracy between 2- and 0-back tasks was plotted on the vertical axis as a function of control and stress conditions for two genotype groups (*COMT* Met-homozygotes and Val-carriers). Note: $^*p < 0.05$; error bars in the graph represent standard error of mean.

rate. The PFC mask was anatomically defined by combination of a gray matter mask and the anatomical automatic labeling (AAL) template of the PFC. Monte-Carlo simulations were implemented in Matlab using methods similar to the AlphaSim procedure. Ten thousand iterations of random 3D images, with the same resolution and dimensions as the fMRI data, were generated. The resulting images with the gray matter mask of interest were smoothed with the same 8 mm FWHM Gaussian kernel used to smooth our fMRI data. The maximum cluster size was then computed for each iteration and the probability distribution was estimated across the 10,000 iterations. The cluster threshold corresponding to a voxel-wise threshold of $p < 0.001$ for height, and a significance level of $p < 0.05$ corrected for multiple spatial comparisons was determined to be 28 voxels. Parameter estimates were extracted from clusters of activation associated with interaction effects to characterize the neural activation patterns of the stress and neutral conditions in the two groups using MarsBar (Brett et al., 2002).

RESULTS

EFFECTIVENESS OF STRESS INDUCTION

Measurements of salivary cortisol, α-amylase, and subjective negative affect were submitted to separate 2 × 2 × 2 repeated measures ANOVAs with stress (stress induction vs. control) and time (pre vs. post) as within-subject factors, and genotype (*COMT* Met-homozygotes vs. Val-carriers) as between-subject factor, and with the order effect of stress manipulation as a covariate of no interest (similarly hereinafter for other ANOVAs including functional imaging data). Time-by-stress interactions were found for salivary cortisol [$F_{(1, 34)} = 4.46$, $p < 0.05$], α-amylase [$F_{(1, 34)} = 8.59$, $p = 0.006$] (**Table 2**), and negative affect [$F_{(1, 37)} = 20.49$, $p < 0.001$]. For cortisol, a decrease was observed from pre- to post-stressor levels in the neutral condition [$t_{(35)} = 5.12$, $p < 0.001$], but no significant change in the stress condition [$t_{(35)} < 1$]. For α-amylase, we observed an increase in the stress condition [$t_{(35)} = 2.33$, $p < 0.03$] and a decrease in the control condition [$t_{(35)} = 2.07$, $p < 0.05$]. Negative affect increased in the stress condition only [$F_{(1, 37)} = 8.23$, $p < 0.01$]. In addition, a two independent samples T test revealed t difference [$t_{(34)} < 1$] in cortisol between Met-homozygotes (7.89 ± 7.92) and Val-carriers (8.04 ± 2.17) at baseline which were collected one day prior to the experiment.

HR data were analyzed with a 2 × 3 × 2 repeated measures ANOVA across averaged measures during the N-back task and the two surrounding movie clips. We found a main effect of stress [$F_{(1, 74)} = 46.62$, $p < 0.001$], and further t-tests confirmed that HR was consistently higher during all three phases of the experiment in the stress condition [all $t_{(38)} > 2.29$, $p < 0.03$].

None of the statistical tests described above revealed significant interaction effects of genotype and order-related effects.

Table 4 | Brain activations related to WM, and modulations of stress and COMT genotype.

Brain regions	L/R	BA	*T* score	Cluster size	MNI coordinates		
					x	*y*	*z*
WM-related activation: 2- vs. 0-back collapsing across conditions and groups							
Inferior parietal cortex	L	40	15.42	7528***	−36	−42	44
	R		14.46		44	−42	48
Superior PFC	L	8	14.83	19642***	−4	14	54
	R		14.12		4	22	50
Dorsolateral PFC	R	9 and 10	12.16		40	36	34
	L		10.40		−50	24	30
Inferior PFC	L	47	13.23		−32	20	−2
	R		15.07		34	26	−2
Striatum	L	–	9.53		−18	−2	14
	R		8.45		16	4	4
Midbrain	L	–	6.91		−6	−24	−10
	R		7.04		6	−24	−8
Cerebellum	L	–	14.03	3389***	−28	−60	−28
	R		14.02		30	−60	−26
Main effect of genotype: Met/Met vs. Val-carriers collapsing across conditions							
Dorsolateral PFC	L		3.94	40*	−42	42	12
	R		5.13	128**	42	8	44
Main effect of genotype: Met/Met vs. Val-carriers collapsing across conditions							
Dorsolateral PFC	R		5.78	169**	44	10	44
Interaction: (stress vs. control) × (Met/Met vs. Val-carriers)							
DLPFC	R	6	4.03	40*	30	30	42

*Note: Only clusters significant at $p < 0.05$ corrected on cluster level were reported. *** $p < 0.05$ FWE whole brain corrected; ** cluster $p < 0.05$ whole brain corrected; * cluster $p < 0.05$ small volume correction using non-stationary suprathreshold cluster-size approach. Stress, stress group; Control, control group; PFC, prefrontal cortex; L, left; R, right; BA, Brodmann Area; MNI, MNI coordinates (SPM5).*

Together, these results consistently confirm that the N-back task was indeed embedded in a stressful context in the stress condition.

WM PERFORMANCE

The mean accuracy and reaction times (RTs) are included in **Table 3**. WM load effects on accuracy and RTs (i.e., differences between 2- vs. 0-back) were submitted to two separate 2 (stress) by 2 (genotype) ANOVAs. For accuracy, we found a main effect of genotype [$F_{(1, 36)} = 4.95$, $p < 0.03$] with worse for Met-homozygotes in general, and an interaction between genotype and stress [$F_{(1, 36)} = 4.47$, $p < 0.04$] (see **Figure 2**). Further analyses revealed that *COMT* Met-homozygotes performed worse than Val-carriers in the stress condition [$t_{(37)} = 2.85$, $p < 0.01$], while no genotype effect was found in the control condition [$t_{(37)} = 1.31$, $p > 0.20$]. For RTs, neither a main effect of genotype nor an interaction effect was found [all F values <1]. To explore potential differences between Val-homozygotes and heterozygotes, we also conducted separately an additional 2-by-3 ANOVA by splitting Val-carriers into heterozygotes and Val-homozygotes, two separate, genotype groups for accuracy and RT data. We found a similar (but weaker) main effect of genotype and an interaction between the factors of genotype and stress. We did not find a significantly larger effect for Val-homozygotes than heterozygotes, likely due to the small sample size. Altogether, these results indicate that there was a larger detrimental effect on accuracy in COMT Met-homozygotes as compared to Val-carriers in the stress condition.

STRESS-BY-COMT GENOTYPE INTERACTION IN WM-RELATED ACTIVATION IN THE DORSOLATERAL PFC

First, by contrasting 2- with 0-back conditions (collapsing across groups), we confirmed activation of a WM-related frontal-parietal network (**Table 4**), indicating robust main effects of WM load. We also found main effect of genotype on the dorsolateral PFC when collapsing across the stress and control conditions, as well as in the control condition alone (**Table 4**). More important for the question at issue, we found a suprathreshold cluster in the right dorsolateral PFC (local maxima at [30, 30, 42], t value = 4.03, cluster $p < 0.05$ small volume correction using non-stationary suprathreshold cluster-size approach) for the interactive effect of stress (control vs. stress) and genotype (*COMT* Met-homozygotes vs. Val-Carriers) on this contrast. There was no reliable activation outside of the PFC in this contrast of stress-by-*COMT* interaction. As shown in **Figure 3**, stress induction had opposite effects on WM-related activity in this region depending on genotype. We also analyzed the data by splitting Val-carriers into heterozygotes and Val-homozygotes, two separate groups. This analysis revealed almost an identical main effect of genotype and interaction between stress and genotype in the dorsolateral PFC. Val-homozygotes showed numerically lower activation in the DLPFC in the control condition, and larger stress-induced positive effect as relative to heterozygotes. These effects, however, do not reach the level of significance applied to the analysis otherwise. This lower reliability is likely due to the small sample size of Val-homozygotes in our present study.

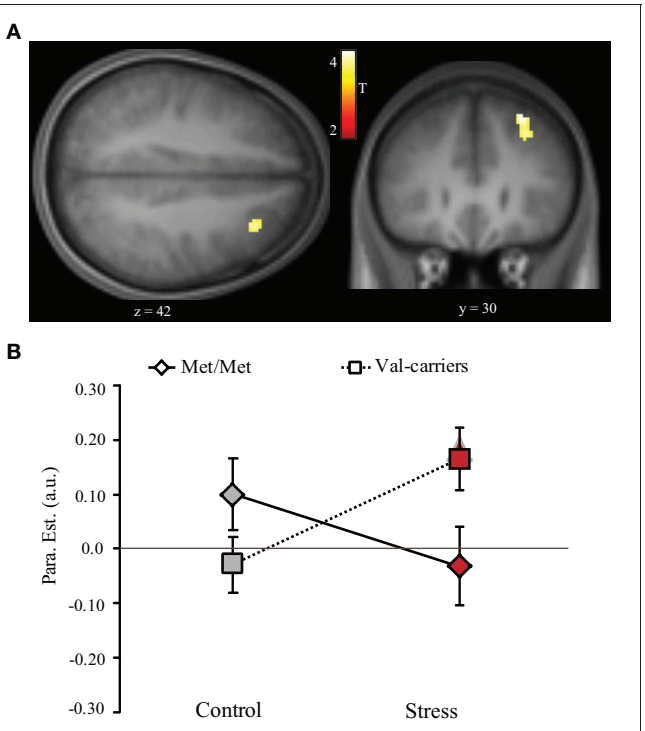

FIGURE 3 | Stress-by-COMT genotype interaction effect on WM-related activity in the dorsolateral PFC. (A) Transversal (left panel) and coronal (right panel) view of activation in the right dorsolateral PFC showing significant stress-by-COMT genotype interaction effect. Statistical parametric maps are superimposed onto spatially normalized and averaged ($n = 39$) high-resolution T1-weighted images (thresholded at $p < 0.001$ uncorrected for visualization purposes). **(B)** Bar graphs representing parameter estimates of WM-related activation under control and stress conditions in Met-homozygotes (Met/Met) and Val-carriers. The data for these bar graphs were only extracted to illustrate the interaction effect. Note: Control, control condition; PFC, prefrontal cortex; Stress, stress condition; error bars in the graph represent standard error of mean; T, color coded t values obtained from the whole brain analysis.

STRESS-BY-COMT GENOTYPE INTERACTION IN WM-RELATED DEACTIVATION IN THE MTL

By contrasting 0- with 2-back conditions (collapsing across groups), we replicated previous findings showing deactivation in regions comprising the "default mode" network (**Table 5**). For the interactive effect of stress (control vs. stress) and genotype (*COMT* Met-homozygotes vs. Val-carriers) on this contrast, we found significant clusters in the bilateral anterior MTL extending into amygdala (local maxima at [−46, 2, −20] and [30, 0, −22], both t values > 4.17, both cluster $p < 0.05$ whole-brain corrected). As shown in **Figure 4**, this interaction exhibits a pattern that is opposite to the one in the dorsolateral PFC—that is, a clear pattern of stress-induced positive and negative effect for Met-homozygotes and Val-carriers, respectively.

DISCUSSION

The present study investigated whether effects of psychological stress on WM-related neural activity are modulated by a genetic variation in catecholaminergic function (determined by *COMT* genotype) in humans. As expected, stress induction resulted in

Table 5 | Brain deactivations related to WM, and modulations of stress and COMT genotype.

Brain regions	L/R	BA	*T* score	Cluster size	MNI coordinates		
					x	*y*	*z*
WM-related deactivation: 2- vs. 0-back collapsing across conditions and genotype groups							
Posterior cingulate cortex	–	31	16.05	7210***	0	−42	36
	L		13.49		−6	54	18
Ventral medial PFC	L	10	12.63	5690***	−4	48	−6
	–		12.34		0	52	14
Hippocampus	L	–	12.03	5201***	−26	−24	−16
	R		11.29	5449***	28	−20	−16
Anterior MTL	L	35/28	9.81		−22	−10	−16
	R		6.98		30	−6	−18
Insula	L	13	9.88		−36	−16	2
	R		10.52		40	−16	18
Interaction: (control vs. stress) × (Met/Met vs. Val-carriers)							
Anterior MTL (extending into amygdala)	L	–	4.17	223**	−46	2	−20
			3.54		−26	−2	−18
	R	–	4.32	103**	30	0	−22
			4.25		40	−2	−24

*Note: Only clusters significant at $p < 0.05$ corrected on cluster level were reported. *** $p < 0.05$ FWE whole brain corrected; ** cluster $p < 0.05$ whole brain corrected. Stress, stress group; Control, control group; MTL, medial temporal lobe; PFC, prefrontal cortex; L, left; R, right; BA, Brodmann Area; MNI, MNI coordinates (SPM5).*

COMT genotype-dependent effects on WM performance and WM-related neural activity in the dorsolateral PFC, with a relatively negative impact of stress in *COMT* Met-homozygotes as opposed to a relatively positive effect in Val-carriers. A similar interaction was found for WM-related deactivation in the anterior MTL, with a stress-induced positive and negative effect for Met-homozygotes and Val-carriers, respectively. As evidenced by elevation of both HR and α-amylase, our stress induction procedure succeeded in triggering an increase of sympathetic and noradrenergic activity, and thus resulted in increased central release of stress-sensitive catecholamines (de Kloet et al., 2005; Joels and Baram, 2009; Ulrich-Lai and Herman, 2009), which has been confirmed by our recent pharmacological fMRI study in humans (Hermans et al., 2011). The effectiveness of the stress induction did not differ between genotype groups. We, therefore, discuss how stress-induced elevation of catecholamines, together with genetic variation in catecholaminergic function, accounts for our observed *COMT* genotype-dependent effects of stress on WM processing.

Our findings of an opposite effect of stress induction in *COMT* Met-homozygotes as compared to Val-carriers are in line with animal models of the role of catecholamines in the neuromodulation of cognition. Such models assume that catecholaminergic activity exhibits an inverted U-shaped relationship with higher-order prefrontal cognitive function, and that optimal performance is reached at moderate levels of catecholamines (Arnsten and Li, 2005; Aston-Jones and Cohen, 2005; Arnsten, 2007, 2009). Thus, these models predict that the effect of stress-induced elevation of catecholaminergic activity may vary depending on the baseline. In humans, homozygous carriers of the Met allele have lower *COMT* availability, presumably resulting in higher catecholaminergic activity at baseline. Our findings show that a moderate level of stress has a relatively negative impact on neurocognitive functioning in these individuals, possibly because an elevation of catecholaminergic activity shifts the PFC functioning toward a supraoptimal state at the right side of the alleged inverted-U shaped curve (see **Figure 5A**). Interestingly, we found an opposite effect in Val-carriers, where a similar amount of stress had a relatively positive effect. To interpret this pattern of results, it is important to consider that the stressor used in this study was relatively mild. For instance, we observed a decrease of cortisol from pre- to post-stressor levels in the control condition but no significant change in the stress condition. Exposure to more stressful situations (i.e., higher levels of cortisol induced) has been found to result generally in detrimental effects on WM processing (Oei et al., 2006; Schoofs et al., 2008, 2009), particularly when high levels of cortisol and noradrenergic activity occurred concurrently (Elzinga and Roelofs, 2005; Schoofs et al., 2008). Moreover, we previously found detrimental effects of acute stress on activity in the dorsolateral PFC across an unselected female sample (Qin et al., 2009), but that study did not implement a crossover design (i.e., repeated testing) and may, therefore, have been slightly more stressful for the participants in the stress condition. It is well possible that higher levels of acute stress would also have a negative impact in COMT Val-carriers. Thus, various (i.e., decreased or improved) effects of acute stress on PFC functions observed in previous studies (Wang et al., 2005; Porcelli et al., 2008; Pruessner et al., 2008; Weerda et al., 2010) may be partly explained by the non-linear relationship between levels of stress-induced catecholamines and prefrontal functioning, and potential interactions with individual differences in basal catecholaminergic availability. In sum, our findings suggest that individuals with high catecholaminergic availability at baseline (COMT Met-homozygotes) are more susceptible to the

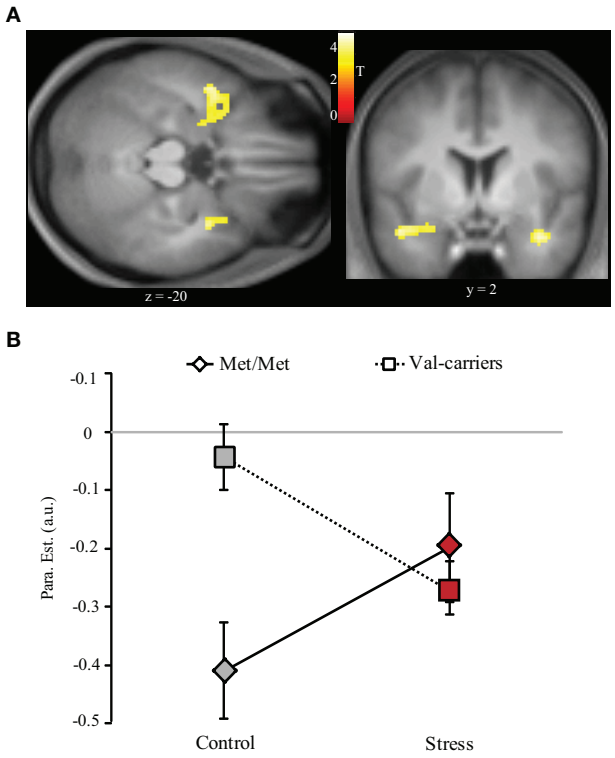

FIGURE 4 | Stress-by-COMT genotype interaction effect on WM-related deactivation in the MTL. (A) Transversal (left panel) and coronal (right panel) view of deactivation in the bilateral anterior MTL showing significant stress-by-COMT genotype interaction effect. Statistical parametric maps are superimposed onto spatially normalized and averaged ($n = 39$) high-resolution T1-weighted images (thresholded at $p < 0.001$ uncorrected for visualization purposes). **(B)** Bar graphs representing parameter estimates of WM-related deactivation under control and stress conditions in Met-homozygotes (Met/Met) and Val-carriers. The data for these bar graphs were extracted illustrating the interaction effect. Note: Control, control condition; MTL, medial temporal lobe; Stress, stress condition; error bars in the graph represent standard error of mean; T, color coded *t* values obtained from the whole brain analysis.

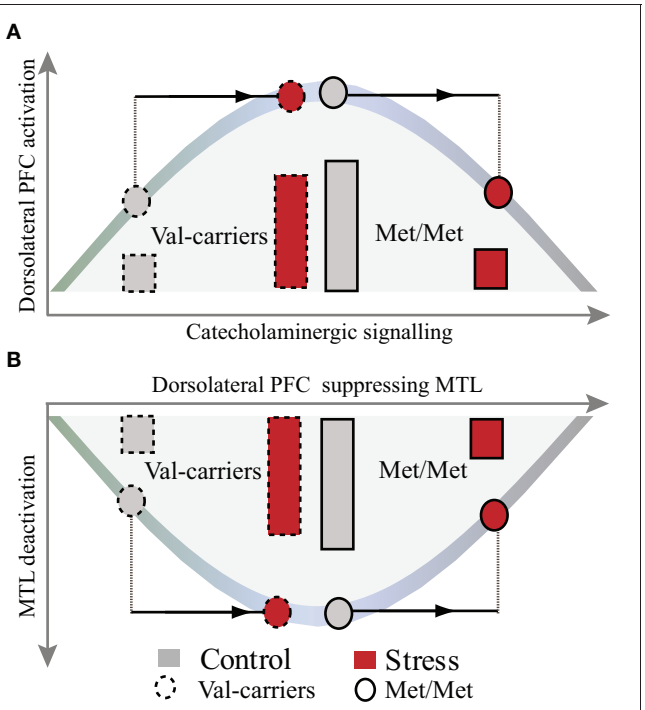

FIGURE 5 | A heuristic model illustrating the effects of *COMT* genotype and stress on WM-related activation in the dorsolateral PFC and deactivation in the MTL. Stress-by-*COMT* genotype interaction on the inverted U-shaped curve between levels of catecholamines and dorsolateral PFC function **(A)** and its suppression of MTL function **(B)**. *COMT* Val-carriers, with presumably lower baseline levels of catecholamines, start from the sub-optimal left end of the inverted U-shaped curve, with suboptimal prefrontal WM function and less MTL suppression. Under moderate psychological stress, elevation of catecholamines may shift catecholaminergic signaling toward an optimal state (strong PFC activation and MTL suppression). In contrast, *COMT* Met-homozygotes, with high baseline catecholamines, might already start closer to the peak of the curve. Stress-induced elevation of catecholamines may therefore more easily shift these individuals toward a supra-optimal state. Note: The bars represent the magnitude of neural activation in the dorsolateral PFC and deactivation in the MTL, respectively. PFC, prefrontal cortex; MTL, medial temporal lobe.

detrimental effects of stress, whereas Val-carriers appear more resilient.

Animal studies have shown that at a cellular level, the prefrontal WM network is strengthened through actions of α2A-adrenoceptors and increased neural firing via inhibition of cAMP-HCN (cyclic adenosine monophosphate-hyperpolarization-activated cyclic nucleotide-gated cation channel) signaling (Wang et al., 2007), while optimal levels of dopamine decrease task-irrelevant neuronal firing by increasing cAMP-HCN signaling (Arnsten, 2007, 2009; Vijayraghavan et al., 2007). Interestingly, recent studies in behaving primates suggest that elevated levels of catecholamines under stress impair prefrontal functioning by excessive cAMP-HCN and phosphatidylinositol-protein kinase C (PKC) intracellular signaling pathways (Arnsten, 2007, 2009). Activation of these two stress-sensitive signaling pathways is thought to be regulated by molecular inhibitors provided by enzymes such as COMT (Arnsten, 2009). The valine-to-methionine substitution at codon 158 in the COMT protein may reduce the ability of COMT to inhibit the activation of these stress-sensitive pathways. By showing a genotype-dependent difference in stress resilience, with relatively stronger stress sensitivity in human carriers of the *COMT* Met allele, our data provide the first evidence for these notions in humans.

Human neuroimaging studies consistently show that WM-related activation of the dorsal frontoparietal "executive" network is accompanied by a reciprocal deactivation in regions comprising the "default mode" network (DMN), including the MTL and amygdala (Selemon and Goldman-Rakic, 1988; Dolcos and McCarthy, 2006; Esposito et al., 2006; Arnsten, 2009). Our data robustly replicate these findings, but moreover reveal an interaction between stress and *COMT* genotype in the bilateral anterior MTL, extending into the amygdala. This interaction shows an opposite pattern to the one observed in the dorsolateral PFC (see **Figures 4** and **5A**,**B**), with less deactivation after stress in *COMT* Met-homozygotes as compared with Val-carriers.

This finding may be a consequence of the concomitant effect on frontal regions, resulting in altered efficacy of these regions to suppress the DMN. An alternative, but partly complementary, explanation of this finding is that stress-sensitive catecholaminergic changes may exert regionally specific effects on PFC functioning (Aston-Jones and Cohen, 2005; Shin et al., 2005; Dolcos and McCarthy, 2006; Etkin and Wager, 2007), but at the same time have their opposite effects on neural processes in limbic regions, particularly the MTL and the amygdala (Coull et al., 2001; de Kloet et al., 2005; Chamberlain et al., 2006; Admon et al., 2009; van Marle et al., 2009). The function of such a large-scale reallocation of neural resources (Bouret and Sara, 2005; Sara, 2009; Oei et al., 2011) may be to effectuate a hypervigilant brain state promoting rapid behavioral adaptation to adverse conditions at the cost of elaborative executive functions.

It is worth noting that our stress induction procedure refers to an emotion focused, moderate acute psychological stressor rather than socially and cognitively oriented stressors such as the Trier social stress test (TSST) and arithmetic calculation with negative evaluation (Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Wang et al., 2005; Pruessner et al., 2008). The reason why we did not observe a reliable increase (but nevertheless a significant difference between stress and neutral conditions) in cortisol lies probably in the specifics of the experimental design. The genetic analysis required a within-subject design reducing the contextual novelty effects substantially. Furthermore, we opted for a short succession of the two conditions for reasons of practicality. Nevertheless, converging evidence from multiple elegant readout measurements in the present study as well as our previous studies, including increase in hear rate and cortisol, changes in pupil dilation responses (Henckens et al., 2009; Qin et al., 2012) and increase in α-amylase and amygdala perfusion (Cousijn et al., 2010, 2012), firmly promote the conclusion that our emotion focused stress induction procedure was effective. That is, our procedure indeed successfully induced a state characterized by hyperactivation of catecholaminergic systems and negative mood (Arnsten and Goldman-Rakic, 1998; Arnsten, 2009; Hermans et al., 2011; Shackman et al., 2011; Weymar et al., 2011).

Behaviorally, we found COMT genotype-dependent effects of moderate acute psychological stress on WM performance, but no main effect of genotype at baseline in the control condition. The lack of a genotype effect on baseline WM performance may be attributed to a lack of sensitivity at a behavioral level (Meyer-Lindenberg and Weinberger, 2006). A pretraining procedure prior to fMRI scanning may also play a role in reducing the potential genotype effect. Nonetheless, we found a robust main effect of genotype on WM-related activity in the dorsolateral PFC, indicating that brain imaging genetics may have higher sensitivity for subtle genetic effects on putative neural activity related to cognition and behavior, and thus serving as so-called intermediate phenotype (Meyer-Lindenberg and Weinberger, 2006).

In conclusion, the present study demonstrates *COMT* genotype-dependent effects of moderate stress on WM performance, WM-related activation of the dorsolateral PFC, and WM-related deactivation in the anterior MTL, with a more negative impact of stress in the genotype that is associated with higher baseline levels of catecholamines. These findings are in line with animal models of catecholaminergic function that assume an inverted U-shaped relationship between catecholaminergic activity and PFC-dependent higher-order cognitive functions.

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On the influence of emotion on conflict processing

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INTRODUCTION

The ability to show coherent goal-directed behavior, even in the presence of distraction, requires the detection and resolution of conflict, for example between opposing action tendencies. This defining feature of cognitive control has been extensively studied with experimental tasks like the Stroop, Simon, or Flanker paradigm (Stroop, 1935; Simon and Rudell, 1967; Eriksen and Eriksen, 1974), which also yielded the description of an underlying neural network for conflict detection and resolution (Fan et al., 2003; Ridderinkhof et al., 2004). Understanding the influence of emotion on this system is particularly important because they are intrinsically tied to one another in real life (Pessoa, 2008). Recent evidence seems to be contradictory with reports of facilitation and impairment effects of emotion on the processing of conflict. On a conceptual basis both accounts can be supported. It may be argued that keeping up goal-directed behavior is especially difficult in emotional situations because of their greater distracting potential. On the other hand, emotional stimuli are also signals of relevance for a situation that might require particularly efficient cognitive control (Scherer, 1994). In line with this latter view, Norman and Shallice (1986) suggested that emotion, along with other instances like novelty or error commitment, might trigger cognitive control processes. The present opinion article aims at elucidating these diverging views by specifying two critical factors – task relevance and individual differences – that result in an enhancing or hindering influence of emotion on the processing of conflict.

TASK RELEVANCE

To study conflict processing, participants are typically given a certain goal related to a target stimulus and need to ignore other irrelevant information. The irrelevant information could be related to peripheral distractor stimuli (e.g., in the Flanker task) or to stimulus-response-associations (e.g., in the Simon task). If this information is incongruent with the given goal the resulting conflict needs to be detected and solved in order to show coherent behavior. A series of recent studies demonstrated that the speed, with which conflict is resolved in such tasks is enhanced, if the presented conflict stimuli are emotional, i.e., emotion speeds up cognitive conflict processing (Kanske and Kotz, 2010, 2011b). This effect is independent of emotional valence and observable for positive and negative stimuli alike (Kanske and Kotz, 2011a). It is also present in the visual and auditory modality (Kanske and Kotz, 2011d) and in Flanker, as well as Simon-type conflict tasks (Kanske and Kotz, 2011b,c). The latter is especially interesting as the mechanisms underlying Flanker and Simon tasks are very different. Conflict in the Simon task is not elicited through peripheral distractor stimuli, but through incompatible stimulus presentation and response side mapping. If, for example participants perform a voice gender discrimination with female voices requiring a right hand response, but the stimulus is presented on the left side, the elicited action tendencies will conflict and responses are prolonged. Even though this task does not require participants to focus on emotions, responses in the incompatible condition are accelerated if the spoken word is emotional (Kanske and Kotz, 2011b). The presence of the emotional modulation of conflict processing across these different conflict tasks and different sensory modalities strongly suggests that it is a general mechanism acting on the supra-modal processing steps of conflict detection and resolution rather than on visual or auditory spatial attention. Critically, however, in each of these studies the emotionally valent stimuli were task-relevant, i.e., the stimuli that participants needed to process and react to in order to solve the task. This contrasts other studies that modulated emotion through the presentation of additional stimuli that were unrelated to the task. For example, when emotional stimuli are presented before the conflict stimuli, conflict resolution is not facilitated, but impaired (Hart et al., 2010). Furthermore, conflict adaptation, i.e., the enhanced processing of conflict after presentation of an incongruent trial, is also compromised if emotional stimuli are presented between conflict trials (Padmala et al., 2011). This pattern of hindering and enhancing effects of emotion on conflict processing suggests that the exact role that emotion plays in a task is crucial for determining its impact. Emotion will only enhance cognitive control if the behaviorally relevant stimuli that participants react to during a task are emotional. Transiently induced emotion by task-unrelated stimuli, in contrast, yields hindering effects (for potentially conflicting results see Birk et al., 2011; Melcher et al., 2012, but see also Cohen and Henik, 2012, in this Research Topic for a discussion). Corroborating evidence for this conclusion also comes from two recent studies on the effects of motivation on conflict processing. Similarly to emotional stimuli that signal importance of a situation, if relevance is increased through reward for correct task performance, cognitive control is triggered resulting in accelerated conflict processing (Padmala and Pessoa, 2011). If, however, the motivational salience of the distractor stimuli is increased, conflict resolution is impaired (Krebs et al., 2010). It may thus be relevance in general that speeds up conflict processing, rather than emotion specifically.

NEURAL UNDERPINNINGS

A crucial node in the neural network underlying cognitive control is the anterior cingulate cortex (ACC), in particular its dorsal portion (Ridderinkhof et al., 2004). The ventral ACC has been shown to be more sensitive to emotion (Bush et al., 2000) and also to conflict between emotional stimuli of different valence (Etkin et al., 2006). This ventral portion is also heavily connected to the amygdala, which is critically involved in emotion detection and generation (Phelps and LeDoux, 2005). In the context of emotional influences on conflict processing, interactions between these three regions seem important. Conflicting stimuli that are emotionally negative activate the ventral ACC in addition to the dorsal portion, which is active for incongruent stimuli irrespective of their emotional status (Kanske and Kotz, 2011b). Furthermore, functional connectivity between the ventral and dorsal ACC, as well as between ventral ACC and the amygdala is increased in incongruent emotional compared to neutral trials (Kanske and Kotz, 2011c). This suggests that the ACC is integrating the need for increased cognitive control in conflicting situations with task-relevant emotional stimuli. The emotional saliency information is signaled by the amygdala and the ACC prioritizes these situations resulting in enhanced conflict processing. The relative speed of this process is apparent in an emotional modulation of the first conflict-related component of the event-related potential of the EEG (Kanske and Kotz, 2011a). Already 200 ms after stimulus onset, emotional incongruent stimuli elicit an enhanced negativity over central electrodes, which has been localized to the dorsal ACC in non-emotional conflict processing (N200; van Veen and Carter, 2002). The effects of task-irrelevant emotional stimuli on reducing conflict processing efficiency are also mediated by the ACC. Activation reduction in this region during emotional distraction correlates with increased response times in the conflict task (Hart et al., 2010). The data on the neural underpinnings of reward-related influences on conflict processing show some similarities with the nucleus accumbens involved in behavioral facilitation of conflict resolution by reward associated stimuli, and a medial frontal region just dorsal to the ACC integrating information on the reward value of distractor stimuli (Krebs et al., 2011).

INDIVIDUAL DIFFERENCES

As individuals differ in sensitivity to emotional stimuli and cognitive control capabilities, there are also variations in the modulation of conflict processing through emotion. A recent correlational study examined this across six experiments on the influence of task-relevant emotional stimuli on conflict processing (Kanske and Kotz, 2012). Individuals high in subclinical depression and anxiety, both emotional states with deficient emotion processing (Kalia, 2005; Li et al., 2008), show a reduced increase in cognitive control for negative emotional stimuli. In contrast, the temperament trait effortful control, which correlates positively with conflict processing and describes the ability for self-regulation (Gerardi-Caulton, 2000) is associated with an enhanced emotion induced facilitation of conflict processing. These relations also translate to the neural level. High depression and anxiety are characterized by a smaller conflict-related increase in ventral ACC activity and N200 amplitude in task-relevant emotional stimuli, while effortful control has the opposite effects. Anxiety might also be related to the impairing effect of task-irrelevant emotional stimuli on conflict processing, but the evidence regarding the direction of this effect is rather mixed (Dennis and Chen, 2007; Dennis et al., 2008). The presence of these individual differences and their systematic relation to emotional states and temperament across different experimental designs (Kanske and Kotz, 2012) may therefore represent an important aspect when explaining the enhancing and hindering effects of emotion on cognitive control.

INTEGRATION

The discussed results suggest a tight integration of emotion and cognitive control in situations that require the resolution of conflict. **Figure 1** illustrates this for conflict processing in neutral stimuli (**Figure 1A**), and for an emotional task-irrelevant (**Figure 1B**) or task-relevant (**Figure 1C**) stimulus. In the well-described situation of conflict in neutral stimuli, cognitive control resources will be recruited and bias information processing in line with current task-demands through amplification of the cortical representation of the task-relevant stimulus (Egner and Hirsch, 2005). If a task-unrelated stimulus is emotional, relevance detectors like the amygdala or nucleus accumbens will divert resources toward the processing of that stimulus, thereby impairing the processing of task-related conflict (Pessoa, 2009). The ACC closely follows this pattern by showing emotion-related activation increase that predicts impaired task performance (Lim et al., 2008). ACC activity related to conflict, however, is decreased under emotional distraction, which also correlates with impaired behavior (Hart et al., 2010). In contrast, when the task-relevant stimulus is emotional, the current task-goal and emotional information signaled through the relevance detector coincide. Therefore, increased cognitive control resources will be recruited yielding an enhanced bias in information processing toward task-relevance. Here, the ACC also follows this pattern with the additional activation of the ventral portion for conflict in emotional stimuli, where the resolution of conflict is accelerated compared to neutral stimuli (Kanske and Kotz, 2011b,c). These interactions are variable, for example with individual differences in emotion-related amygdala reactivity and limbic-prefrontal connectivity in depression and anxiety (Johnstone et al., 2007; Kanske and Kotz, 2012). Here, the altered relevance detection seems to result in the dysfunctional integration of emotion and current task-goals apparent in reduced ventral ACC activation. This consequently leads to impaired performance.

CHALLENGES AND QUESTIONS

The evident pattern might show some valence specificity. Even though negative and positive emotional stimuli yield comparable behavior and EEG results (Kanske and Kotz, 2010, 2011a), there is less data yet on the neural mechanisms underlying the influence of positive emotion on conflict processing. As depression and anxiety selectively affect the influence of negative, but not positive emotional stimuli on conflict processing (Kanske and Kotz, 2012), the mechanisms that mediate the influence on conflict processing might be different (see also Prehn et al., 2011). For positive emotion they might resemble more the pattern observed for reward-related stimuli with nucleus accumbens involvement (Krebs et al., 2011). The mechanisms might also differ for highly salient emotional stimuli, as suggested by Pessoa (2009). This notion is supported by the observed

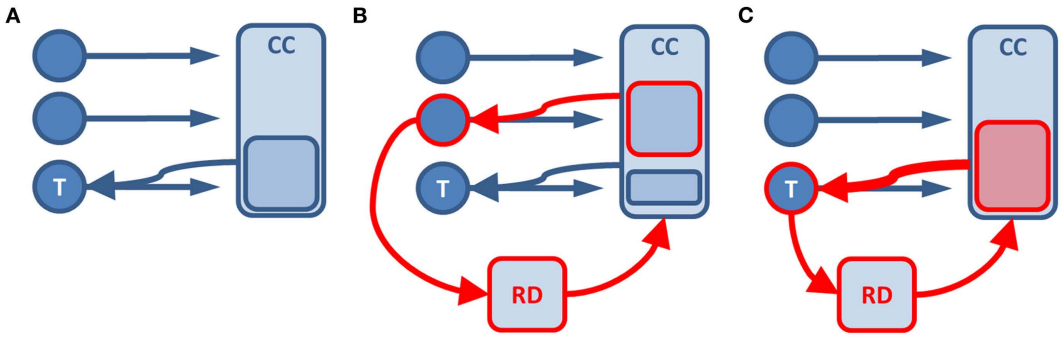

FIGURE 1 | Illustration of the functional integration of emotion and cognitive control in conflict processing. The situation for neutral **(A)** and emotional task-irrelevant **(B)** or task-relevant stimuli **(C)** is displayed. Circles represent stimuli. Rectangles stand for processing units. Red frame color indicates an emotional stimulus or emotion induced processing. T, task-relevant stimulus; CC, cognitive control; RD, relevance detector.

effects for anxiety and depression, which are characterized by increased sensitivity to negative emotional stimuli and increased related amygdala responding (Kanske and Kotz, 2012). The similarity of the results for motivation and emotion suggests that it may be relevance in general that yields enhanced conflict processing. This question should be followed up by direct comparisons of differently salient stimuli. Lastly, the relation of emotion and cognitive control is not uni-directional, rather, different levels of control may also affect emotion. There is some indication that individuals with high emotion regulation capacity attenuate emotional processing when cognitive control is recruited for conflict processing (Cohen et al., in press). The challenge for future investigations will be to concurrently study these reciprocal relations and their underlying neural mechanisms.

CONCLUSION

Conflict processing is directly influenced by emotion, with individual differences in temperament and emotional state, as well as the task-relevance of the emotionally valent stimuli critically determining if this influence is an enhancing or a hindering one. The resulting pattern is highly evolutionary adaptive as the time that conflict yields an organism incapable of responding to potentially dangerous negative or reward-signaling positive stimuli is reduced. In contrast, if stimuli are present that are not relevant to current task-goals, but may still be relevant to higher order goals because of their danger- or reward-value, their processing is prioritized over task-performance. In consequence, the flexibility of behavior is greatly enhanced with slower and faster processing routes depending on current task-related and overarching goals.

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Do irrelevant emotional stimuli impair or improve executive control?

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Our behavior is constantly influenced by emotional stimuli. These stimuli can enhance (i.e., improve) or impair performance, depending on their specific interaction with situational demands (Dolcos et al., 2011). This paper examines factors that mediate the influence of task-irrelevant negative stimuli on executive control (EC). We demonstrate how similar results of emotion-cognition interactions might be interpreted according to opposing theories, following the use of different analysis methods.

Executive control is responsible for monitoring, controlling, and regulating irrelevant information, in order to enable goal-directed behavior (Norman and Shallice, 1986). Recently, there is growing debate regarding the influence of negative stimuli on EC (Hu et al., 2012). Specifically, compared to neutral stimuli, negative stimuli were found to impair (i.e., elongated reaction times – RT), improve (i.e., facilitated RT), or have no influence (i.e., similar RT) on EC. Herein we will first suggest that descriptions of *improved* or *impaired* EC may be misleading, and then discuss three factors that modulate links between EC and emotion: available resources, attentional breadth, and top-down modulation.

TACKLING THE TERMS *IMPAIRED* AND *IMPROVED* EC

Two tasks widely used to examine EC are the Stroop (1935) and flanker (Eriksen and Eriksen, 1974). In the Stroop task, participants are presented with colored words written in colored ink and need to name the ink color and ignore the word. This task usually contains congruent, incongruent, and neutral targets (e.g., BLUE, RED, XXXX, respectively where the response should be "blue"). In the flanker task, participants need to respond to a target and ignore distracting stimuli. For example, in the arrow-flanker task, participants respond to the direction of the middle arrow and ignore the two flanker arrows. This task also contains congruent (→→→→→), incongruent (→→←→→), and neutral (--→--) targets. Although the Stroop and flanker tasks differ in several aspects (Magen and Cohen, 2002), both create conflict situations during incongruent targets (although, see Goldfarb and Henik, 2007, for discussion of conflict also during congruent trials). This conflict situation activates EC mechanisms designed to detect and solve the conflict.

Studies presenting neutral and negative stimuli prior to Stroop or flanker tasks (Dennis and Chen, 2007a,b; Dennis et al., 2008; Hart et al., 2010; Cohen et al., 2011, 2012; O'Toole et al., 2011; Hu et al., 2012; Melcher et al., 2012) usually analyze the influence of these stimuli on the congruity effect (i.e., RT incongruent minus RT congruent). A larger congruity effect is usually interpreted as impaired EC, while a smaller congruity effect is usually interpreted as improved EC. However, this analysis does not distinguish between different effects of negative stimuli on congruent and incongruent targets separately. This distinction is important due to the presence of conflict (and hence, activation of EC) mainly during incongruent targets. Without showing a significant difference between negative and neutral stimuli influence on incongruent targets, it might be problematic to claim negative stimuli impair or improve EC. Importantly, this difference should not appear in congruent or neutral targets of the EC task (this would imply a main emotional effect on RT).

We recently showed that compared to neutral stimuli, negative stimuli delayed RTs for congruent flanker targets, but had no influence on incongruent targets (Cohen et al., 2011, 2012). Although these findings indicate a smaller congruity effect following negative stimuli, we did not interpret them as improved EC, but as attenuation of the emotional effect during conflict situations. Nevertheless, our paper was cited as evidence for improved EC (Birk et al., 2011). It is possible that this pattern (i.e., incongruent trials not affected by negative stimuli) is caused by improved EC. However, it is also possible that other mechanisms are responsible for this null effect (see Cohen et al., 2011; Hu et al., 2012, for debate regarding interpretation of their results). Similarly, interpretations of impaired EC may be misleading when data does not indicate delayed RTs for incongruent targets following negative compared to neutral stimuli.

Figure 1 illustrates typical results (not based on empirical data) that can be found in experiments presenting negative and neutral stimuli prior to an executive task. **Figures 1A,B** demonstrate results suggesting impaired (i.e., larger congruity effect) EC, while **Figures 1C,D** demonstrate results suggesting improved (i.e., smaller congruity effect) EC following presentation of negative stimuli. A similar congruity effect is found in **Figures 1A,B**, and a similar congruity effect is found in **Figures 1C,D**. However, these similar effects are produced in different ways (e.g., the impaired congruity effect in **Figure 1A** is due to elongated RT in negative incongruent trials, whereas the impaired congruity effect in **Figure 1B** is due to facilitated RT in negative congruent trials, with no change in the incongruent trials).

The following sections present three factors that might account for these different interaction patterns. In addition, we will demonstrate how similar results might be interpreted differently, depending on the analysis used.

AVAILABLE RESOURCES

According to the dual competition model (DCM), highly threatening stimuli impair EC since they consume resources required for resolving conflict (Pessoa, 2009). In accordance with this model, several studies demonstrated negative stimuli impair performance in a Stroop-like task (Hart et al.,

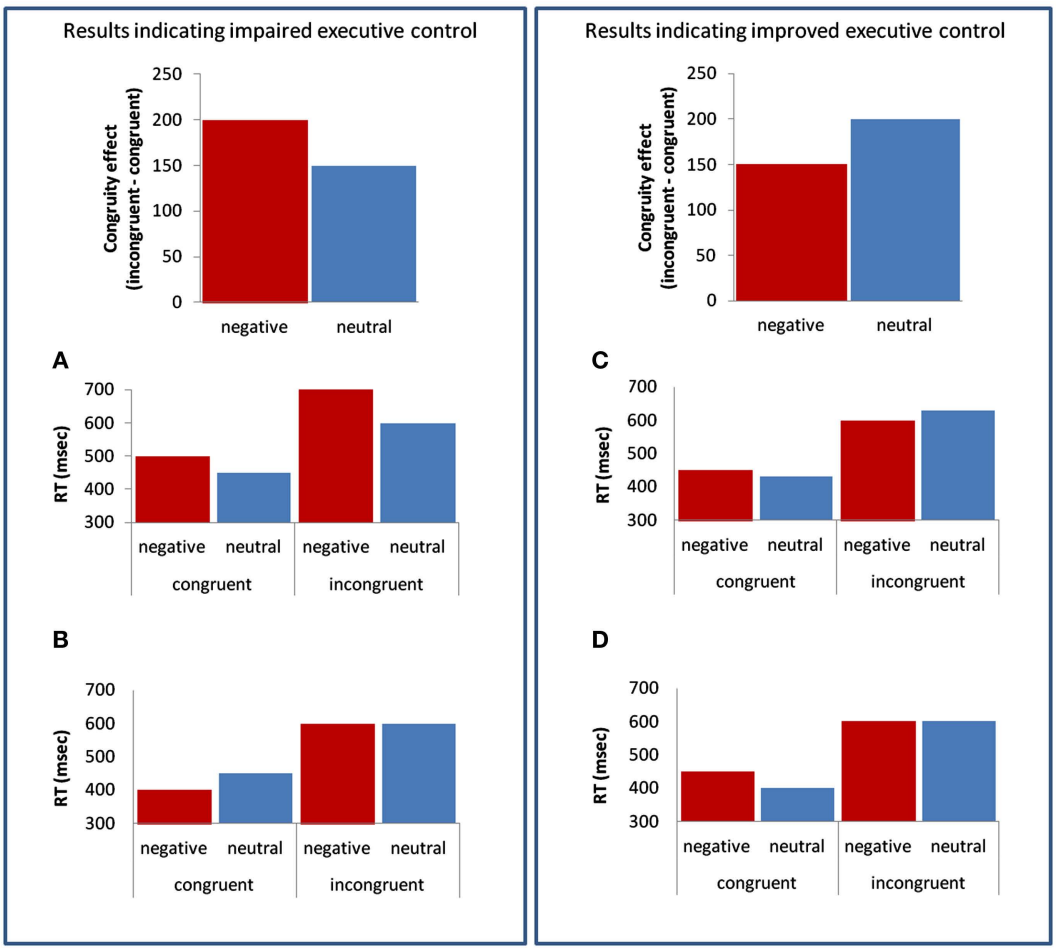

FIGURE 1 | Illustration of "impaired" (A,B) and "improved" (C,D) executive control following negative, compared to neutral, stimuli.

2010; Melcher et al., 2011; Padmala et al., 2011) and in the flanker task (Dennis et al., 2008). Although these studies reported impaired EC, close examination of the data of several of them may imply an alternative interpretation for the results.

Support for the DCM is found in studies reporting increased RTs for incongruent targets following negative compared to neutral stimuli (Hart et al., 2010; Melcher et al., 2011; see **Figure 1A**), thus demonstrating negative stimuli impair EC. In contrast, other studies interpreted results as being a consequence of impaired EC although their data did not show increased RTs for incongruent targets following negative stimuli. For example, examining RTs in the study of Dennis et al. (2008) may imply the increased congruity effect found after presentation of negative stimuli (and interpreted as impaired EC), resulted from facilitated RTs for negative compared to neutral stimuli in congruent trials, while RTs for incongruent trials following negative and neutral stimuli were very similar (Dennis et al., 2008; see **Figure 1B**). Findings of facilitation or lack of emotional interference in congruent trials (Dennis et al., 2008; Hart et al., 2010) are inconsistent with data showing delayed RTs in discrimination tasks following irrelevant emotional stimuli (Hartikainen et al., 2000; Buodo et al., 2002). Moreover, the DCM (Pessoa, 2009) would have predicted that resources devoted for processing emotional stimuli would cause delay both in congruent and in incongruent targets (although to a greater extent in incongruent targets; see **Figure 1A**, and Blair et al., 2007, for debate regarding this notion).

The study of Dennis et al. (2008) is an example of our claim that analyzing difference scores (i.e., congruity effect) might lead to incomplete or inaccurate interpretation of results. We suggest that under some circumstances emotional stimuli impair EC, thus supporting the DCM. However, there is also evidence emotional stimuli improve or have no influence on EC (see below). Hence, more data is needed to uncover the specific situations in which this impairment occurs.

ATTENTIONAL BREADTH

The DCM discussed above emphasizes the importance of available resources for solving a cognitive conflict. In contrast, attentional breadth theories (e.g., Easterbrook, 1959) emphasize the impact of negative information on attentional allocation. These theories claim negative stimuli narrow attention and hence, reduce interference of distracting or irrelevant information (Derryberry and Tucker, 1994; Chajut and Algom, 2003; van Steenbergen et al., 2011).

Indeed, a smaller congruity effect following negative compared to neutral stimuli is often driven by facilitation of incongruent targets (see example in **Figure 1C**), as a result of reduced attention to distractors (in the flanker task) or the irrelevant dimension (in the Stroop task).

Evidence regarding improved EC following presentation of negative stimuli is found in Birk et al.'s (2011) study. The authors found reduced RTs for incongruent flanker targets following presentation of fearful compared to neutral faces (see **Figure 1C**). Several other studies also suggested emotion improves EC (Dennis and Chen, 2007b; Hu et al., 2012; Melcher et al., 2012). However, in contrast to Birk et al.'s study, the reduced congruity effect in the latter studies did not result from reduced RTs in incongruent targets. For example, in a Stroop-like task, Hu et al. (2012) found that compared to neutral situations, negative situations (shock anticipation) delayed RTs in congruent trials, but no difference between neutral and negative situations was found in incongruent trials (see **Figure 1D**). The authors suggested the overall slowdown following shock anticipation was contrasted by the facilitation effect caused by attentional narrowing. Importantly, they based their claim on results showing delayed RTs during neutral Stroop trials (e.g., XXX where the response should be "red"). As discussed in their paper, adding neutral Stroop trials may help unravel different effects of attentional narrowing and available resources on EC.

Hence, it seems that under specific circumstances, negative stimuli improve EC. In addition, it seems that findings of a null emotional effect in incongruent targets are sometimes interpreted as improved EC and sometimes as impaired EC (as described earlier). We suggest this null emotional effect in incongruent targets may result from a top-down regulation mechanism (see supporting explanation below).

TOP-DOWN MODULATION

Decreased emotional response during or following executive activation led to the suggestion EC can trigger top-down mechanisms that inhibit the effect of emotion (Etkin et al., 2006; Blair et al., 2007; Cohen et al., 2011, 2012). Etkin et al. (2006) presented a modified Stroop task where participants had to respond to the emotionality of a face (happy or fearful) and ignore a superimposed word (that was congruent or incongruent with the face emotion). They demonstrated a conflict adaptation effect in which the response for an incongruent target attenuated the response of the following incongruent target. This decrease in emotional conflict was related to a connection between brain areas known to be activated during conflict monitoring (e.g., anterior cingulate cortex) and emotional areas (e.g., amygdala). Similarly, we recently showed that when an executive task *precedes* an emotional stimulus, incongruent trials can attenuate emotional response both behaviorally (Cohen et al., 2011, 2012; see **Figure 1D**) and physiologically (Cohen and Henik, Submitted). In addition, there is evidence that this inhibitory connection characterizes healthy individuals and is deficient in people suffering from depression (Johnstone et al., 2007; for review, see Rogers et al., 2004) or anxiety (Bishop et al., 2004; Etkin et al., 2010). Taken together, there is strong evidence that activation of EC might result in decreased emotional response and hence, in a diminished emotional effect during incongruent targets.

CONCLUSION

We presented several factors that might account for the various relationships between emotion and EC. In addition, we suggested that the use of difference scores (i.e., the congruity effect) might lead to different interpretations, even in face of similar data sets. We offer two important conclusions:

1. The effect of emotion on EC is modulated by several factors. Negative stimuli impair EC if they consume resources available for resolving the conflict, improve EC if attention is narrowed, or have no influence on EC if top-down processes are activated. Additional factors, such as relevance of the negative stimuli to current goals (Kanske and Kotz, 2011a,b; see also Kanske, in press, in this Research Topic), task demands (Shafer et al., 2012), and individual differences, may also modulate the effects of emotion on EC (for review, see Okon-Singer et al., 2012). More research is required to unravel how all these factors are orchestrated to shape the emotion-executive relationship.
2. Researchers tend to analyze the influence of emotion on the congruity effect and by doing so, miss important information. A good example for inconsistent interpretation occurs when researchers find a null emotional effect for incongruent targets. This null effect is sometimes interpreted as impaired, and sometimes as improved EC, depending on the effect of emotion on congruent trials (compare **Figures 1B,D**, respectively). Hu et al. (2012) suggested that adding neutral trials to the EC task might help distinguish between impairing and enhancing effects. However, as discussed above this null effect may also result from top-down regulation of the emotional system. This top-down effect should be directly examined by conducting a sequential analysis (Cohen et al., 2011) or by presenting the EC task before the emotional stimuli (Cohen et al., 2012).

Future studies should strive to uncover the specific factors that modulate emotional effect on conflict vs. non-conflict situations. Defining the interactions between these factors could uncover how emotion and EC are mutually linked in order to generate adaptive behavior. On a broader perspective, the use of difference scores, such as the congruity effect, in various cognitive domains (e.g., spatial attention, implicit attitudes, affective priming) may lead to an incomplete view of emotion-cognition interactions, thus hindering the research in this field.

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Neurocognitive correlates of the effects of yoga meditation practice on emotion and cognition: a pilot study

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Mindfulness meditation involves attending to emotions without cognitive fixation of emotional experience. Over time, this practice is held to promote alterations in trait affectivity and attentional control with resultant effects on well-being and cognition. However, relatively little is known regarding the neural substrates of meditation effects on emotion and cognition. The present study investigated the neurocognitive correlates of emotion interference on cognition in Yoga practitioners and a matched control group (CG) underwent fMRI while performing an event-related affective Stroop task. The task includes image viewing trials and Stroop trials bracketed by neutral or negative emotional distractors. During image viewing trials, Yoga practitioners exhibited less reactivity in right dorsolateral prefrontal cortex (dlPFC) to negative as compared to neutral images; whereas the CG had the opposite pattern. A main effect of valence (negative > neutral) was observed in limbic regions (e.g., amygdala), of which the magnitude was inversely related to dlPFC activation. Exploratory analyses revealed that the magnitude of amygdala activation predicted decreased self-reported positive affect in the CG, but not among Yoga practitioners. During Stroop trials, Yoga practitioners had greater activation in ventrolateral prefrontal cortex (vlPFC) during Stroop trials when negative, compared to neutral, emotional distractor were presented; the CG exhibited the opposite pattern. Taken together, these data suggest that though Yoga practitioners exhibit limbic reactivity to negative emotional stimuli, such reactivity does not have downstream effects on later mood state. This uncoupling of viewing negative emotional images and affect among Yoga practitioners may be occasioned by their selective implementation of frontal executive-dependent strategies to reduce emotional interference during competing cognitive demands and not during emotional processing *per se*.

Keywords: mindfulness, fMRI, emotion-cognition

INTRODUCTION

Hatha Yoga is a 600 year old practice that integrates physical poses (i.e., asana), meditation, breath work (i.e., pranayama), study of tantric philosophy and community outreach. The practice of yoga is shown to improve cognition in healthy (Manjunath and Telles, 2004) and clinical populations including multiple sclerosis (Velikonja et al., 2010) and major depressive disorder patients (Sharma et al., 2006). Yoga has also proven effective for improving emotional function in healthy (Hartfiel et al., 2011) and in clinical populations including reducing negative affect (Vadiraja et al., 2009), anxiety (Vadiraja et al., 2009; Streeter et al., 2010), depression (Banerjee et al., 2007), and improving emotional well-being (Moadel et al., 2007). These observed beneficial effects on cognitive and emotional health are thought to result in part from increased mindfulness arising from various yoga practices (Salmon et al., 2009).

Hatha yoga involves mindfulness *practice*, that is, repeated placement of attention onto an object while alternately acknowledging and letting go of distracting thoughts and emotions. Within the Hatha yoga tradition, mindfulness practice occurs both during the physical postures as well as during formal mindfulness meditation on one's breathing, where the object of mindfulness practice might include proprioceptive or interoceptive sensations stemming from physical posture or respiration, respectively. In turn, mindful yoga practices may generate the *state* of mindfulness, which, when evoked recurrently through repeated practice, may accrue into *trait* or *dispositional* mindfulness (Chambers et al., 2009; Garland et al., 2010). The state of mindfulness is characterized by a nonjudgmental and metacognitive monitoring of moment-by-moment cognition, emotion, perception, and sensation without fixation on thoughts of past and future (Kabat-Zinn, 1982; Garland, 2007; Lutz et al., 2008). Correspondingly, trait mindfulness is characterized as the tendency to adopt a nonjudgmental awareness of one's thoughts, emotions, experiences, and actions in everyday life (Baer et al., 2006). Trait mindfulness can be promoted

by recurrent mindfulness practice. For example, individuals participating in an eight-week Mindfulness-Based Stress Reduction course evidenced increases in trait mindfulness which mediate the effects of training on clinical outcomes (Carmody and Baer, 2008; Greeson et al., 2011). Moreover, participants in a yoga intervention exhibited significant increases in trait mindfulness after eight weeks of training (Shelov et al., 2009).

Insofar as the practice of mindfulness generates state mindfulness via intentional attending to emotions without cognitive fixation or elaborative processing of emotional experience, this practice may produce positive effects on emotion-cognition interactions. For example, mindfulness practice has been shown to result in improved ability to regulate negative emotions (Chiesa and Serretti, 2010), enhanced attentional orienting (Jha et al., 2007; Lutz et al., 2008), and increased cognitive flexibility (Wenk-Sormaz, 2005; Zeidan et al., 2011). In light of these short-term benefits, long-term mindfulness practice has the potential to promote durable alterations in trait affectivity and attentional control with resultant effects on well-being and cognitive function. These salutary, trait-level effects may be observed in identified positive associations between trait mindfulness and enhanced affect regulation (Chambers et al., 2009), attentional control (Moore and Malinowski, 2009), and autonomic recovery from emotional provocations (Garland, 2011). Plausibly, such lasting functional improvements may derive from mindfulness-induced neuroplasticity in brain regions instantiate cognition and emotion (Hölzel et al., 2011).

NEUROCOGNITIVE MODEL OF EMOTION-COGNITION INTERACTIONS

Outside of the context of yoga, meditation, or mindfulness, a prevailing neurobiological model posits that affective and cognitive processes are coordinated via an interaction between a dorsofrontal executive network and a ventral-affective circuit (Mayberg, 1997; Drevets and Raichle, 1998). Task-relevant targets activate the dorsolateral prefrontal cortex (dlPFC), whereas emotional distractors activate the amygdala (Yamasaki et al., 2002). Exerting cognitive control over emotional processes leads to increased activation in the dlPFC, with corresponding reciprocal deactivation in the amygdala (Ochsner et al., 2002; Ochsner and Gross, 2008).

A nascent database has emerged on the neurocognitive correlates of yoga and meditation practice. Neuroimaging research has demonstrated differences in task-related brain function between experienced meditation practitioners and meditation naïve controls. For example, fMRI analyses indicate that meditation practitioners exhibit greater meditation-related neural activation in brain regions involved in attentional control (e.g., prefrontal cortex), conflict resolution (e.g., dorsal anterior cingulate cortex) and emotional processing (e.g., medial/orbitofrontal cortices) (Hölzel et al., 2007; Baron Short et al., 2010). Moreover, compared to non-meditators, mindfulness practitioners evidence attenuated electrophysiological activation in frontal scalp regions to negative emotional stimuli during passive picture viewing (Sobolewski et al., 2011), and yoga meditation practitioners (YMP) exhibit sustained reductions in the late positive brain potential during cognitive reappraisal of negative emotional stimuli (Gootjes et al., 2011) and reduced power in high-frequency EEG spectrum during negative emotional information processing (Aftanas and Golosheykin, 2005). In addition, on an auditory oddball task, mindfulness meditation reduced N1, P2, and P3a amplitude to distractor stimuli (Cahn and Polich, 2006). Taken together, these findings suggest that meditation practitioners evidence significantly different neural responses in cognitive and affective brain circuitry than non-meditators which may mediate the identified salutary effects of mindfulness practice on attentional and emotional processes. Though these data provide important neural clues for the effects of Yoga meditation (YM) practice on emotional and cognitive processes, the precise neural mechanisms underlying the effects of YM on emotion-cognition interactions (e.g., emotional information processing; emotional interference on cognition) remain largely unknown.

CURRENT STUDY

The present study investigated the neurocognitive correlates of emotional interference on a cognitively demanding task within a sample of meditation practitioners and matched controls. In the present study, we sought to investigate the effects of YM on emotion-cognition interactions. YMP and a matched control group (CG) of yoga and meditation naïve subjects underwent fMRI scanning while performing an Affective Stroop Task (Blair et al., 2007; Vythilingam et al., 2007; Hasler et al., 2009; Mueller-Pfeiffer et al., 2010; Froeliger et al., 2011, 2012), a modified version of the Number Stroop task (Pansky and Algom, 2002). The Affective Stoop task was designed to evaluate emotional information processing and its effects on cognitive conflict resolution. We hypothesized that YMP, as compared to the CG, would exhibit less brain activation [i.e., Blood-oxygenation-level-dependent (BOLD) response] during negative emotional information processing and greater brain activation during Stroop trials in the executive control system (e.g., PFC).

MATERIALS AND METHODS

PARTICIPANTS

Fourteen [7 Hatha YMP, 7 Hatha yoga and meditation-naïve control (CG)] participants between the ages of 18 and 55 years were enrolled. MP participants reported engaging in mindfulness meditation on average 7 days per week [0] over the course of the previous 5.7 yrs [3.8]. In addition, participants in the YMP group were also involved in an active and ongoing hatha yoga practice (>45-min a day, three-four times per week, >3 years). The matched CG reported no current or past dedicated meditation or yoga practice. In addition, all participants were right-handed, free of any psychiatric condition or any major medical condition that would make participation unsafe or uncomfortable. Additional exclusionary criteria included current alcohol or drug abuse, use of tobacco or nicotine products and positive urine drug screen. Female participants were required to have a negative urine pregnancy test at screening and within 12 h prior to the fMRI scan. The protocol was approved by the institutional review board at Duke University Medical Center, and all participants provided written informed consent before participating in study-related activities.

PROCEDURES

After screening, eligible participants completed one training session during which they practiced the experimental task and were placed in a mock scanner in order to habituate to the scanning environment. Following training, participants completed one fMRI session.

ASSESSMENT OF TRAIT AND STATE AFFECT

Baseline measures included assessment of depressive symptoms with the Center for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977) and anxiety symptoms with the Beck Anxiety Inventory (BAI). State-dependent mood was measured using the 20-item positive and negative affect schedule (PANAS) (Watson et al., 1988). This measure results in two orthogonal scales—Positive Affect (attentive, proud) and Negative Affect (distressed, angry).

AFFECTIVE STROOP TASK

The Affective Stroop Task used in the present study was similar to that used in other studies evaluating emotion-cognition interactions (Blair et al., 2007; Vythilingam et al., 2007; Hasler et al., 2009; Mueller-Pfeiffer et al., 2010; Froeliger et al., 2011). During each imaging session, participants performed two runs of the task (**Figure 1**). Stimuli consisted of number grids and distractor images. The number grids consisted of numerals (1's through 6's) randomly presented within a 9-point grid-field. Distractor

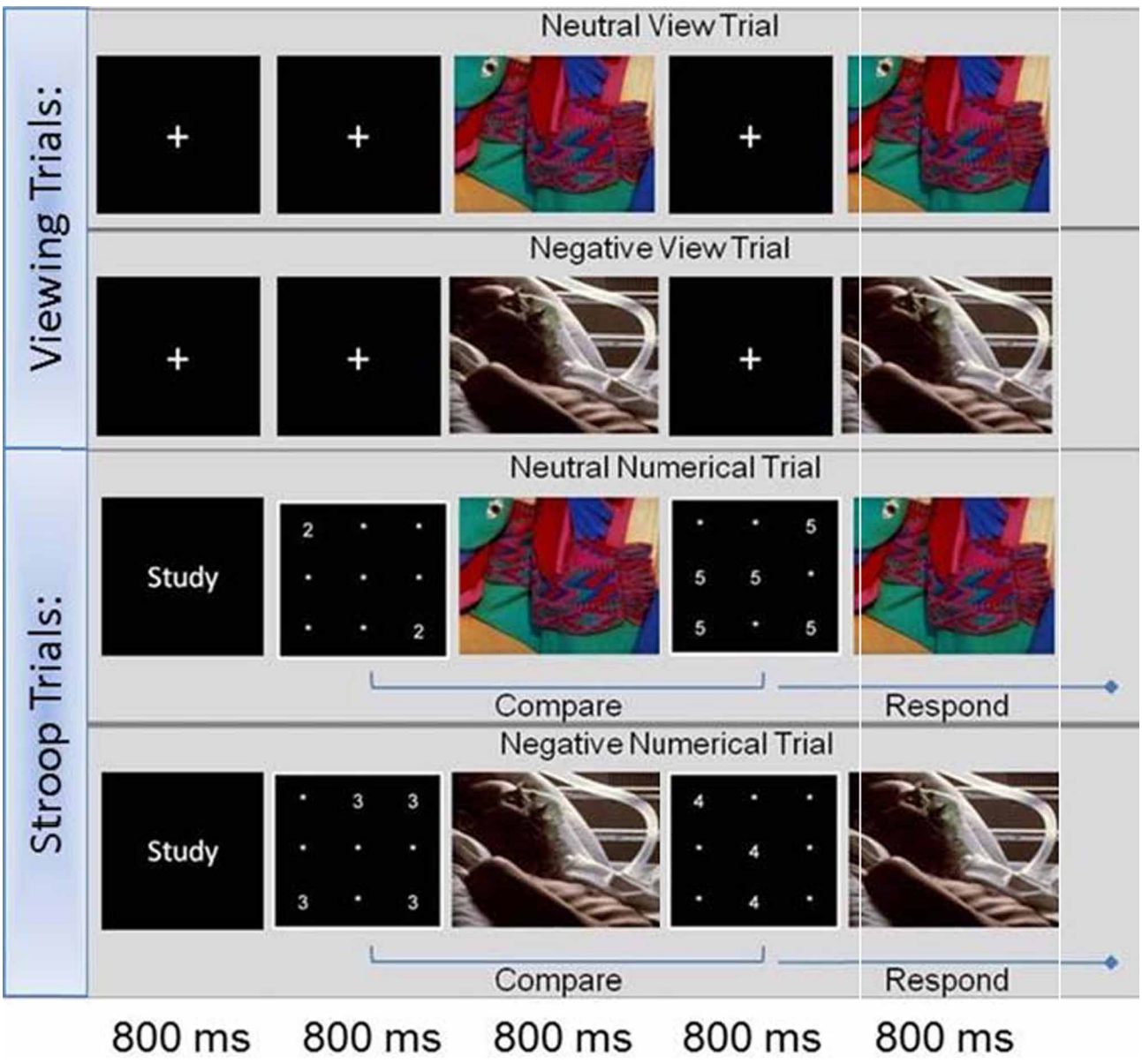


FIGURE 1 | Affective Stroop task.

stimuli were negative and neutral valence images selected from the International Affective Picture Series (IAPS) (Lang et al., 1997) on the basis of 9-point arousal (1-lowest, 9-highest) and valence (1-negative, 5-neutral, 9-positive) scales. Valence and arousal ratings for chosen images did not overlap across categories (Negative, Valence <3, Arousal >6; Neutral, Valence 4 to 6, Arousal <3) and were matched on mean luminance, chromatic features, and scene complexity. Within the aST, two primary types of trials are randomly presented, Stroop trials that contain numerical grids and distractor images, and viewing trials—requiring the participant to only view images (**Figure 1**). The Stroop trials began with a fixation cross, followed by a number grid, a negative or neutral distractor image, a unique number grid, and concluded with the re-presentation of the distractor image each for 800 ms. Participants were instructed to report by button press which number grid presented (1st or 2nd) contained greater numerosity (the quantity of numbers presented) as quickly and accurately as possible. Stroop trials were further broken down into two subcategories: congruent and incongruent trials. During congruent trials, the number grids presented numerals with a face value congruent with the numerosity (e.g., two 2's; five 5's). During the incongruent trials, the face value of the numerals did not match the numerosity (e.g., four 3's; three 4's). Response accuracy and reaction times (RT's) were recorded for each trial. During the viewing trials the numerical grids were replaced with a crosshair and no responses were recorded. Finally, numerical trials began with a brief (800 ms) instruction "Study"; whereas emotional information processing trials began with a brief (800 ms) instruction "View". During each 8 1/2 min run, six event types (negative congruent, negative incongruent, neutral congruent, neutral incongruent, negative view, and neutral view) were each randomly presented equally (15 events), resulting in a total of 30 events per type during each scanning session.

ANALYSIS OF BEHAVIORAL DATA

Analyses of the effects of group on overall task response RT and accuracy during the Stroop trials were conducted using a 2 (Group: YMP, control) × 2 (Task Condition: congruent, incongruent) × 2 (Distractor Valence: negative, neutral) ANOVA. Behavioral analysis of the effects of group and emotional distractor valence on Stroop [incongruent-congruent] accuracy and RT were evaluated in a 2 (Group: YMP, control) × 2 (Valence: negative, neutral) ANOVA.

fMRI METHODS

A 3T General Electric Signa EXCITE HD scanner (Milwaukee, WI) equipped with 40 mT/m gradients was used for image acquisition. At the start of each fMRI session, a high-resolution three-dimensional fast spoiled gradient recalled echo (3D-FSPGR) anatomical sequence was collected (FOV = 25.6 cm, matrix = 256^2, flip angle = 12°, 166 slices, slice thickness = 1 mm). BOLD functional images were collected for 34 contiguous slices parallel to the horizontal plane connecting the anterior and posterior commissures. A gradient-recalled inward spiral pulse imaging sequence was used (34 slices, TR = 1500 ms, TE = 30 ms, FOV = 25.6 cm, matrix = 64 × 64, flip angle = 60°, slice thickness = 3.8 mm, resulting in 4 × 4 × 3.8 mm voxels).

Preprocessing was conducted using statistical parametric mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London) to attenuate noise and artifacts. The first four volumes of each run were discarded to allow for T1 stabilization. All functional images underwent correction for acquisition timing and for head motion using rigid-body rotation and translation (Friston et al., 1994). Each participant's data was then subsequently warped into a standard stereotaxic space (Montreal Neurological Institute) with an isotropic 2 mm voxel size and smoothed with an 8 mm FWHM Gaussian filter.

fMRI DATA ANALYSIS

Participant's data from each session was entered into a first-level, whole-brain analysis using the General Linear Model (Friston et al., 1994) to examine BOLD response to each of the six trial types; negative view, neutral view, negative congruent, neutral congruent, negative incongruent, neutral incongruent. For the first-level model, each event of each trial was modeled as a delta regressor at the onset of the event and convolved with a canonical hemodynamic response function. Motion was removed through rigid body rotation and translation and included as covariates, and a high-pass filter (128 s; 0.008 Hz) was applied to remove slow signal drift. Statistical images were thresholded with a mask containing regions of interest (ROI) that have been previously found to play a role in emotion-cognition interactions (Drevets, 2000; Ochsner et al., 2002, 2004; Yamasaki et al., 2002; Dolcos and McCarthy, 2006; Wang et al., 2008). These included bilateral posterior, dorsal and paracingulate cortices; inferior, middle and superior frontal gyri; inferior parietal lobule (IPL); insula and amygdala. These ROI's were obtained from automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) in Marina (Walter et al., 2003). The goal of the analyses were to identify effects of YM experience (YMP, controls) on (1) emotional information processing [e.g., viewing emotional images (negative, neutral)] and (2) emotional distraction on Stroop-BOLD response.

Analysis of group, emotional distraction and stroop effect

To examine the effects of group and emotional distraction on the neurocorrelates of the Stroop effect, a Stroop contrast image (incongruent-congruent) of the second numerical grid in the trial (decision making event) was created separately for (1) negative and (2) neutral emotional distractors trials at the first level—resulting in two contrast images; negative emotional and neutral emotional distractor Stroop contrast maps. Regressors for each event were entered into a 2 (Group: YMP, control) × 2 (Valence: negative, neutral) random effects ANOVA. Main effects of Group and Valence; and Group × Valence interactions were evaluated.

Analyses of group and emotion reactivity

To examine between group differences in brain activity while viewing negative emotional images, regressors for each event of interest (1st presentation of an image during a trial; negative, neutral) were entered into a 2 (Group: YMP, control) × 2 (Valence: negative, neutral) random effects ANOVA. Main effects of Group and Valence; and Group × Valence interactions were evaluated.

Results were thresholded using the total number of voxels from the complete set of ROI's (i.e., one ROI mask containing all regions indicated in the Materials and Methods). In all analyses, voxels were considered significant if they passed a statistical threshold of $p < 0.05$ cluster-corrected. Cluster size for the comparisons was determined using AlphaSim and running 1000 Monte Carlo simulations (Ward, 2000) ($p < 0.005$, uncorrected; 432-μL cluster of contiguous significant voxels).

Exploratory analysis of affect and BOLD response

To examine the relationship between change in affect during performance of the Affective Stroop task and BOLD response during negative emotional viewing trials, a zero-order correlation was computed between % BOLD signal change in the amygdala cluster identified in the main effects model and the change score in positive affect (pre-post task self-report). We further explored this association using a multiple regression model to test whether the relationship between change in affect and BOLD response during negative emotional viewing was moderated by meditation experience. We regressed change in positive affect on the following set of variables: % signal change (BOLD response) to negative emotional viewing (the independent variable), a dichotomous variable coded 1 for controls and 2 for YMP (the moderator), and a group membership X BOLD response to negative emotional viewing interaction term. The significance of the interaction term indicated the presence of a moderation effect which was then explored graphically by plotting the regression lines (Baron and Kenny, 1986).

RESULTS

STUDY PARTICIPANTS

YMP and CG participants did not significantly differ with regard to demographics or measures of trait and state affect (see **Table 1**). Among the YMP group, age was not significantly correlated with years of meditation practice ($r = -0.01$, $p = 0.98$) or yoga ($r = -0.27$, $p = 0.55$).

Table 1 | Subject demographics and self report.

	Yogis ($n = 7$)	Controls ($n = 7$)	
# Female	6	6	
Mean Age (SD)	36.4 (11.9)	35.5 (7.1)	
Years of Education (SD)	15.5 (2.5)	15.3 (2.3)	
Years of Yoga (SD)	9.3 (2.4)	0	
Years of Meditation (SD)	5.6 (4.2)	0	
BASELINE MOOD			
BAI	14.4 (2.5)	12.5 (1.9)	*ns* [>0.15]
CESD	3.4 (3.8)	2.6 (3.2)	*ns* [>0.6]
MAAS	4.9 (0.3)	5.0 (0.4)	*ns* [>0.5]
PANAS: Positive	35.6 (9.0)	36.1 (10.3)	*ns* [>0.9]
PANAS: Negative	10.4 (0.8)	10.7 (1.9)	*ns* [>0.7]
STATE MOOD			
PANAS: Positive	33.6 (10.8)	36.4 (7.6)	*ns* [>0.6]
PANAS: Negative	10.4 (0.8)	10.3 (0.5)	*ns* [>0.7]

BEHAVIORAL DATA

No significant differences in Stroop RT were observed: there was no main effect of group [YMP (11.65 ms), and controls (14.3 ms)] or valence [negative distractor (15.7 ms) and neutral distractor (10.3 ms)], nor was there a significant group X valence interaction on RT (all p-values > 0.1). Similarly, no significant differences in Stroop Accuracy were observed: there was no main effect of group [YMP (0.002), and controls (0.04)] or valence [negative distractor (0.02) and neutral distractor (0.02)], nor was there a significant or group X valence interaction on accuracy (all p-values > 0.2) (**Table 2**).

ANALYSIS OF BOLD RESPONSE DURING VIEWING TRIALS

Interaction results

BOLD response to distractor images was modulated by a group X distractor valence interaction in right dlPFC [i.e., middle frontal gyrus] (effect size: $d = 2.09$) [see **Table 3**; **Figure 2**]: the CG were found to have greater activation to negative as compared to neutral emotional images, whereas the YMP group exhibited comparatively decreased activation to both negative and neutral emotional images.

Main effects

A significant main effect of distractor valence was identified in left hippocampus and amygdala and right insula, characterized by greater activation to negative as compared to neutral images [see **Table 3**; **Figure A1**]. No main effect of group was found.

Exploratory correlational analyses

Exploratory analyses were performed to evaluate correlations between % signal change in dlPFC and amygdala clusters identified in the prior analyses during viewing trials. Across YMP and CG participants, a significant negative correlation was found between % signal change in the dlPFC and amygdala during negative ($r = -0.575$, *p.03 2-tailed*) but not neutral ($r = -0.05$, p.8) distractor images.

ANALYSIS OF THE EFFECTS OF EMOTIONAL DISTRACTION ON STROOP-BOLD RESPONSE

Interaction results

Stroop-BOLD response was modulated by a group X distractor valence interaction in left ventrolateral prefrontal cortex (vlPFC) [i.e., inferior frontal gyrus] (effect size: $d = 2.4$) [see **Table 4**; **Figure 3**]: YMP exhibited greater Stroop-BOLD when negative, as compared to neutral emotional distractor images were presented, whereas the CG had greater Stroop-BOLD response during trials that presented neutral as compared to negative emotional distractors.

Main effects

A significant main effect of group was identified in left superior frontal gyrus (SFG), such that the CG had greater Stroop-BOLD response as compared to the YMP group [see **Table 4**]. A significant main effect of distractor valence on Stroop-BOLD response was identified in left vlPFC and bilateral anterior cingulate cortex (ACC), such that negative distractor Stroop trials elicited greater activation than neutral distractor Stroop trials [see **Table 4**].

Table 2 | Affective Stroop task: behavioral stroop performance (incongruent-congruent).

Negative		Neutral		Valence × Group Interaction		Main effect of Group				Main effect of Valence			
Yogis	**Controls**	**Yogis**	**Controls**	**F**	***p***	**Yogis**	**Controls**	**F**	***p***	**Negative**	**Neutral**	**F**	***p***
REACTION TIMES													
30.8 (108)	0.7 (63)	−7.5 (56)	28 (54)	2.2	0.16	11.6	14.3	0.007	0.9	15.7	10.3	0.06	0.8
ACCURACY													
0.03 (0.11)	0.01 (0.07)	0.04 (0.1)	0.00 (0.08)	0.14	0.7	0.002	0.04	1.8	0.2	0.02	0.02	0.02	0.8

Table 3 | BOLD response to viewing trials.

Contrast	Side	Lobe	Brain Region	Brodmann Area	MNI (*x, y, z*)	Cluster Size (mm^3)	*Z* (max)	Effect Size (d)
GROUP × VALENCE INTERACTION								
	R	Frontal	dlPFC (MFG)	8	28 28 40	840	3.53	2.09
MAIN EFFECT OF GROUP								
				none				
MAIN EFFECT OF VALENCE								
Neg > Neut	L	Limbic	Hippocampus		−30 2 −16	648	4.1	
			Amygdala		−24 −4 −14			
	R	Limbic	Insula (posterior)	13	38 −16 14	552	4.11	
	R	Frontal	Insula (anterior)		44 14 −10	1272	3.75	
Neut > Neg				none				

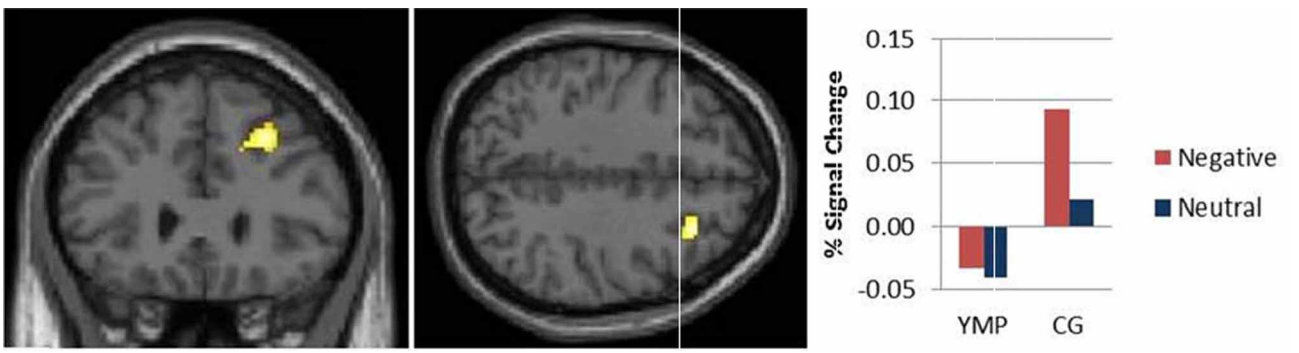


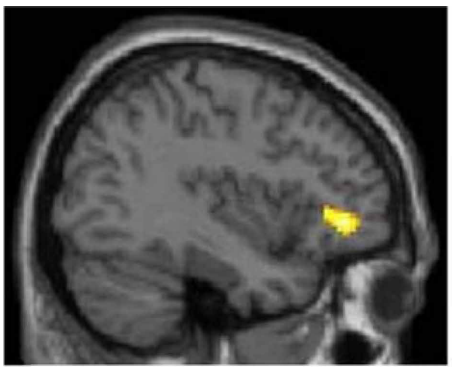
FIGURE 2 | fMRI contrast of the Group × Valence interaction on BOLD response during viewing emotional images. Among the control group, activation was greater during negative versus neutral images and as compared to YMP in right middle frontal gyrus (MFG) ($x = 28$, $y = 28$, $z = 40$).

EXPLORATORY ANALYSIS OF SELF-REPORTED AFFECT AND EMOTIONAL VIEW TRIAL BOLD RESPONSE

No significant main effects of time or group X time interaction effects were observed for change in negative affect from baseline through completion of the Affective Stroop task. In contrast, a significant main effect of time on positive affect was observed; across YMP and controls, positive affect decreased significantly from baseline through completion of the Affective Stroop task, $[F_{(1,\ 12)} = 5.54,\ p = 0.04]$. The group X time interaction was nonsignificant, $[F_{(1,\ 12)} = 0.78,\ p = 0.40]$. Across the entire sample, change in positive affect from baseline through completion of the Affective Stroop task was significantly correlated with BOLD response to negative distractors in the left amygdala, $r = 0.\ 58$, $p = 0.03$ (**Figure 4**). Yet, in exploratory moderation analyses, a significant group X emotional view-BOLD interaction on change in positive affect was observed, $B = -3.31$, $SE = 1.17$, $p = 0.018$ (see **Figure 3**). Graphical inspection of the plot of the interaction effect and *post-hoc* probing of the simple slopes (Aiken and West, 1991) indicated that among controls, higher BOLD response to viewing negative emotional images was significantly related to larger decreases in positive affect during participation in the Affective Stroop task ($t = 3.75$, $p = 0.004$). Simple slopes analysis revealed no such significant relationship between BOLD response to viewing negative emotional images and affective reactivity among YMP ($t = 1.13$, $p = 0.29$).

Table 4 | Stroop-BOLD response.

Contrast	Side	Lobe	Brain Region	Brodmann Area	MNI (*x, y, z*)	Cluster Size (mm^3)	*Z* (max)	Effect Size (d)
STROOP EFFECT:GROUP × VALENCE INTERACTION								
	L	Frontal	vlPFC (IFG)	10	−38 40 −2	824	3.67	2.45
Main EFFECT OF GROUP								
CG > YMP	L	Frontal	Superior Frontal Gyrus	10	−12 60 20	960	3.44	
YMP > CG					none			
MAIN EFFECT OF VALENCE								
Neg > Neut	L	Frontal	vlPFC (IFG)	9	−38 6 26	2488	3.94	
	L	Frontal	Anterior Cingulate	32	−8 12 34	856	3.63	
	R	Frontal	Anterior Cingulate	32	12 20 32	656	3.17	
Neut > Neg					none			



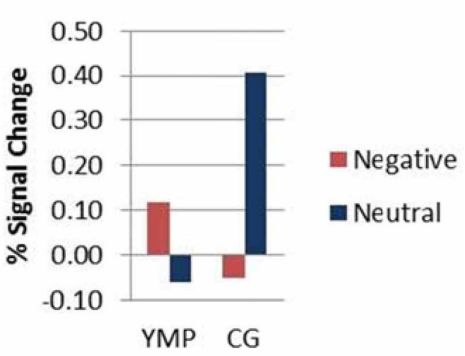
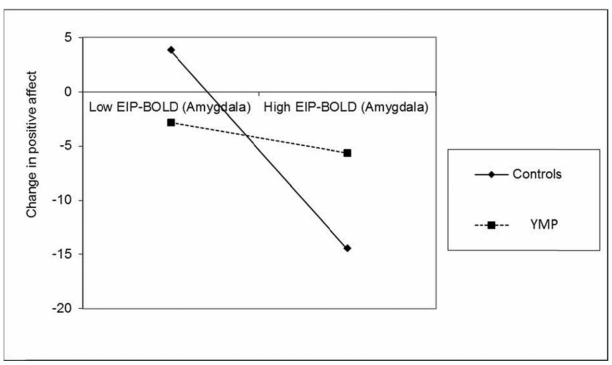


FIGURE 3 | fMRI contrast of the Group × Distractor Valence interaction on Stroop-BOLD response. Among Yoga Meditation Practitioners (YMP), Stroop-BOLD was greater during negative, as compared to neutral distractor trials in left Inferior Frontal Gyrus (IFG) [$x = -38$, $y = 40$, $z = -2$], whereas the opposite pattern was observed among the Control Group (CG).

DISCUSSION

The present study represents one of the first attempts to discriminate YMP from meditation-naïve subjects on the basis of the neural substrates of negative emotional reactivity and emotion-cognition interactions. Though the study failed to identify any significant task-related behavioral findings, it did identify a number of significant task-related neural differences between groups—suggesting within the context of this study that the groups differed from one another, not on *how well* they performed the task, but rather on *how* they performed the task. The study yielded three main findings. First, YMP were less reactive in right dlPFC (i.e., MFG) during viewing negative emotional images. Secondly, during a cognitively demanding task, the presence of emotionally irrelevant distractor images resulted in greater vlPFC (i.e., IFG) activation in YMP. Thirdly, among meditators amygdala activation to negative emotional distracters was uncoupled with task-related changes in affect, unlike non-meditators whose decreases in positive affect were correlated with increased amygdala activation. Taken together, these data suggest that YMP may selectively recruit dissociable frontal executive-dependent strategies in response to emotionally salient information as a function of cognitive demands and not during emotional processing *per se*. Furthermore, bottom-up driven emotional responding among YMP does not have downstream effects on later mood state, dissimilar to that observed among controls.



[a] EIP= Emotional information processing (negative viewing trials)
[b] YMP= Yoga Meditation Practioners.

FIGURE 4 | Plot of interaction between meditation experience and BOLD response in the amygdala to viewing negative emotional images on change in positive affect during participation in the Affective Stroop task[ab].

SELECTIVE RECRUITMENT OF FRONTAL EXECUTIVE MECHANISMS

Emotional information processing

In the present study, YMP exhibited less activation in right dlPFC (i.e., MFG) in response to all distractors images, whereas controls had heightened activation to negative emotional distractors.

The MFG is involved in attention (Cabeza and Nyberg, 2000), cognitive control (Kerns et al., 2004), goal directed processes (Blair et al., 2007) and exerting cognitive control over emotional processes (e.g., emotion regulation) (Ochsner et al., 2002; Ochsner and Gross, 2008). With regard to emotion regulation, the mediation hypothesis posits that executive circuitry (e.g., dlPFC) reduces negative affective response by top-down modulation of affective circuitry (Wager et al., 2008), marked by activation in dlPFC that is inversely related to activation in the amygdala. The current study finding that % signal change in dlPFC was negatively correlated with % signal change in the amygdala during negative, but not neutral, image trials is consistent with the meditation hypothesis model. Moreover, though controls exhibit a reciprocal pattern of executive-limbic BOLD response during viewing negative emotional images, YMP do not. Though the experimental task was not designed to probe *how* subjects processed the emotional images, this pattern of brain activation is consistent with the notion that mindfulness, whether generated via yoga postures or sitting meditation, increases attention toward emotion without active attempts to cognitively restructure affective experience (Hölzel et al., 2011). Recent neuroimaging evidence suggests that mindfulness practitioners evidence decreased fronto-executive activation during processing of emotionally aversive experiences (e.g., pain) (Gard et al., 2011). Such attention to emotional information without cognitive control may reflect the attitude of acceptance and nonjudgment that is held to be an essential component of yoga and mindfulness.

Emotion-cognition interactions

With regard to the effects of negative emotion processing on cognition, YMP had greater Stroop-Bold response in left vlPFC (i.e., IFG) when negative, as compared to neutral, emotional distractors were presented; whereas controls exhibited the opposite pattern. The vlPFC (i.e., IFG) is part of a network involved in inhibitory control (Aron and Poldrack, 2006; Aron et al., 2007), social emotional processes (Carr et al., 2003), and cognitive control over emotional distraction (Dolcos and McCarthy, 2006). Plausibly, the observed pattern of brain activation may indicate that YMP selectively recruited neurocognitive resources to disengage from negative emotional information processing and engage the cognitive demands presented by the Stroop task. Increased activity in the vlPFC may prevent working memory functions from becoming disturbed by incoming sensory input stemming from negative emotional stimuli by deactivating emotional information processing signals ascending from subcortical routes to the amygdala (Austin, 2009). In contrast, CG participants marshaled comparatively fewer frontal-executive resources to resolve emotional interference in the face of this demanding task.

In conjunction, these findings suggest a brain model associated with YM practice whereby frontal executive-dependent strategies to reduce emotional processing are selectively implemented as a function of whether competing cognitive demands are presented. In other words, in the absence of concurrent task performance, YMP appear to process emotional information without effortful cognitive control; however, when emotional experience occurs within the context of a demanding task situation, YMP may resolve emotional interference via recruitment of regions of cortex that subserve cognitive control. Plausibly, this strategy would ensure neurocognitive resource efficiency and confer significant behavioral advantages, such as the psychological benefits observed in clinical and non-clinical samples (Chiesa and Serretti, 2010).

IMPACT OF LIMBIC RESPONSE ON SUBSEQUENT AFFECT

Exploratory analyses revealed that Affective Stroop performance was associated with degradation of positive affect over time and non-significant effects on negative affect. This decrease in positive state affect was likely the result of exposure to aversive images coupled with engagement in a cognitively demanding task. These findings are consistent with prior literature on emotion-cognition interactions (Holdwick and Wingenfeld, 1999; Calkins et al., 2011). For example, Calkins et al. (2011) found that individuals participating in a cognitive control task experienced a significant decrease in positive affect after a negative mood induction, but reported a trend toward a lower induction of negative mood following mood induction. Hence, cognitive control tasks may operate as a buffer from subsequent negative mood induction, by virtue of the fact that they engage regions of prefrontal cortex involved in downregulation of negative emotion. Such prefrontal control could protect individuals from negative emotional reactivity in the context of a cognitive and affective challenge. Alternatively, lack of significant task-related changes in negative affect may stem from low statistical power driven by the modest sample size in this study.

During viewing negative emotional images, CG participants exhibited a stereotypic limbic-mediated affective response, such that increased activation in amygdala to negative emotional distractors predicted greater decay of positive affect over the task session. In contradistinction, YMP amygdala responses during viewing negative emotional images were uncoupled with changes in positive affect. Conceptually, this finding complements the lack of dlPFC activation observed among YMP during exposure to negative emotional distractors. If YMP can process emotional information without effortful cognitive control through mindful awareness and acceptance of experience, they may avoid the negative consequences of response-focused forms of emotion regulation like suppression (Wenzlaff and Wegner, 2000; Gross, 2002; Campbell-Sills et al., 2006), which has been shown to deplete neurocognitive resources during affective cue-exposure (Garland and Roberts-Lewis, 2012).

CONCLUSION AND LIMITATIONS

The present study included a well-controlled, matched sample of YMP and YM naive subjects and a neuroimaging paradigm that allows for modeling of the interactive effects of emotion on cognition—an area of research currently underrepresented in the literature.

However, limitations included a relatively small sample size and the use of a cognitive paradigm with sufficient task difficulty to subjects which may have attenuated the ability to detect behavioral Stroop effects. The small sample may have limited the reliability of study findings on the observed impact of limbic responses on subsequent affect, and thus this analysis

should be replicated in studies with larger sample sizes. Moreover, the cross-sectional design of the current study cannot elucidate whether the observed group differences in neurocognitive function reflect trait-level factors linked with the initiation and maintenance of long-term YM practice, or whether these differences are the result of recurrent yoga practice over time. However, if these findings reflect differences that are a result of recurrent practice over time, they suggest that yoga mediation practice may provide putative therapeutic benefits for individuals with dysregulated affect and/or cognitive control deficits. One such example may be individuals with a substance abuse disorder. For example, the extant research on the neurobiology of substance abuse disorders posits that chronic drug use is associated with dysregulated prefrontal-dependent cognitive control function, which may play a key role in negative affect and inhibitory control (Koob and Volkow, 2010). To test these hypotheses, large-scale longitudinal studies are needed to follow individuals as they initiate the discipline of YM practice and cultivate progressively deeper states of mindfulness over time.

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APPENDIX

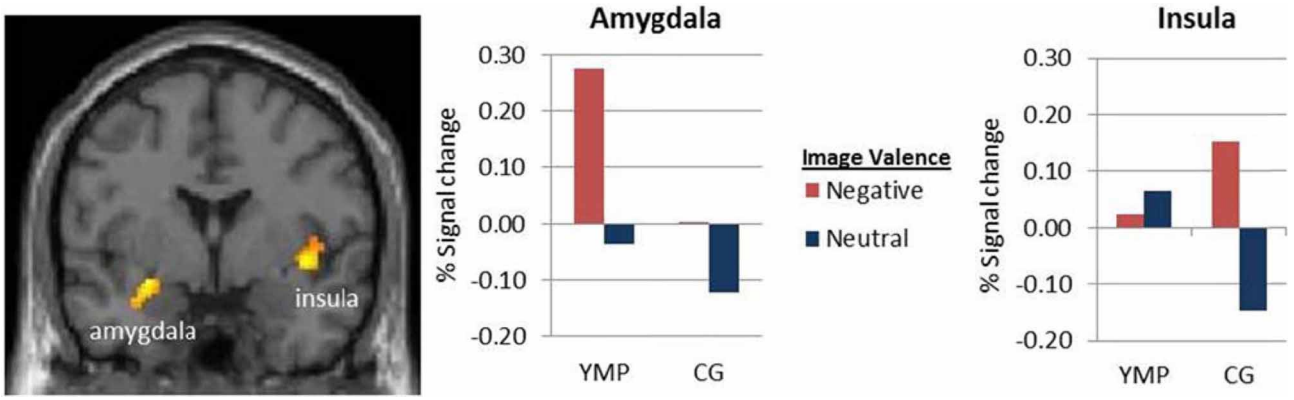

FIGURE A1 | fMRI contrast of the main effect of valence on viewing emotional images. BOLD response was greater during negative, as compared to neutral emotional images in left Amygdala [$x = -24$, $y = -4$, $z = -14$] and right Insula [$x = 38$, $y = -16$, $z = 14$] $p < 0.05$ (cluster corrected).

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Reasoning, cognitive control, and moral intuition

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Recent Social Intuitionist work suggests that moral judgments are intuitive (not based on conscious deliberation or any significant chain of inference), and that the reasons we produce to explain or justify our judgments and actions are for the most part *post hoc* rationalizations rather than the actual source of those judgments. This is consistent with work on judgment and explanation in other domains, and it correctly challenges one-sidedly rationalistic accounts. We suggest that in fact reasoning has a great deal of influence on moral judgments and on intuitive judgments in general. This influence is not apparent from study of judgments simply in their immediate context, but it is crucial for the question of how cognition can help us avoid deleterious effects and enhance potentially beneficial effects of affect on judgment, action, and cognition itself. We begin with established work on several reactive strategies for cognitive control of affect (e.g., suppression, reappraisal), then give special attention to more complex sorts of conflict ("extended deliberation") involving multiple interacting factors, both affective and reflective. These situations are especially difficult to study in a controlled way, but we propose some possible experimental approaches. We then review proactive strategies for control, including avoidance of temptation and mindfulness meditation (Froeliger et al., 2012, this issue). We give special attention to the role of slow or "cool" cognitive processes (e.g., deliberation, planning, and executive control) in the inculcation of long-term dispositions, traits, intuitions, skills, or habits. The latter are critical because they in turn give rise to a great many of our fast, intuitive judgments. The reasoning processes involved here are distinct from *post hoc* rationalizations and have a very real impact on countless intuitive judgments in concrete situations. This calls for a substantial enlargement of research on cognitive control, drawing on work in developmental psychology, automatization, educational theory, and other fields.

Keywords: intuition, reasoning, decision neuroscience, affect, neurosciences

It seems obvious that on occasion people make impulsive judgments or decisions and live to regret it. What to do about this is less obvious, but traditionally common sense and philosophy have agreed that reason offers some hope: "think it over before you decide," "look before you leap." Most people are inclined to think that reasoning, if given half a chance, can help us recognize some impulses or intuitions as foolish and others as sound. We can then give due weight to sound intuitions and use various means to counter the force of foolish ones. But does reasoning actually have this much influence? Recent work by "Social Intuitionists" on decision-making and moral judgment in particular (Haidt, 2001; Greene, 2007) suggests that almost everybody, almost all the time, exercises moral judgment via quick, intuitive (non-deliberative), "hot" (affect laden) processes. The reasons people produce to explain or justify their moral judgments are for the most part *post hoc* rationalizations, and not the actual basis or cause of those judgments. There are exceptions, but these are scarce in everyday life and as a rule restricted to people specifically trained to think through moral judgments, conflicts or dilemmas. The same holds in many domains: people often cannot give coherent explanations of their judgments or actions at all, yet cling to those judgments nonetheless [see Mills and Keil (2004) for experimental evidence]. The real explanation for their inability to produce a coherent, defensible account is that their judgments are not based on reasoning, but are intuitive and the result of processes not available to conscious reflection. This is the basic Social Intuitionist picture of moral judgment.

Our view is that although there is much truth in this picture, there is also much left out. Above all it underestimates the causal influence of slower, controlled cognitive processes on affect and emotion on at least three fronts: first, reactive strategies for

control of impulse, intuition, or emotion; second, proactive measures to avoid unwanted impulses from arising in the first place, to prepare for coping with them if they do arise, or to actively arouse affect that might in turn have enhanced effects on action or cognition; and third, proactive inculcation, (re)shaping, or elimination of the underlying bases of many of our fast, intuitive or "gut" responses. These bases include character traits, habits of perception, expertise of various sorts, dispositions to intense gut reactions such as disgust, and others. In this third area we also review interesting new work on mindfulness meditation and its influence on the downstream effects of emotional processing.

In the larger picture we see these causal roles for reasoning as part of a general theory of cognition/affect interaction that incorporates rather than contests recent work by Social Intuitionists. Our reservations about Social Intuitionism have to do not with the claim that most of our moral judgments are intuitive, but that it takes too narrow a view of the potential role of reasoning in generating or shaping those intuitive judgments, hence in influencing them for better or worse.

REACTIVE REGULATION OF AFFECT AND EMOTION

STRATEGIES FOR COGNITIVE CONTROL

There are several experimentally established reactive strategies for cognitive control, including suppression, distraction, distancing (adopting a third-party view of a conflict), and reappraisal of a conflict situation, especially of the option favored by impulse or intuition (see the reviews by Ochsner et al., 2002; Kim and Hamann, 2007; Goldin et al., 2008). We focus here on reappraisal. The object of an intuitive or impulsive response—for example, my next cigarette—may initially appear to me as a source of pleasure ("Satisfying, and they are mild!"). But if I am trying to quit smoking I can consciously reappraise the cigarette as a "coffin nail," or think of smoking as a "smelly, obnoxious habit." Reappraisal is pervasive in advertising, political campaigns (Lakoff and Johnson, 1980) and elsewhere, and often plays a role in moral decision-making. Social Intuitionists would rightly point out that reappraisals frequently amount to rationalizations. At times these rationalizations can be quite self-serving: "If I don't take over Joe's old job (after Joe has been unjustly fired) someone else will; so I might as well do it." In fact I may already intend to take the job. But in light of my self-serving rationalization, taking the job appears not as acquiescence or participation in an injustice, but as something that is for all practical purposes harmless. And my refusing the job now appears not as a protest against injustice but as a pointless sacrifice on my part. I may well even believe that these rationalizations explain and justify my taking the job, when in fact the real explanation is simply that I am an opportunistic cad.

Reappraisal is not limited to internally generated rationalizations, however. As Social Intuitionists point out, (re)appraisal often works by means of one person triggering a gut or intuitive response in someone else. Thus, an anti-abortionist displays a photo of a 6-months-old fetus to a freedom-of-choice advocate: "Abortion until the last trimester allows the killing of a living creature such as this." This may stimulate a new gut reaction and a different intuitive moral judgment. But we suggest a major addition to this characterization of the new judgment as "intuitive." For the strategy of showing such photos, or of erecting billboards graphically depicting the internal ravages of smoking, may itself have been well-researched, long-planned and executed, by epidemiologists, statisticians, social activists, publicists, legislators, and so on. The end result may well be a fast, non-deliberated, affect laden reaction on someone's part—or millions of such responses if a campaign of public education is widely successful. But these automatic, intuitive reactions are to a significant extent the causal effects of previous slow, controlled processes of thought and planning. Thus for the purpose of discovering how reasoning might influence affect, impulse, or intuitive judgment, it is crucial to go beyond the fact that a given response considered in its immediate context is fast and intuitive rather than deliberated. This holds whether or not people are aware of how their own intuitions were shaped.

Recent work on reappraisal indicates that people who use this strategy more frequently also use it more effectively (Cohen et al., 2012). This result raises further questions for investigation, including that of whether people can through practice improve their ability to use this strategy. Interestingly, Kanske (2012, this issue) finds that "temperament trait effortful control" correlates with "enhanced (task-relevant) emotion-induced facilitation of conflict processing," and that this translates to the neural level. Given this, along with Cohen's et al. (2012) suggestive results, research into the plasticity and educability/trainability of temperament trait effortful control could lead to methods of improving this important ability in "normals" and perhaps methods of addressing individual or group deficiencies.

Further, if people can through practice improve their ability to use reappraisal effectively, can they eventually automatize it, so that it becomes "second nature"? These questions could in fact be pursued in the case of any strategy for cognitive control. And clearly they bring the study of cognitive control into contact with work on individual differences in ability, on habit or skill acquisition, and on the shift from conscious control and practice to automatic activation [see Logan (1988) on two competing psychological models of automatization]. A related question for further investigation is whether one can improve in the use of a given strategy by mental rehearsal (i.e., via imaginative simulation of anticipated situations of decision or action) as one can with many motor skills (see Gunaratana, 2002; Lutz et al., 2009).

Regarding neural underpinnings, it would be particularly interesting to know whether the system of executive control involved in the practice or application of reappraisal was the same in different domains. Does it differ, for example, depending on whether the process to be cognitively controlled is itself psychological (as in cognitive control of affect or of unwanted thoughts), or physical (as with consciously monitored practicing in sports or music)? Comparison of research on cognitive control of affect with results in other domains would bear also on the question of whether or not there is a single, general-purpose system of executive control, and if so, how it relates to domain-specific systems of cognitive control. Indeed, accumulating neuroscience evidence indicates that executive control functions are not implemented within a unitary system but may instead reflect the operation of multiple information processing systems (Koechlin et al., 1999, 2000; Miller and Cohen, 2001; Braver et al., 2003; Sakai

and Passingham, 2003; Curtis and D'Esposito, 2004; Braver and Barch, 2006; Crone et al., 2006; Dosenbach et al., 2006; Koechlin and Summerfield, 2007; Barbey et al., 2012).

This brings us to an example of contemporary research with the kind of broad scope we think necessary in the long run. Posner et al. (2008) investigate the genetic and neural basis of a human executive attention network. More specifically, their work combines recent developments in genetics, fMRI, and behavioral testing to track the development of an attentional network in early childhood. The neural systems involved coincide with results of fMRI studies of cognitive control in adults, at least insofar as it includes anterior cingulate cortex and portions of lateral prefrontal cortex; for reviews see Botvinick et al. (2001), Miller and Cohen (2001), Ramnani and Owen (2004), Barbey et al. (2009), and Barbey and Patterson (2011). The experimenters also correlated their results with parental reports of children's ability for self-regulation of cognition and emotion. One long-range goal was to investigate the role of genes and experience in the emergence of this network in 4-year-olds, and how it might constitute a general foundation for acquiring a series of more specific skills during early school years. From our point of view such a network would be an important element also in the development and exercise of any of the strategies for cognitive control surveyed so far. This would be particularly important if ways were found to systematically strengthen such a system of executive attentional control, whether in children or adults.

Finally, the case of reappraisal already suggests ways in which psychological and neuropsychological research itself can make important if indirect contributions to direct practical efforts at cognitive control in concrete circumstances. These potential contributions include (1) discovering or verifying experimentally the efficacy of a given strategy for cognitive control; (2) evaluating experimentally the pros and cons of different strategies (e.g., the potential undesirable "rebound" effect of suppression (Wegner et al., 2004); (3) exploring the effectiveness of different strategies with respect to control of different types of affect (e.g., anger management, stress reduction, curbing one's enthusiasm); (4) exploring the possible plasticity and educability of the ability to use a given strategy; (5) investigating individual and group differences with respect to capacities for control (Kanske, 2012, this issue), along with possible ways to address deficiencies [e.g., in very young or old populations; see esp. Braver (2012)]; (6) testing methods by which different strategies might be taught, learned, practiced, and even perhaps routinized so they themselves become second nature. Cognitively controlled research in all these areas can potentially discover effective means of cognitive control and explore possibilities for helping children and adults improve their ability to exercise particular strategies of control.

COGNITIVE CONTROL IN EXTENDED DELIBERATION

The strategies for control surveyed so far treat conflict between reasoning and affect as a simple one-on-one encounter. But when a decision is important and an agent has the time, and the cognitive and imaginative resources to think things through, the factors involved can multiply quickly. This "extended deliberation" predictably produces a mix of reasons and intuitions/impulses/emotions on both sides of the question. (By "extended deliberation" we mean roughly a process of identifying and weighing all the significant pros and cons pertaining to a particular judgment or choice—or at least, the significant factors an agent can find by making an honest and unhurried but not clinically obsessive effort.) Extended deliberation typically includes multiple forms of interaction among those various factors, and multiple points in time at which these interactions occur. In addition, different factors and interactions may well engage different neural mechanisms if different specific forms of cognitive control come into play. Extended deliberation is more difficult to study, either behaviorally or via neuroimaging, than specific, "one-on-one" control strategies. After analyzing the process a bit further we will venture some suggestions about how it might nonetheless be approached empirically. For present purposes we will look more closely at deliberation arising from a conflict between one's "better judgment" and an affective impulse, but bear in mind that it can also arise from conflict between affective impulses, or even from conflicting reasons.

Reasoning recruiting affect

One frequent feature of extended deliberation is the recruitment of supporting affect by reasoning. When we try to think of the reason(s) in favor of or against some judgment or action we ordinarily think of the consequences that would or would not ensue, depending on whether or not we performed the action. These consequences are typically valenced—i.e., they include positive or negative affect. A common mechanism for the evocation of affect is the imaging or mental simulation of actions and their likely consequences (Aristotle and Barnes, 1984; Barsalou, 1999). Do we go to the birthday party as promised, or do we accept the free tickets to the ball game we were just unexpectedly given? Suppose we have an emotional impulse to go to the ball game (it is a "big game" against our arch-rival) and don't really want to go to the party anyway (last year's was extremely boring). On the other hand, we ought morally speaking to attend the party, not only because we said we would, but also based on the imagined responses of other attendees—their delight if we show up, their disappointment if we do not. Other emotionally valenced considerations then naturally present themselves, e.g., the shame or guilt we would feel if we broke our promise, or the guilt we would feel at disappointing the hostess, who has always treated us well. So already the option favored by moral reasoning has recruited two "rational" considerations ("a promise was made and must be honored"; "you shouldn't mistreat someone who has treated you well"), but also a variety of emotionally charged scenarios to bolster those rational factors and to counter our emotional impulse to go to the ball game. Real-life extended deliberation will usually be more complex still, since the initial gut response will also recruit both affect and reasoning to its cause.

In a nutshell, in extended deliberation both (or all) sides of a conflict will recruit both affect and "cooler" considerations. Moreover, as deliberation develops over time, opposing factors will interact: although some newly recruited factors will be simply additional considerations meant to add cumulative force to one side or the other, some will be direct responses to considerations advanced on behalf of the opposing viewpoint while still others will be replies to those responses.

Scanners in the fog of war

These are not mere possibilities, but facts of life when an individual, a pair of agents such as a married couple, or a group of people must think through a difficult decision, trying to identify and evaluate the pros and cons of various possible options. These cases raise an obvious problem for the use of brain imaging studies to address the question of the possibility and manner of interaction between affect and cognition. The problem is not just the perennial one of whether and how one can make a clear cut distinction between affective and cognitive processes. The further problem is that even if we are able to determine during actual deliberation that one sort of underlying neural system or structure (e.g., dorsolateral prefrontal cortex vs. amygdala) shows a greater increase in activity at a given time than the other, this will not tell us *which* particular reasons or which affects actually account for the observed increase in activity (for a review, see Dolcos et al., 2011). After all, there will be both sorts of factors on both (or all) sides. Moreover, heightened activity in either the dorsolateral prefrontal cortex or the amygdala might well reflect more than one simultaneous process of cognition or feeling.

Future research into these matters might well begin by using experimental material suitable for extended deliberation, preferably issues that people actually do deliberate and debate. Then keep a running, temporally fine-grained self-report record of conscious steps of deliberation while the underlying brain activity is being recorded. Recent work on social interaction suggests a promising variant on the usual one-participant-at-a-time setup: include two participants, each in a scanner and each able to communicate with the other via keyboard and screen as they discuss some question that is of actual concern to them (for a review of the technique and some of its technical problems, see Montague et al., 2002). Comparison of sufficiently precise neuroimaging data with real-time records of deliberation could potentially throw light on some—though probably not all—of the questions listed in the previous paragraph.

Among the many additional questions raised by extended deliberation we mention only the most fundamental of these, and note that it applies also to the simpler cases of cognitive control reviewed above under "Reactive Regulation of Affect and Emotion." Can reasoning itself have causal or motivational force, for example in countering affect or impulse, or must it arouse/recruit affect in order to have such influence? On the surface extended deliberation appears to pit reasons against reasons, affect against affect, and reasons against affect. We tend to think of valenced affect as itself motivational. But are we to think of "rational considerations" as possessing some kind force or weight in and of themselves?

Philosophers have debated this question for centuries, but today it may at least in part be addressed empirically. Relatively simple cases of control such as reappraisal or distraction might already shed light on the issue, for in each type of cognitive control one could ask whether its conscious exercise involves arousal of affect in its own support. Neuroimaging evidence would be critical, since it could in principle reveal activity in affective systems even if an agent did not report any conscious experience of affect arising in support of the initial "cooler" side of the conflict. It would be important also to compare successful attempts at control with unsuccessful ones, to see whether they correlated systematically with greater or lesser activity or some change in patterns of activity in affective systems. As usual, however, matters quickly grow more complicated. Should consciously felt *effort* at control be counted as affect—e.g., exerting "will power" in the face of temptation, or "maintaining resolve" through a prolonged effort? If so, is the feeling of exerting effort the sort of affect that reason must rely on if it is to have causal influence on judgment or behavior? If so, how (neurally speaking) does reasoning summon this sort of exertion? On the other hand, would reasoning not in fact have to have some other source of influence in cases where we do not experience any feeling of effort? Or do we then postulate unconscious effort and look for neural underpinnings? Along the same lines, if people can through practice become better at using a particular strategy of control should we not predict that they will with increased mastery be able to exercise *greater* control with *less* effort? There are many more related questions awaiting investigation, but since this paragraph was supposed to formulate "just one," we will leave off here, and turn to proactive strategies for control.

THINKING AHEAD: PROACTIVE COGNITIVE CONTROL

PREVENTATIVE MEASURES

In everyday experience it is not necessary to be entirely reactive with respect to emotion. [We borrow the terminology of "reactive" and "proactive" from (Braver, 2012), but give it much broader application.] As Aristotle pointed out (Aristotle and Barnes, 1984), people are often aware of their own susceptibilities and weaknesses, and they can take reasonable steps to avoid situations that are likely to arouse unwanted impulses or thoughts. An alcoholic may avoid drinking parties, or take one route home rather than another to avoid passing directly by the corner tavern.

A quite different means of control is described in a very recent pilot study of the effects of mindfulness meditation on emotion and cognition (Froeliger et al., 2012, this issue). Experimental results suggest that although practitioners exhibit limbic reactivity to negative emotional stimuli, this reactivity appears not to have the usual downstream effects on later mood states. Especially interesting is the authors' finding concerning these practitioners' performance on the Stroop test following presentation of potentially interfering negative emotional images: yoga practitioners may employ "selective implementation of frontal executive-dependent strategies to reduce emotional interference during competing cognitive demands and not during emotional processing *per se*." Further research is needed to determine whether meditation can enhance capacity for control with regard to additional sorts of contexts, tasks, and potential distractors.

POSITIVE AFFECT AND THE GOLDILOCKS EFFECT

Proactive measures are not always aimed at potentially deleterious affect. If we are aware that appropriate emotion would be useful in enhancing thought or action we may try to stimulate that emotion. Knowing that a blasé attitude is detrimental to cognitive performance, a student might try to "get psyched" for an exam (via self-exhortation, perhaps with caffeine supplement). Some very recent work supports experimentally the familiar notion that an appropriate level of stress can enhance performance by

enhancing attentional focus or raising one's energy level (Minois, 2000). We take this case as representative of the "Goldilocks" effect, in which cognitive control aims not at suppression, distraction, etc., but at just the right level of affect—not too hot and not too cold, but just right for cognitive or motor performance. We hypothesize that this applies to other sorts of affect as well (e.g., anger, confidence) and consider the ability to tune affect by regulation up or down to be an additional area for future research. One challenge will be to identify specific strategies for modulation of affect, analogous to research on strategies for the type of cognitive control discussed in section "Reactive Regulation of Affect and Emotion" above. These tuning or modulatory strategies would presumably be different than those for simple suppression, distraction, etc., since their aim is to modify and make use of affect rather than to eliminate it from consciousness or block its effect. They would also include strategies for both raising or lowering levels of affect, where agents might well need different strategies for raising than for lowering, even with regard to the same type of affect (stress, anger, fear). A key overarching question will be *how* this modulation of affect proves helpful or the opposite: is it a matter of supporting (or interfering with) desirable levels of attention, energy, or motivation? If so, are there better, perhaps more direct or more reliable methods for achieving this? Answering these questions could have large practical implications.

PRESENT AT THE CREATION: INCULCATION (OR EXTINCTION) OF INTUITION, HABITS, TRAITS, AND DISPOSITIONS

Not all traits or dispositions to quick responses of a given type are acquired, and not all acquired ones are acquired through the deliberate application of cooler processes of planning, training, etc. But some are, and in particular situations these deliberately acquired or shaped dispositions and habits give rise in turn to a great many fast, intuitive, or "hot" responses. Thus, slow, controlled cognitive processes that lead to underlying traits, or dispositions to a certain type of intuitive response, can have a large impact at least indirectly on particular intuitive or gut responses. We suggest that this is the single most important source of cognitive control of affect and intuition.

We sometimes consciously and on the basis of reflection decide to alter our own behavioral patterns, as with "New Year's Resolutions." And sometimes we actually follow through. An extreme example is Benjamin Franklin's systematic program of identifying desirable and undesirable habits and personal traits, then performing actions calculated to inculcate or root them out, keeping a real-time written record of his relevant actions.

But more often the cooler processes of deciding what habits and traits we should have, as well as any thinking about how those habits are to be taught and learned, is done by others. Much of it is in fact exercised in our "upbringing" and early education in everything from correct table manners and habits of personal hygiene to virtues such as generosity, honesty, and good citizenship. The aim is to make these things second nature, so that they have a "learned naturalness" (Boyer, 1994). When that is achieved, they issue naturally, and without need for deliberation, in "intuitive" or "instinctive" judgments and actions when triggered by relevant circumstances. Here cognitive control meets developmental psychology, educational policy, "parenting," moral development, social planning, legislation, law enforcement, and transmission of culture in general.

The processes of enculturation are numerous and closely intertwined. This is where some Social Intuitionists rightly speak of "immersion in cultural complexes" (Haidt, 2001). Still, we maintain that some of the most important aspects of these cultural complexes consist of slow, controlled cognition in various forms. To cite just a single important American example, one can point to the continuing influence of the "wisdom of the Founding Fathers" as expressed in the Constitution. That document's ideas about the basic structure of good government and certain ideals of citizenship in a democracy have been inculcated continuously ever since. In part the institutions of inculcation themselves (e.g., a system of public education) have been established along lines long ago deliberated, decided, and even built into our collective experience by deliberated legislation (e.g., laws requiring a certain level of schooling) and curriculum decisions (e.g., requiring a course in "civics"). Occasionally substantial changes have been made to the system (Amendments to the Constitution), such as extending voting rights beyond white adult males. These changes, too, have been deliberated and adopted in accordance with considered procedures set out in the Constitution itself. In addition, major issues of interpretation have arisen and been settled through deliberation and voting by the Supreme Court (e.g., rulings establishing a broad interpretation of "free speech" under the First Amendment). All these instances of deliberation and carefully weighed decision-making have had a large impact on the habits of perception, thought and action of millions of people. This is true even for those who have paid little conscious attention to these processes and would be hard pressed to explain them coherently. In the present example much of the reasoning involved occurred quite a long time ago; but its impact on our intuitions here and now in the twenty-first century is very real nonetheless. Again, although it is important to note that our latter-day judgments are often intuitive, this is only the beginning of the story, and overlooks important ways in which reasoning helps shape and control a great many of our affective responses (e.g., to voter suppression or voter fraud) and intuitive judgments (e.g., about proper political process or the scope of civil rights).

SOMATIC MARKERS AND ALARM BELLS

Finally, we consider briefly two additional proactive and long-term sources of gut responses. The first is what Antonio Damasio calls "somatic markers" (Damasio, 1996). Damasio points out that many of our decisions, judgments, and actions are at least constrained by emotionally valenced neural representations of events and associations implanted by relevant experience. Once established, they serve to circumscribe the range of viable responses or decision-making alternatives by nipping the "frame problem" in the bud. That is, cognitive or behavioral problems typically can in principle be addressed in an unlimited number of ways, whereas an agent does not have the time, resources, or need to investigate them all. Thus, the problem must be "framed" so as to limit the possibilities to a manageable field of alternatives. Agents clinically deficient in this regard tend to engage in

extreme—and exasperatingly extended—processes of deliberation (Damasio, 1996). Somatic markers make normal decision-making possible by automatically closing off various alternatives without our having expressly to consider them. At the same time they can bias one option over another by automatically giving it a positive or negative valence.

These markers are sometimes distinguished from more intensely valenced automatic responses, especially aversive ones, such as disgust or moral repugnance. Greene and colleagues (Greene et al., 2001; Greene, 2007) relate the difference between somatic markers and alarm bells to the traditional philosophical distinction between deontological and utilitarian ethical judgments. Roughly put, deontological judgments are based on specific and "absolute" rules or principles; e.g., "it is impermissible to kill an innocent bystander even in order to save five lives, because murder is always wrong." Utilitarian judgments allow specific moral rules to be overridden by considerations of the "greatest good for the greatest number"; e.g., "it is permissible to kill an innocent bystander to save five lives, because the overall good outweighs the harm." The "Trolley Problem" has been familiar in philosophy for a few decades and has recently formed the basis of numerous psychological experiments. We put aside for present purposes the question of how much the Trolley Problem can tell us about actual moral choices. In any event there are now many variants on the problem, but the most basic version is this: You see a trolley car headed toward a group of five people standing on the tracks. If you don't do something the trolley will kill them all. However, you can throw a switch and divert the trolley onto a side track, so that it will only kill one person. Do you intervene, or just let things take their course? Most respondents say it is morally permissible to intervene in order to save the greater number. Now vary the scenario: you can save the five people only by directly pushing a large person off a bridge and onto the trolley track. Is it permissible to push him off or not? Most people say they do not think this permissible. Why is that, if in both cases it is a matter of sacrificing one person to save five? Some philosophers and psychologists suggest that the throwing-the-switch scenario activates only a cooler (i.e., somatic marker based judgment) utilitarian judgment, whereas the pushing-a-man-off-the-bridge scenario triggers a basic gut aversion (i.e., alarm bell response) to harming someone through direct personal action.

Greene and colleagues found that fMRI scans suggest a systematic neural difference in the type of affective input commonly linked to these two styles of judgment: deontological-style assessments are commonly driven by alarm bell responses, whereas utilitarian-style judgments are influenced by relatively more subtle somatic markers (Greene et al., 2001). However, from the point of view of how reasoning can influence affect/intuition/gut response, it perhaps goes without saying by now that the main issues are the extent to which somatic markers and alarm bells can be implanted deliberately under the control of executive processes, the extent to which they are open to beneficial modification by top–down executive processes, and the like. No doubt somatic markers and alarm bells are sometimes established by experience willy-nilly—as when one receives a conk on the noggin from a playground swing, or an indignant reproof from a proper young lady (e.g., a slap in the face, if that is not entirely a thing of the past). But just as with habits, somatic markers and alarm bells need not be acquired or inculcated thoughtlessly. We suggest that in fact they are often established as a result of deliberated, reasoned judgment on the part of others—for example, parents who give thought to what sort of markers ought to be established in their children, and to how these markers are to be established. Punishment and reward, admonition and encouragement, censure and praise, succeed in part by deliberately establishing appropriate somatic markers that help guide future decisions and actions. If successfully implanted, these markers in turn contribute to the shaping of many intuitive responses in concrete situations. The obvious parallel with traits or habits is not coincidental, since the selective laying down of somatic markers and subsequent repeated activation of them is part and parcel of much of our habit formation.

The same holds for "alarm bells," even though they may seem more deeply visceral, inflexible, and perhaps more closely tied to evolved genetic origins. The example of disgust is a good case in point. It is one of our loudest alarm bells, and one closely allied with certain moral responses (see, for example, Nichols, 2004). Some of our disgust reactions (e.g., to the smell of putrefying flesh) are evolved, and are extremely resistant to any process of extinction. But some, including reactions of disgust, fear, etc., are just as clearly cultural, as with Mary Wollstonecraft's moral disgust at the sight of "a fine lady clasping a lap dog to her bosom" (Wollstonecraft, 1792). Behind this intuitive alarm bell of moral disgust lies a good deal of experience, and reflection on the moral fatuousness (or worse) of "fine" ladies. Such reflection can help change the way we conceive a type of person or situation, so as to trigger an alarm bell that it did not trigger in the past. There was a time, perhaps, when we admired the fine lady, and intuitively found it endearing that she clasped her little dog to her bosom.

The neuroscience evidence just mentioned (Greene et al., 2001; Greene, 2007) does, however, raise one new and important issue. With regard to types or styles of moral judgment in particular we would caution against thinking of deontological and utilitarian approaches as exhaustive alternatives. Moral traits and habits, including those we label "virtues" and "vices," constitute a very important source of moral perceptions, judgments and actions, and they do not fit easily into a simple deontic/utilitarian scheme. Moral philosophy has in recent decades seen a resurgence of interest in "virtue ethics" as an alternative to deontic and utilitarian theories of how one is to live a morally good life. The approach goes back to Plato, Aristotle, Aquinas, et al. A pivotal modern work is Mac Intyre (1984) but there is now a voluminous literature on the topic. In virtue ethics, virtues and vices are construed along the general lines of habits or character traits. Consequently we have strong reservations about framing psychological or neurological research—or interpreting the data from such research—in terms of a deontological vs. utilitarian dichotomy.

As for the use of scanning evidence to support such a dichotomy, we suggest that although the Trolley Problem may in fact pose a fairly clear conflict between deontological and utilitarian principles, other sorts of moral judgment do not. Moreover, in many circumstances the same moral conclusion would be consistent with both deontological and utilitarian principles.

For present purposes, however, let it suffice to say that future research should recognize the option for interpretation afforded by virtue ethics (and still others would be possible), and consider carefully how differing responses to given types of experimental materials might correlate with different underlying bases of moral judgments. Certainly recognizing the importance of moral traits and habits opens the door to a great deal of further research, and to the forging of connections with already established research on learning, practice, and automatization of moral and other responses.

CONCLUSION

Our point of departure for a broad consideration of cognitive control was a particular interpretation of moral judgment as virtually always intuitive. We conclude that although there is much truth in this description of such judgments considered in their immediate context, it is necessary to look beyond that context when addressing the question of whether and how reasoning might potentially influence moral and other intuitions, or whether rational control in this area is an illusion (Haidt, 2001). A broader perspective reveals numerous ways in which reasoning can and very often does influence affective response and intuitive judgment, even if that influence is in many cases indirect. Much of our discussion, especially that of measures for proactive control, constitutes a response to the question, "Where do our intuitive judgments come from?" Putting aside other factors, we have focused for present purposes on ways in which reasoning, planning, cognitive monitoring, and the like play a substantial role in establishing the underlying sources of intuitive judgments. Chief among these sources are the diverse habits, traits, skills, expertise, and dispositions that give rise to fast, automatic, sometimes "hot" responses in particular circumstances. Of course these sources are not inculcated entirely through slow, cognitively controlled processes. But many are acquired or shaped to a significant extent in that way, and this constitutes a larger field for the control of the fast and hot by the slow and cool than do the reactive strategies that have up to now received more attention in the literature on cognitive control.

In addition there is a great deal of work to be done on related issues regarding cognitive control: strategies for up-regulation of affect as well as for suppression, reappraisal, etc.; modulation or tuning of affect to enhance cognition or action; strategies for improving or automatizing abilities to apply strategies for modulation or control; and others. These all bear on situations of moral judgment, but they in fact apply to perception, judgment and action of all sorts and call for further investigation as important aspects of the wide and complex domain of cognitive control.

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When does stress help or harm? The effects of stress controllability and subjective stress response on Stroop performance

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The ability to engage in goal-directed behavior despite exposure to stress is critical to resilience. Questions of how stress can impair or improve behavioral functioning are important in diverse settings, from athletic competitions to academic testing. Previous research suggests that controllability is a key factor in the impact of stress on behavior: learning how to control stressors buffers people from the negative effects of stress on subsequent cognitively demanding tasks. In addition, research suggests that the impact of stress on cognitive functioning depends on an individual's response to stressors: moderate responses to stress can lead to improved performance while extreme (high or low) responses can lead to impaired performance. The present studies tested the hypothesis that (1) learning to behaviorally control stressors leads to improved performance on a test of general executive functioning, the color-word Stroop, and that (2) this improvement emerges specifically for people who report moderate (subjective) responses to stress. Experiment 1: Stroop performance, measured before and after a stress manipulation, was compared across groups of undergraduate participants ($n = 109$). People who learned to control a noise stressor and received accurate performance feedback demonstrated reduced Stroop interference compared with people exposed to uncontrollable noise stress and feedback indicating an exaggerated rate of failure. In the group who learned behavioral control, those who reported moderate levels of stress showed the greatest reduction in Stroop interference. In contrast, in the group exposed to uncontrollable events, self-reported stress failed to predict performance. Experiment 2: In a second sample ($n = 90$), we specifically investigated the role of controllability by keeping the rate of failure feedback constant across groups. In the group who learned behavioral control, those who reported moderate levels of stress showed the greatest Stroop improvement. Once again, this pattern was not demonstrated in the group exposed to uncontrollable events. These results suggest that stress controllability and subjective response interact to affect high-level cognitive abilities. Specifically, exposure to moderate, controllable stress benefits performance, but exposure to uncontrollable stress or having a more extreme response to stress tends to harm performance. These findings may provide insights on how to leverage the beneficial effects of stress in a range of settings.

Keywords: stress, executive function, controllability, contingency

INTRODUCTION

Stress is part of life. Pursuing goals despite exposure to stressors, or better yet, showing enhanced functioning in response to stress, are abilities that are fundamental to survival and resilience (Maier and Watkins, 2010). For a broad range of daily goals, it is critical to know what type of stress can help or harm behavioral functioning. Musical concerts, athletic competitions, and academic testing are all settings in which stress may either impair performance or fuel pursuit of goals. To perform optimally, healthy humans must expose themselves to the types of stress that promote the most enhanced functioning possible.

The effects of stress on cognitive functions, specifically, may mediate the helpful and harmful effects of stress in complex domains such as those described above. Stress research with humans has yielded evidence for both positive and negative effects of stress and stress hormones on cognitive functions (Lupien et al., 1999). This research has revealed that working memory, a function thought to be very important for executive function (EF), is particularly sensitive to such effects (Lupien et al., 2007). Several studies show that stress exposure (Duncko et al., 2009; Weerda et al., 2010) or naturalistic stress (Lewis et al., 2008) can lead to improved performance on tests of working memory. However, other studies have demonstrated that the same types of stress exposure can cause

impaired performance on working memory tasks (Oei et al., 2006; Schoofs et al., 2008, 2009; Luethi et al., 2009), as do higher levels of naturalistic stress (Sliwinski et al., 2006). Finally, a third set of research results show no differences in performance on working memory tasks between conditions of stress or no-stress exposure (Kuhlmann et al., 2005; Porcelli et al., 2008; Qin et al., 2009). What might explain these mixed findings?

One possibility is that these research endeavors have often focused on group differences (e.g., stress group versus no-stress group) without examining individual differences in response to those stressors (either subjective stress response or physiological reactivity). When researchers have monitored physiological reactivity to stress, several studies have found that cortisol and performance on working memory tasks are negatively correlated (Qin et al., 2009; Schoofs et al., 2009) especially when adrenergic activity is also high (Elzinga and Roelofs, 2005). Animal research has demonstrated that the effects of stress intensity on behavior are characterized by an inverted-U-shaped function: while low or high levels of stress lead to performance impairment on tests of vigilance and working memory, a moderate level of stress leads to performance improvement (Lupien et al., 2007; Arnsten, 2009). Neurobiological studies suggest that these quadratic effects are related to levels of stress hormones (e.g., glucocorticoids) and adrenergic activity (e.g., catecholamines) in the brain, especially in prefrontal cortex (PFC) regions (Arnsten and Goldman-Rakic, 1998; Mizoguchi et al., 2004; Lupien et al., 2007; Hains and Arnsten, 2008; Arnsten, 2009), which are critically involved in working memory and EF processes. Examining individual responses to stress, and how these responses relate to subsequent cognitive functioning (in either linear or quadratic relationships), is thus critical for clarifying the question of when stress may help or harm behavioral performance.

Controllability of stressors is also a key factor that influences how stress affects behavioral performance (Dickerson and Kemeny, 2004; Arnsten, 2009). Controllability is a characteristic of stress that has been explored in "learned helplessness" research. This research typically uses a triadic design in which two groups are exposed to equivalent stress but differ on whether or not it is possible to learn to control stressors, and a third (control) group is not required to learn control and usually is not exposed to stress. After these manipulations, participants are tested on learning or problem-solving tasks, and comparison of performance between groups reveals the effects of stress exposure and controllability. Learned helplessness research has provided evidence for the harmful effects of exposure to uncontrollable stress, as well as the protective effects of having behavioral control over stressors. Specifically, while exposure to uncontrollable stress leads to passivity, negative affect, and disrupted performance on subsequent cognitively demanding tasks, being able to learn how to behaviorally control the same stressor buffers the individual from these negative effects (see Maier and Seligman, 1976, for review). An extensive literature documents learned helplessness effects in a range of animal species (see Seligman, 1972; Maier, 1984 for reviews) and the neural mechanisms inhibiting the stress response under conditions of controllability are well defined in rodents (Maier and Watkins, 2005). Research with humans has replicated the behavioral effects of controllability, showing that uncontrollable situations, in which behavioral responses cannot affect outcomes, lead to poorer performance on subsequent learning and anagram tasks (Hiroto, 1974; Hiroto and Seligman, 1975; Jones et al., 1977; DeVellis et al., 1978; Hirt and Genshaft, 1981; Kofta and Sedek, 1989) and possibly a higher cortisol response (Peters et al., 1998).

Thus, controllability of, and individual responses to, stressors influence the effects of stress exposure on cognitive and behavioral functioning. However, several intriguing questions about the nature of these effects remain unexplored. First, the question of what types of stress exposure can enhance cognitive functioning remains only partially resolved. While some promising evidence suggests that exposure to moderately intense stress predicts improved working memory performance, the dearth of research on individual differences, and inconsistencies in group-level effects, make this association far from conclusive. Furthermore, the question remains open whether exposure to controllable stress can enhance behavioral functioning. A number of studies documented the impairing effects of uncontrollable stress, but failed to find any benefit of exposure to controllable stress (Hiroto, 1974; Hiroto and Seligman, 1975; Jones et al., 1977; DeVellis et al., 1978; Hirt and Genshaft, 1981). However, several other studies demonstrated that people exposed to controllable stress show improved learning and cognitive ability in comparison to people exposed to either uncontrollable stress or no-stress (Thornton and Jacobs, 1971; Thornton and Powell, 1974; Benson and Kennelly, 1976; Eisenberger et al., 1976, 1979). We have yet to determine whether, and how, controllable stress exposure may enhance cognitive and behavioral functioning.

Second, although controllability of stress and individual differences in stress response have been investigated separately, little research has examined the interaction of these factors. One research study showed that participants who appraised stressors as challenging performed better on an active coping task than participants who appraised the same stressors as threatening (Tomaka et al., 1993), suggesting that subjective reactions predict performance differences in a context of controllable stress. However, because the passive coping task used in this study for comparison had no measure of performance, it is not possible to determine whether subjective reaction would predict a different pattern in the context of uncontrollable stress. Another study identified an interaction between dosage of stress and individual differences in locus of control in predicting performance on an anagram task (Pittman and Pittman, 1979), although individual responses to stressors were not assessed. In sum, existing research supports the robust influences of controllability and stress reactivity in moderating the effect of stress on cognitively demanding tasks, but investigation of interactions between these factors remains sparse.

Third, our understanding of the cognitive abilities affected by stress controllability and level of stress response remains imprecise. Although both human and animal research suggests that the effects of controllability on cognitive function are mediated by underlying systems fundamental to learning (Maier and Watkins, 2005), the exact nature of those systems in humans is unclear. The most consistently replicated consequences of uncontrollable stress are impaired performance on novel, goal-directed learning tasks or complex tasks such as anagrams (reviews by Oakes, 1982;

Tennen, 1982). Deficits on these complex tasks may have a number of sources ranging from slowed processing speed to reduced ability to direct and sustain attention. Hence, until research is conducted using tasks that isolate particular cognitive abilities, it is not possible to determine which abilities are affected by controllability and which are not. Several pieces of evidence suggest that EF may be the most likely underlying cognitive function impaired by exposure to uncontrollable stress. EF refers to a set of abilities including holding abstract goals in mind, using goals to provide "top-down" direction for attentional allocation, and inhibiting the processing of sensory information, thoughts or actions that are irrelevant to or incompatible with current goals. EFs are often recruited for tasks requiring complex cognition, including the various learning and problem-solving tasks that have been traditionally administered in stress controllability research. Of note, EF abilities are supported by systems in PFC, which is particularly sensitive to the effects of stress hormones and catecholamines (Arnsten, 2009).

Most of the research investigating effects of stress intensity or reactivity has focused on working memory ability. However, it is not known whether stress specifically affects working memory, or EF more broadly. EFs are best characterized as separable but related cognitive processes, with both unique and shared individual differences, genetic influences, and neural substrates (e.g., Miyake et al., 2000; Collette et al., 2005; Friedman et al., 2008). Impairment on working memory tasks could arise either from impairment of processes specific to working memory, or from impairment of processes common across multiple aspects of EF, namely the ability to actively maintain goal information (*common EF*; Friedman et al., 2008). Initial research supports the theory that stress affects executive abilities more broadly; researchers detected a larger difference between stressed and control subjects in performing a Sternberg working memory task when subjects had to ignore emotional distractors presented during a delay (Oei et al., 2009). In other research, scientists found that Trier stress exposure predicted impaired performance on tests of cognitive "flexibility" such as remote associates or anagrams tasks (Alexander et al., 2007) and that inducement or blockade of physiological arousal served to respectively impair or improve performance on such tasks (Beversdorf et al., 1999). Thus, stress appears to have effects across tasks that vary in the aspects of EF they tap, suggesting that stress may affect working memory abilities, at least in part, because stress affects processes that are common across EF tasks. This previous research suggests that common EF processes may be key cognitive functions affected by stress exposure.

To explore common EF processes in the current research, we administered the "gold standard" of EF tasks (MacLeod, 1992), the Stroop task (Stroop, 1935). In this task, participants must identify the color of ink in which a word is printed while ignoring the meaning of the word, which may contain competing color information (e.g., *BLUE* written in red ink). Hence, one must maintain the goal of identifying ink color in the face of highly distracting information (as in the competing color information conveyed by word meaning). Latent variable analysis has demonstrated that the Stroop task loads strongly on a common EF factor (Friedman et al., 2008), suggesting that this measure is suitable for examining general executive ability.

In sum, the current research investigated the helpful or harmful effects of stress on common EF, as assessed by the Stroop task. Specifically, this research explored the (linear or quadratic) relationship between individual differences in stress response and Stroop performance, and whether these effects depend on controllability of stress exposure.

EXPERIMENT 1

STUDY GOALS

This study tested the hypothesis that controllability of stress, and individual differences in subjective stress, are factors that interact to affect EF. Our stress manipulation included two sources of psychological stress to which participants were exposed while performing a choice-RT task: social-evaluative stress in the form of performance pressure, and sensory stress in the form of noise exposure.

Previous research has shown that uncontrollable, social-evaluative stress is the most potent form of psychological stress (Dickerson and Kemeny, 2004). Researchers have defined *uncontrollability* as non-contingency between instrumental actions and outcomes (Oakes and Curtis, 1982), as repeated failure feedback regardless of responses (Klein et al., 1976; Jones et al., 1977; Kilpatrick-Tabak and Roth, 1978; Hirt and Genshaft, 1981) or as both non-contingency and failure (Hiroto, 1974; Hiroto and Seligman, 1975; Benson and Kennelly, 1976; Klein and Seligman, 1976; Miller and Seligman, 1976; Price et al., 1978; Kofta and Sedek, 1989). We structured the manipulation of uncontrollability to include both non-contingency and increased rates of failure. This decision was based on research indicating that this conjunction of stressors generates the most robust perception of uncontrollability, while the conjunction of true contingency and a high rate of success is the strongest generator of perceived control (Gernigon et al., 2000). This body of research also suggests that explicitly manipulating performance feedback makes the absence of contingency more obvious, and overrides the normal bias to assume one is controlling events when desired outcomes (here, shorter noises as opposed to longer noises) are frequent (Vallee-Tourangeau et al., 2005).

Social-evaluative stress occurs when an important aspect of self-identity is (or could potentially be) negatively judged by other people. Social-evaluative stress has been operationalized experimentally as pressure to succeed in active performance situations, e.g., on tasks that require overt or cognitive responses (Dickerson and Kemeny, 2004). We designed our stress manipulation to include social-evaluative stress by including trial-by-trial performance feedback, and by testing each participant individually in the presence of an experimenter.

As a result of the above considerations, we manipulated stress exposure between groups in the following manner. In our controllable stress condition (CSt), participants received accurate, feedback regarding their performance (fast responses elicited success feedback), and could learn to control the duration of noise stressors by responding quickly to stimuli. In our uncontrollable stress condition (USt), participants were exposed to two sources of uncontrollability. First, the type of noise and nature of performance feedback received for each trial were not contingent on responses. This non-contingency made it impossible for these

participants to learn how to control the duration of the noise stress or reliably predict success versus failure feedback. Second, people in this group received a higher proportion of (inaccurate) failure feedback. This biased performance feedback suggested to participants that their responses were, overall, not fast enough to successfully perform the task. Importantly, the CSt and USt groups did not differ on noise exposure, task stimuli, or response requirements. Finally, we included a third, no-stress condition (NSt), in which people were required to respond to identical stimuli as the other two groups, but received no performance feedback or noise exposure.

In this study, participants completed the Stroop task at the beginning of the research session to assess their baseline ability to exert general EF. After completing one of the three stress task conditions described above, participants completed the Stroop task a second time. This design allowed us to control for baseline differences in EF by examining changes in Stroop performance from pre- to post-stress exposure.

MATERIALS AND METHODS

Participants

Participants were 109 undergraduate volunteers ages 18–24 from introductory psychology courses at the University of Colorado Boulder (**Table 1**). Participants provided informed consent and were treated in accordance with procedures approved by the University of Colorado Boulder Institutional Review Board. Participants were tested individually in private rooms.

PROCEDURE

Participants were informed of the study procedures at the beginning of the research session, provided written consent, and were randomly assigned to one of the three stress conditions (USt, $n = 41$; CSt, $n = 42$; NSt, $n = 26$)[1]. The sequence of an experimental sessions was: (1) PANAS-X pre-testing, (2) Stroop, (3) stress manipulation, (4) Stroop, (5) PANAS-X post-testing, (6) assessments of subjective stress response, perceived control, and Beck Depression Inventory II (BDI-II; **Table 2**). At the conclusion of the research session, all participants were given written debriefing information. Participants exposed to uncontrollable stress were debriefed verbally about such uncontrollability.

Materials

A computer system captured accuracy and reaction time (RT) via millisecond-accurate keyboard press for all trials. Participants assigned to stress conditions that included an auditory stressor (either 2000 or 4000 ms in duration) listened to stimuli through headphones, with volume calibrated at 72–80 dB.

Test of executive functioning: color-word Stroop. On each trial of the Stroop task a word written in one of four ink colors (green, yellow, red, or blue) appeared in the center of the screen for 2000 ms and participants identified the ink color as quickly as possible by hitting the corresponding button on the keyboard. Prior to beginning the first Stroop task, participants were given 16 practice trials in which XXXX stimuli were presented to familiarize the participant with the task demands and location of the response keys for each of the four colors. During the task, trials were presented in two blocks (48 trials each; 38% incongruent and 62% neutral across blocks). Incongruent words feature conflict between ink color and word meaning (e.g., *RED* written in blue ink), while neutral (non-color) words do not (e.g., *SUM* written in blue ink). Comparing RT to incongruent versus neutral words isolates the individual's ability to exert cognitive control in the face of highly distracting information, over and above basic perceptual processing abilities and response speed. Therefore, the calculation of percent difference in incongruent versus neutral RT [(incongruent RT − neutral RT)/neutral RT] yields an interference score that indexes general executive functioning. This method of calculating Stroop interference (as a percentage of neutral trial RT) controls for scaling effects in RT measures, in which RT differences tend to scale with the magnitude of RT latency (Lansbergen et al., 2007).

Stress manipulation. Participants performed a choice-RT task and either were (USt and CSt groups) or were not (NSt group) exposed to concurrent psychological stress. The choice-RT task required participants to choose behavioral responses based on perceptual features in the display (**Figure 1**).

For each trial, an arrow pointing either left or right appeared inside a white fixation box on the computer monitor. Participants responded to the direction of the arrow as quickly as possible by pressing the corresponding button on the keyboard. All

[1]Original recruitment included a sample size of 127 participants; however, 3 participants in the CSt condition and 1 participant in the USt condition failed to complete the experiment due to computer error, and 14 participants in the NSt condition failed to complete self-report measures due to experimenter error. For these reasons, analyses were performed on a sample size of $n = 109$.

Table 1 | Demographics and descriptive statistics for Experiment 1.

Condition	Sample *n* (*n* female)	Self-report			Cognitive tasks		
		Subjective stress *M* (SD)	Subjective control *M* (SD)	BDI score *M* (SD)	Pre-stress Stroop interference *M* (SD)	Post-stress Stroop interference *M* (SD)	Change in interference *M* (SD)
CSt	42 (29)	17.07 (4.67)	6.71 (1.47)	11.51 (6.54)	0.0119 (0.0101)	0.0074 (0.0094)	−0.0045 (0.0108)
USt	41 (24)	19.02 (4.43)	4.32 (1.84)	9.73 (6.86)	0.0107 (0.0103)	0.0096 (0.0090)	−0.0011 (0.0106)
NSt	26 (10)	14.56 (5.28)	n/a	8.65 (8.20)	0.0132 (0.0110)	0.0106 (0.0091)	−0.0026 (0.0101)
Total	109 (63)	17.16 (5.00)	5.53 (2.04)	10.15 (7.11)	0.0118 (0.0103)	0.0090 (0.0092)	−0.0027 (0.0106)

participants completed a practice block (20 trials) without any stress exposure, to familiarize themselves with the choice-RT task.

In the two testing blocks (80 trials each), participants in the CSt and USt groups had two performance goals: (1) to respond accurately and fast enough to beat a challenging time limit, for which they received performance feedback indicating success (yellow fixation box) or failure (blue fixation box; blocks 1 and 2); and (2) to learn how their responses controlled the duration of a noise stressor that was evoked by each response (block 2 only). Participants in the NSt condition completed the same task, but with no feedback or noise stress. This task was based on classic manipulations of instrumental control in which participants must learn how to control a noise by pushing a sequence of buttons (Hiroto, 1974; Hiroto and Seligman, 1975).

For the CSt group, feedback and noise exposures were controllable: fast, accurate responses elicited short noises accompanied by success feedback, while slow or inaccurate responses elicited long noises coupled with failure feedback. A moving-window for response speed ensured that every participant was able to beat the time limits on 80% of trials, and participants received success feedback and short noises on these trials. When participants failed to beat the time limit (20% of trials) they received failure feedback and long noises.

For the USt group, feedback and noise exposures were uncontrollable, both (1) because feedback and noises were not contingent on response speed, and (2) because feedback was biased to indicate a higher rate of failure (blue fixation box for 50% of trials, regardless of response speed or accuracy). The CSt and USt groups were matched on their true response success and noise exposure: as in the CSt group, a moving-window for response speed ensured that every participant was actually able to beat the time limits

Table 2 | Experimental procedure (Experiments 1 and 2).

Task or measure	Time (minute)
EXPERIMENT PROCEDURE	
Rating of state affect (PANAS-X)	2
Assess baseline general executive functioning (color-word Stroop)	5
Stress manipulation	16
Assess post-stress general executive functioning (color-word Stroop)	5
Rating of state affect (PANAS-X)	2
Rating of subjective stress, control	2
Report depression (BDI-II)	5
Total	37

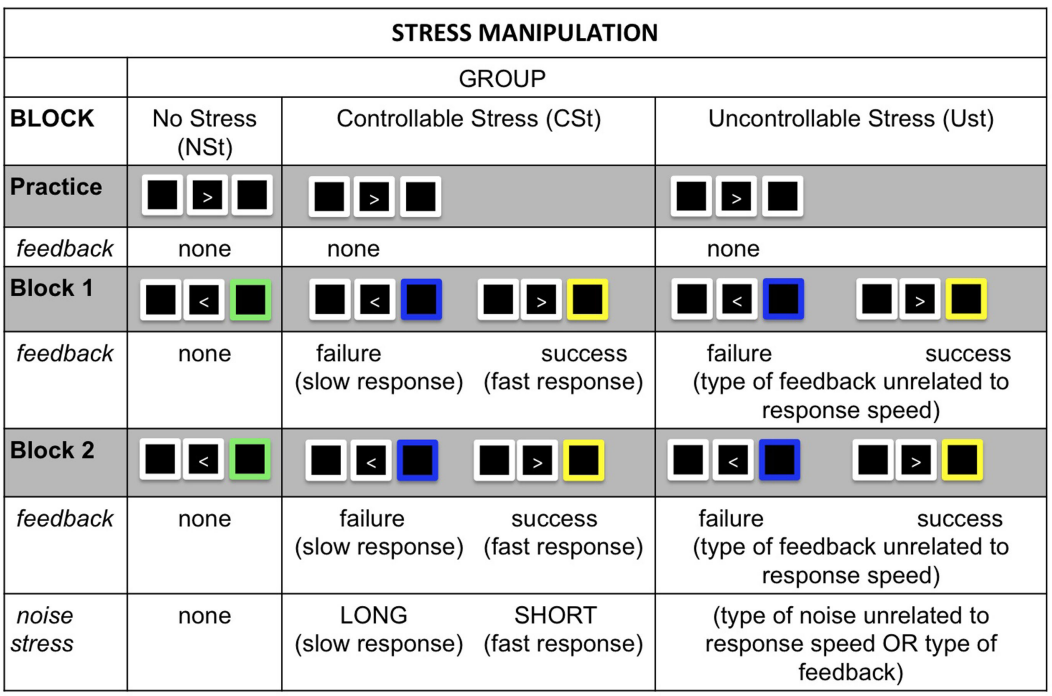

FIGURE 1 | Stress manipulation: In both Experiments 1 and 2, all groups completed a simple choice-RT task that either was accompanied by psychological stress in the form of performance feedback and noise exposure (controllable stress: CSt group and uncontrollable stress: USt group) or was not accompanied by these forms of stress (no-stress: NSt group). The manipulation consisted of a practice block that was identical across groups, followed by two testing blocks that varied between groups. Performance feedback (blocks 1 and 2): the NSt group received no performance feedback; the CSt group received accurate feedback indicating success or failure in responding fast enough to beat a time limit; the USt group received performance feedback that was unrelated to their response speed and either featured an exaggerated proportion of failure feedback (Experiment 1) or was equated on feedback with the CSt group (Experiment 2). Noise exposure (block 2): the NSt group received no noise exposure; the CSt group was able to learn that short noises were contingent on responding fast enough to beat time limits; the USt group was exposed to non-contingent noises unrelated to response speed or performance feedback, and the amount of short and long noises were equated with the CSt group.

on 80% of trials, and every participant received a short noise on 80% of trials. However, unlike the CSt group, the USt participants received non-contingent performance feedback that was biased for failure (success feedback for only 50% of trials) and short and long noises were random and unrelated to their response speed or performance feedback[2].

Finally, for the NSt group, participants received no performance feedback (green fixation box after every response, regardless of response accuracy or speed) and were not exposed to noise (**Figure 1**).

Assessment of subjective stress response. At the end of testing, participants reported subjective ratings of stress to provide a measure of individual differences in response to the stress exposure. Participants rated the following on a 1 (low) to 9 (high) scale: (1) level of stressfulness of the noise exposures (CSt and USt only), (2) level of stressfulness of the task (choice-RT) demands, (3) degree to which you believe someone else would have performed better than you (social comparison), (4) degree to which you believe you performed well on the task. The scores for these scales were summed to yield a composite score of subjective stress for each participant. Because they did not rate the noise exposure item, scores for participants in the NSt condition were multiplied by 4/3 to make this group comparable to the CSt and USt groups. Across the sample, scores were mean-deviated for the purpose of regression analyses.

Assessment of perceived control. Self-reported perception of control was also assessed at the end of testing, with ratings reported from 1 (low) to 9 (high). This measure was collected to confirm that our manipulation of controllability was successful in eliciting differences between groups.

Assessment of mood and affect. We used well-validated measures of current depression and state affect to confirm that groups were equivalent on these dimensions at baseline, and to investigate whether participants experienced changes in affect over the course of testing.

Participants reported level of depression in the past two weeks using the BDI-II (Beck et al., 1996). Previous research has shown that current depression can moderate the effects of controllable stress on cognitive task performance (Klein et al., 1976; Miller and Seligman, 1976; Price et al., 1978). In addition, sex differences in physiological and psychological responses to stress are consistently noted in stress research (e.g., Ordaz and Luna, 2012). Therefore, for all analyses, we also conducted regressions including BDI-II score and participant sex as covariates. Unless otherwise indicated, the significance of the results was not altered by the addition of these covariates and we report simple analyses only.

In addition, they completed the Positive and Negative Affect Questionnaire (PANAS-X; Watson and Clark, 1999) both before and after cognitive testing as a measure of state affect.

RESULTS

Data processing and analyses

For the Stroop tasks, RT analyses were conducted by calculating an average for each trial type. Incorrect trials and trials on which RTs were less than 200 ms or exceeded 3 standard deviations above the within-subject mean were excluded from analyses. RTs were natural log transformed to reduce the skew common to RT data and which violates the statistical assumption of normal distribution necessary for analysis. Accuracy analyses were conducted by calculating the total correct for each trial type pre- and post-stress manipulation.

Data were analyzed with multiple-regression analyses. For group comparisons, two orthogonal contrast-coded predictors were entered in the regression model: controllability (CSt = 1, USt = −1, NSt = 0) and stress exposure (CSt = −1, USt = −1, NSt = 2). For group by subjective stress response (linear or quadratic) interactions, these contrast codes were multiplied by the subjective stress score (controllability × subjective stress and stress exposure × subjective stress) or square [controllability × (subjective stress)^2 and stress exposure × (subjective stress)^2].

Outlier detection was accomplished in two ways: (1) observations on self-report measures that exceeded 3 standard deviations above or below the group mean were excluded from analyses; (2) for any significant regression effects, standardized df beta was calculated to detect observations that had undue influence on the analysis according to the standard threshold (df beta $> 2/(\sqrt{n})$).

Effects of controllability on perceived control and subjective stress

As a manipulation check, we compared self-reported perceived control between the CSt and USt groups (note: members of the NSt group did not rate this item, as they were not asked to learn to control outcomes). Confirming that the controllability manipulation was effective, the CSt group ($M = 6.71$) reported a higher level of perceived control during the stress manipulation than the USt group ($M = 4.32$), $t(1,81) = 6.57$, $p < 0.001$, $R^2 = 0.35$.

We conducted analyses to examine whether our stress manipulation affected subjective ratings of stress. Including sex as a covariate revealed a significant difference in subjective stress responses between men and women, across groups; women reported higher stress ($M = 19.44$) than men ($M = 13.43$), $F(1,98) = 35.09$, $p < 0.001$, $R^2 = 0.26$. Controlling for sex, there was a significant effect of stress exposure on subjective ratings of stress. Participants who were not exposed to noise or performance pressure stress (i.e., the NSt group) reported lower subjective stress ($M = 14.56$) than participants exposed to stress ($M = 18.05$), $F(1,98) = 4.79$, $p = 0.031$, $R^2 = 0.05$. However, there was a no effect of controllability on subjective stress, $F(1,98) = 1.62$, $p = 0.21$, and no interactions between sex and stress exposure or stress controllability (p's > 0.34). These analyses suggest that female participants experienced our research task as being more stressful than male

[2]We expected that response speed on choice-RT trials would vary between groups, given that the no-stress group did not receive performance feedback and therefore may have been less motivated to respond quickly on choice-RT trials. Analyses revealed an effect of stress exposure, in which the NSt group had slower response times in both testing blocks than the CSt or USt group (p's < 0.001), who did not differ from one another (p's > 0.2). However, response speed on choice-RT trials was unrelated to subjective stress (p's > 0.1) or Stroop interference (p's > 0.5), and including choice-RT speed as a covariate in the Stroop analyses failed to alter any statistical effects. Therefore we report simple analyses only.

participants, but that the nature of the relationships between controllability and subjective stress were similar between the sexes.

Finally, because subjects in the uncontrollable stress group received a higher rate of failure feedback, we might expect their performance ratings to be more negative than the ratings of subjects in the other groups. This is reflected in their slightly higher composite ratings of subjective stress (see **Table 1**), although as noted above, when controlling for sex differences in stress response, the difference in subjective stress between controllability groups was not significant. Furthermore, because our analyses were conducted via multiple-regression, in which the effect of each predictor variable is detected over and above variance shared between predictors, such relationships between stress condition and subjective response variables are controlled. However, we also conducted analyses using a revised subjective stress composite that only included ratings of noise and task stress. The pattern of results was consistent with that reported above: there was a significant difference between men and women's reports of subjective stress ($p < 0.001$), and a significant effect of stress exposure on subjective stress ($p = 0.01$) but no effects of controllability or interactions with sex (p's > 0.37). Moreover, analyses of stress effects on executive functioning using the revised subjective stress composite measure yielded the same pattern of results as those with the full 4-scale composite measure. Because these patterns remained consistent, and due to the higher reliability of a composite stress measure that includes four, as compared with two, rating scales, all subsequent analyses used the full 4-scale composite measure.

Effects of stress controllability and subjective stress on executive functioning

We conducted a regression predicting changes in Stroop interference by the following: group contrast codes (controllability and stress exposure), the linear effect of subjective stress, the quadratic effect of subjective stress, and interactions between group predictors and stress response effects (**Table 3**). All effects are controlling for all other variables in the regression model.

There was a significant difference in Stroop interference changes between the controllable and uncontrollable stress groups, $F(1,98) = 7.76$, $p = 0.006$, $R^2 = 0.07$. This result indicates that when participants are equated on subjective stress, exposure to controllable stress is related to greater improvements in Stroop performance than exposure to uncontrollable stress. In addition, there was a significant quadratic relationship between subjective stress and changes in Stroop interference, $F(1,98) = 5.33$, $p = 0.023$, $R^2 = 0.05$. While low and high levels of subjective stress were related to increased interference, a moderate level of subjective stress was related to reduced interference (improved Stroop performance).

There was a significant interaction between stress controllability and the quadratic effects of subjective stress in predicting change in Stroop interference, $F(1,98) = 5.37$, $p = 0.023$, $R^2 = 0.05$. This result indicates that the quadratic relationship between subjective stress and Stroop performance varies between the controllable and uncontrollable stress conditions. Follow-up analyses were conducted to determine the nature of this difference. Specifically, there was a significant quadratic relationship within the CSt group, $F(1,38) = 7.72$, $p = 0.008$, $R^2 = 0.17$, showing that while low or high levels of subjective stress were related to impaired Stroop performance, moderate levels of subjective stress were related to improved Stroop performance. In contrast, there was no quadratic relationships between subjective stress and interference change within the USt group, $F(1,38) = 0.064$, $p = 0.8$, or within the NSt group, $F(1,23) = 0.088$, $p = 0.7$ (**Figure 2**).

We conducted analyses to confirm that baseline differences in Stroop performance did not drive the effects of group noted above. A regression predicting baseline interference scores by group contrast codes confirmed that there were no significant differences in Stroop performance between subjects randomly assigned to each of the three stress conditions, $F(2,106) = 0.48$, $p = 0.6$.

We conducted analyses to investigate whether experimental groups differed in Stroop accuracy, either at baseline or over the

Table 3 | Regression table for Experiment 1, model predicting change in Stroop interference (post-pre stress manipulation) by group status (controllability: compares CSt versus USt groups; stress exposure: compares NSt group versus the average across CSt and USt groups); subjective stress response (subjective stress: the linear effect of subjective stress; subjective stress^2: the quadratic effect of subjective stress); and interactions between these factors.

Source	SS	df	MS	*F*	*p*	R^2
Model	0.002	8	0.000	1.817	0.083	0.129
(Constant)	0.001	1	0.001	12.222	0.001	0.111
Controllability	0.001	1	0.001	7.762	0.006	0.073
Stress exposure	0.000	1	0.000	0.209	0.648	0.002
Subjective stress	0.000	1	0.000	1.664	0.200	0.017
Subjective stress^2	0.001	1	0.001	5.327	0.023	0.052
Controllability × subjective stress	0.000	1	0.000	0.015	0.903	0.000
Stress exposure × subjective stress	0.000	1	0.000	0.808	0.371	0.008
Controllability × subjective stress^2	0.001	1	0.001	5.373	0.023	0.052
Stress exposure × subjective stress^2	0.000	1	0.000	1.863	0.175	0.019
Error	0.012	98	0.000			
Total	0.014	106	0.000			

[a] *$R^2 = 0.129$ (adjusted $R^2 = 0.058$).*

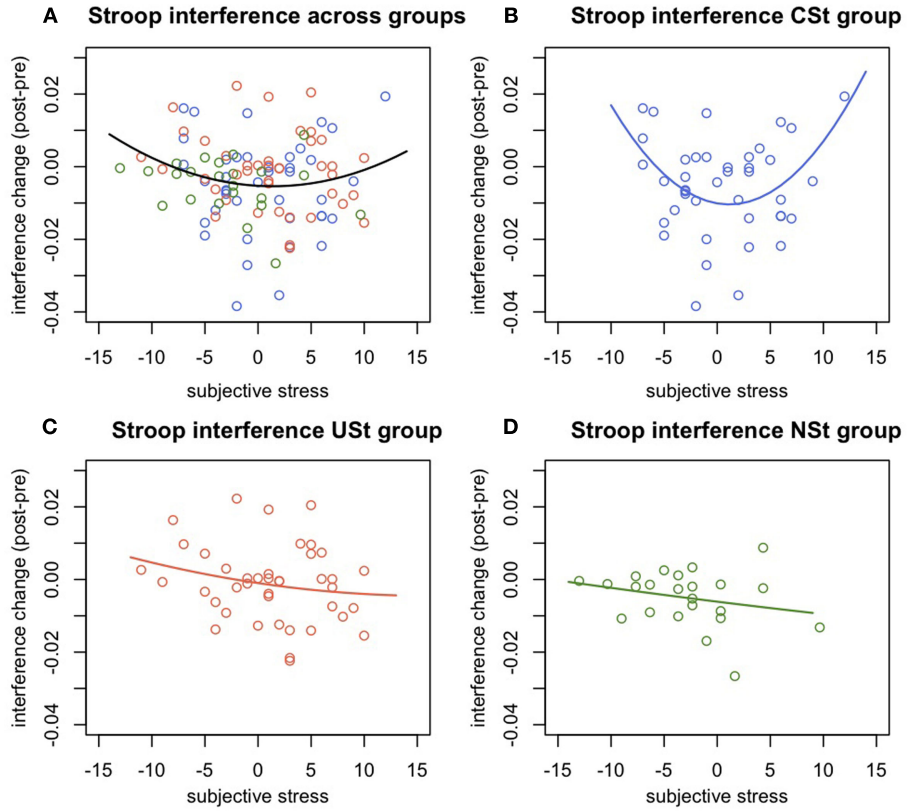

FIGURE 2 | Experiment 1: Change in Stroop interference predicted by subjective stress and controllability. Change in Stroop interference (post-pre stress manipulation) predicted by individual differences in subjective stress and by group. **(A)** Quadratic relationship between subjective stress and change in Stroop interference across all groups. **(B)** Quadratic relationship between subjective stress and change in Stroop interference within the group of participants with behavioral control over stressors. **(C)** Absence of a significant relationship between subjective stress and Stroop interference changes for the group of people exposed to uncontrollable stress, or **(D)** to no-stress.

course of testing. There were no differences in baseline incongruent or neutral trial accuracy between groups (p's > 0.15). Next we examined changes in incongruent trial accuracy from before to after the stress manipulation. There was no effect of stress exposure on changes in incongruent trial accuracy: subjects in the no-stress group showed no changes on this measure ($M = -0.19$), and their performance did not differ from that of subjects exposed to stress ($M = -0.32$), $F(1,106) = 0.24$, $p = 0.8$. However, there was a significant difference detected between controllability groups: subjects who were exposed to controllable stress showed more of an improvement in accuracy on incongruent trials ($M = 0.26$) than subjects exposed to uncontrollable stress, who showed a slight decrease in accuracy ($M = -0.88$), $F(1,106) = 4.71$, $p = 0.03$, $R^2 = 0.04$. There were no changes in neutral trial accuracy over the course of testing, and no differences in such accuracy change between groups (p's > 0.7).

We conducted a full regression in which changes in incongruent trial accuracy were predicted by group contrast codes, the linear and quadratic effects of subjective stress, and interactions between these variables. This analysis revealed a marginal difference in accuracy change between the CSt and USt groups in which having behavioral control predicted a greater improvement in incongruent trial accuracy, $F(1,99) = 2.80$, $p = 0.09$, $R^2 = 0.03$.

Mood and affect

All groups showed similar positive affect ($M = 28.63$), $F(2,106) = 0.004$, $p = 0.9$, and negative affect ($M = 14.68$), $F(2,106) = 1.57$, $p = 0.2$, at baseline. We also conducted analyses to investigate whether changes in affect (post-testing affect – pre-testing affect) over the course of testing were significantly different between groups. On average, participants reported minimal changes in negative ($M = -0.66$) and positive affect ($M = -5.88$), and there were no differences between groups, $F(2,106) = 1.16$, $p = 0.3$ and $F(2,106) = 1.37$, $p = 0.3$. In addition, all groups showed comparable, and low, current levels of depression as assessed by the BDI-II, ($M = 10.15$), $F(2,105) = 1.41$, $p = 0.2$.

DISCUSSION

The results of Experiment 1 suggest that controllability of stress, as well as individual differences in subjective response to stress, together influence the impact of stress exposure on executive functioning in the color-word Stroop. Specifically, these results show that characteristics of stress exposure such as controllability and subjective response can cause stress to have either beneficial or harmful effects on cognitive abilities. Exposure to controllable stress improved executive functioning only when that stress was experienced as moderate. In contrast, stress response had

no relationship with executive functioning when stress exposure was uncontrollable. Furthermore, when equating participants on levels of subjective stress, those who learned to control stressors showed improved Stroop performance compared to those exposed to uncontrollable stress.

Although these results suggest the importance of controllability in moderating the effects of stress on EF, it is not clear from this study which aspects of controllability are essential to this relationship. The question of specifying which aspects of controllability actively drive effects has been controversial. Some studies have suggested that differing rates of failure account completely for learned helplessness effects (Matute, 1994, 1995), while others have demonstrated that non-contingency is the crucial factor, and failure is unnecessary, in evoking learned helplessness (Oakes and Curtis, 1982; Tennen et al., 1982b; Kofta and Sedek, 1989). A third body of research suggests that these factors have additive or interactive effects on behavior (Koller and Kaplan, 1978; Tennen et al., 1982a). In considering the results of Experiment 1, one possibility is that the ability to learn contingencies between actions and outcomes caused moderately reactive participants to respond adaptively to controllable stress, while the inability to learn contingencies eradicated this relationship for people exposed to uncontrollable stress. Another possibility is that differences in performance feedback contributed to the moderating effect of controllability: people exposed to uncontrollable stress received biased feedback indicating a higher rate of failure, which may have caused them to feel discouraged or lose motivation (although all groups reported similar affect before and after testing). With the goal of clarifying which aspects of uncontrollability generated the effects observed in Experiment 1, we conducted Experiment 2, in which rates of failure feedback were held constant across groups exposed to stress.

EXPERIMENT 2

STUDY GOALS

To test the hypothesis that non-contingency between behavioral actions and stressors is critical to the effects we observed in Experiment 1, we equated our controllable and uncontrollable stress groups on performance feedback, so that participants in both groups would receive the same total amount of success and failure feedback over the course of testing. However, it was once again impossible for participants in the uncontrollable condition to learn how to control stressors or accurately anticipate the type of feedback they received for each trial.

METHOD

Participants

Participants were 90 undergraduate volunteers ages 18–24 from introductory psychology courses at the University of Colorado Boulder (**Table 4**). Participants provided informed consent and were treated in accordance with procedures approved by the University of Colorado Boulder Institutional Review Board. Participants were randomly assigned to one of three stress conditions (USt, $n = 28$; CSt, $n = 30$; NSt, $n = 32$)[3].

Procedure

Study procedures were the same as in Experiment 1.

Materials

Individual testing and materials were the same as in Experiment 1, except as noted.

Stress manipulation. The stress manipulation was modified for Experiment 2 to hold the rates of success and failure feedback constant across CSt and USt groups. Every research participant responded to identical choice-RT trials, and a moving-window for response speed ensured that everyone was able to beat the time limits on 70% of trials. Again, the NSt group never received performance feedback (green fixation box after every response). The CSt participants received accurate, response-contingent performance feedback (success feedback for 70% of trials), and received short noises on successful trials (70%) and long noises on failed trials (30%). The USt participants received an identical rate of success feedback (70%) that was, however, not contingent on response speed, and were exposed to short (70%) and long (30%) noises that were unrelated to their response speed or to performance feedback. Noise exposures were once again equated between the CSt and USt groups, so participants in these groups received the same total number of short and long noises.

Participants in the CSt and USt groups completed a practice block (20 trials) without noise exposure or feedback, a feedback block (60 trials) that included performance feedback as described above but no noise exposure, and a stress block (60 trials) that included performance feedback and noise exposure as described

[3]Recruitment included an additional two participants in the USt group, however, these participants failed to complete the experiment due to (1) computer error, and (2) one participant reported color-blindness that caused him to be unable to perform the Stroop task.

Table 4 | Demographics and descriptive statistics for Experiment 2.

Condition	Sample *n* (*n* female)	Self-report			Cognitive tasks		
		Subjective stress	Subjective control *M* (SD)	BDI score *M* (SD)	Pre-stress Stroop interference *M* (SD)	Post-stress Stroop interference *M* (SD)	Change in interference *M* (SD)
CSt	30 (18)	17.13 (4.32)	5.57 (1.33)	9.20 (6.78)	0.0159 (0.0091)	0.0105 (0.0090)	−0.0054 (0.0101)
USt	28 (14)	15.26 (5.38)	2.61 (2.64)	9.46 (5.79)	0.0118 (0.0127)	0.0073 (0.0101)	−0.0045 (0.0155)
NSt	32 (16)	12.99 (4.03)	n/a	11.16 (5.89)	0.0165 (0.0137)	0.0100 (0.0104)	−0.0065 (0.0151)
Total	90 (48)	17.16 (5.00)	4.14 (2.54)	9.97 (6.17)	0.0149 (0.0120)	0.0094 (0.0098)	−0.0055 (0.0135)

above. These trial blocks were shorter in Experiment 2 to minimize the amount of noise exposure per participant, and equate the amount of long noises (reported in pilot testing as considerably more stressful) experienced by each participant across Experiments 1 and 2. Participants in the NSt group completed the same task but did not receive feedback or noise stress during any block[4].

Other measures. All assessments of executive functioning, mood, affect, and subjective stress response, were conducted in Experiment 2 with the same measures as implemented in Experiment 1. Again, we also conducted regressions including BDI-II score and participant sex as covariates. Unless otherwise indicated, the significance of the results was not altered by the addition of these covariates and we report simple analyses only.

RESULTS

Data processing and analyses

Data processing and analyses were the same as for Experiment 1.

Effects of controllability on perceived control and subjective stress

Confirming that the controllability manipulation was effective, the CSt group ($M = 5.57$) reported a higher level of perceived control during the stress task than the USt group ($M = 2.61$), $t(1,56) = 5.44$, $p < 0.001$, $R^2 = 0.35$.

Next we investigated the effects of stress exposure and controllability on subjective stress responses. Again, including sex as a covariate revealed a significant difference in subjective stress responses between men and women, across groups; women reported higher stress ($M = 17.20$) than men ($M = 13.46$), $F(1,79) = 12.04$, $p = 0.001$, $R^2 = 0.13$. Controlling for sex, participants who were not exposed to noise or performance pressure stress reported lower levels of stress ($M = 12.99$) than participants who were exposed to stress (CSt, $M = 17.13$ and USt, $M = 15.26$), $F(1,85) = 4.44$, $p = 0.038$, $R^2 = 0.05$. However, there was no effect of controllability on subjective stress, and no interactions between sex and stress exposure or controllability (p's > 0.14).

Effects of stress controllability and subjective stress on executive functioning

To examine the interactive effects of stress controllability and subjective stress on executive functioning, we conducted regression analysis in which change in Stroop interference was predicted by group contrast-coded predictors, subjective stress (both linear and quadratic effects), and the interactions of these predictors (**Table 5**). All effects are controlling for all other variables in the regression model.

There was a significant interaction between stress controllability and the linear effect of subjective stress, $F(1,17) = 5.00$, $p = 0.028$, $R^2 = 0.061$. This result indicates, again, that the relationships between subjective stress and Stroop performance varied by controllability of stress exposure. However, in this analysis, it was the linear effect of stress that varied between groups. Follow-up analyses were conducted to determine the nature of the linear effects of subjective stress within groups. Within the CSt group, there was a significant linear effect of stress on Stroop interference such that at higher levels of subjective stress, performance became impaired, but at moderate levels of stress, performance was improved $F(1,27) = 6.92$, $p = 0.014$, $R^2 = 0.20$. There were no linear or quadratic relationships between subjective stress and interference change within the USt group, $F(1,23) = 0.89$, $p = 0.4$, or within the NSt group, $F(1,27) = 0.88$, $p = 0.4$ (**Figure 3**).

In the full regression described above, there were no quadratic effects of subjective stress detected when controlling for group

[4]As in Experiment 1, the NSt group had slower response times in both testing blocks than the CSt or USt group (p's < 0.001), as expected. In the second testing block, the CSt group had faster response times than the USt group ($p = 0.03$) but this difference did not emerge in the first testing block ($p = 0.8$). Response speed on choice-RT trials was unrelated to subjective stress (p's > 0.1) or Stroop interference (p's > 0.3), and including choice-RT speed as a covariate in the Stroop analyses failed to alter any statistical effects. Therefore we report simple analyses only.

Table 5 | Regression table for Experiment 2, model predicting change in Stroop interference (post-pre stress manipulation) by group status (controllability: compares CSt versus USt groups; stress exposure: compares NSt group versus the average across CSt and USt groups); subjective stress response (subjective stress: the linear effect of subjective stress; subjective stress^2: the quadratic effect of subjective stress); and interactions between these factors.

Source	SS	df	MS	*F*	*P*	R^2
Model	0.002[a]	8	0.000	1.092	0.378	0.102
(Constant)	0.003	1	0.003	16.933	0.000	0.180
Controllability	0.000	1	0.000	0.229	0.633	0.003
Stress exposure	0.000	1	0.000	0.160	0.691	0.002
Subjective stress	0.000	1	0.000	0.052	0.820	0.001
Subjective stress^2	0.000	1	0.000	0.359	0.551	0.005
Controllability × subjective stress	0.001	1	0.001	4.991	0.028	0.061
Stress exposure × subjective stress	0.000	1	0.000	0.371	0.544	0.005
Controllability × subjective stress^2	0.000	1	0.000	0.035	0.852	0.000
Stress exposure × subjective stress^2	0.000	1	0.000	0.011	0.918	0.000
Error	0.014	77	0.000			
Total	0.016	85	0.000			

[a] *$R^2 = 0.102$ (adjusted $R^2 = 0.009$).*

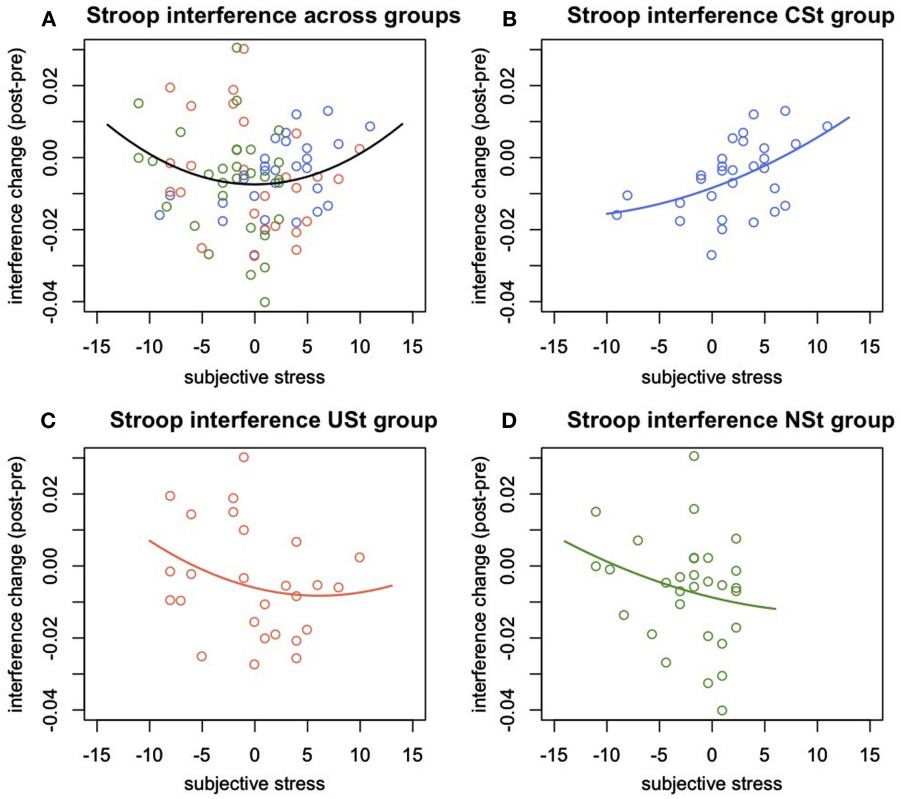

FIGURE 3 | Experiment 2: Change in Stroop interference predicted by stress reactivity and controllability. Change in Stroop interference (post-pre stress manipulation) predicted by individual differences in subjective stress and by group. **(A)** Quadratic relationship between subjective stress and change in Stroop interference across all groups. **(B)** Linear relationship between subjective stress and change in Stroop interference within the group of participants with behavioral control over stressors. **(C)** Absence of a significant relationship between subjective stress and Stroop interference changes for the group of people exposed to uncontrollable stress, or **(D)** to no-stress.

and group interactions. This result could indicate that different groups clustered on different parts of the quadratic curve, so that equating participants on group status simply washed out the quadratic effect. In consideration of this possibility, and to examine the effects of stress response on executive functioning across groups, we conducted a regression predicting change in Stroop interference by the linear and quadratic effects of subjective stress. Examined this way, there was a significant quadratic effect such that moderate levels of stress predicted reduced Stroop interference while low or high levels of subjective stress predicted increased Stroop interference, $F(1,86) = 4.27$, $p = 0.042$, $R^2 = 0.047$.

To determine whether there were group differences in Stroop performance at baseline that could contribute to these effects, we regressed baseline interference scores on group contrast codes. This analysis confirmed that participants randomly assigned to each of the three stress conditions showed comparable Stroop interference at baseline, $F(2,87) = 1.10$, $p = 0.4$.

We conducted analyses to investigate whether experimental groups differed in Stroop accuracy. There were no differences in baseline incongruent or neutral trial accuracy between groups (p's > 0.2). In addition, there was no effect of stress exposure on incongruent trial accuracy: the accuracy of subjects in the no-stress group did not change over testing ($M = 0.03$), and their performance did not differ from subjects exposed to stress ($M = 0.55$), $F(1,86) = 0.53$, $p = 0.5$. However, there was a significant difference between controllability groups: subjects who were exposed to controllable stress showed an improvement in accuracy on incongruent trials ($M = 1.13$) while subject exposed to uncontrollable stress showed no change in accuracy ($M = -0.04$), $F(1,86) = 4.33$, $p = 0.04$, $R^2 = 0.05$. There were no changes in neutral trial accuracy over the course of testing, and no differences in neutral trial accuracy change between groups (p's > 0.6).

We conducted a full regression in which changes in incongruent trial accuracy were predicted by group contrast codes, the linear and quadratic effects of subjective stress, and interactions between these variables. This analysis revealed a significant difference in accuracy change between the CSt and USt groups in which having behavioral control predicted a greater improvement in incongruent trial accuracy, $F(1,80) = 5.55$, $p = 0.02$, $R^2 = 0.07$.

Mood and affect

All groups showed comparable, and low ($M = 9.97$), current levels of depression as assessed by BDI-II scores, $F(2,86) = 0.90$, $p = 0.4$. In addition, all groups showed similar negative affect at baseline, $F(2,86) = 1.29$, $p = 0.3$. Although participants reported similar levels of positive affect at baseline across groups,

$F(2,86) = 2.24$, $p = 0.12$, a marginal difference emerged between the CSt ($M = 27.10$) and the USt ($M = 29.96$) groups indicating that people randomly assigned to uncontrollable stress also had higher positive affect at baseline, $F(1,86) = 2.98$, $p = 0.09$, $R^2 = 0.03$. Including baseline positive affect in subsequent analyses, however, failed to alter any results; therefore we report simple analyses only. Finally, there were no differences between groups in change in negative, $F(2,86) = 1.66$, $p = 0.2$, or positive, $F(2,86) = 0.18$, $p = 0.8$, affect over the course of testing.

DISCUSSION

These results support the view that non-contingency is an active ingredient in the effects of uncontrollability on the relationship between subjective stress and executive functioning. Once again, stress response only predicted Stroop interference in the group exposed to controllable (contingent) stressors.

GENERAL DISCUSSION

Stress is ubiquitous, and previous research suggests it can have both negative (Oei et al., 2006; Schoofs et al., 2008, 2009) and positive (Duncko et al., 2009; Weerda et al., 2010) effects on cognitive function. However, from this previous research it was not clear what determines whether stress enhances or impairs function. The goal of the current studies was to investigate two important factors that may moderate the effect of stress on executive functioning: controllability of stress, and individual differences in subjective response to stress. Our results suggest that controllability and subjective response interact to determine whether stress exposure will impair or enhance Stroop performance: exposure to controllable stress that was experienced as moderately intense predicted improved performance (reduced interference), but subjective stress was unrelated to performance when stress exposure was uncontrollable. In addition, people exposed to controllable stress showed greater improvement in accuracy on incongruent trials than people exposed to uncontrollable stress, a result that further supports the benefits of behavioral control.

These results are consistent with previous research suggesting the importance of controllability (Dickerson and Kemeny, 2004; Arnsten, 2009) and intensity (Lupien et al., 1999, 2007) in moderating the effects of stress exposure on behavioral functioning. Importantly, our findings extend this literature to examine how these dimensions interact. In addition, this research uses experimental manipulations of controllability together with assessment of individual differences in subjective stress response to permit detection of linear and quadratic effects of stress on EF. In Experiment 1, there was a quadratic relationship between subjective stress and Stroop performance across the full sample, and this effect was strongest within the group exposed to controllable stress. In Experiment 2, a similar quadratic relationship was detected across the full sample, but the group exposed to controllable stress showed a linear effect of subjective stress on Stroop performance. Because the dosage of controllable stress (proportion of trials that were failure/long noise) was higher in Experiment 2, this linear effect could reflect the fact that this group was shifted higher on the U-shaped subjective stress curve than similar participants in Experiment 1, and our analyses thus captured the upward slope of this quadratic relationship. The average subjective response to controllable stress in Experiment 1 was 0.50 standard deviations above the response reported by the no-stress group, but in Experiment 2 the response to controllable stress was 0.85 standard deviations above that reported by the no-stress group. Together, these results support the hypothesis that exposure to moderate and controllable stress causes improved functioning, while exposure to (subjectively) more intense or uncontrollable stress impairs functioning.

In addition, these results demonstrate for the first time that controllability and subjective stress influence the effect of stress on a measure of general EF (i.e., common EF; Friedman et al., 2008), providing more precise evidence for the specific cognitive systems affected by these factors. Previous research investigating the effects of stress on cognitive functioning has largely focused on declarative or working memory tasks, but prefrontal cortical systems that are sensitive to stress and undergird aspects of working memory also support other types of EFs. For example, EFs include the ability to hold goals in mind and resist interference from distractors. To investigate the effects of stress on common EF processes in this research, the color-word Stroop was used because it has been shown to load strongly on a common EF factor (Friedman et al., 2008). We would expect that performance on the Stroop would improve with practice (Logan, 1988) and indeed participants who were not exposed to stress showed improved performance over testing. However, the predictive relationship between subjective stress and Stroop performance emerged only for subjects exposed to controllable stress. These results support the hypothesis that controllability and subjective stress moderate the effect of stress on core cognitive abilities that are recruited not only for working memory tasks, but also for other tasks that require EFs.

Comparing Experiments 1 and 2 leads to some tentative conclusions regarding the critical aspects of controllability that affect behavioral functioning. Specifically, these results suggest that non-contingency between behavioral responses and stressors is sufficient to alter the relationship between subjective stress and Stroop performance, as demonstrated by Experiment 2. These results are consistent with the theory that exposure to non-contingency causes disruption to basic learning systems (Oakes, 1982; Oakes and Curtis, 1982).

The results of these experiments raise several questions. First, the current study is limited by the absence of physiological measures of stress reactivity, which would enable us to compare subjective and objective individual differences in stress responses. Previous research has shown that subjective ratings are related to physiological reactions, but are not perfectly correlated (Elzinga and Roelofs, 2005; Alexander et al., 2007; Schoofs et al., 2009). Our stress manipulation may have evoked responses in key stress systems, e.g., the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS), but it is not possible to determine the degree or timing of such responses without physiological measures. Assessing multiple indices of physiological stress response would provide insight on the correspondence between subjective and objective reactivity to controllable or uncontrollable stress exposure. In addition, such biological measures would help improve understanding of how controllable

versus uncontrollable stress may affect the complex balance of activation within and between stress systems, and interactions between stress mediators (e.g., cortisol, catecholamines) as they affect cognition. Previous work has suggested that the effect of stress on cognitive functioning depends on the relative levels of cortisol and adrenergic activity, which are related but not perfectly correlated (Okuda et al., 2004; Elzinga and Roelofs, 2005; Roozendaal et al., 2006). Furthermore, one study suggested that controllable stress leads to greater adrenergic activity, while uncontrollable stress leads to greater cortisol response (Peters et al., 1998). Exploring how controllability affects relative recruitment of stress systems may provide insight on why controllability moderates the relationship between subjective stress and cognitive functioning.

Second, it remains an open question why subjective response to stress was related to Stroop performance in the group exposed to controllable stress, but not in the group exposed to uncontrollable stress. One possibility is that uncontrollable stress leads to different neural responses than controllable stress, and thus does not affect EF performance in the same way. In rodents, the inability to learn to escape a stressor is related to decreased activity in neural systems responsible for down-regulating activity in stress-response regions; thus stress responses are permitted to occur unchecked, ultimately leading to a sensitized arousal system that reacts more readily to mild provocation (Maier and Watkins, 2005). In humans, similar regulatory brain systems are involved in tuning down arousal and affect, and research on emotion regulation strategies has demonstrated that these systems are recruited in the service of purposeful regulation of emotion (Delgado et al., 2008). It may be that in humans, the presence of contingency associations along with moderately intensive stress enables recruitment of prefrontal brain systems that regulate arousal in a top-down manner. This active and successful top-down regulation may extend beyond regulation of arousal to a more general enhancement of top-down control processes, and hence improved EF. However, if an individual experiences those stressors as extreme, top-down regulation may be unsuccessful and therefore yield no benefit. Meanwhile, the absence of contingency for people exposed to uncontrollable stress could remove this source of top-down regulation, so that the biological stress response of these people is more related to individual differences in bottom-up reactivity and thus does not predict the ability to recruit top-down control in a subsequent EF task. However, note that this explanation fails to explain the poorer Stroop performance on average across the uncontrollable stress group in Experiment 1 (which, however, did not replicate in Experiment 2). Research incorporating neurobiological methods in humans is thus needed to test this theory.

Finally, in these experiments we detected no effects of mood or affect. Because this research was conducted with a non-clinical sample, and the majority of participants (71%) reported scores below the cut-point for mild dysphoria (BDI > 12; Kendall et al., 1987; Beck et al., 1996), the absence of statistically significant depression effects may be unsurprising. The absence of stress effects on affect may be due to the delay between exposure and administration of the state-affect measure; any mood effects of stress, or controllability, may have tapered while participants completed the Stroop task. Use of a self-report measure that queries about emotions experienced during the stress manipulation may provide a more sensitive assessment of affect (as in the subjective ratings of stress, which were retrospective). Alternately, it may be that the absence of group differences in affective change accurately reflects the absence of controllability or exposure effects on emotion in these experiments. As has been pointed out by previous researchers (e.g., Lupien et al., 2007), stress and emotion are not isomorphic; clarifying the relationships between stress responses (both subjective and objective), controllability, and emotion, remains an important target of clinical research.

The results of this research are relevant for anyone who wants to capitalize on the potential of stress to enhance goal-directed behavior, while minimizing the negative effects of stress. In particular, this research is relevant as we set physical or academic goals for ourselves that are tuned to our individual appraisals of difficulty and controllability. Future studies investigating controllability and reactivity in settings such as education or clinical treatment may provide insight on how stress exposure can be a powerful source of benefit for students, clients, and others hoping to reap the helpful effects of stress.

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Perceiving control over aversive and fearful events can alter how we experience those events: an investigation of time perception in spider-fearful individuals

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We used a time perception task to study the effects of the subjective experience of control on emotion and cognitive processing. This task is uniquely sensitive to the emotionality of the stimuli: high-arousing negative stimuli are perceived as lasting longer than high-arousing positive events, while the opposite pattern is observed for low-arousing stimuli. We evaluated the temporal distortions of emotionally charged events in non-anxious (Experiments 1 and 5) and spider-fearful individuals (Experiments 2–4). Participants were shown images of varying durations between 400 and 1600 ms and were asked to report if the perceived duration of the image seemed closer to a short (400 ms) or to a long (1600 ms) standard duration. Our results replicate previous findings showing that the emotional content of the image modulated the perceived duration of that image. More importantly, we studied whether giving participants the illusion that they have some control over the emotional content of the images could eliminate this temporal distortion. Results confirmed this hypothesis, even though our participant population was composed of highly reactive emotional individuals (spider-fearful) facing fear-related images (spiders). Further, we also showed that under conditions of little-to-no control, spider-fearful individuals perceive temporal distortions in a distinct manner from non-anxious participants: the duration of events was entirely determined by the valence of the events, rather than by the typical valence × arousal interaction. That is, spider-fearful participants perceived negative events as lasting longer than positive events, regardless of their level of arousal. Finally, we also showed that under conditions of cognitive dissonance, control can eliminate temporal distortions of low arousal events, but not of high-arousing events, providing an important boundary condition to the otherwise positive effects of control on time estimation.

Keywords: feeling of control, time perception, spider-fearful, emotion and cognition, emotion regulation

INTRODUCTION

It is agreed that the feeling of control that we experience over external events in the world and over our behaviors, thoughts, emotions, cognitions and beliefs, fosters mental health, physical health, and is hence crucial for evolutionary survival (e.g., Shapiro et al., 1996). This feeling of wellbeing arises from a complex interaction involving psychological, psycho-sociological, and biological factors, that altogether foster mental health, physical health, and psychosocial functioning (Lefcourt, 1973; Langer and Rodin, 1976; Bandura, 1977; Thompson, 1981; Burger, 1985; Wiedenfeld et al., 1990; Armfield and Mattiske, 1996; Shapiro et al., 1996; Bandura et al., 2003; Leotti et al., 2010; Allman and Meck, 2012). Importantly, this subjective experience of control is not necessarily related to an actual causal control over the world (Langer, 1975). A consistent finding across different species (e.g., humans, non-human primates, rats, dogs, for a review, see Lefcourt, 1973) is that the perception of control can alter the aversive quality of an external stressor (e.g., Glass et al., 1969). Recently, it was suggested that the perception of control plays a critical role in regulating the emotional response triggered by environmental stressors, in such a way that it buffers our emotional reactions to aversive stimuli (Leotti et al., 2010; Mereu and Lleras, in press). In the present report, we tested this hypothesis in a highly reactive emotional group of participants (sub-clinical spider-fearful individuals) within the context of a time perception task. Because it is well known that the emotional content of an event influences how long we experience that event (e.g., Angrilli et al., 1997; Droit-Volet and Meck, 2007; Smith et al., 2011), we evaluated whether having a feeling of control over emotional and fear-related events altered the manner in which those events were experienced.

EXPERIENCING ILLUSORY CONTROL OVER EXTERNAL EVENTS

People like to believe that their choices or actions affect the events around them, even in uncontrollable situations (a phenomenon referred to as the illusion of control by Langer, 1975; see also Presson and Benassi, 1996 for a meta-analytical review). For example, one may push several times the elevator "call" button and as a result may feel that the elevator arrived sooner because of one's actions. This feeling is also evidenced in superstitious behavior (e.g., Skinner, 1948). A feeling of control can be experienced when outcomes (i.e., events in the world) are entirely independent of one's choices, provided that the person concerned is sufficiently

motivated to achieve the outcome and that the desired outcome occurs often (Jenkins and Ward, 1965; Alloy and Abramson, 1979; Thompson, 1999). For instance, in an experiment a person may be given a choice between two keys (key 1 or 2) and one of two outcomes (happy or sad face) may occur after their keypress. Imagine a situation in which participants are asked to press buttons 1 and 2 in such a way as to maximize the occurrence of happy faces. If a happy face appears 75% of the time, *irrespective of the button chosen*, participants will report having had control (though not perfect) over the outcome. If on the other hand, a happy face occurs rarely (e.g., 25% of the time), they will report having little-to-no control over the events. This belief that one's actions impact the world in probabilistic or deterministic fashion is very common (Taylor and Brown, 1994; Presson and Benassi, 1996; Thompson, 1999), and occurs as soon as one is given the opportunity to exert a choice and is put in a position of being an active agent in a situation (Langer, 1975; Langer and Rodin, 1976; Thompson, 1999; Leotti et al., 2010). Taylor and Brown (1988, 1994) considered the illusion of control as being a "positive" illusion (or cognitive bias) that promotes individual's wellbeing by fostering, for instance, good copying strategies, high motivation in various aspect of the life, high productivity, and positive social exchanges.

BENEFITS OF PERCEIVED CONTROL OVER EXTERNAL STRESSORS

A feeling of control over an external stressor has substantial beneficial effects on the period preceding the occurrence of the external stressor (Stotland and Blumenthal, 1964; Geer et al., 1970; Geer and Maisel, 1972; Gatchel and Proctor, 1976). For instance, participants that were provided with a feeling of control showed decreased physiological arousal and reported less discomfort and less anxiety compared to participants that were not given a feeling of control in the period preceding the administration of a painful stimulation (e.g., electric shocks, loud tones, Geer et al., 1970; Gatchel and Proctor, 1976), the presentation of high-arousing negative images (Geer and Maisel, 1972), and the administration of a series of tests (Stotland and Blumenthal, 1964). See Thompson (1981) for a review of different methods used to study the effects of perceived control on aversive stimulation.

Most remarkable, compared to participants that were not given any feeling of control over stressful situations, participants provided with a feeling of control over the stressors showed better performance on later cognitive tasks (puzzle solving and proofreading tasks) that did *not* involve any manipulations of control nor any stressors (Glass et al., 1969). This type of long-lasting benefits of perceived control over stressful events has also been shown in animals. In rats, experiencing heightened levels of control during aversive events can increase emotional resilience to future social-stressors that are themselves uncontrollable. For example, rats that learned to turn the wheel for a specific amount of turns to escape a series of electric shocks and that 7 days later were faced with social-stress (i.e., confronted with an alpha male rat) handled the stress much like rats that were never electrocuted: they showed a normal rate of defeat/submission behaviors. In comparison, rats that were not given the possibility to escape the electric shocks showed an abnormal increase of defeat/submission behaviors when facing the alpha male rat (Amat et al., 2010). Finally, studies on monkeys showed that control helps to reduce the negative lasting impact of previous stressors on physical health (Weiss, 1971). Thus, experiencing a sense of control over a potentially traumatic event (electric shock) can provide a measure of psychological resilience to future stressful events and diminish the sequelae of those events.

It is important to note that while the feeling of control seems to have a strong influence on the period preceding the aversive event, there are conflicting results as to whether it can actually alter the perception of the aversive event itself: both increases and decreases in physiological arousal in response to the aversive event have been found when control was increased (e.g., Corah and Boffa, 1970; Geer et al., 1970; Geer and Maisel, 1972; Gatchel and Proctor, 1976) and no benefit has been observed in the overall estimation of pain and stress (e.g., Pervin, 1963; Stotland and Blumenthal, 1964; Glass et al., 1969). That said, participants that are given a feeling of control over a painful stimulus are willing to endure more painful stimulation and show higher pain tolerance than those deprived of a sense of control (e.g., Glass et al., 1969).

In sum, research that evaluated the impact of perceived control on external stressors indicates that some aspects of the aversive quality of the stimulus can be decreased by providing participants with a feeling of control and the possibility to exert choice. This indicates that the feeling of control may play an important role in the cognitive reappraisal of aversive events. As proposed by Leotti et al. (2010), we believe that having a sense of control over the aversive events can provide a buffering effect on the otherwise strong impact of emotion on our cognitive processes (see also Mereu and Lleras, in press).

GOAL OF THE PRESENT STUDY

Here, we studied the impact of perceived control on one perceptual aspect of the aversive stimulation: its duration. We chose to study time perception because it provides us with an experimental platform to test the effects of the feeling of control on a cognitive process that is uniquely sensitive to the emotionality of the event being judged (e.g., Angrilli et al., 1997; Smith et al., 2011). Specifically, when judging the duration of high-arousing events, people perceive negative events (e.g., images of dismembered bodies) as lasting longer than positive events (e.g., erotic images). When judging the duration of low-arousing events, people perceive negative events (e.g., a dirty mop) as lasting shorter than positive events (e.g., a pretty flower). In sum, time perception shows sensitivity to both arousal and valence in a very distinct pattern, which we can now leverage to study the impact of perceived control on emotional processing. Moreover, the study of time perception is interesting on its own right because these emotion-induced time distortions can be frequently experienced in everyday life. For example, the time spent waiting for a loved one seems longer than the one spent with them. We also frequently experience daily events as lasting overly long, when we are in a hurry and there are obstacles in our way (e.g., traffic lights seem to take overly long to turn to green). The goal of our research is to study whether the subjective feeling of control can alter these temporal distortion effects. The rationale is that, if a feeling of control can buffer our cognition from our emotional reactions to emotional events (see Leotti et al., 2010; Mereu and Lleras, in press), then performance on the time estimation task (a cognitive task) will no longer be influenced by the emotionality of the images themselves.

Here we use a time bisection task (Penney et al., 2008) to evaluate temporal distortions elicited by emotional stimuli. In a time bisection task, participants are initially taught to discriminate between two standard durations (one short and one long). Then they are shown events of varying duration and asked to judge whether the duration of the event is closer to the short or to the long standard. This procedure allows one to estimate a psychophysical curve relating the real duration of events to participants' perceived duration of that event (by plotting the likelihood that a given event is perceived as more similar to the long standard). One can compute separate psychophysical curves for different types of events and thus estimate whether time is perceived differently across those different types of events. The key measure to compare these curves is the bisection point (BP): the point at which participants are equally likely to report an event as being more similar to the short or long standards. Let's take as examples high-arousing positive images and high-arousing negative images. Typically, high-arousing negative images are perceived as lasting longer than high-arousing positive images. In the psychophysical curve, this means that for any given event duration, participants are more likely to respond long for negative compared to positive high-arousing images. Therefore, the psychophysical curve for the negative images is shifted to the left compared to that for the positive images. Consequently, the BP for negative images is smaller than the one for positive images. In other words, a smaller BP indicates an earlier transition from events being perceived as short to events being perceived as long, and therefore indicates an overestimation of time in that condition.

Mereu and Lleras (in press) first tested the impact of perceived control on the duration of high-arousing emotional events by using images from the International Affective Picture System (IAPS images, Lang et al., 2008). Their results showed that under a condition of low perceived control, participants evaluated negative events as lasting longer than positive events (replicating Angrilli et al.'s, 1997 results), whereas participants under conditions of high perceived (illusory) control experienced no temporal distortions. Here, we aim to extend those initial findings in two important directions: (1) we wanted to perform a stronger test of our hypothesis by investigating whether this buffering effect of control on time perception would also be observed in a highly emotionally reactive population: spider-fearful participants confronted with spider images; (2) we wanted to determine some of the boundaries of this effect.

The overall structure of the paper is as follows. Experiment 1 replicates the temporal distortion effects typically observed in non-anxious individuals, deprived of control, when faced with emotional images, including a subset of spider images. We used these results as a benchmark. Experiment 2 tested sub-clinical spider-fearful individuals, also deprived of control, on the same set of images. We observed large temporal distortions driven by emotional content, though the pattern of temporal distortions was different from that of non-anxious individuals. Experiment 3 was our critical experiment in which we tested the influence of high levels of control on time perception in this highly reactive population. No time distortion effects were observed. Experiment 4 provided an experimental control condition in which spider-fearful individuals experience the same images as those in Experiment 3, but were once again, deprived of any feeling of control. Time distortions were again evident, replicating Experiment 2. Finally, Experiment 5 tested whether high levels of perceived control, alone, are sufficient to eliminate time distortion effects. They are not: in a condition of high cognitive dissonance, non-anxious participants showed temporal distortions of high-arousing events.

EXPERIMENT 1: 25% OF POSITIVE IMAGES – NON-ANXIOUS INDIVIDUALS

We used a time bisection task to evaluate time distortion effects in non-anxious individuals *under conditions of low experienced control over the events*. Participants were shown images that varied along their arousal and valence dimensions. According to previous studies (Jenkins and Ward, 1965; Alloy and Abramson, 1979), the subjective experience of control can be diminished by reducing the occurrence of a desired outcome. Thus, in Experiment 1, we presented a high percentage of negative pictures (75%) and instructed participants to try to *minimize* the occurrence of negative images by selecting one of two buttons at the beginning of each trial. Importantly, the occurrence of pleasant and unpleasant images was entirely independent of participants' choices. Thus, the sense of control over the events was not real, just illusory, and given the low percentage of positive images, we anticipated participants experiencing low levels of control over the emotionality of the pictures.

The aim of this first experiment was to provide a replication of previous findings in the time perception literature (Angrilli et al., 1997; Smith et al., 2011) by using a new subset of pictures (spiders) in addition to images taken from the IAPS (Lang et al., 2008) in a group of normal, non-anxious, and non-spider-fearful individuals. The IAPS pictures were categorized into three sets: high-arousing positive, high-arousing negative, and low-arousing positive. The spider images were expected to be judged as being low-arousing and slightly negative or neutral by non-anxious individuals (see Buetti et al., 2012). Thus, we expected that non-anxious participants would overestimate the duration of high-arousing negative images compared to arousal-matched positive images (i.e., BP for negative images will be smaller than for positive images). Conversely, for low-arousing images, positive pictures should be perceived as lasting longer than spider images (i.e., BPs for positive images will be smaller than for negative images).

METHODS

Participants

Participants were students at the University of Illinois. Sixteen non-anxious individuals (14 females, 2 males, mean age of 20.8 years, 1.9 of mean at the Fear of Spiders Questionnaire, FSQ) participated in the study in exchange for one psychology course credit. They were selected on the basis of their scores at the FSQ (Szymanski and O'Donohue, 1995). All participants were naïve regarding the selection criteria and questionnaires scores, and had normal or corrected-to-normal vision. The study was approved by the university IRB board.

Stimuli and design

We used two types of stimuli to train participants to discriminate between two standard durations, that is, a short (400 ms) and

a long (1600 ms) duration. First, short and long durations alternated across trials ($N = 8$) and participants reported the perceived duration of a pink oval displayed on the center of the screen. Second, short and long durations were randomized and participants reported the perceived duration of eight IAPS neutral pictures (on both arousal and valence dimensions). In this second training task, participants were given feedback about their performance and they were required to reach 100% of correct answers before continuing to the next task.

In the *time bisection task*, we used seven stimulus durations (400, 600, 800, 1000, 1200, 1400, and 1600 ms) and participants were asked to report if the perceived duration was more similar to the short or to the long standard duration. The stimuli consisted in four sets of pictures ($25.5^\circ \times 21^\circ$). Three sets were chosen from the IAPS: low-arousing positive pictures (arousal score: 3.8, valence score: 7.1), high-arousing positive pictures (6.5, 6.5) and high-arousing negative pictures (6.2, 2.0). The fourth set consisted of spider pictures[1] that were taken from the internet and that were evaluated by the participants at the end of the experiment using the same method used to rate the IAPS pictures (Self-Assessment Manikin, Lang, 1980). This method allowed us to obtain three mean scores describing the level of arousal, valence, and domination experienced by participants when confronted with our set of spider pictures. Responses were given on a 1–9 scale and scores were recoded so that low and high scores on the *arousal dimension* indicate low and high levels of arousal, respectively; on the *valence dimension*, low and high scores refer to negative and positive valence, respectively; and on the *dominance dimension*, low and high scores indicate that participants felt controlled or in control when confronted to the spider pictures.

For the time bisection task, we chose 8 IAPS low-arousing positive pictures, 8 IAPS high-arousing positive pictures, 24 IAPS high-arousing negative pictures, and 24 spider pictures. See Appendix for a list of the IAPS images used. In order to better estimate the BP in the psychophysical curve, all pictures were shown for each of the three central time durations (800, 1000, and 1200 ms). To diminish the number of trials in the session, we reduced the number of pictures for the two shortest (400 and 600 ms) and the two longest (1400 and 1600 ms) time durations. Indeed, long and short categorization was much easier for those time durations compared to the three central time durations. **Table 3** provides the actual number of trials per condition, for Experiments 1–5.

Overall, across the whole experiment, participants completed a total of 352 trials, presented in a random order. All stimuli were displayed on a white background at the center of the screen.

Procedure

The experimental session contained the following tasks. First, participants completed three questionnaires in the following order: Short Depression-Happiness Scale (SDHS, Joseph et al., 2004), short form of the State Anxiety Inventory (s-STAI, Marteau and Bekker, 1992), FSQ (Szymanski and O'Donohue, 1995). Second, they were trained to discriminate between short and long standard durations, first with the pink oval stimulus and then with IAPS neutral pictures. The training trials started with a black fixation cross displayed on the centre of the screen for a random duration, varying between 400 and 900 ms. Then, the training-stimulus was presented for 400 or 1600 ms. Three-hundred milliseconds later, the message "Was the duration of the oval/image short or long?" was shown and the participants responded "short" and "long" by pressing one of two buttons (key 4 or 6), that were counterbalanced across participants. Visual feedback ("Correct" or "Wrong answer") was provided in the training trials with the neutral IAPS images.

Third, participants performed the *time bisection task* that included a manipulation aimed to induce a sense of control at the beginning of each trial (see **Figure 1**). Participants were asked to choose between one of two keys (1 and 3) to try to *decrease the occurrence of negative images*: they were instructed to try to find out different combinations of keypresses that would yield a high rate of positive images. Across all experiments, some participants failed to comply with these instructions (e.g., they pushed just one key along the whole experiment), and those were not considered for further analysis. Importantly, there was no contingency between the selection of one of the two keys and the outcome. Because in this experiment negative pictures occurred on 75% of the trials, we expected participants to experience a low level of control over the image content (i.e., the valence). Each trial started with the message "Make your choice: 1 or 3" and once one of the two keys was pressed, the fixation cross was presented for a random interval between 400 and 900 ms. Afterward, an image was displayed for one of the seven time durations (400, 600, 800, 1000, 1200, 1400, and 1600 ms) and 300 ms after the image disappeared, the message "Was the duration of the image short or long?" was presented. Participants were asked to judge whether the duration of the presented image was more similar to the duration of the short or long standard interval by pressing one of two keys (4 or 6). A 500 ms blank screen preceded the next trial. Participants completed 8 blocks of 44 trials, for a total of 352 trials, with a pause after each block.

At the end of the time bisection task, participants were asked to respond to the following questions (in order) by means of a continuous scale going from 0 to 100%: (1) how often did positive images appear?; (2) Did you feel at any point of the experiment that you had control over the images?; and (3) How liberal are you? Then, they completed the s-STAI a second time. Afterward, they completed the Desirability of Control DC Scale (Burger and Cooper, 1979) and finally, they rated the valence, arousal, and domination for each of the spider pictures by using the nine-point scale of the Self-Assessment Manikin (Lang, 1980). The entire session lasted about 50 min.

RESULTS

Questionnaires and evaluation of the spider pictures

Scores from the different questionnaires are reported in **Table 1**. Overall, non-anxious participants were not afraid of spiders (FSQ = 1.9), had relatively low state anxiety levels that did not significantly vary between the first and second assessment [STAIs mean before and after the bisection task: 11.5 and 11.9; $t(15) = -0.32$, $p = 0.75$], and were not at risk for depression (SDQ = 13). At the end of the time bisection task, non-anxious

[1]The full set of spider images can be requested by contacting the corresponding author.

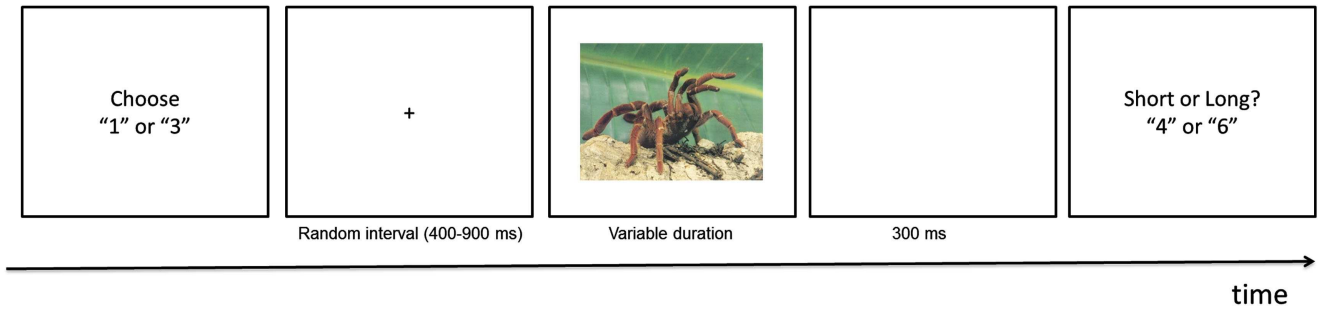

FIGURE 1 | Schematic of the trial events in the experiments. Trials started with the choice display where participants had to choose either the "1" or "3" key in order to try to influence the valence of the subsequent image. The display remained on the screen until a choice was recorded. A fixation display was then presented for a random interval anywhere between 400 and 900 ms. This variable interval was followed by the presentation of the emotional picture which was presented for one of seven possible durations (400, 600, 800, 1000, 1200, 1400, and 1600 ms). The image then was replaced by a blank screen for 300 ms. Then participants were prompted to categorize the image duration as short of long on the final display.

participants reported that positive images occurred in 29% of the trials. They considered themselves as being relatively liberal (67%). More importantly, they reported experiencing very low levels of control over the image content (13%).

In the *evaluation of the spider pictures*, the means observed for the three dimensions of the Self-Assessment Manikin scale, arousal, valence, and dominance, were 3.8, 5.2, and 5.4, respectively (see **Table 2**). Thus, non-anxious participants considered spider pictures as being low-arousing and neutral in valence. Because spider pictures were not considered as being positive in valence by non-anxious participants, for these participants, 25% of images were highly positive. Notice that participants were quite accurate at reporting this frequency when they estimated the percentage of positive images at the end of the experiment (29%)[2].

Time bisection task

Temporal judgments for each set of images were examined by calculating the BPs from the individual psychometric functions obtained after running a logistic regression. The BP represents the duration at which the psychophysical curve crosses the "50% Long" likelihood. To test for temporal distortion effects we ran two separate ANOVAs on BPs with Valence as within-subjects factors and compared arousal-matched conditions (IAPS high-arousing positive images vs. IAPS high-arousing negative images; and IAPS low-arousing positive images vs. low-arousing neutral spider images).

The results indicated that for high-arousing stimuli, negative pictures (BP = 905 ms) were perceived as lasting longer than positive pictures (BP = 961 ms), $F(1,15) = 9.47$, $p < 0.01$, while for low-arousing stimuli, positive stimuli (BP = 897 ms) were perceived as lasting longer than neutral stimuli (BP = 957 ms), $F(1,15) = 5.46$, $p < 0.05$ (see **Figure 2A**).

DISCUSSION

In Experiment 1 we tested non-anxious, non-spider-fearful participants to measure time distortion effects for different sets of emotional pictures under conditions of low level of experienced control, including a set of spider images. Including a set of spider images was important to establish a baseline to compare their performance to that of spider-fearful individuals (Experiment 2). As expected, with a high proportion of negative pictures (75%) and the instruction of reducing the proportion of negative images, participants experienced very low feelings of control over the events in the experiment (13%). Importantly, under this condition of low level control, we successfully replicated previous findings from the literature with non-anxious individuals for whom the perceived duration of emotional events is determined by both arousal and valence (Angrilli et al., 1997; Smith et al., 2011): high-arousing negative stimuli were perceived as lasting longer than arousal-matched positive images and low-arousing positive stimuli were perceived as lasting longer than arousal-matched but less positive stimuli (neutral spider pictures).

EXPERIMENT 2: 25% OF POSITIVE IMAGES – SPIDER-FEARFUL INDIVIDUALS

In Experiment 2, we sought to establish a baseline response from spider-fearful individuals when judging the duration of emotional images that included a subset of spider images (fear-related stimuli), under conditions of low perceived control. This baseline will serve as a comparison to Experiment 3, in which we increased the level of perceived control over the images experienced by spider-fearful participants. The events were identical to those in Experiment 1. We anticipated temporal distortions to be evident because of the low levels of perceived control. Specifically, we expected high-arousing positive images to be perceived as lasting shorter than both high-arousing negative and spider's images (i.e., BP for positive images would be larger than the ones for negative and fear-related images).

There is conflicting evidence in the literature regarding how time is experienced when faced with high-arousing threat stimuli compared to high-arousing aversive images. A recent study found that high-arousing negative images representing disgust (e.g., mutilated bodies) were overestimated compared to arousal-matched images representing fear (e.g., attacking animal; Gil and Droit-Volet, 2012). That said, Tipples (2011) showed that

[2]Overall, in Experiment 1, participants were shown 37.5% of high-arousing negative images, 37.5% of low-arousing neutral images, 12.5% of high-arousing positive images, and 12.5% of low-arousing positive images.

Table 1 | Mean scores (standard errors in parentheses) from the experimental questions and questionnaires completed in Experiments 1–5.

	Experiment 1 ($N = 16$)	Experiment 2 ($N = 16$)	Experiment 3 ($N = 16$)	Experiment 4 ($N = 16$)	Experiment 5 ($N = 16$)
FSQ	1.9 (0.2)	5.6 (0.2)	5.6 (0.2)	5.1 (0.2)	2.1 (0.2)
SDQ	12.8 (0.7)	13.3 (0.7)	14.4 (0.7)	13.4 (0.9)	13.6 (0.8)
STAIs-pre	11.5 (0.9)	12.7 (0.9)	10.4 (0.9)	11.8 (1.2)	11.3 (1.1)
STAIs-post	11.9 (0.7)	15.8 (1.1)	13.3 (0.9)	16.5 (1.1)	12.9 (1.0)
DC	93.1 (2.9)	94.9 (3.5)	98.2 (3.5)	99.8 (3.4)	96.1 (0.4)
% Positive images	28.9 (2.2)	28.2 (2.7)	62.8 (4.4)	63.4 (2.8)	26.1 (2.9)
% Participant in control	12.6 (3.7)	16.1 (4.1)	53.9 (4.4)	11.2 (2.8)	54.6 (5.6)
% Computer in control	–	–	–	85.5 (3.5)	–
% Liberal	67.2 (6.2)	67.2 (6.7)	66.2 (5.0)	63.5 (5.2)	65.9 (5.1)

FSQ, Fear of Spider Questionnaire; SDQ, Short Depression-Happiness Scale; STAIs-pre: short form of the State Anxiety Inventory filled out before the Time Bisection Task; STAIs-post: short form of the State Anxiety Inventory filled out after the Time Bisection Task; DC, Desirability of Control Scale; % Positive images: participants were asked to report how often did positive images appear in the experiment?; % Participant in control: participants were asked to report if they felt that at any point in the experiment they felt that they had control over the emotional content of the images; % Computer in Control: participants were asked to report how much the computer choice influenced the image content (only assessed in Experiment 4); % Liberal: participants were asked to report the extent to which they estimated themselves as being liberal.

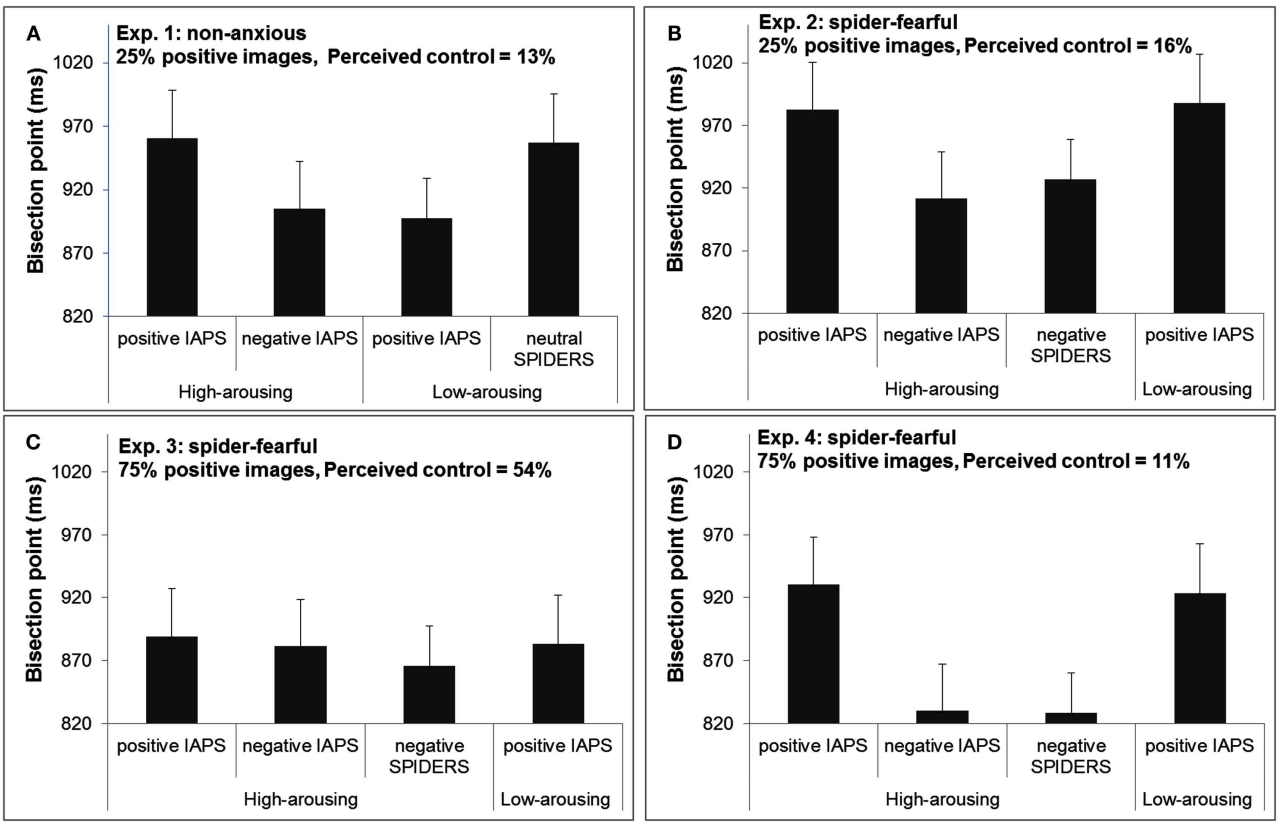

FIGURE 2 | Bisection points in Experiments 1–4 [(A–D), respectively], as a function of emotional content of image events. Note that when comparing two bisection points, the smaller bisection point corresponds to images in that category having been perceived as lasting longer than the images with a larger bisection point. Error bar indicates the standard error of the means.

fearful and threatening faces were perceived as lasting the same amount of time. However, Tipples found that high levels of fearfulness (as assessed by the Emotionality Activity Sociability Temperament Survey, Buss and Plomin, 1984) were associated with higher overestimations of threat-related facial expressions. This overestimation was driven by participants' fearfulness and was independent from other personality variables (e.g., level of distress, trait anxiety). Therefore, it appears that fear can

have an independent effect on time perception, separate from anxiety.

A critical difference between our study and these past studies was the population tested. Whereas these past studies focused on normal individuals, we are now interested in investigating these effects in a highly reactive population of sub-clinical spider-fearful population. Recent studies have shown that for these individuals, there is an automatic, overlearned aversive response toward spider pictures. For instance, Buetti et al. (2012) investigated rapid reaching movements in spider-fearful individuals who were asked to reach either toward or away from a spider image. In both conditions, participants showed very early avoidance of the spider images in the execution of the reaching response. The initial segment of the reaching trajectory in which the effects were observed is thought to reflect the motor plan assembled prior to movement execution. Therefore, this finding was interpreted as reflecting overlearned, automatic motor responses to fear-related images. Because of the existence of overlearned automatic reactions related to fear-relevant objects compared to other high-arousing negative images (e.g., mutilated bodies), one might expect that spider-fearful participants perceive spider pictures as lasting even longer than arousal-matched negative stimuli, in line with the results of Gil and Droit-Volet (2012). On the other hand, if Tipples (2011) is correct, one might expect that the level of fear of spiders in an individual will be positively correlated with their temporal overestimation of spider images (i.e., negatively correlated with the BP for spider images).

METHODS

Participants

Sixteen participants from the same pool as in Experiment 1 participated in Experiment 2. However, this time we tested 16 sub-clinical spider-fearful participants (14 females, 2 males, mean age of 19.9 years, 5.6 of mean at the FSQ).

Stimuli, design, and procedure

Stimuli, design, and procedure were the same as in Experiment 1.

RESULTS

Questionnaires and evaluation of the spider pictures

Spider-fearful individuals were very scared of spiders (FSQ = 5.6) and were not at risk for depression (SDQ = 13.3). The level of state anxiety increased from the first to the second assessment, indicating that the images presented in the bisection task affected participant's anxiety (12.7 vs. 15.8), $t(15) = -2.13$, $p < 0.05$. Participants reported that positive images occurred on 28% of the trials. They considered themselves as being relatively liberal (67%). Importantly, they reported experiencing very low levels of control over the image content (16%).

As expected, spider pictures were evaluated by spider-fearful participants as being highly arousing (mean: 6.5), extremely negative (2.7), and as exerting high domination (3.3). It is important to note that the set of spider images matched the levels of arousal and valence of the IAPS high-arousing negative picture set[3].

[3]Overall, spider-fearful participant were shown 25% of highly positive images (12.5% being low-arousing and 12.5% high-arousing) and 75% of high-arousing negative images.

The Pearson's correlations between the mean arousal, valence, and domination observed at the evaluation of the spider pictures and the mean at the FSQ, indicated that the more spider-fearful participants were afraid of spiders the more they felt aroused ($r = 0.54$, $p = 0.015$) and dominated by the aversive pictures ($r = -0.48$, $p = 0.029$), and the more they evaluated the pictures as being negative (-0.47, $p = 0.032$), which constitutes a good validity check for the FSQ score.

Time bisection task

To evaluate whether there was a difference between the three sets of high-arousing images, we ran an ANOVA on the BPs with Image type (IAPS-positive, IAPS-negative, spider) as within-subject factor, remembering that these three groups of images were matched in overall arousal. The results showed a significant main effect, $F(2,30) = 4.77$, $p < 0.05$. The *t*-tests indicated that Spider and IAPS-negative pictures were perceived as lasting the same time (BP of 927 and 912 ms, respectively), $t(15) = -0.64$, $p = 0.53$, but importantly, both Spider and IAPS-negative pictures were perceived as lasting longer than IAPS-positive pictures (BP of 983 ms), $t(15) = 2.22$, $p < 0.05$ and $t(15) = 3.04$, $p < 0.01$, respectively.

Finally, a visual inspection of **Figure 2B** reveals that the BPs of positive images from the IAPS were almost identical for high- and low-arousing positive images. A *post hoc* comparison confirmed no significant difference between those two conditions (BP of 983 vs. 988 ms, respectively), $t(15) = -0.20$, $p = 0.85$.This *post hoc* finding was unexpected and it indicates that for spider-fearful individuals, perceived duration was only a function of valence (positive vs. negative), with no contribution from arousal. This pattern was also replicated in Experiment 4. The BPs for the four sets of images are shown in **Figure 2B**.

Finally, we obtained a significant and negative correlation between scores on the FSQ and BPs for the spider picture set ($r = -0.56$, $p = 0.012$), indicating that the more fearful of spiders a participant was, the longer she/he overestimated the duration of spider pictures.

Between experiment comparison (Experiment 1 vs. 2)

Participants in Experiments 1 and 2 were exposed to the same sets of stimuli and both saw 25% of highly positive stimuli. However, spider-fearful individuals were faced with a higher percentage of high-arousing negative images than non-anxious individuals (75 vs. 37.5%), half of them representing their object of fear. Thus, overall, the spider-fearful group was exposed to a more stressful experimental context than the non-anxious group.

To ensure that the spider-fearful group only differed with respect to their fear of spiders from the non-anxious group, we compared their responses on the different questionnaires (means and standard errors are shown in **Table 1**). The *t*-tests clearly indicated that spider-fearful and non-anxious participants only differed on the FSQ (the first group being scared of spiders and the second not), $t(30) = -14.19$, $p < 0.001$ and on their level of state anxiety after performing the time bisection task (spider-fearful participants showed a higher state anxiety than control participants after completing the task), $t(30) = -3.1$, <0.01. The two groups of participants did not differ on the Short Depression Questionnaire, $t(30) = -0.48$, $p = 0.63$, on the first assessment of

the State Anxiety Inventory, $t(30) = -0.92$, $p = 0.36$, nor on the DC Scale, $t(30) = -0.41$, $p = 0.69$. Furthermore, at the end of the time bisection task, the two groups reported having been exposed to a similar percentage of positive images, $t(30) = 0.21$, $p = 0.83$, and having experienced similar levels of perceived control over the images, $t(30) = -0.63$, $p = 0.53$. Finally, we also compared their performance on the time bisection task on the two sets of images that were identical across groups: high-arousing positive and high-arousing negative IAPS pictures. When considering these two sets of images, non-anxious and spider-fearful participants showed comparable time distortion effects: an ANOVA on the BPs for IAPS high-arousing positive and negative images with Group as between-subjects factor indicated that neither the main effect of Group was significant (BP of 933 and 948 ms, respectively), $F(1,30) = 0.11$, $p = 0.75$, nor was there an interaction between valence and Group, $F(1,30) = 0.28$, $p = 0.60$.

In spite of the many resemblances between the two groups, in terms of their initial anxiety, as well as in terms of how they reacted to the high-arousing IAPS pictures, we observed a fundamental change in how these two groups judged time: whereas non-anxious participants' time estimates were sensitive to both arousal and valence, for spider-fearful individuals, time estimates were only a function of the valence of the image (positive images were perceived as shorter than negative images). To anticipate the results of Experiment 4, this difference was not due to the emotional context in the task, as determined by differences in the number of negative images the two groups experienced: in Experiment 4, we found this pattern again, using a very different emotional context.

Thus, we can conclude that the difference in the pattern of results was uniquely due to differences in spider-fearfulness between the two groups.

DISCUSSION

In Experiment 2 we tested time distortion effects in a highly emotional reactive group of participants under conditions of low levels of perceived of control. Self-report measures of perceived control confirmed that spider-fearful participants experienced a low level of control (16%) in the current experiment. The results from the time bisection task indicated that spider-fearful participants perceived IAPS high-arousing negative images as lasting longer than IAPS high-arousing positive images, just as non-anxious participants did. Supporting previous findings by Tipples (2011), the temporal overestimation observed for IAPS high-arousing negative images was similar to the one observed for high-arousing threat-related images. In addition, the results showed that the more participants were scared of spiders, the longer was the overestimation of the duration of spider images. This result is consistent with Tipples' results that highly fearful participants overestimate the duration of fearful faces more so than less fearful individuals.

EXPERIMENT 3: 75% OF POSITIVE IMAGES – INCREASED LEVEL OF CONTROL

Experiments 1 and 2 provided the general framework to test the hypothesis of most interest to us. We have now established that (a) our spider images give rise to strong temporal distortion effects (both in non-anxious and spider-fearful individuals) and further (b) that the degree of fearfulness toward spiders actually predicts the magnitude of the temporal distortion experienced by spider-fearful individuals. Therefore, our paradigm is robust and sensitive to both the stimulus set that we have chosen and to the personality traits of our participants. The question of interest is then: can a manipulation aimed at increasing the feeling of control in this highly reactive population eliminate the temporal distortion effects observed in Experiment 2? If so, this result would provide strong evidence in support of the hypothesis that perceived control can play an emotion buffering effect and minimize the impact of the emotionality of events on our cognitive processes, as implicitly indexed by the time perception task (Leotti et al., 2010; Mereu and Lleras, in press).

To increase the perceived level of control in our participants, we presented a high proportion of positive images (75%) and a low proportion of negative images (25%) and asked participants to maximize the occurrence of positive images. That is, compared to Experiments 1 and 2, the desired outcome was over-represented in the world's events, which should lead to a robust feeling of illusory control (Jenkins and Ward, 1965; Alloy and Abramson, 1979). It is important to note that even though we changed the proportion of positive and negative images, we chose the pictures in a way that allowed us to keep the mean arousal and valence comparable across all experiments (see **Table 2**).

If an increased level of perceived control can buffer the participants' reactions toward aversive stimuli (Leotti et al., 2010), then one would no longer expect any differences in temporal estimations (i.e., similar BP) across the four image sets.

METHODS

Participants

Sixteen (new) spider-fearful participants from the same pool as in Experiment 2 participated in Experiment 3 (16 females, mean age of 19.1 years, 5.6 of mean at the FSQ).

Stimuli, design, and procedure

The experimental session was the same as in Experiments 1 and 2. The images from the IAPS and spider images used in Experiment 3 matched the mean arousal and valence of the images presented in Experiments 1 and 2 (see **Table 2**). See **Table 3** for the number of trials per condition. The procedure was the same as in Experiments 1 and 2 with the exception that participants were instructed to maximize the occurrence of positive images. At the end of the session, participants evaluated the spider images using the Self-Assessment Manikin scale (Lang, 1980), starting with the 8 images used in this experiment, and later rating an additional 16 spider images.

RESULTS

Questionnaires and evaluation of the spider pictures

Scores from the different questionnaires are reported in **Table 1**. Overall, spider-fearful individuals showed high scores at the FSQ (5.6) and were not at risk for depression (SDQ = 14.4). The level of state anxiety increased from the first to the second assessment (10.4 vs. 13.3), $t(15) = 2.84$, $p = 0.012$. At the end of the time bisection task, spider-fearful participants reported that positive images occurred in 63% of the trials. Participants also considered themselves as being relatively liberal (66%). They evaluated the eight

Table 2 | Mean arousal and valence (standard deviation shown in parenthesis) of the four image sets used in Experiments 1–5.

Image set	Dimension	Experiment 1	Experiment 2	Experiment 3	Experiment 4	Experiment 5
IAPS high-arousing positive	Arousal	6.5 (2.1)	6.5 (2.1)	6.5 (2.1)	6.5 (2.1)	6.5 (2.1)
	Valence	6.5 (1.9)	6.5 (1.9)	6.8 (1.8)	6.8 (1.8)	6.5 (1.9)
IAPS high-arousing negative	Arousal	6.2 (2.3)	6.2 (2.3)	6.3 (2.4)	6.3 (2.4)	6.2 (2.3)
	Valence	2.0 (1.3)	2.0 (1.3)	1.9 (1.3)	1.9 (1.3)	2.0 (1.3)
IAPS low-arousing positive	Arousal	3.8 (2.2)	3.8 (2.2)	3.8 (2.2)	3.8 (2.2)	3.8 (2.2)
	Valence	7.1 (1.4)	7.1 (1.4)	7.0 (1.5)	7.0 (1.5)	7.1 (1.4)
Spider pictures	Arousal	3.8 (1.2)	6.5 (2.1)	6.7 (0.4)	7.4 (0.3)	3.9 (0.3)
	Valence	5.2 (1.4)	2.7 (1.4)	1.8 (0.2)	2.2 (0.4)	4.8 (0.3)

Table 3 | Number of trials per condition.

Experiment	Time duration (ms)	IAPS high-arousing positive	IAPS high-arousing negative	IAPS low-arousing positive	Spider pictures
Experiments 1, 2, 5	400	5	15	5	15
	600	5	15	5	15
	800	8	24	8	24
	1000	8	24	8	24
	1200	8	24	8	24
	1400	5	15	5	15
	1600	5	15	5	15
Experiments 3, 4	400	15	5	15	5
	600	15	5	15	5
	800	24	8	24	8
	1000	24	8	24	8
	1200	24	8	24	8
	1400	15	5	15	5
	1600	15	5	15	5

Note that in Experiments 1, 2, and 5, for the two shortest (400, 600 ms) and longest (1400, 1600 ms) time durations, we randomly selected 15 pictures among the 24 IAPS high-arousing negative pictures as well as 15 pictures among the 24 spider pictures; and for the IAPS high- and low-arousing positive pictures we randomly selected 5 among the 8 pictures from our set. Similarly, for Experiments 3 and 4, for the two shortest and longest time durations, we randomly selected 5 pictures among the 8 IAPS high-arousing negative and spider pictures, and 15 pictures among the 24 IAPS high- and low-arousing positive pictures. Appendix 1 shows the list of the IAPS images used in Experiments 1–5.

experimental spider pictures as being highly arousing (mean: 6.0), extremely negative (2.2), and as exerting high domination (4.0); and the whole set as being highly arousing (6.7), extremely negative (1.8), and as exerting high domination (3.8). Critically, participants reported sensing a high level of control over the images (54%), as we had expected, which was significantly higher than in Experiments 1 and 2 (ps < 0.001).

Unlike Experiment 2, *Pearson's correlations* no longer showed a significant correlation between participants' score on the FSQ and any of the ratings of the spider images (arousal, valence, and domination, all ps > 0.1). Note that participants rated the images *after* having experienced the images during the experiment and while feeling a high sense of control over the images.

Time bisection task

We ran an ANOVA on the BPs measured for high-arousing images with Image type (IAPS-positive, IAPS-negative, spider) as within-subject factor. Unlike Experiment 2, there was no effect of Image type on the magnitude of the BPs, $F(2,30) = 0.22$, $p = 0.80$, see **Figure 2C**. The BPs for IAPS-positive, IAPS-negative, and spider images were 889, 881, and 866 ms, respectively. The BP for IAPS low-arousing images was 883 ms. As can be seen from the Figure, there was also no difference in BPs between high-arousing positive images and low-arousing positive images (BP of 889 vs. 883 ms), $t(15) = 0.27$, $p = 0.79$.

It is critical to our interpretation of this experiment to measure not only whether the null hypothesis was rejected (it was not), as in traditional Null Hypothesis Significance Testing, but more so, to evaluate the degree of adherence to the null hypothesis. To evaluate this, we used Bayesian statistics (see Masson, 2011), and more specifically, we computed p_{BIC}: the probability that quantifies the evidence in support of the null hypothesis to any alternative hypothesis, given the data. p_{BIC} for Experiment 3 was 0.996, which according to Raftery (1995) provides very strong support in favor of the null hypothesis. In sum, we can confidently conclude that the emotional content of images in Experiment 3 really had no effect whatsoever on time perception.

Finally, in contrast to Experiment 2, *Pearson's correlations* indicated no significant correlation between the score on the FSQ and the BP observed for the spider pictures set ($p = 0.21$).

DISCUSSION

The results of Experiment 3 show a substantial contrast with respect to those obtained in Experiment 2. Not only were there no temporal distortion effects across image types obtained, but also, the scores on the Fear of Spider Questionnaire no longer predicted how participants experienced the duration of the spider images during the experiment, nor how they rated the images with the Self-Assessment Manikin scale (Lang, 1980) at the end of the session. Together, these results provide support to our hypothesis that the feeling of control (even if illusory) buffers our cognition (as indexed by performance in the time perception task) from the emotionality of events. Indeed, the effect of control was restricted to a cognitive measure (time judgments): control did not preempt a rise in anxiety during the experiment. This result helps us constraint the boundaries of the buffering effects of perceived control on behavior. That said, these conclusions can only be seen as preliminary given that participants actually experienced more positive images in Experiment 3 than in Experiment 2. Thus, the differences in performance across the two experiments can be ascribed to either the increase in perceived control or the increase in the rate of positive images. Experiment 4 was designed to address this important confound.

EXPERIMENT 4: 75% OF POSITIVE IMAGES – LOW LEVEL OF CONTROL

The aim of this experiment was to rule out the possibility that the absence of an effect of image type on time perception was due to the overall emotional context of the images in Experiment 3. That is, in Experiments 1 and 2, where strong effects of image type on time perception were obtained, the overall rate of positive images was small (25%), whereas in Experiment 3, where no such effects were found, the overall rate of positive images was much higher (75%). Thus, it is possible that when participants find themselves in an overall "positive" context, that image type no longer affects time perception. To rule out this possibility, we re-ran Experiment 3 with a small variation aimed at taking away the sense of control that participants experienced over the images, while maintaining the same high rate of positive images. To do so, participants in this experiment were no longer instructed to try to maximize the occurrence of positive images. Rather, they were told that the computer had an algorithm that was trying to pick as many positive images as possible and that they were to evaluate the computer's success in this endeavor. They were told that the computer would convey its choice by picking one of two keys and they should simply press the key chosen by the computer. This manipulation was proven to diminish feelings of control in non-anxious individuals on a different study (Mereu and Lleras, in press). As a result, we expected this manipulation to greatly diminish the participant's sense of control over the events, in spite of the high rate of positive images in the experiment. Because we believe that it is the sense of control (and not the rate of positive images) that was responsible for the absence of time distortions in Experiment 3, we predicted that strong time distortion effects would once again be observed, replicating the results of Experiment 2.

METHODS

Participants

Sixteen (new) non-anxious participants from the same pool as in Experiment 1 participated in Experiment 4 (16 females, mean age of 19.5 years, 5.1 of mean at the FSQ) either in exchange for credit in a psychology class (2 participants) or for monetary compensation ($8, 14 participants).

Stimuli, design, and procedure

Stimuli, design, and procedures were the same as in Experiment 3. The only difference between Experiments 3 and 4 was the instruction given to participants. Instead of being asked to choose between two keys to try to maximize the occurrence of positive image, participants were instructed to press the key indicated by the computer at the start of each trial. They were told that the computer had an algorithm to try to maximize the occurrence of positive images from a set of positive and negative images and that the key represented the computer's image choice. So, in this experiment, the trials begun with a display telling them which key to press ("Press the 1 key"; or "Press the 3 key"). The remaining of the instruction were the same as in Experiment 3, with the exception that we asked the following four questions at the end of the time bisection task: (1) How much did the computer choice influence the image content?; (2) Did you feel at any point of the experiment that your choices (instead of those of the computer) influenced the type of images that were presented in the experiment (positive vs. negative images)?; (3) How often did positive images appear?; 4) How liberal are you?

RESULTS

Questionnaires and evaluation of the spider pictures

Our spider-fearful participants scored high at the FSQ (5.1). They were not at risk for depression (SDQ = 13.4). The level of state anxiety was higher in the second than first assessment (STAIS-s = 16.5 vs. 11.8), $t(15) = -3.61$, $p < 0.01$. At the end of the time bisection task, participants reported that about 63% of the images in the experiment were positive[4]. Participants also considered themselves as being relatively liberal (64%). Participants evaluated the eight experimental spider pictures as being highly arousing (mean: 7.3), extremely negative (2.4), and as exerting high domination (2.7); and the whole set as being highly arousing (7.4), extremely negative (2.2), and as exerting high domination (2.9). Critically, they reported that the computer choices were very much responsible for the valence of the images (86%) in the experiment, whereas they themselves felt very little control over the experimental events (11%).

As in Experiment 2, *Pearson's correlations* between participants' scores on the FSQ and their ratings of the spider images were related: the higher the score on the FSQ, the higher they rated the mean arousal of the spider images ($r = 0.45$, $p = 0.040$), and

[4]Overall participants saw 37.5% of IAPS high-arousing positive images, 37.5% of IAPS low-arousing positive images, 12.5% of IAPS high-arousing negative images and 12.5% of high-arousing threatening images.

the more dominated they felt by the spider images ($r = -0.51$, $p = 0.023$). We did not find a significant correlation between the FSQ scores and the valence score ($r = 0.13$, $p = 0.31$). Finally, although the FSQ score showed once again a negative correlation with the BPs observed for spider images, in this experiment that relationship did not reach significance ($r = -0.26$, $p = 0.16$). It is possible that we failed to find a significant correlation here because of a lack of power.

Time bisection task

We ran an ANOVA on the BPs with Image Type (IAPS-positive, IAPS-negative, Spiders, with comparable levels of arousal) as within-subjects factors. The results indicated a significant main effect, $F(2,30) = 4.99$, $p = 0.013$, see **Figure 2D**. A planned t-test confirmed no difference between IAPS high-arousing negative images and high-arousing spider images (BPs 830 and 829 ms), $t(15) = 0.05$, $p = 0.96$. Both sets of high-arousing negative images were temporally overestimated compared to high-arousing positive images (BP 930 ms), $t(15) = 2.56$, $p < 0.05$ and $t(15) = 2.63$, $p < 0.02$, respectively. Interestingly, as in Experiment 2, temporal estimations were similar among high- and low-arousing positive images (BPs 930 and 924 ms), $t(15) = 0.24$, $p = 0.82$.

Between experiment comparison (Experiment 2 vs. 4)

A cross-experiment comparison of the two participant groups showed that the two groups were matched in all respects ($ps > 0.09$), except for the reported level of positive images perceived in the experiment, which was significantly higher in Experiment 4 than in Experiment 2 (63 vs. 28%), $t(30) = 9.10$, $p < 0.001$.

With respect to performance on the time bisection task for high-arousing images, we ran an ANOVA on BPs with Image type (IAPS-positive, IAPS-negative, and spider) as within-subjects factors and Experiment as between-subject factor. As before, the results showed that a main effect of Image type, $F(2,60) = 9.29$, $p < 0.001$. More importantly, the main effect of Experiment and the interaction between Experiment and Image type were not significant ($Fs < 0.56$). Furthermore, the BPs for the four sets of images did not differ between Experiment 2 and 4 ($ps > 0.1$).

DISCUSSION

The results of Experiment 4 replicated the results of Experiment 2, in spite of the large difference in the rate of positive images that participants experienced during the time bisection task. That is, in both experiments, spider-fearful participants experienced large time distortion effects that were driven uniquely by the valence of the images: negative images were perceived as lasting longer than positive images, and both sets of positive images were perceived in similar (shorter) fashion, in spite of the large difference in arousal between these two sets of images. We can now confidently conclude that the overall emotional context of the images in an experiment (few vs. many positive images) does not fundamentally alter the direction of the time distortion effects experienced by our participants. More importantly, the results of Experiment 3 can now be more clearly interpreted: we can confidently argue that it was the increase in participants' feelings of control over the experimental events that eliminated the temporal distortions in that experiment (and not the high rate of positive images).

In sum, we have found strong evidence in favor of the hypothesis that the perception of control over emotional events can have a buffering effect over our cognitive assessments of those events, as indexed here by performance on the time bisection task. That said, this buffering effect did not extend to anxiety: across experiments, and irrespective of the level of control, our spider-fearful participants consistently felt more anxious after being faced with the spider images in the time bisection task, than before. No such increase was found with non-anxious, non-spider-fearful individuals (Experiment 1). Experiment 5 was designed as a final test of the effects of control on the interaction between cognition and emotion.

EXPERIMENT 5: HIGH LEVEL OF CONTROL AND COGNITIVE DISSONANCE

In Experiments 1–3, the participants' task was consistent with the participants' general inner goals. That is, participants were asked to minimize negative events or maximize positive events, which are both goals that are compatible with a human being's general aim of maintaining or moving toward a positive state of wellbeing (e.g., Thorndike, 1933). When participants felt successful in the choice task (Experiment 3), this sense of achievement was compatible with their personal desires of avoiding negative states and aversive events. Under these conditions, their sense of control produced a buffering effect such that the emotionality of events no longer influenced their cognitive decisions in the time bisection task. At first glance, one may want to conclude that *in general* a sense of control will always have a positive effect on our cognition. However, it is easy to design a scenario where participants feel in control over the events, yet, those events lead to a negative internal state. Take for example the instruction: "Try to maximize the occurrence of *negative* images." Perceived success in this task would lead participants to feel responsible for all the highly aversive images that they are seeing, which presumably, at some level, they do not want to, see. This state of cognitive dissonance may over-ride the otherwise positive effects of perceived control on cognition. Experiment 5 tested this condition in non-anxious, non-spider-fearful participants.

All experimental procedures were identical to those in Experiment 1, with the single exception of the change in instructions. If a sense of control can over-ride the state of cognitive dissonance, one would expect (a) that participants will feel a high level of control and (b) that this simple change in instructions would lead to the absence of time distortion effects (i.e., similar BPs across image sets), even though everything about the procedure and images is identical to Experiment 1, where robust distortion effects were found. If, on the other hand, the state of cognitive dissonance prevents the sense of control from providing some buffering to the participants, then one might expect to replicate Experiment 1 and obtain large distortion effects, in spite of participants having a large sense of control over the experimental events.

METHOD

Participants

A total of 16 non-anxious participants from the same pool as in Experiment 1 participated in Experiment 5 (16 females, mean age of 19.1 years, 2.1 of mean at the FSQ). We should note that six

of our participants had to be replaced. One because she scored too high on the FSQ (5.6) and we wanted to only test non-spider-fearful individuals. Five others were excluded because our instruction manipulation failed to induce a sense of control in them (scores at or near 0%).

Stimuli, design, and procedure

Stimuli, design, and procedures were the same as in Experiment 1. The only difference between Experiments 5 and 1 was the instruction given to participants. Instead of being asked to choose between two keys to try to maximize the occurrence of positive image, participants were told to try to *maximize the occurrence of negative events*. Because positive events occurred rarely (25%), we anticipated participants would feel a high level of control over the image content.

RESULTS

Questionnaires and evaluation of the spider pictures

The non-anxious participants were not scared of spiders (FSQ = 2.1) and were not at risk of depression (SDQ = 13.6). The levels of state anxiety were marginally higher during the second than the first assessment (12.9 vs. 11.3), $t(20) = -1.92$, $p = 0.069$. After the time bisection task, participants reported that 26% of the images in the experiment were positive. Participants considered themselves relatively liberal (66%). The evaluation of the spider pictures indicated that they considered the spider images as being low-arousing (3.9), as being neutral (4.8), and as producing moderate feelings of domination (5.5). Critically, participants reported sensing a high level of control over the images (55%).

Time bisection task

To test time for distortion effects we ran two separate ANOVAs on BPs with Valence as within-subjects factors and compared arousal-matched conditions (IAPS high-arousing positive images vs. IAPS high-arousing negative images; and IAPS low-arousing positive images vs. low-arousing neutral spider images).

The results indicated that despite the high level of perceived control, high-arousing negative images were still perceived as lasting longer than arousal-matched positive images (BPs 858 vs. 941 ms, respectively), $F(1,15) = 6.89$, $p = 0.019$. On the other hand, BPs did not significantly differ between low-arousing positive and neutral (spiders) images (BPs 948 vs. 899 ms, respectively), $F(1,15) = 1.71$, $p = 0.21$ (see **Figure 3**). A visual inspection of the results also suggested that we should do a *post hoc* analysis to compare BPs of positive images (high arousal vs. low arousal). Unlike Experiment 1, this comparison revealed no significant difference between these two conditions, $t(15) = -0.29$, $p = 0.78$. In sum, this pattern of results shows that a significant temporal distortion effect was observed only for high-arousing negative IAPS pictures.

Between experiment comparison (Experiment 1 vs. 5)

A cross-experiment comparison of the two participant groups, showed that the two groups were matched in all respects ($ps > 0.42$), except for their level of perceived control over the events, which was significantly higher in Experiment 5 (55%) than in Experiment 1 (13%), $t(30) = 6.24$, $p < 0.001$. We ran two ANOVAs on BPs with Valence as within-subjects factors and Experiment as between-subject factor for each level of arousal separately

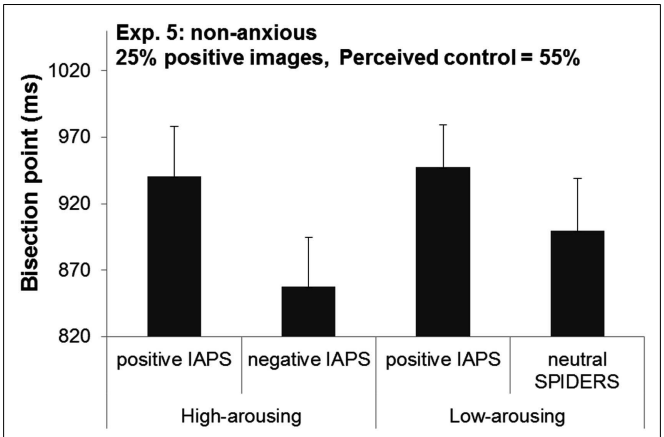

FIGURE 3 | Bisection points in Experiment 5 as a function of the emotional content of the image events.

(high and low). For high-arousing images, the results indicated that only the main effect of Valence was significant: negative images were perceived as lasting longer compared to positive images (BPs 881 vs. 951 ms, respectively), $F(1,30) = 14.49$, $p < 0.001$. The main effect of Experiment and the interaction between Valence and Experiment did not reach significance ($Fs < 0.56$).

For low-arousing images, the BPs did not differ between Experiments 1 and 5 (BPs 927 vs. 924 ms, respectively) and between positive and neutral images (BPs 922 vs. 928 ms, respectively), $Fs < .0.07$, $ps > 0.79$. However, the interaction between Valence and Experiment was significant, $F(1,30) = 5.79$, $p = 0.022$, indicating that participants experienced low arousal images in a different fashion across the two experiments: whereas in Experiment 1, positive images were perceived as lasting longer than negative images, that time distortion effect was not observed in Experiment 5.

DISCUSSION

The results of Experiment 5 provided a qualified answer to the question: does perceived control help cognition under conditions of cognitive dissonance? We successfully induced a sense of control in our participants, in spite of the cognitive dissonance that they certainly experienced. With this high sense of control, participants experienced temporal distortions in only one condition: high-arousing negative images were perceived as lasting longer than the other image types. In other words, perceived control seemed to inoculate participants from experiencing temporal distortions when viewing low-arousing images. But at high levels of arousal, the valence of the images did alter how subjects experienced them.

Overall, comparing Experiments 1 and 5, the results suggest that experiencing heightened levels of control once again affected the manner in which we processed emotional events. That said, the effects of control were less strong than in Experiment 3, and the critical difference was the goal state of the task: in Experiment 3, participants tried to achieve a positive goal, whereas here, they maximized the occurrence of a negative outcome. Thus the manner in which one elicits control seems to be critical in determining the effect that control will have on cognitive processing, when faced

with emotional events. This makes sense because the perception of control is generally considered to be a positive illusion (Taylor and Brown, 1988, 1994), with the adaptive role of moving individuals toward positive moods and states. Thus, the task in Experiment 5 clashes with this adaptive role of experiencing control: asking participants to maximize the number of aversive events puts them in "control" of an environmental situation that is moving them away from a desirable end state (positive mood). From this perspective, it is actually quite remarkable that experiencing control actually had any effects on participants at all.

GENERAL DISCUSSION

The goal of the present study was to test the hypothesis that having a sense of subjective control over experimental emotional events alters the way humans judge the duration of those events. We predicted that having a sense of control would work as an emotional buffer, blocking the effects of emotionality on our cognitive processes (Leotti et al., 2010; Mereu and Lleras, in press). As a strong test of this hypothesis, we chose a population that is very emotionally reactive (sub-clinical spider-fearful individuals) and used fear-related images as stimuli in the time perception task. Our results demonstrated that experiencing a sense of control over the emotional events changed the way these participants judged the duration of those events: whereas in situations of little-to-no control (Experiments 2 and 4), their judgments were influenced by the valence of images (negative images judged to be longer than positive images), once we elicited a sense of control in these participants, the effect of valence on their temporal judgments was eliminated. In fact, when participants experienced little-to-no control, their fearfulness of spiders predicted the time distortion effects, and this correlation was eliminated under conditions of high levels of perceived control.

Two important qualifying results to our conclusions were found. First, whereas the experience of control had a positive effect on cognition (as indexed by performance in the time perception task), it did not change participants' anxious response to the images: consistently, our spider-fearful participants felt significantly more anxious after the time perception task than before. This finding was robust to differences in the overall emotional contexts of the tasks (in Experiment 2, 75% of images were negative whereas in Experiment 4, 75% were positive) and to the varying sense of control that participants experienced (low control in Experiments 2 and 4, high control in Experiment 3). This finding is consistent with prior findings indicating that the experience of control does not necessarily alter all aspects of our responses to stressing stimuli: the overall estimation of pain and stress is not impacted by the experience of control (Pervin, 1963; Stotland and Blumenthal, 1964; Glass et al., 1969). And whereas control can decrease arousal on the interval preceding the stressful event, no straightforward effect of control has been found on the physiological response to stressors during the stimulation itself (e.g., Corah and Boffa, 1970; Geer et al., 1970; Geer and Maisel, 1972; Gatchel and Proctor, 1976). It is worth remembering that our participants in Experiments 2, 3, and 4 were sub-clinical spider-fearful and thus had a life-long, well established aversion toward spiders. In that sense, it is not a surprise that they consistently reported being more anxious at the end of the experimental session (after being confronted with spider images) than at the beginning. The s-STAI questionnaire (Marteau and Bekker, 1992) that we used is an explicit self-assessment tool to measure state anxiety and therefore it is subject to response biases. As a result, the s-STAI scores may not have been sufficiently sensitive to measure specific responses that participants had to specific spider images throughout the experiment. These phasic anxiety responses may have been modulated by perceived control on a trial by trial basis, but we had no way of measuring such effects. Follow-up studies using different anxiety measuring techniques as well as physiological arousal measures are warranted to better assess the impact of perceived control on anxiety. On the positive side, the time perception task represents an implicit measure of the effects of emotional stimuli on our participants' cognitive system. Participants were not asked directly to judge or respond to the emotionality of each image in the task, they simply reported whether the image duration seemed closest to the shorter or to the longer standards. This implicit measure successfully showed an effect of perceived control on the cognitive task of time estimation.

A second qualifying result to our overall conclusion that a sense of control can protect our cognitive processes (here, time judgments) from the usual effects of emotional stimuli relates to the conditions in which the sense of control is obtained. Given that, in our experiments, eliciting a sense of control depends on asking participants to exert a choice, the choice must be one that seeks to obtain an outcome aligned with participants' inner sense of wellbeing. When participants are asked to seek goals that run counter to their wellbeing (Experiment 5), the effects of control are diminished and the emotionality of events does seem to end up altering cognition (at least for high-arousing stimuli). Put simply, the experience of control is not a magic bullet: simply asking participants to play an active role in emotional situations will not ensure that emotions will not influence their cognitive mechanisms.

TIME PERCEPTION

Models of time perception differ on whether they posit the existence of an internal clock (or pacemaker) that can be sampled to estimate time (e.g., Gibbon, 1977; Gibbon et al., 1984) or whether they do without an internal clock (Church and Broadbent, 1990; Matell and Meck, 2004). Though the existence of an internal clock is a matter of debate (see Gorea, 2011), the vast majority of the literature on time perception uses the SET model which does incorporate an internal clock (Gibbon et al., 1984). Within this framework, temporal distortions are easily modeled: they can arise because the internal clock has changed its ticking rate (typically, an effect ascribed to manipulations of arousal) or because the extent to which one can attend to the counting process itself has been manipulated. That is, if we seldom pay attention to the counting process, then time will appear to have gone quickly (few samples were taken), if we often pay attention to the counting process, then time will appear to slow down (many tic samples were taken).

Droit-Volet and colleagues (e.g., Droit-Volet et al., 2004; Droit-Volet and Meck, 2007; Droit-Volet and Gil, 2009) have published substantially on the topic of how emotions affect our estimation of time. The results obtained in this literature are as follows:

for high-arousing events, negative events are perceived as lasting longer than positive events because of attentional avoidance. When faced with highly aversive stimuli, our attention quickly turns inward, and the counting process begins quickly. In contrast, high-arousing positive events do not cause this quick avoidance reaction, and thus less attention is available for time estimation. In contrast, for low-arousing images, the effects are reversed. Negative images actually tend to capture attention. But, given the absence of threat in the environment, there is no need to quickly disengage from the image, which delays attention to the counting process. More recent studies have started to better differentiate different types of aversive stimuli: fear, disgust, threat are now being considered independently (Tipples, 2011; Gil and Droit-Volet, 2012).

Within the framework proposed by Droit-Volet et al. (2004) the effect of perceived control on time perception fits best with an "attentional locus." It is as if, under high levels of perceived control in Experiment 3, participants can better engage and disengage from the images, or at least do so in a similar fashion across all image types. Perhaps, success in the control task allows participants to focus on a positive aspect of their ongoing experience (their success), allowing them to be less vulnerable to the attentional pull of emotional events. We hasten to add that the task we used to induce the feeling of control ("maximize events of type X") was the same across all experiments. Thus, it is not the inclusion of this new task that changed the attentional engagement to the various images, but the perceived level of success in that task. Further, when control was high, but the experience was not positive (Experiment 5), perceived control did not fully protect participants against temporal distortions. Overall, it is possible that the "buffering" effect proposed by Leotti et al. (2010) is attentional in nature: when we feel in control, we might attend differently to world events. This issue is now the focus of investigation in our laboratory.

Our results provide an important contribution to the time perception literature. First, Experiment 1 replicated the standard modulations of time judgments by valence and arousal (Angrilli et al., 1997; Smith et al., 2011). Furthermore, the results of Experiments 2 and 4 provide additional support regarding the stability of these effects: the overall emotional context of a task does not impact the specific effect of image type on BPs. That is, both when negative events were frequent and when they were rare, the valence of the image being judged on a given trial determined whether this image would be perceived as relatively longer or shorter than other image types in that experiment. Another important result from our experiments was the replication of Tipples' (2011) observation that individual differences in fearfulness predict differences in time perception: the more fearful participants were of spiders, the longer they perceived the duration of spider images. This finding was obtained when participants felt little-to-no control over experimental events.

Finally, the results of Experiments 2 and 4 represent a new departure from the literature on one important point: we twice failed to, see an effect of arousal on the perceived duration of positive images. That is, whereas it is typically observed that highly arousing positive images are perceived as lasting a short time and low-arousing positive images as lasting a relatively longer period of time, here we found no such difference. In fact, our results suggested that our participants' perception of time was entirely driven by valence, with positive events being judged as lasting shorter than both aversive and threatening events. We can speculate that our participants were probably highly aroused throughout the experiment because of the anticipation of having to face spider pictures (in an unpredictable fashion). Thus, perhaps *all* events were perceived as occurring in a state of high arousal. If that is true, then that would explain why only an effect of valence was found.

POSSIBLE LIMITATIONS OF THE PRESENT FINDINGS

There are several potential limitations to this study that should be acknowledged. First, with respect to the selection of stimuli, McGraw et al. (2010) recently published a study showing that bipolar scales for measuring emotional valence (as it is done in the IAPS ratings) are inappropriate because they do not reflect the psychological difference in intensity between positive and negative emotions. That is, a score of 3 in the IAPS valence scale is 2 units away from the neutral point in the scale (5), but the intensity of this negative emotion is larger than the intensity of a positive image with a score of 7. Thus, it is possible that our group of negative images were therefore psychologically more intense than the groups of positive images. Fortunately, the main point of the current paper does not rest on perfectly equating valences across image sets. Rather, our design and experimental logic lay on the direct comparison of performance by participants looking at the exact same images (see comparison between Experiments 3 and 4). Thus, the key in the logic is that emotional images that usually produce distortions in time perception (as we verified in Experiments 1, 2, and 4) failed to do so when one judges them under conditions of high perceived control (Experiment 3).

The between-subject structure of our design also presents limitations to the current findings. Although we successfully equalized the participant groups across experiments, experiments were run at different times during the semester and some participants received monetary compensation for participation. Thus, one cannot be entirely certain that there were not "unmeasured" differences between groups. To assuage these concerns, we should point out that our results replicated previous results in the literature (Experiment 1 replicates Angrilli et al., 1997; Smith et al., 2011), and also replicated within this study (Experiments 2 and 4). Thus, we can feel confident that our results are robust and replicable. We should also note that the null result we obtained in Experiment 3 should be interpreted with a measure of caution. Even though we (a) predicted a null result, (b) replicated a null result from a different study (Mereu and Lleras, in press), and (c) provided a quantitative measure to estimate the adherence of the null hypothesis (Masson, 2011), one can never be certain as to the reasons why a null result is found in an experiment.

CONCLUSION

In this manuscript, we studied one way in which emotions can impact cognition, specifically, how the emotional content of an

event alters how we estimate the duration of that event. Such time distortions have been interpreted as a negative effect of emotions on cognitive processing: the emotionality of an event alters the manner in which our attention system engages in the task of counting time. Here, we demonstrated that the manner in which participants engage with the stimuli can significantly modulate this deleterious effect of emotions on cognitive processing: when participants feel a high degree of control over the emotionality of events in the experiment, they seem to better control their attention system, such that the emotionality of the image no longer impacts their cognitive assessment of that image. Given that in most if not all current experiments investigating the effects of emotion on cognition, participants are put into a situation where they have no control over the emotional events in the experiment, our results indicate that it may be worthwhile and fruitful to study the impact of emotion on cognition in situations where participants can feel some degree of control over the emotional events.

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APPENDIX

List of the IAPS images (Lang et al., 2008) used in Experiments 1–5.

In *Experiments 1, 2, and 5* we chose 8 low-arousing positive pictures (1441, 1450, 1600, 2057, 5030, 5040, 5210, 5725), 8 high-arousing positive pictures (4607, 4647, 4649, 4651, 4652, 4656, 4668, 4670), and 24 high-arousing negative pictures (3000, 3001, 3010, 3030, 3053, 3061, 3062, 3063, 3064, 3068, 3071, 3101, 3103, 3120, 3131, 3140, 3150, 3168, 3185, 3190, 3191, 3225, 3250, 3261).

In *Experiments 3–4* we chose 24 low-arousing positive pictures (1333, 1419, 1441, 1450, 1600, 1602, 1620, 2040, 2057, 2060, 2153, 2302, 2304, 2306, 2358, 2388, 5001, 5030, 5040, 5210, 5725, 5764, 5831, 7325), 24 high-arousing positive pictures (4607, 4608, 4611, 4631, 4647, 4649, 4651, 4652, 4656, 4664, 4668, 4670, 5621, 5629, 7405, 8033, 8080, 8179, 8180, 8185, 8186, 8370, 8490, 8492), 8 high-arousing negative pictures (3000, 3001, 3010, 3030, 3061, 3062, 3150, 3168).

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Controllability modulates the anticipatory response in the human ventromedial prefrontal cortex

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Research has consistently shown that control is critical to psychological functioning, with perceived lack of control considered to play a crucial role in the manifestation of symptoms in psychiatric disorders. In a model of behavioral control based on non-human animal work, Maier et al. (2006) posited that the presence of control activates areas of the ventromedial prefrontal cortex (vmPFC), which in turn inhibit the normative stress response in the dorsal raphe nucleus and amygdala. To test Maier's model in humans, we investigated the effects of control over potent aversive stimuli by presenting video clips of snakes to 21 snake phobics who were otherwise healthy with no comorbid psychopathologies. Based on prior research documenting that disrupted neural processing during the anticipation of adverse events can be influenced by different forms of cognitive processing such as perceptions of control, analyses focused on the anticipatory activity preceding the videos. We found that phobics exhibited greater vmPFC activity during the anticipation of snake videos when they had control over whether the videos were presented as compared to when they had no control over the presentation of the videos. In addition, observed functional connectivity between the vmPFC and the amygdala is consistent with previous work documenting vmPFC inhibition of the amygdala. Our results provide evidence to support the extension of Maier's model of behavioral control to include anticipatory function in humans.

Keywords: controllability, anticipation, vmPFC, amygdala, fMRI, PPI, phobia

INTRODUCTION

Emotion and cognition interact in numerous ways that affect psychopathology. Importantly, resilience has the potential to significantly mitigate human suffering related to psychopathology (Garmezy, 1971; Masten, 2001, 2011; Casey, 2011). The capacity to perceive control, to identify controllable situations, and to exert effortful control is involved in the complex process leading to resilience (Staudinger et al., 1995; Chorpita and Barlow, 1998; Kumpfer, 1999; Maier et al., 2006; Eisenberg and Sulik, 2012). Moreover, perceived control can dampen emotional responses to aversive events, which in turn would mitigate any impairing effects of emotion on cognition. Indeed, controllability has been a core concept in empirical and theoretical work on psychopathology (e.g., Freud, 1936; Mandler and Watson, 1966; Barlow, 2002) and resilience (Kumpfer, 1999; Zimmerman et al., 1999; Bandura et al., 2003; Yi et al., 2005; Rutter, 2008).

Although multiple aspects of controllability are distinctively human (Abramson et al., 1978; Bandura, 1989; Bandura et al., 2003), research with non-human animals has provided important insights about the mechanisms involved in behavioral control. Influential work in non-human animals has demonstrated differential behavioral phenotypes in response to electrical shock dependent on the animal's perception that it can or cannot escape/avoid the shock (Overmier and Seligman, 1967; Seligman and Maier, 1967; Seligman et al., 1968; Seligman and Beagley, 1975; Seligman et al., 1975). The inescapable response phenomenon, termed *learned helplessness* (Seligman et al., 1975), has generated numerous lines of research. The extension of Seligman's learned helplessness model to humans (Hiroto and Seligman, 1975) required refinement precisely because humans are a meaning-making species and attribute helplessness to a cause, whether "stable or unstable, global or specific, and internal or external" (Abramson et al., 1978, p. 49). This reformulation made Bandura's (1969, 1977, 1986, 1997) social learning and social cognitive theories essential for an understanding of causal attributions, including controllability, when humans perceive themselves to be helpless under adverse or potentially adverse circumstances. This led to demonstrations that affective self-regulation (which may be perceived as internalized/implicit control) is essential to positive psychological adaptation (Bandura et al., 2003; Eisenberg and Sulik, 2012). Thus, any cogent extension of non-human animal research to human neurobiology must acknowledge the role of

social cognition/self-efficacy in making causal attributions about perceived helplessness in humans.

Research on external control in non-human animals has uncovered many of the neurobiological mechanisms involved (Weiss, 1991; Maier et al., 2006). This provides insights into which neuroanatomical structures should be investigated in explorations of control in humans. In particular, increased serotonergic response in the dorsal raphe nucleus (DRN) is necessary for learned helplessness (Maier et al., 1993, 1995); input to the DRN is almost exclusively from the infralimbic and prelimbic areas of the ventromedial prefrontal cortex (vmPFC; Jankowski and Sesack, 2004; Gabbott et al., 2005); and activation of the vmPFC decreases the learned helplessness response, whereas inhibition of the vmPFC increases the learned helplessness response (Amat et al., 2005, 2006). Furthermore, activity in the vmPFC inhibits the normative stress response in relevant midbrain, limbic, brainstem, and cortical areas such as the DRN (Amat et al., 2005) and amygdala (Maier et al., 2006). These findings led Maier et al. (2006) to posit that the presence of control and top-down feedback by the vmPFC are critical for resilient behavior.

Research extending these findings to the human vmPFC has been minimal. Two fMRI studies on pain have demonstrated alterations in the neural response to pain when subjects perceive that they have control over the duration of the painful stimulus (Salomons et al., 2004; Wiech et al., 2006). Of particular importance for investigating controllability in humans is anticipatory function, as the ability to anticipate threatening situations is critical to the survival of any organism. The capacity of anticipating the future is further highlighted in Bandura's views on self-efficacy and resilience, with an emphasis on predicting beneficial as well as aversive consequences, setting goals, and planning actions to arrive at desired outcomes (Bandura, 1989; Bandura et al., 2003). In humans, excessive anticipation of negative events has been shown to be maladaptive and to contribute to psychiatric disorders (Mackiewicz et al., 2006; Nitschke et al., 2006, 2009; Straube et al., 2007; Sarinopoulos et al., 2010). Therefore, we posit that the debilitating effects of anxious anticipation in psychiatric disorders may be the result of, or compounded by, the perceived uncontrollability of the event. Furthering our understanding of the relationships between control and anticipation are of paramount importance in human research and the development of therapeutic interventions that can increase resilience.

To investigate the neural underpinnings of controllability in humans, we designed a study that robustly elicited aversion in a scenario that provided a strong test of control. A sample of 21 snake phobics who were otherwise healthy with no comorbid psychopathologies viewed video clips of moving snakes. On half the trials, an anticipatory cue indicated that they could avert the video presentation (controllable) if they responded quickly enough to a target. For the other half of the trials, the cue indicated that their response times to the target had no impact on the video presentation (uncontrollable). The controllable condition is tightly linked to the concept of perceived control, which has been identified as central to resilience research.

We hypothesized heightened vmPFC activity during the anticipation of controllable snake (cS) videos and increased functional connectivity of the vmPFC with the amygdala (Carlsson et al., 2004; Larson et al., 2006; Maier et al., 2006; Straube et al., 2006; also reviewed in Etkin and Wager, 2007). In the current study, connectivity was operationalized using a new method of context-dependent connectivity (McLaren et al., 2012) building on psychophysiological interactions (PPI; Friston et al., 1997; Gitelman et al., 2003). Support for these hypotheses would demonstrate that Maier et al.'s (2006) model of behavioral control over responses to stress and aversion extends to anticipatory responses in humans, which has important consequences on how emotion modulates cognition.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-one snake phobic participants (17 females, mean age 21.8, range 18–46), without any comorbid psychopathologies, were recruited to this study from the University of Wisconsin at Madison undergraduate population and surrounding community. All participants were right-handed and neurologically normal. Participants were diagnosed with specific phobia (of snakes) using the Structured Clinical Interview for the DSM-IV (SCID; First et al., 2002) and had never taken any prescribed psychotropic medications or participated in behavioral therapy. Participants provided informed written consent and were paid for their participation. The study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board in accordance with the Declaration of Helsinki.

EVENT-RELATED EXPERIMENTAL PARADIGM

Each trial began with an anticipation epoch containing a colored letter cue signal plus a variable delay period (**Figure 1**). The S cue indicated that a phobogenic stimulus of a snake video clip (e.g., one snake crawling) might follow. The F cue indicated that a neutral stimulus of a fish video clip (e.g., one fish swimming) might follow. Each video was equalized for several physical attributes (brightness, contrast, scene complexity, and movement). Videos were selected from 90 videos (30 snake videos, 27 fish videos, and 33 disgust videos) that were rated by 19 adults (7 females) with a median age of 25.5 (range 19–58). Participants rated each video for: valence, arousal, fear, disgust, certainty (of viewed content), complexity, familiarity. The 78 videos in the present study were selected based on the stability of their ratings. Examples of each video type can be found in the Supplemental Material. Videos were presented to participants using the entire viewing area provided by a Silent Vision System (Avotec, Inc., Jensen Beach, FL, USA).

The anticipation epoch was further divided into a perceived controllable and a perceived uncontrollable condition. A blue cue indicated the participant had control over whether the video would be seen or not (controllable trial), while a yellow cue indicated the participant had no control over whether the video would be seen or not (uncontrollable trial). After the variable delay period, a target red square was presented that the participant was told to press a button to as quickly as possible. For all trials, the instructions were the same: "Press the button as fast as possible when the target red square appears." The target was followed by either a video clip or a fixation cross. When a participant had a controllable trial they were informed that if they responded fast enough to the red target square, they would see a fixation cross instead of

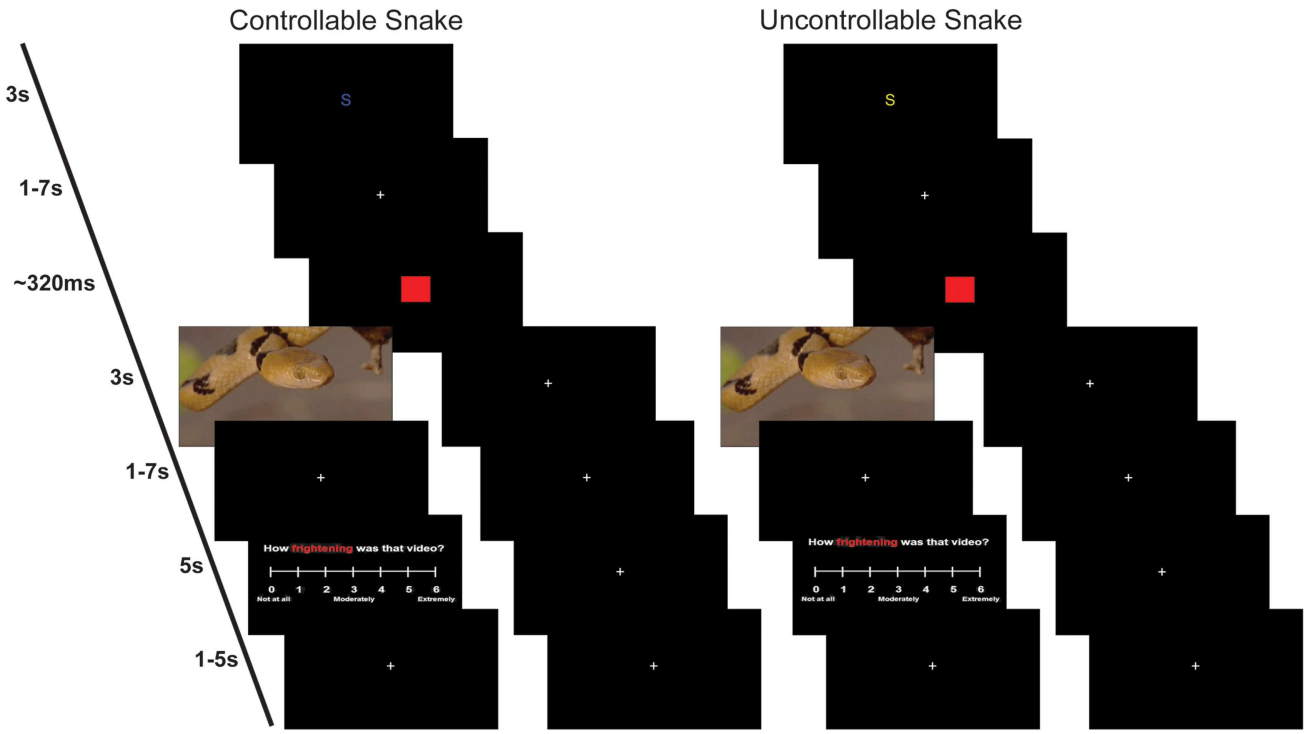

FIGURE 1 | Example trials. Left: a controllable snake trial where participant did not press the button fast enough and saw a video of a snake (left branch) or where participant pressed the button fast enough and did not see a video of a snake (right branch). Right: an uncontrollable snake trial where participant saw a video of a snake (left branch) or where participant did not see a video of a snake (right branch). The cue, presented for 3 s, was either yellow indicating an uncontrollable trial or blue indicating a control trial. The letter S indicated the potential video contained a snake. Following the cue, a fixation cross appeared for 1–7 s. We modeled the anticipation period as the time of the cue plus fixation cross. Following the fixation cross, a red square would appear, and the participant pressed a button as quickly as possible. Depending on the trial type and speed of the response, either a video or fixation cross would appear for 3 s. This was followed by another fixation cross for 1–7 s. If the participant saw a video, then they had 5 s to answer a rating question using a Likert scale. The scale was followed by a final fixation cross for 1–5 s before the onset of the next trial.

the video; however, if they were not fast enough, they would see a video. When a participant had an uncontrollable trial, they were informed a video clip would follow on half the trials and a fixation cross would follow on the other half of the trials. To ensure that participants were only able to avoid the videos on approximately 50% of the control trials, the target presentation time was adjusted on a trial-by-trial basis using DMDX software (Jonathan Forster, University of Arizona). If a participant failed to respond fast enough to avoid the video on one trial, the target presentation of the subsequent trial was lengthened by 17–149 ms. Conversely, if a participant responded fast enough to avoid the video, the target presentation of the subsequent trial was shortened by 16–100 ms. Videos were presented for 3 s followed by a variable delay period. Following the presentations of videos, one Likert online rating about the nature of the stimulus was collected per trial: (a) valence; (b) arousal; (c) disgust; and (d) fear. Participants had 5 s to make their rating, which was then followed by a variable inter-trial interval. Colors and rating questions were counterbalanced. In summary, this manuscript focuses on four conditions: (1) cS, anticipation epoch that precedes a potential snake video where the participant can avoid the video; (2) cF, anticipation epoch that precedes a potential fish video where the participant can avoid the video; (3) uS, anticipation epoch that precedes a potential snake video where participant response does not affect video presentation; (4) uF, anticipation epoch that precedes a potential fish video where participant response does not affect video presentation.

DATA ACQUISITION

All participants underwent fMRI scanning during four runs of the experimental paradigm consisting of 132 trials. The breakdown of trial types was as follows: 22 controllable snake (cS), 22 uncontrollable snake (uS), 22 controllable fish (cF), and 22 uncontrollable fish (uF). Two weeks prior to fMRI scanning, participants underwent a mock scan during which they viewed an abbreviated version of the experimental paradigm using different videos from those used in the actual fMRI scan. Of note, disgust trials were also included in the paradigm, with the D cue indicating that a disgust video clip (e.g., moving maggots, vomiting) might follow. The corresponding 22 controllable and 22 uncontrollable disgust trial types were modeled at the first-level, but not utilized in the group analyses. Disgust trials were not analyzed at the group level because participants' self-reports during debriefing immediately following the fMRI scan revealed mixed responses on how they viewed the disgust trials, including morbid fascination and excited

curiosity. Moreover, the behavioral responses to the target did not show the expected pattern of reduced reaction times to controllable than uncontrollable aversive stimuli. Thus, the disgust trials were excluded because they were not universally aversive.

A 3.0 Tesla GE SIGNA Scanner (Milwaukee, WI, USA) with a quadrature birdcage head coil was used to collect anatomical and functional images. Two sagittal GRE field maps were acquired in order to correct warping of the experimental echo planar imaging (EPI) scans around tissue-air interfaces such as the forehead, the brainstem, and the sinuses (Cusack et al., 2003), with the following parameters: repetition time (TR) = 700 ms, echo time (TE)1/TE2 = 7/10 ms, field-of-view (FOV) = 24 cm, flip angle = 60°, number of excitations (NEX) = 1, matrix = 256 × 128, 30 sagittal slices of 4.0 mm, and a gap of 1.0 mm. Functional data was collected using a sagittal, T2*-weighted, blood oxygen-level dependant (BOLD) EPI sequence with the following parameters: TR = 2 s, TE = 30 ms, FOV = 24 cm, flip angle = 90°, NEX = 1, matrix = 64 × 64, voxel size = 3.75 mm, 30 slices, slice thickness = 4.0 mm, gap = 1.0 mm. Each of the four functional runs was 267 TRs. Finally, we collected a 3D T1-weighted inversion-recovery fast gradient echo sequence with the following parameters: TR = 8.9 ms, TE = 1.8 ms, inversion time = 600 ms, FOV = 24 cm, flip angle = 10°, NEX = 1, matrix = 256 × 192, voxel size = 0.9375 mm, 124 slices, slice thickness = 1.2 mm.

IMAGE PREPROCESSING

Images underwent the following preprocessing steps in Analysis of Functional Neuroimages (AFNI; Medical College of Wisconsin, WI, USA): (1) slice time correction; (2) motion correction; (3) field map correction; and (4) conversion to percent signal change.

FIRST-LEVEL TASK ACTIVATION ANALYSES

General linear models (GLM) in SPM8 (University College London, UK) were used to derive single subject activations. The design matrix was formed by separately convolving the canonical HRF from SPM8 with the presence of the stimuli for the anticipation, video, and rating periods. For anticipation, the presence was defined as the time between the cue onset and the target red square, which could be thought of as an epoch. The design matrix also included the motion parameters, a constant term, autoregressive (AR1) term, and a high-pass filter. In AFNI, the contrast images for each anticipation period (cS, uS, cF, uF) were spatially normalized to the Talairach atlas (Talairach and Tournoux, 1988) and resampled to 1 mm^3 voxels.

SECOND-LEVEL TASK ACTIVATION ANALYSIS

Hypotheses examining differences in neural activation during the anticipation of controllable and uncontrollable snake and fish videos were tested using planned contrasts in AFNI. Significant clusters ($p < 0.05$) were defined as clusters contained at least 224 contiguous voxels with a p-value of $p < 0.005$ or at least 337 contiguous voxels with a p-value of $p < 0.01$ based on 3dClustSim (AFNI) within a controllability mask ("Nitschke_Lab" in the peak_nii toolbox)[1].

FIRST-LEVEL PSYCHOPHYSIOLOGICAL INTERACTIONS ANALYSES

Percent signal change images were spatially normalized to the Talairach atlas (Talairach and Tournoux, 1988), resampled to 2 mm isotropic voxels, and smoothed with a 6 mm FWHM Gaussian filter. Generalized psychophysiological interactions (gPPI) were used to evaluate context-dependent connectivity, based on their improved sensitivity and specificity in detecting connectivity effects (McLaren et al., 2012), with the vmPFC. The vmPFC seed region was defined as a 3-mm radius sphere around the peak voxel of the cS minus uS contrast (Talairach: 5, 46, −7). We used the automated gPPI toolbox[2] to estimate the PPI effects for each subject. This analysis was limited to the 12 participants who had full coverage in the region based on the mask generated by SPM8, rather than using variable seed regions for each participant. These 12 did not differ from the remaining nine participants for sex or age (all ps > 0.10).

SECOND-LEVEL PSYCHOPHYSIOLOGICAL INTERACTIONS ANALYSIS

Hypotheses examining functional connectivity via PPI were tested using one-sample t-tests of contrasts comparing two conditions (equivalent to paired t-tests). Significant clusters ($p < 0.05$) were defined as clusters contained at least 35 contiguous voxels with a p-value of $p < 0.005$ based on 3dClustSim within a controllability mask ("Nitschke_Lab" in the peak_nii toolbox, see text footnote 1).

RESULTS

BEHAVIORAL RESULTS

As a manipulation check for perceived control, we tested whether reaction times differentiated the controllable and uncontrollable conditions. A 2 × 2 repeated-measures ANOVA examining controllability and stimulus revealed a significant interaction ($p = 0.038$). *Post hoc* paired t-test analyses of this interaction revealed that cS reaction times (mean = 458.77 ms; SEM = 24.89 ms) were significantly faster than uS reaction times (mean = 481.91 ms; SEM = 28.01 ms; $p = 0.003$). By contrast, there was not a significant difference between cF (mean = 488.15 ms; SEM = 27.30 ms) and uF reaction times (mean = 494.89 ms; SEM = 27.47 ms; $p = 0.367$). Additional comparisons revealed that cS reaction times were significantly faster than cF reaction times ($p < 0.001$) and that uS reaction times were significantly faster than uF ($p = 0.035$). These results show that controllability had a larger effect when the stimulus was aversive.

fMRI ACTIVATION RESULTS

A paired t-test revealed greater anticipatory activation in the vmPFC for cS compared to uS (**Figure 2**, **Tables 1** and **4**). No other significant clusters were found for this comparison, nor were any significant clusters found in the opposite direction.

A paired t-test revealed greater anticipatory activation during the uF compared to cF in the posterior mid-cingulate cortex (pMCC), the right anterior insula, and the pons (**Table 4**). No significant clusters were found in either the vmPFC or amygdala, nor were any significant clusters found the opposite direction.

[1] http://www.nitrc.org/projects/peak_nii

[2] http://www.nitrc.org/projects/gppi

Within these regions, no interactions were found between controllability and stimuli, suggesting that the controllability effects were sub-threshold for non-aversive stimuli. Interestingly, there was an interaction in the left anterior insula (**Table 4**). *Post hoc* paired *t*-test analyses were conducted using values extracted from the left anterior insula cluster. These revealed that activity during cS was greater than that during uS ($p = 0.015$), whereas the activity during uF was greater than during cF ($p = 0.004$). Anticipatory activity during cS was greater than cF ($p = 0.002$), whereas the comparison for activity during uS compared uF was not significant ($p = 0.624$).

Valence effects collapsing across controllability were also assessed. A paired *t*-test revealed greater activity during the S compared to F in the vmPFC, the pregenual anterior cingulate cortex (pACC), a cluster spanning the anterior mid-cingulate cortex (aMCC), and ACC, a second cluster in the aMCC, bilateral anterior insula, and bilateral thalami (**Figure 3**, **Tables 2** and **4**). No significant effects were found in the opposite direction.

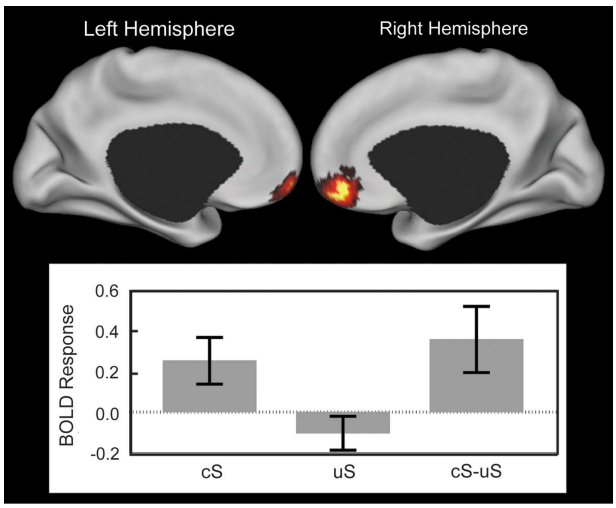

FIGURE 2 | Anticipatory ventromedial prefrontal cortex (vmPFC) response showing the effect of controllability. Top: cortical surface renderings of the controllable snake (cS) minus uncontrollable snake (uS) contrast using multi-fiducial mapping in CARET with the strongest voxel within 2.5 mm of the surface (Van Essen, 2005). Results were thresholded at $p < 0.05$ cluster corrected. Brighter colors represent stronger effect or more overlap between the surfaces in the multi-fiducial map and can be interpreted as the most likely area of a strong effect. Bottom: the BOLD response in the cluster for cS, uS, and their difference. Error bars are SEM.

Table 1 | Anticipation of controllable snake videos > uncontrollable snake videos.

Cluster size (mm^3)	Peak location[a]	Talairach coordinates			Peak *t*-statistic	*p*-Value
		x	*y*	*z*		
389	vmPFC	−5	61	−10	4.613	<0.001
	vmPFC	5	46	−7	4.612	<0.001
	vmPFC	2	56	−11	3.796	<0.001

[a]*Table includes all significant peaks of activation that are more than 8 mm apart within significant clusters ($p < 0.05$ corrected). vmPFC, ventromedial prefrontal cortex.*

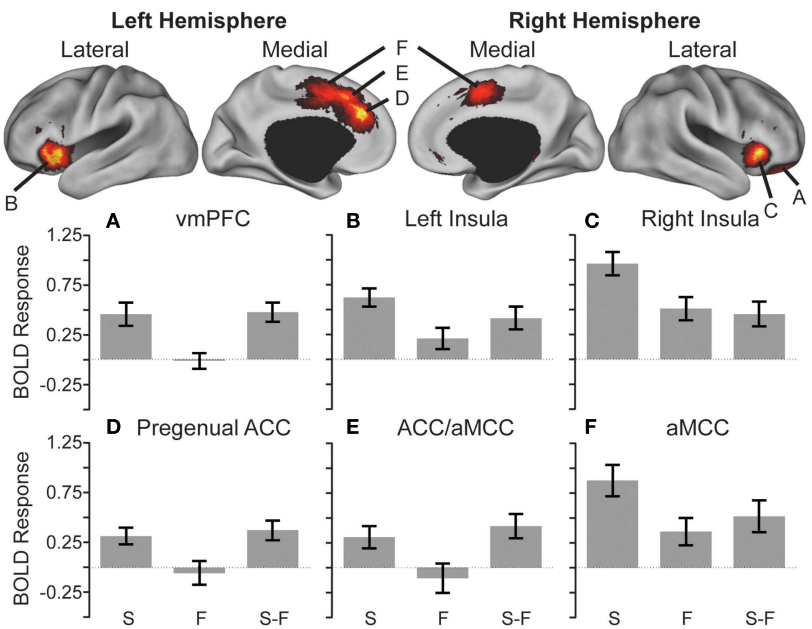

FIGURE 3 | Anticipatory activations showing the effect of stimulus. Cortical surface renderings of snake (S) minus fish (F) contrast using multi-fiducial mapping in CARET with the strongest voxel within 2.5 mm of the surface (Van Essen, 2005). Results were thresholded at $p < 0.05$ cluster corrected. Bottom: heightened anticipatory activity reflected in greater activation in the ventromedial prefrontal cortex (vmPFC) **(A)**, bilateral anterior insula **(B,C)**, pregenual anterior cingulate cortex (ACC) **(D)**, regions spanning from the ACC to the anterior mid-cingulate cortex (aMCC) **(E)**, and bilateral aMCC **(F)** preceding snake videos compared to fish videos (S > F).

Table 2 | Anticipation of snake videos > fish videos.

Cluster size (mm^3)	Peak location[a]	Talairach coordinates			Peak *t*-statistic	*p*-Value
		x	*y*	*z*		
2727	Right thalamus	13	−9	13	5.534	<0.001
	Right thalamus	7	−27	6	5.339	<0.001
	Right thalamus	19	−14	17	5.335	<0.001
	Right thalamus	13	−20	16	4.738	<0.001
	Right thalamus	2	−6	8	3.841	<0.001
	Right thalamus	3	−19	9	3.418	0.001
	Right thalamus	17	−13	4	3.240	0.002
737	Left thalamus	−1	−7	8	4.082	<0.001
	Left thalamus	−10	−3	12	3.939	<0.001
	Left thalamus	−16	−11	17	3.608	<0.001
	Left thalamus	−16	−10	7	3.418	0.001
	Left thalamus	−6	−17	15	3.083	0.003
781	Left thalamus	−14	−25	12	3.714	<0.001
	Left thalamus	−15	−15	12	3.131	0.003
669	Left anterior insula	−29	24	4	4.249	<0.001
	Left anterior insula	−39	20	10	3.588	<0.001
	Left anterior insula	−35	11	3	3.574	0.001
	Left anterior insula	−30	17	−6	3.272	0.002
	Left anterior insula	−31	24	13	2.936	0.004
548	Right anterior insula	36	22	4	3.933	<0.001
495	vmPFC	18	37	−8	4.727	<0.001
	vmPFC	20	45	−8	4.265	<0.001
475	pACC	−4	32	26	4.717	<0.001
518	aMCC	−4	17	42	3.685	<0.001
	ACC	−5	26	37	2.777	0.006
729	aMCC	−6	2	45	3.504	0.001
	aMCC	6	3	47	3.090	0.003

[a]*Table includes all significant peaks of activation that are more than 8 mm apart within significant clusters ($p < 0.05$ corrected). ACC, anterior cingulate cortex; aMCC, anterior mid-cingulate cortex; pACC, pregenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.*

fMRI CONTEXT-DEPENDENT CONNECTIVITY/GPPI RESULTS

A paired *t*-test revealed that the vmPFC contributed more to the activity in the pMCC during cS compared to uS (389 mm^3; **Table 4**). There were no significant clusters where the connectivity was greater during uS compared to cS.

A paired *t*-test revealed that the vmPFC contributed more to the activity in the bilateral amygdala, pMCC, posterior cingulate, and bilateral thalami during cS compared to cF (**Figure 4**, **Tables 3** and **4**). There were no significant clusters where the connectivity was greater during cF compared to cS.

A paired *t*-test did not reveal any significant connectivity differences with the vmPFC between uS and uF.

DISCUSSION

This paper reports the first exploration of the neural basis for mediating the impact of perceived controllability on the anticipatory response to aversive stimuli. We found that in humans the vmPFC region is critical to behavioral control while anticipating aversive stimuli. Moreover, this area showed strong functional coupling with the amygdala, consistent with prior work implicating it in top-down regulation of the amygdala (Phelps et al., 2004; Urry et al., 2006; Johnstone et al., 2007; Maier and Watkins, 2010). This extends to humans the behavioral control model that Maier et al., 2006 based on their work with animals, the core of which emphasizes vmPFC regulation of the amygdala, and other brain areas that respond to stress. Based on our work and others results, we conclude that these brain regions are involved in mediating the impact of perceived control on emotional responses to adversity that can have enhancing or impairing effects on various domains of cognitive function.

Experiments dating back to the 1960s and 1970s have documented the effects of perceived control on behavioral responses (Seligman, 1975; Weiss, 1991; Barlow, 2002; Maier et al., 2006). These studies are pivotal because they demonstrated that: (1) there is a potential temporal dependence in learned helplessness (Overmier and Seligman, 1967; Seligman et al., 1975); (2) learned helplessness can be mitigated by prior escapable trials that induce perceived control (Seligman and Maier, 1967); and (3) learned helplessness can be reversed by showing that shocks are escapable (Seligman et al., 1968). These findings provided the impetus for investigating the neural basis for learned helplessness. Petty et al. (1994) demonstrated that learned helplessness

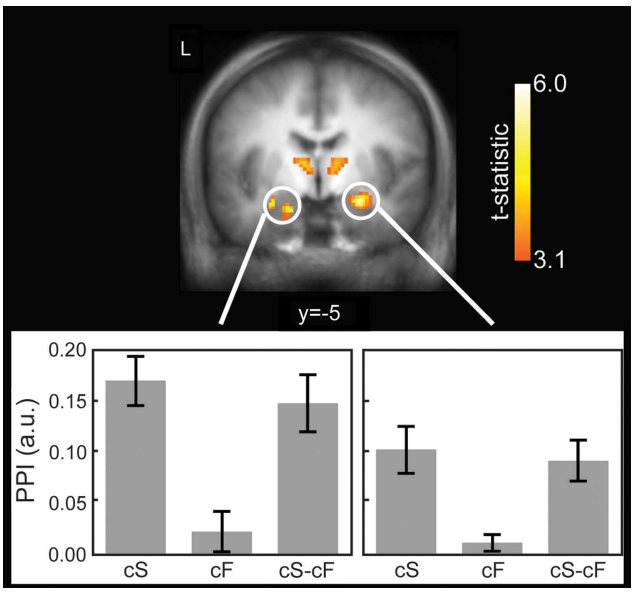

FIGURE 4 | Functional connectivity using generalized psychophysiological interactions (gPPI). Top: significantly greater connectivity during controllable snake (cS) compared to uncontrollable snake (uS) shown in a coronal slice through the amygdala and thalamus. Results were thresholded at $p < 0.05$ cluster corrected. Bottom: plots for the left and right amygdala clusters showing the PPI values. Error bars are SEM. a.u. = arbitrary units.

correlated with serotonin levels in the vmPFC post-shock, but not basal pre-shock level, providing evidence that changes occur during the stressor. Subsequent studies demonstrated that vmPFC activity during inescapable shock correlated with later social exploration/escape behavior (Amat et al., 2005, 2006; Christianson et al., 2009) and that inhibiting vmPFC activity during, but not after, a forced swim test prevented the learned helplessness behavior the following day (Scopinho et al., 2010). Similar findings led Maier et al. (2006) to posit that the presence of control and its activation of the vmPFC are critical in determining behavior. In essence, the vmPFC modulates the stress response by top-down feedback.

The present study utilized a novel design to investigate the circuitry recruited by behavioral control in humans by exposing snake phobics to the very object on which their diagnosis is based. When they anticipated the snake videos, only the vmPFC showed a differential response between controllable and uncontrollable trials. Thus, the vmPFC has substantial potential to provide top-down feedback and aid in down regulation of the amygdala and stress-related responses. Consistent with this idea, we observed changes in connectivity with a number of brain regions, most notably the amygdala. In sum, the exact significance of the vmPFC is the implementation of perceived control in humans via its regulation of the stress response system.

Although the direction of the association between the vmPFC and amygdala cannot be conclusively determined on the basis of PPI alone (Friston et al., 1997; Banks et al., 2007), vmPFC inhibition of the amygdala is of considerable significance for translational neuroscience. Hypothetically, the vmPFC controls decrements in fear response and strengthens extinction memory formation (Quirk and Mueller, 2008). Non-human animal research has consistently demonstrated this top-down inhibition of the amygdala by the vmPFC during fear extinction (Morgan et al., 1993; Milad and Quirk, 2002; Quirk et al., 2003; Rosenkranz et al., 2003; Delgado et al., 2008). Verifying vmPFC inhibition of the amygdala in humans will require further development of fMRI-based causality models (Etkin et al., 2006; McFarlin et al., 2012). Using dynamic causal modeling to indicate directionality between these regions in humans, Etkin et al. (2006) were able to demonstrate that pregenual ACC activity (adjacent to the vmPFC activity found here) predicted reductions in amygdala activity when the previous trial was incongruent (more emotional conflict). Structural equation modeling (SEM) on time-series data has provided further support for medial PFC regulation of the amygdala (Meyer-Lindenberg and Zink, 2007). Despite not directly assessing causality, the present study extends prior work documenting heightened amygdala responses in specific phobia (Etkin and Wager, 2007) by highlighting the importance of the vmPFC and its connectivity with the amygdala for both the development and treatment of specific phobic (Maier and Watkins, 2010).

Additionally, a growing number of studies have implicated the vmPFC in emotional functions other than regulation (Hartley et al., 2011; Myers-Schulz and Koenigs, 2012). More specifically, the vmPFC region found here corresponds to the perigenual vmPFC section described by Myers-Schulz and Koenigs (2012) to be involved in positive affect. The identification of this area provided further support for the hypothesis that this area is involved in the psychologically beneficial effects provided during the anticipation of behavioral control over an aversive stimulus in phobics, perhaps related to down regulation of the amygdala and stress-related responses by the vmPFC.

Precisely because excessive anticipation of negative events has been shown to be maladaptive and contribute to psychiatric disorders (Mackiewicz et al., 2006; Nitschke et al., 2006, 2009; Straube et al., 2007; Sarinopoulos et al., 2010), this study investigated the neural basis for perceived control in humans to provide the proverbial "missing links" between learned helplessness (Seligman, 1975), social cognitive theory (Bandura, 2002), and the neuroscientific basis of resilience (Curtis and Cicchetti, 2003). As demonstrated by Seligman and colleagues, it is the perception of control that determines the behavioral response to a stressor. In particular, high resilience – the knowledge and prior experience of escapable shocks – reduced the learned helplessness behavior (Overmier and Seligman, 1967; Seligman and Maier, 1967). Furthermore, an animal's resilience can be increased through behavioral treatment (Seligman et al., 1968). Thus, humans have an innate ability to change their capacity to perceive and exert control, in part due to their unique ability to attribute causality to aversive events that directly contribute to resilience (Abramson et al., 1978). The central role of perceived control in resilience (Staudinger et al., 1995; Chorpita and Barlow, 1998; Kumpfer, 1999; Maier et al., 2006) in conjunction with findings here indicate a prominent role for the vmPFC in the neurobiology of resilience. Coupling the neural circuitry for perceived control in humans with the underappreciated

Table 3 | gPPI: functional connectivity between vmPFC and ROI during anticipation of controllable snake videos > controllable fish videos.

Cluster size (mm^3)	Peak location[a]	Talairach coordinates			Peak *t*-statistic	*p*-Value
		x	*y*	*z*		
984	Right ventral amygdala	23	−7	−12	6.028	<0.001
	Right extended amygdala	13	−11	−10	4.021	0.001
784	Left ventral amygdala	−19	−5	−16	4.773	<0.001
	Left extended amygdala	−27	−11	−10	4.699	<0.001
2832	Left pMCC	−13	−21	32	5.634	<0.001
	Left PCC	−11	−35	36	4.743	<0.001
504	Right PCC	15	−33	32	4.900	<0.001
3672	Left thalamus	−9	−9	10	4.695	<0.001
	Left thalamus	−13	−19	0	4.282	<0.001
	Right thalamus	11	−3	10	4.012	0.001
	Left thalamus	−13	−27	8	3.889	0.001
	Left thalamus	−17	−31	0	3.869	0.001
	Left thalamus	−23	−25	0	3.816	0.001
	Left thalamus	−13	−19	16	3.734	0.002
	Right thalamus	3	−11	6	3.529	0.002
472	Right thalamus	21	−23	0	3.926	0.001
	Right thalamus	15	−23	16	3.402	0.003
	Right thalamus	21	−31	10	3.147	0.005
312	Right PCC	5	−47	42	3.533	0.002

[a]*Table includes all significant peaks of activation that are more than 8 mm apart within significant clusters ($p < 0.05$ corrected). pMCC, posterior middle cingulate cortex; PCC, posterior cingulate cortex.*

Table 4 | Summary of results.

Anatomical location	Paired *t*-tests											
	cS-uS		cF-uF		(cS-uS)-(cF-uF)		S-F		cS-uS		cS-cF	
	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH
ACC							+					
aMCC							+	+				
pACC							+					
pMCC				−							+	
PCC									+		+	+
vmPFC	+	+					+					
Anterior insula				−	−		+	+				
Amygdala												
Ventral amygdala											+	+
Extended amygdala											+	+
Thalamus							+	+			+	+
Pons			−	−								

NOTES: black, fMRI results; red, gPPI results; +, significant positive cluster; −, significant negative cluster; ACC, anterior cingulate cortex; aMCC, anterior mid-cingulate cortex; pACC, pregenual anterior cingulate cortex; PCC, posterior cingulate cortex; vmPFC, ventral medial prefrontal cortex; LH, left hemisphere; RH, right hemisphere.

potential of human resilience points to the necessity of neuroscience in designing studies to enhance resilience in the face of adversity (Garmezy, 1971; Masten, 2001, 2011; Huber and Mathy, 2002; Casey, 2011).

LIMITATIONS

Signal dropout was observed in a number of subjects in the vmPFC as is commonly reported in other studies. In the present study, the dropout extended into our functionally defined ROI

in nine subjects, which led them to be excluded from the PPI analysis. Although the smaller sample limits the generalizability of the PPI results, it is unlikely that excluding these subjects biased the results because the extent of signal dropout was not associated with differences with demographic or psychological variables. Moreover, reducing the sample limits the statistical power for detecting the hypothesized effect here, lending support for the importance of the functional coupling found in the small sample. Another limitation is that we were not able to test whether the effects observed here for anticipation were also present for the video presentation. Analogous analyses for the video period were not possible due to insufficient trials per cell: only half the trials included a video as a result of the experimental manipulation of controllability.

CONCLUSION

This first study of behavioral control investigating anticipatory responses directly extends Maier's model of behavioral control to humans. The anticipatory vmPFC activation observed for perceived control has ramifications for the emotional response to aversive events and consequent effects of emotion and cognitive function. A new advance in functional connectivity, gPPI (McLaren et al., 2012), provided evidence of the dynamic relationships between nodes of the network, in particular the vmPFC and amygdala. The identification in humans of these brain areas in perceived controllability under aversive conditions clearly suggests that resilience is not only ordinary (Masten, 2001), but innate and potentially universal. As such, a neurological mechanism has evolved in humans to enable coping with extreme adversity, whether natural or social, and to perceive the controllability of our environment and emotional responses.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Emotion_Science/10.3389/fpsyg.2012.00557/abstract

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Individual differences in delay discounting under acute stress: the role of trait perceived stress

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Delay discounting refers to the reduction of the value of a future reward as the delay to that reward increases. The rate at which individuals discount future rewards varies as a function of both individual and contextual differences, and high delay discounting rates have been linked with problematic behaviors, including drug abuse and gambling. The current study investigated the effects of acute anticipatory stress on delay discounting, while considering two important factors: individual perceptions of stress and whether the stressful situation is future-focused or present-focused. Half of the participants experienced acute stress by anticipating giving a videotaped speech. This stress was either future-oriented (speech about future job) or present-oriented (speech about physical appearance). They then performed a delay discounting task, in which they chose between smaller, immediate rewards, and larger, delayed rewards. Their scores on the Perceived Stress Scale were also collected. The way in which one appraises stressful situations interacts with acute stress to influence choices; under stressful conditions, delay discounting rate was highest in individuals with low trait perceived stress and lowest for individuals with high trait perceived stress. This result might be related to individual variation in reward responsiveness under stress. Furthermore, the time orientation of the task interacted with its stressfulness to affect the individual's propensity to choose immediate rewards. These findings add to our understanding of the intermediary factors between stress and decision-making.

Keywords: delay discounting, stress, decision-making, future orientation, perceived stress

INTRODUCTION

Delay discounting refers to the tendency for individuals to prefer immediate rewards over rewards received after a delay, even if the magnitude of the delayed reward is larger (Kirby et al., 1999; Berns et al., 2007). This tendency can often be maladaptive when making intertemporal choices; for example, one might choose to forego future health in order to enjoy the immediate pleasure afforded by fatty foods. While most individuals exhibit some degree of delay discounting, the rate at which people discount future rewards can vary widely from individual to individual, and even from context to context (Peters and Buchel, 2011). For instance, many studies have shown that drug addicts have higher discounting rates than non-drug users (Kirby et al., 1999; Kirby and Petry, 2004; Businelle et al., 2010), and people from Western cultures have higher discounting rates than those from Eastern cultures (Takahashi et al., 2009). Contextual influences on delay discounting rate include a gambling context among pathological gamblers (Dixon et al., 2006) and episodic future thinking in normal subjects (Peters and Buchel, 2010; Benoit et al., 2011).

Given that many important decisions are made under stressful circumstances, our aim in the present study is to determine the effect of acute stress on delay discounting rate. A few studies have begun to investigate how stress might influence decision-making about delayed rewards and uncertain rewards. Participants under stress have been shown to make more risky choices in a risk-taking paradigm (Porcelli and Delgado, 2009), and exogenous cortisol administration has been shown to increase risk-seeking (Putman et al., 2010). While these findings point to more risky decision-making under stress, which may translate to higher delay discounting, high basal cortisol levels have actually been associated with less risky behavior on the Iowa Gambling Task (van Honk et al., 2003), as well as with lower delay discounting rates (Takahashi, 2004). Stress has also been found to increase risky decision-making in a driving task in older adults, but not in younger adults (Mather et al., 2009), and a few studies have reported gender differences in decision-making under stress (Preston et al., 2007; Lighthall et al., 2009; van den Bos et al., 2009; Takahashi et al., 2010).

These mixed findings highlight the importance of considering not only the presence of an acute stressor, but also how people perceive and appraise stressful situations. A growing literature shows that individuals may interpret stressful situations as either challenging or threatening, and that this might affect their choices (e.g., Kassam et al., 2009). The degree to which an individual tends to perceive stressful situations as uncontrollable, unpredictable, and severe can be measured by the Perceived Stress Scale (PSS; Cohen et al., 1983). High scores on this measure have been associated with blunted hedonic capacity (Pizzagalli et al., 2007), especially in the presence of acute stress (Bogdan and Pizzagalli, 2006). This decreased reward responsiveness may affect the way in which immediate rewards are construed, and decisions are made, in a

delay discounting paradigm. In the present study, we administered the PSS in order to measure participants' general perception of life events as stressful. This trait perceived stress might represent an important intermediary factor in the relationship between acute stress and delay discounting; likewise, acute stress may mediate the relationship between trait perceived stress and delay discounting.

In addition to varying in the way they are interpreted by the individual, stressful situations may also vary in their time orientation. That is, they may be future-focused (e.g., thinking about future encounters or job interviews) or present-focused (e.g., worrying about how one appears to others). Since intertemporal choice involves making decisions about the future, and since perception of time is an important factor in determining delay discounting rates, it is critical to take into account how stress interacts with time orientation to affect decisions involving delayed rewards. Individuals who perceive future events as being farther away in time are more likely to discount rewards at a higher rate (Takahashi, 2005; Zauberman et al., 2009). In addition, prospection about future events has been found to reduce bias toward immediate reward in delay discounting tasks (Peters and Buchel, 2010; Benoit et al., 2011). Prospection about future events in a stressful context may have a different effect on delay discounting, in that a bleak view of the future might invite a preference for immediate reward. Likewise, stress that is present-focused may decrease delay discounting rate by decreasing responsiveness to immediate reward (Bogdan and Pizzagalli, 2006). In order to control for effects of time orientation on delay discounting, we included manipulations that varied in both stressfulness and time orientation.

Another important consideration is the distinction between risk-taking and delay discounting. While delay discounting carries a risk-taking component (since future rewards may be interpreted as uncertain), the inability to wait for future rewards is a well-documented and well-defined dimension of impulsivity (Kirby and Finch, 2010). Risk-taking is often found to be correlated with preference for immediate reward (Reynolds et al., 2004), and there may be similarities between the discounting functions for delayed and probabilistic rewards (Rachlin et al., 1991; Green and Myerson, 2004). However, probability discounting (i.e., tendency for risk-taking) and delay discounting likely have distinct neural underpinnings and mechanisms (Cardinal, 2006), and other variables may affect these two constructs differently (Green et al., 1999; Green and Myerson, 2004). Therefore, in order to examine whether stress affects delay discounting, probability discounting, or both, this study also included a choice paradigm in which participants made decisions between certain and probabilistic rewards. Higher probability discounting rates were indicative of greater risk-taking, or a greater propensity to discount odds against receiving an uncertain reward.

In summary, the current study explored the effects of acute stress on delay discounting rate and probability discounting rate, while taking into consideration individual differences in trait perceived stress and time orientation of the stressor. Each of four groups was treated with a different manipulation, designed to induce some combination of time orientation and acute stress. Additionally, PSS scores were collected for all participants. Due to previously discussed evidence of reduced reward responsiveness in high PSS individuals during acute stress exposure, we predicted that delay discounting rate under stressful conditions would be differentially affected in individuals with varying levels of trait perceived stress.

MATERIALS AND METHODS

PARTICIPANTS

A total of 120 males participated in this experiment; they were randomly assigned to each of the four groups. Smokers were excluded, because smoking has been linked with high delay discounting rates (Businelle et al., 2010), as well as increased base cortisol levels (Kirschbaum et al., 1992). Only males were included because of reported menstrual and contraceptive effects on cortisol levels (Kudielka et al., 2004). Limiting analysis to one gender is a common approach in the stress and cognition literature (e.g., al'Absi et al., 2002; Henckens et al., 2009). In addition, the experiment was always conducted between the hours of 1:00 and 5:00 PM, as stress levels have been shown to fluctuate throughout the day (Izawa et al., 2010) and to control for circadian fluctuations in circulating cortisol (Federenko et al., 2004). Seven individuals were excluded from data analysis due to misunderstanding of instructions ($n = 2$), refusal to consent to video recording ($n = 2$), and naïveté issues (i.e., having done a similar stress-induction study previously; $n = 3$). Therefore, final analysis was conducted on 113 participants (mean age = 20.46 years, SD = 3.74). All participants gave written, informed consent. They were compensated with course credit, and all were aware that they might be selected to perform a stressful speech-giving exercise while being videotaped. The study was approved by the Institutional Review Board of Rutgers University.

WORKING MEMORY TASK

Prior research has demonstrated that lower working memory capacity may be related to increased delay discounting (Hinson et al., 2003; Shamosh et al., 2008; Bobova et al., 2009). Thus, we included a variant of the Sternberg item-recognition task (Sternberg, 1966), often used in past research to measure maintenance of information in verbal working memory (Rypma et al., 2002; Narayanan et al., 2005; Porcelli et al., 2008). Participants completed this task directly after a baseline cortisol measurement was taken (for study timeline, see **Figure 1**). On each of forty trials, subjects were presented with a string that was either three or six letters in length. After a brief pause, they were shown a single random letter and were asked to indicate whether or not this letter had appeared in the previous string by pressing "1" (for "yes") or "2" (for "no").

STRESS AND FUTURE ORIENTATION MANIPULATION

After the participants completed the working memory task, they were told whether or not they had been randomly selected to give a speech. In our factorial design, participants were exposed either to acute stress in the form of anticipating a videotaped speech or a non-stressful control procedure (Stress, Non-Stress). Additionally, participants' time orientation was manipulated to be either future- or present-focused (Future, Present). Therefore, there were four distinct manipulations, detailed below, which varied on these two axes. The anticipatory stress manipulation was adapted from

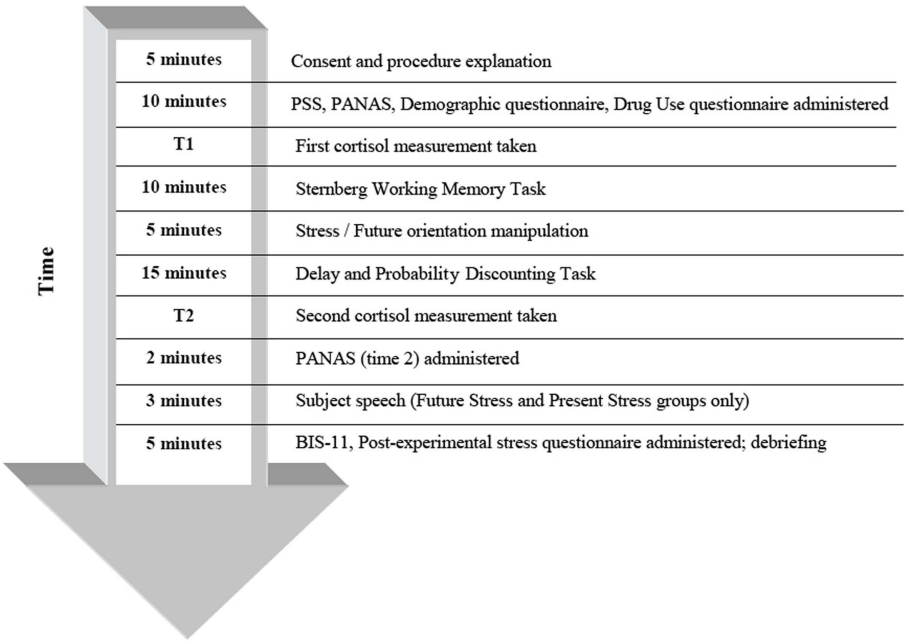

FIGURE 1 | Timeline for procedure.

a previous study on stress and decision-making (Preston et al., 2007).

If the participants were in the future-oriented stress (FS) group, they were told that they would be giving a 3-min speech in front of a video camera. The speech would be recorded, and later viewed and judged by the experimenters. The instructions for the speech were, "Pretend that you are in front of an interview committee for your future dream job. Talk about your strengths and weaknesses, and please explain why you should get this job despite your weaknesses. You will be ranked relative to your peers based on your articulation, clarity, defensiveness, openness, and organization." The participants were then given 5 min to prepare their speeches before the next task. This speech topic is commonly used as part of the Trier Social Stress Test (Kirschbaum et al., 1993), a manipulation that reliably elicits self-reported stress and cortisol release.

In the present-oriented stress (PS) group, the instructions were similar, but the topic of the speech was "Please talk about what you dislike about your body and physical appearance." It was emphasized that participants should focus only on physical traits. Preston et al. (2007) found that this speech topic elicited stress in both men and women.

Both stress conditions included a similar speech-giving exercise that involved some level of social evaluative stress. We chose these procedures because their validity and effectiveness in inducing stress has been demonstrated in previous studies (e.g., Kirschbaum et al., 1993; Preston et al., 2007). Although time orientation was not the only factor that differed between the two conditions, we did not want to make the time orientation manipulation transparent to subjects, nor did we wish to include a new manipulation that might not have been effective in inducing stress.

In the future-oriented non-stress (FN) group, participants were told to relax and to make a list of events within the next 6 months that they were looking forward to (e.g., school vacations).

If the participants were randomly selected to be in the present-oriented non-stress (PN) group, they were asked to relax and sit quietly while listening to music (Winston, 1984, track 4). Listening to relaxing music is often used as a non-stressful control task in studies that involve stress manipulation (e.g., van den Bos et al., 2009).

DELAY AND PROBABILITY DISCOUNTING TASK

The delay and probability discounting task administered following the stress and time orientation manipulations was a computerized question-based measure used in past research to study choice behavior (Richards et al., 1999). In the series of delay trials, participants were presented with questions asking about their preferences between $10 to be received after one of the delays (1, 2, 30, 180, and 365 days) or a smaller amount (e.g., $2) to be received immediately. For each trial, they were instructed to click on the reward they preferred. Time to choose was unlimited, and after each response participants were asked, "Are you sure about your response?" If they indicated uncertainty, they were permitted to go back to make a different choice; if they were sure, the program continued to the next question. For each delay, the immediate reward amount was increased or decreased in value (±$0.50) based on previous responses until an indifference value was reached. An indifference value is defined as the smallest amount of money chosen to be received immediately instead of waiting the specified delay in order to receive the $10 standard. A random adjusting-amount procedure was programmed to use the answers to previous questions to restrict the range of values from which the immediate value for

the next question was selected. This procedure was unlikely to be transparent to participants, because delay trials were interspersed with probability trials (see next section), and the algorithm for determining the adjusted value for subsequent questions was not readily predictable. No participant indicated that he detected the adjusting nature of the task.

Interspersed with delay trials were probability trials. In these trials, participants were presented with a choice between $10 to be received at varying levels of probability (25, 50, 75, and 90%) or a smaller amount with a 100% chance of receipt. As in the delay trials, the smaller amount was increased or decreased in value (±$0.50) based on previous responses until an indifference value was reached. The initial adjusted value was randomized, and the range of potential indifference values was restricted with every response. An indifference value for each probability was defined as the smallest amount of money chosen to be received with certainty instead of taking the probabilistic $10. The task automatically terminated once an indifference value was calculated for each delay and for each probability (for more details on this procedure, see Richards et al., 1999).

To increase the saliency and relevance of their choices, participants were told at the outset that one of their responses would be randomly selected and that they would receive the amount they chose at the delay specified, or with the probability specified. That is, if they chose the immediate reward on the randomly selected trial, they would receive the money as additional compensation after the session; conversely, if they chose the larger, delayed reward, they would receive the money either by mail, or by returning to the laboratory, after the delay specified. If the randomly selected trial was a probability trial, they would either receive a reward at the end of the session (if they chose the "definite" option) or they would draw a token from a bag containing two colors of tokens in the proportion that reflected the probability of their selection, thereby possibly receiving compensation at the end of the session. After completing this procedure, participants were asked to rate their certainties for receiving the delayed rewards (e.g., "If you had chosen the money delayed by 365 days, were you sure you would actually get that money if it was the randomly selected answer? How sure were you that you would get the money in 365 days if you chose it?"; Richards et al., 1999).

Following this task, salivary cortisol was sampled (T2). Participants in the stress condition were then asked to give the 3-min speech, while participants in the non-stress condition were informed of their winnings in the delay discounting task. Participants in the stress condition were not informed about their winnings until after the speech.

CORTISOL

Salivary free cortisol levels correspond well with plasma free cortisol levels. Therefore, collection of saliva is an easy and non-invasive means to obtain an index of the biologically active fraction of this hormone (Kirschbaum and Hellhammer, 1989). Participants were instructed to refrain from eating and consuming caffeine and alcohol for at least 2 h before study participation. Saliva samples were collected using Salimetrics Oral Swabs (SOS) after the first set of questionnaires (T1) and approximately 20 min after the stress manipulation (T2). Cortisol levels corresponding to the stress response tend to peak at this time (Kirschbaum et al., 1993). Subjects chewed on the SOS for about 60 s, after which they were placed in vials and stored in a freezer until later processing. Cortisol samples were assayed at Salimetrics, LLC (State College, PA, USA).

SELF-REPORT QUESTIONNAIRES

Self-report questionnaires administered at the beginning of the experiment included the PSS (Cohen et al., 1983) and the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). The PSS measures the degree to which situations in one's life are appraised as stressful (Cohen et al., 1983). Higher scores indicate higher perceived stress in response to stressful situations. The PANAS contains items that measure current negative affect and positive affect. High negative affect is characterized by subjective distress, nervousness, and overall unpleasant engagement. Positive affect, on the other hand, represents the degree to which the individual engages with the environment with positive emotions, such as enthusiasm and alertness (Watson et al., 1988). Demographic and income information were also collected at this time, and drug and alcohol use were assessed. The first cortisol measurement was taken as soon as these questionnaires were completed (T1).

Directly after the delay discounting task, participants completed the PANAS one more time. At the end of the experiment, the Barratt Impulsiveness Scale Version 11 (BIS-11; Patton et al., 1995) and a post-task questionnaire assessing stress during the experiment were administered. The BIS-11 provides a measure of real-world impulsivity (e.g., "I charge more than I earn") and has been found to possess satisfactory reliability and validity (Patton et al., 1995).

RESULTS

DATA REDUCTION

The indifference values determined in the delay discounting task were used to produce a delay discounting curve and to compute the area under the curve (AUC; Myerson et al., 2001) for each subject. The indifference values and delay values (1, 2, 30, 180, and 365 days) were used as x-coordinates and y-coordinates, respectively, to construct a graph of the discounting data. Vertical lines were then drawn from each data point to the x-axis, subdividing the graph into a series of trapezoids. The area of each trapezoid is equal to $(x_2 - x_1)[(y_1 + y_2)/2]$, where x_1 and x_2 are successive delays, and y_1 and y_2 are the indifference values associated with these delays (for the first trapezoid, the value of x_1 and y_1 are defined as 0 and 1). The area under the empirical discounting function is equal to the sum of the areas of these trapezoids.

Area under the curve values range from 0 to 1; higher AUC values indicate lower discounting by delay (i.e., a preference for delayed, larger rewards), while lower AUC values correspond to steeper, or more impatient, discounting (i.e., a preference for smaller, more immediate rewards). The AUC served as the measure of delay discounting rate in this study. As a theoretically neutral measure of delay discounting, the AUC makes no explicit assumptions regarding the form of the indifference curve. In this way, it is applicable to a wider range of indifference curves than other quantitative models, such as hyperbolic or exponential delay discounting models. This approach is common in studies of delay discounting (e.g., Dixon et al., 2006; Shiels et al., 2009).

For the probability choice data, AUC was also computed (Myerson et al., 2001), using indifference values for each probability as the *y*-coordinate, and the odds against receiving a reward as the *x*-coordinate. AUC was used as the measure of probability discounting rate. Here, smaller area values indicate greater discounting by odds against receiving a reward; therefore, participants with lower AUC values were relatively risk-averse, while higher AUC values indicated greater risk-taking behavior.

We tested for Pearson correlation between participants' scores on the working memory measure and delay discounting rate and probability discounting rate, as well as between BIS-11 scores and these variables. No significant relationships were found between working memory capacity and delay discounting rate ($r = 0.06$, $p = 0.55$) or probability discounting rate ($r = 0.08$, $p = 0.41$). There were also no significant associations between scores on the BIS-11 and delay discounting ($r = -0.05$, $p = 0.64$) or probability discounting ($r = 0.01$, $p = 0.96$). Therefore, these variables were dropped from further analyses.

EFFECTS OF ACUTE STRESS MANIPULATION

Two participants' cortisol data were excluded due to sample contamination, leaving 111 subjects in this analysis. There was an effect of acute stress manipulation on change in cortisol from T1 to T2, with stress groups showing significantly greater increases in cortisol than non-stress groups [$F_{(1, 110)} = 5.17$, $p = 0.025$; change in cortisol for future stress group: $M = 0.005\,\mu g/dL$, $SD = 0.116\,\mu g/dL$, range: -0.28 to $0.28\,\mu g/dL$; for present stress group: $M = -0.003\,\mu g/dL$, $SD = 0.073\,\mu g/dL$, range: -0.19 to $0.14\,\mu g/dL$; for present non-stress group: $M = -0.04\,\mu g/dL$, $SD = 0.068\,\mu g/dL$, range: -0.2 to $0.17\,\mu g/dL$; for future non-stress group: $M = -0.028\,\mu g/dL$, $SD = 0.053\,\mu g/dL$, range: -0.19 to $0.06\,\mu g/dL$]. There was also a main effect of stress manipulation group on change in negative affect from T1 to T2 [$F_{(1, 110)} = 8.99$, $p = 0.003$], indicating presence of greater negative affect after the stress manipulation than before it. There was no significant relationship between change in negative affect and change in cortisol, neither across all subjects ($r = 0.05$, $p = 0.60$) nor for participants in the stress groups ($r = -0.04$, $p = 0.80$). Not all participants completed the post-task questionnaire, assessing the stressfulness of the manipulation; therefore, this explicit measure was not considered in the manipulation check.

Between the two stress groups, FS and PS, no differences in cortisol ($t_{54} = 0.29$, $p = 0.77$,) or negative affect ($t_{55} = 1.09$, $p = 0.28$) were observed, implying that participants in these groups exhibited similar stress reactivity associated with the two manipulations. The groups did not differ with regard to changes in positive affect ($t_{55} = 1.23$, $p = 0.23$) from pre- to post-manipulation. Furthermore, there were no differences in change in positive ($t_{54} = -0.15$, $p = 0.89$) or negative affect ($t_{54} = -0.93$, $p = 0.36$) from T1 to T2 between the two non-stress groups, PN and FN, demonstrating that they were similarly emotionally influenced by the non-stress manipulations.

ACUTE STRESS INTERACTS WITH TRAIT PERCEIVED STRESS TO AFFECT DELAY DISCOUNTING

To investigate how individual differences in trait perceived stress might interact with acute stress to determine decision-making patterns, a moderated multiple regression approach was used (Aguinis, 2004). A one-way ANOVA indicated that PSS did not significantly vary by group ($F = 0.315$, $p = 0.814$). Mean-centered PSS scores, the dummy-coded acute stress exposure variable (non-stress = comparison group), and the dummy-coded time orientation variable (present = comparison group) were entered into the first step of the regression, with the interaction term between PSS score and acute stress manipulation entered in the second step. Delay discounting rate and probability discounting rate were entered as dependent variables in two separate analyses. This analysis showed that the interaction between acute stress and PSS significantly predicted delay discounting rate [PSS range: 8–43, $M = 23.56$, $SD = 6.57$; $\Delta R^2 = 0.06$, $\Delta F_{(1, 108)} = 6.71$, $p = 0.016$; **Figure 2**], better than the model that included PSS, acute stress exposure, and time orientation of the stressor. When including certainty about receiving delayed rewards (as assessed by the post-task questionnaire) as another control variable in the first step of this analysis, the interaction remains significant ($\Delta R^2 = 0.06$, $\Delta F_{(1, 107)} = 5.29$, $p = 0.007$). Delay discounting was highest (i.e., AUC value is lowest) in individuals with low trait perceived stress when they were under acute stress, and lowest for individuals with high trait perceived stress when they were under acute stress. In the first step of this regression, a model containing mean-centered PSS scores and the dummy-coded acute stress exposure and time orientation variables was not sufficient to predict delay discounting rate ($R^2 = 0.05$, $F_{(1, 109)} = 1.80$, $p = 0.15$). The multiple regression analysis revealed null results when probability discounting rate was entered as a dependent variable [$\Delta R^2 = 0.01$, $\Delta F_{(1, 108)} = 0.230$, $p = 0.19$].

As a confirmatory analysis, a three-way ANOVA was performed, with Time Orientation (Future, Present), Acute Stress (Stress, Non-Stress), and median-split PSS score (High PSS, Low PSS) as factors, and with delay discounting rate as the dependent variable. There were no significant main effects of any of the factors, but the interaction between PSS score group and acute stress group was significant [$F_{(1, 112)} = 5.188$, $p = 0.025$].

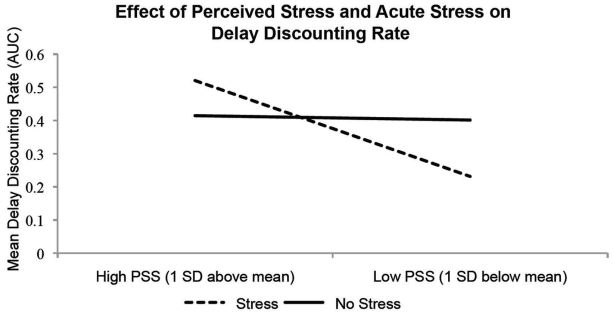

FIGURE 2 | Mean delay discounting rates for individuals with PSS scores 1 standard deviation above and below the mean, stratified by stress manipulation group (Stress, Non-stress; *N* = 113). There is a significant interaction of acute stress manipulation and trait perceived stress level on delay discounting rate (AUC). Higher AUC values indicate lower delay discounting rates (i.e., more later/larger rewards chosen). When no stress is present, participants with differences in trait perceived stress make similar choices on the delay discounting paradigm. When faced with an acute stressor, subjects with high PSS scores discount rewards at a lower rate, and subjects with lower PSS scores exhibit increased discounting.

EFFECT OF TIME ORIENTATION AND ACUTE STRESS ON IMMEDIATE REWARD BIAS

In a 2 × 2 ANOVA, the effects of stress [$F_{(1,112)} = 1.36$, $p = 0.25$] and time orientation manipulation on choices about probabilistic rewards in this paradigm did not reach significance [although there was a trend for future orientation; $F_{(1,112)} = 3.63$, $p = 0.06$]. There was no overall significant effect of future orientation on delay discounting rate [$F_{(1,112)} = 0.37$, $p = 0.55$], nor was there an overall effect of acute stress [$F_{(1,112)} = 0.55$, $p = 0.46$]. All interactions were also non-significant [for probability discounting: $F_{(1,112)} = 1.25$, $p = 0.27$; for delay discounting: $F_{(1,112)} = 0.41$, $p = 0.53$].

Due to evidence that future-thinking manipulations can decrease delay discounting rate (e.g., Benoit et al., 2011), the lack of a significant relationship between time orientation and delay discounting rate in this study was puzzling. Thus, in an additional analysis, we quantified participants' *immediate reward bias*, by calculating the choice index, or the ratio of the frequency of immediate reward options chosen to all options chosen (Boettiger et al., 2007; Benoit et al., 2011) for each subject. This immediate reward bias measure is distinct from the delay discounting rate, since it reflects participants' overarching preference for immediate reward, regardless of the delay intervals. Past studies (e.g., Ebert and Prelec, 2007) have shown that manipulations of time sensitivity may affect choices for the near-future and far-future differently, thereby changing delay discounting in a way that might not be captured by the AUC measure.

A 2 × 2 ANOVA was conducted with Time Orientation (Future, Present) and Acute Stress (Stress, Non-Stress) as factors and immediate reward bias as the dependent variable. No significant main effect of future orientation on the percentage of immediate reward choices was observed [$F_{(1,112)} = 0.47$, $p = 0.50$], nor was there a main effect of acute stress [$F_{(1,112)} = 0.88$, $p = 0.35$]. However, there was a significant interaction between time orientation manipulation and stress manipulation [$F_{(1,112)} = 56.63$, $p < 0.001$; **Figure 3**], whereby immediate reward bias was highest when a future-oriented situation was stressful (FS) or a present-oriented situation was non-stressful (PN), and it was lowest when a future-oriented situation was non-stressful (FN) or a present-oriented situation was stressful (PS). *Post hoc* t-tests revealed that the PN group exhibited significantly higher immediate reward bias than the PS group ($t_{55} = 4.44$, $p < 0.001$) and the FN group ($t_{54} = 4.61$, $p < 0.001$). In addition, the FS group demonstrated higher immediate reward bias than the PS group ($t_{55} = 6.10$, $p < 0.001$) and the FN group ($t_{54} = 6.34$, $p < 0.001$). There were no differences between the FS and PN groups in immediate reward bias ($t_{52} = -0.16$, $p = 0.87$), nor was there a significant difference between the FN and PS groups on this measure ($t_{55} = 1.18$, $p = 0.24$). The ANOVA remains significant even after entering certainty about receiving future rewards as a covariate [$F_{(1,111)} = 55.82$, $p < 0.001$]. However, we found that participants in the PS group were significantly less certain that they would receive a reward after 365 days than members of the other groups (compared to FN: $t = -2.63$, $p < 0.05$; FS: $t = -2.09$, $p < 0.05$; PN: $t = -2.04$, $p < 0.05$). This difference between groups is worthy of note.

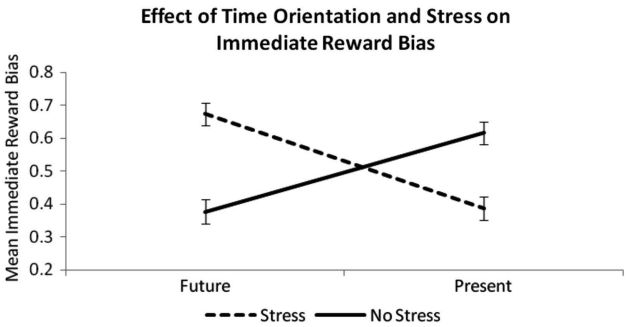

FIGURE 3 | Means of immediate reward bias (i.e., percentage of immediate options chosen) for each group (Future Stress, Future Non-stress, Present Stress, Present Non-stress). There is a significant interaction between time orientation manipulation and acute stress manipulation on this variable [$N = 112$; $F_{(1,111)} = 56.63$, $p < 0.001$], showing that future orientation increases choices for immediate reward when the stressor is present, but decreases immediate reward bias when the stressor is absent.

This finding should be interpreted with caution, as the percentage of immediate rewards chosen was strongly correlated with the number of choices that participants faced in this staircase paradigm ($r = 0.609$, $p < 0.001$). Indeed, if the first immediate reward amount randomly generated by the task was very high, then it would have been more likely to be followed by more immediate reward choices; if the first number was low, then there would be fewer immediate choices at the beginning. This source of noise is potentially problematic, but due to its random nature, it is unlikely to be at the root of group differences. It is plausible, however, that another mechanism (such as more consistent choices among subjects in the FN and PS groups) may be driving this effect. To investigate this possibility further, we fit a q-exponential model to the data to determine estimates of q (inconsistency) and k_q (delay discounting rate) using R statistical language (www.r-project.org). This function is based on Tsallis' statistics, and was computed as:

$$V(D) = A/\left[1 + \left(1 - q\right) k_q D\right]^{1/(1-q)} \quad (1)$$

where A is the amount of the reward at D, D is the delay to reward, k_q is a parameter of delay discounting at delay D, and the q parameter can be used to assess a subject's consistency in intertemporal choice (Cajueiro, 2006; Takahashi et al., 2007). Note that Eq. 1 is equivalent to the simple hyperbolic discount function [$V(D) = A/(1 + kD)$] when $q = 0$. Critically, in the current dataset, the q-exponential function could not be fitted in 26 participants due to an infinity value. After excluding these subjects, a one-way ANOVA revealed no group differences in the consistency parameter q ($F = 0.513$; $p = 0.679$) or in the discounting parameter k_q ($F = 0.487$; $p = 0.692$). The lack of quantifiable differences in consistency between groups indicates that this finding most likely arises from a change in bias toward immediate reward. However, in this staircase procedure, it is important to bear in mind that the immediate reward bias index is a less reliable measure than AUC.

EFFECT OF CORTISOL ON DELAY DISCOUNTING

Collapsing across all groups, there was a significant negative correlation between change in cortisol concentration from T1 to T2 and delay discounting AUC ($r = -0.19$; $p < 0.05$), whereby higher discounting of delayed rewards (smaller AUC) was associated with a larger increase in cortisol after the manipulation. That is, individuals who experienced an increase in cortisol, regardless of manipulation, were more likely to select smaller, sooner rewards. When inspecting the stress groups only, however, this relationship does not hold ($r = -0.16$, $p = 0.23$), although the direction of the effect is the same. There was no significant relationship between change in cortisol and probability discounting ($r = -0.06$; $p = 0.512$), or with immediate reward bias ($r = 0.14$; $p = 0.16$).

DISCUSSION

Many decisions are made under stressful circumstances, including decisions in which small, immediate rewards are weighed against larger, delayed rewards. The results of the present study carry strong implications regarding the effects of acute stress on intertemporal choice. In this investigation, we found that the interaction between trait perceived stress and acute stress had a significant effect on rate of delay discounting, regardless of the time orientation of the stressor. Based on our findings, we can conclude that individuals with high and low trait perceived stress made different choices when faced with acute stress. Those who are more likely to perceive stressful situations as such show a preference for larger, delayed rewards, while those with low perceived stress discount delayed rewards at a higher rate. When there was no acute stressor present, individuals who differed in PSS levels made similar choices in this paradigm. It is possible, then, that individual differences in stress appraisal may affect reward responsiveness under stress. When these same analyses were performed on probabilistic choice data, null effects were observed.

The finding that choices under stress were differentially affected by *a priori* level of trait perceived stress speaks to the complexity of stress as a construct, and the importance of studying individual differences in this domain. The challenge versus threat literature on stress (Blascovich and Tomaka, 1996; see also Henry, 1980; Frankenhaeuser, 1986) differentiates "good stress" from "bad stress" during active, goal-relevant tasks. Whether an individual perceives a stressful situation as a challenge or a threat may affect the decisions that one makes in such a situation (e.g., Kassam et al., 2009). In addition, the perceived controllability of a stressor can influence executive functioning under stress (Henderson et al., 2012). A plausible mechanism in the current study is that those who are more likely to perceive situations as stressful are more likely to interpret the stress manipulation as threatening. Accordingly, they might experience a decrease in their reward response to immediate reward and make more delayed reward choices. This decrease in reward responsiveness has been documented in previous studies (Bogdan and Pizzagalli, 2006), and the association between blunted reward response and reduced delay discounting has also been found previously (Lempert and Pizzagalli, 2010). Those with low trait perceived stress, on the other hand, may feel more control over the stressor, and even see the situation as a challenge with a positive valence. Thus, they may experience an increased immediate reward response and choose more immediate rewards. In addition, high trait perceived stress has been shown to be hereditary (Bogdan and Pizzagalli, 2009) and associated with a serotonin transporter genotype that is linked with depression following stress (Otte et al., 2007). Given serotonin's role in delay discounting processes (Schweighofer et al., 2008), the interplay between serotonin levels, stress, and decision-making is an interesting future avenue of research.

In this study, we also found that the interaction between time orientation and acute stress had a significant effect on bias toward immediate reward. Participants tended to make far-sighted choices when they experienced present stress or when they thought about the future in a stress-free light. Conversely, when participants thought about a future situation that was stressful (in this case, a future job interview), they showed a greater preference for immediate – albeit smaller – rewards. These findings suggest that induction of a future orientation is not sufficient to reduce delay discounting rate. Past studies that have found an effect of prospection on discounting rate (Peters and Buchel, 2010; Benoit et al., 2011) focused only on positive future events. Framing a future situation as stressful, however, might precipitate a bleak view of the future, which, in turn, shifts a participant's motivation toward increasing immediate reward. Changes in mood might be involved in this process (Hirsh et al., 2010; Augustine and Larsen, 2011). In our study, it is impossible to disentangle effects of mood from effects of stress; in fact, negative affect increased significantly more for all participants who underwent a stress manipulation relative to those in the non-stress conditions.

Another methodological limitation of our study is that there might be differences between our future non-stress and present non-stress groups independent of time orientation itself (e.g., arousal state may be different for listing positive future events than for listening to music). Similarly, there may be differences between the stress groups that are unrelated to time orientation; in the present stress condition, participants are socially evaluated for more superficial qualities (physical appearance), whereas in the future stress condition, they are evaluated for deeper qualities. Although there were no significant differences between the two stress conditions in cortisol increase, participants may have also felt more stressed in the present stress condition, due to the uncontrollability of the speech topic (subjects had more freedom to choose a topic in the "future job" speech condition). The aim of the current study was to investigate the effects of acute stress on delay discounting, while controlling for the potential confound of time orientation. Therefore, statistical differences in decision-making based on time orientation should be interpreted with caution. Future studies are warranted to further clarify the contributions of time orientation and stress to delay discounting.

While future orientation and stress, in combination, affected immediate reward bias, they did not have any effect on *rate* of delay discounting. This finding is unusual, given that these two variables were derived from the same choice procedure, and that they are correlated ($r = -0.604$, $p < 0.01$). However, the percentage of small-immediate rewards chosen does not fully represent an individual's tendency to choose more proximal rewards versus more distal ones. Only delay discounting rate takes into account the various delays used in the paradigm, which ranged from 1 to 365 days. It is possible that certain manipulations, such as

our future orientation manipulation, may induce an ephemeral tendency toward choosing either immediate or future rewards, without affecting the more stable variable of discounting rate, characterized in this study by AUC. For example, Ebert and Prelec (2007) found that manipulations of time sensitivity affected the valuation of near-future and far-future rewards differently.

With our AUC measure of delay discounting, it is not clear if the differences reported above are due to effects on the discount parameter (i.e., to what degree are sooner rewards valued more than later rewards), or effects on the participants' utility functions (i.e., how the objective reward amounts correspond to participants' subjective values). Previous studies have found that delay discounting behavior can be explained by a combination of diminishing marginal utility and preference for sooner reward (Andersen et al., 2008; Pine et al., 2009). It is also possible that our manipulations influenced time perception in these subjects, which then modulated their delay discounting (Takahashi, 2005; Zauberman et al., 2009). Future research will be necessary to clarify the effects of stress on time perception, marginal utility, and time discounting.

Stress hormones, such as cortisol, are known to influence a number of brain regions related to decision-making. They seem to impair prefrontal cortex (PFC) function and executive control (Hains and Arnsten, 2008), but they activate different receptors in PFC depending on the level of stress, and depending on the time of day (see Lupien et al., 2007 for a review). One limitation of the current study is that, even though we always conducted the study in the afternoon, we did not assess participants' sleep habits. Acute stress might affect glucocorticoid activity in early risers and late-risers differently; furthermore, late-risers and early risers may differ in their decision-making patterns (e.g., Tonetti et al., 2010). However, all participants in the study were students, and most had similar class schedules, so it is unlikely that their sleeping patterns varied widely. Stress hormones can also impair hippocampal function and neurogenesis (McEwen, 1999). White matter volume in the hippocampus has been shown to be positively associated with delay discounting rate (Yu, 2012), and the hippocampus is involved in future-directed thinking during delay discounting (Peters and Buchel, 2010). Determining the relationship between stress, hippocampal activity, and delay discounting is a promising avenue for future research.

Unlike previous studies on stress and decision-making (e.g., Porcelli and Delgado, 2009), we found no significant effect of acute stress on choices in the probability portion of the decision-making paradigm. However, differences in experimental procedures, including stress application and actual paradigm, might be responsible for this discrepancy. In contrast with many risk-taking tasks, in our task, participants made decisions about a large range of probabilities under no time pressure. There were also no correlations found between delay discounting and working memory capacity or BIS-11 scores, but these null findings are unsurprising, since this study examined manipulations of delay discounting, and not trait delay discounting. That is, any correlations across all participants may have been overwhelmed by larger, between-group differences.

The inclusion of males only in this study can be seen as both a strength and a limitation. While it is a standard practice in stress research, and we were able to rule out gender effects on the hormonal data, gender differences have been observed in studies that utilize stress manipulations (Preston et al., 2007; Lighthall et al., 2009; van den Bos et al., 2009; Takahashi et al., 2010). Because gender is an important variable of interest in studies of stress and decision-making, we felt that excluding its consideration in this already complex study was warranted. It is premature, however, to generalize our results about the effects of stress on decision-making in this sample to the general population; future studies should aim to uncover gender differences if they exist.

The present study provides important evidence that a general outlook toward stress can affect decision-making under stress. This finding is relevant to the prevention of substance dependence and other disorders of impulsivity (e.g., attention deficit/hyperactivity disorder, pathological gambling). Both high delay discounting (Yoon et al., 2007; Harty et al., 2011) and stress (Sinha, 2001) have been shown to be vulnerability factors for addiction and relapse. It has also been hypothesized that stress might elicit suicidal behavior and other impulsive behaviors in depression, through modulation of delay discounting (Takahashi, 2011). By addressing how individuals handle stress, and manipulating the way that immediate rewards are perceived under stress, it may be possible to intervene in the development of maladaptive and dangerous behaviors.

In conclusion, the presence of acute stress interacts with general perceived stress to influence discounting of delayed rewards. Furthermore, future orientation and acute anticipatory stress show interactive effects on bias toward immediate reward. Whether one is contemplating the present or the future during intertemporal choice affects the likelihood with which one chooses immediate rewards, but this effect is tempered by the stressfulness of the context. Countless crucial decisions are made under stress every day. The current findings add to our understanding of the mediating factors that act between acute stress and decision-making.

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Cognitive and neural aspects of information processing in major depressive disorder: an integrative perspective

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Researchers using experimental paradigms to examine cognitive processes have demonstrated that Major Depressive Disorder (MDD) is associated not with a general deficit in cognitive functioning, but instead with more specific anomalies in the processing of negatively valenced material. Indeed, cognitive theories of depression posit that negative biases in the processing of information play a critical role in influencing the onset, maintenance, and recurrence of depressive episodes. In this paper we review findings from behavioral studies documenting that MDD is associated with specific difficulties in attentional disengagement from negatively valenced material, with tendencies to interpret information in a negative manner, with deficits in cognitive control in the processing of negative material, and with enhanced memory for negative material. To gain a better understanding of the neurobiological basis of these abnormalities, we also examine findings from functional neuroimaging studies of depression and show that dysfunction in neural systems that subserve emotion processing, inhibition, and attention may underlie and contribute to the deficits in cognition that have been documented in depressed individuals. Finally, we briefly review evidence from studies of children who are at high familial risk for depression that indicates that abnormalities in cognition and neural function are observable before the onset of MDD and, consequently, may represent a risk factor for the development of this disorder. By integrating research from cognitive and neural investigations of depression, we can gain a more comprehensive understanding not only of how cognitive and biological factors interact to affect the onset, maintenance, and course of MDD, but also of how such research can aid in the development of targeted strategies for the prevention and treatment of this debilitating disorder.

Keywords: depression, MDD, neuroimaging, amygdala, interpretation bias, attention bias, memory bias, cognitive control

INTRODUCTION

Major Depressive Disorder (MDD) is a debilitating psychiatric condition that is characterized by a range of emotional, cognitive, and behavioral symptoms, including core features of persistent depressed mood and decreased interest or pleasure in usually enjoyable activities. MDD is also highly prevalent; almost 20% of the American population will experience at least one clinically significant episode of depression in their lifetime (Kessler and Wang, 2009). Further, more than 75% of these individuals will go on to experience a subsequent episode of depression, often within the first two years of recovery (Boland and Keller, 2009). Given these alarming statistics, it is important for researchers to elucidate the cognitive and neurobiological factors that are involved in the onset, maintenance, and recurrence of this disorder.

Beck's (1976) cognitive model of depression has advanced our understanding of depression and has served as the foundation for multiple lines of research. This model posits that early adverse events, in combination with other (e.g., genetic, personality) factors, can lead to the development of depressive self-referential schemas that influence information processing through negative biases in attention, memory, and cognition. These biases then confer vulnerability for depression by leading individuals to interpret their experiences in systematically negative ways.

Since the formulation of this model, a wide body of research has amassed examining the cognitive mechanisms of depression and refining cognitive theories of this disorder (Ingram, 1984; Teasdale, 1988; Mathews and MacLeod, 2005). In this paper we review important findings from this work, focusing in particular on research demonstrating that depression is characterized by negative biases in attention, interpretation, memory, and cognitive control. We also present and discuss findings from studies using functional magnetic resonance imaging (fMRI) to elucidate the neural underpinnings of these biases, and review how cognitive and neural dysfunction in depression may influence emotion regulation and inform the development of new treatments. Finally, we briefly discuss the implications of findings of extant research for the prevention of depression.

ATTENTIONAL BIASES

EARLY STAGES OF PROCESSING

The question of whether depression is associated with biases during the initial orienting to emotion-relevant information has been examined in studies that use subliminal or very rapid presentations

of affective material. For example, in the dot-probe task, two stimuli (one neutral, the other positively or negatively valenced) are presented simultaneously for a brief duration (e.g., 14 ms). A dot then appears in the previous location of one of the two stimuli and participants must indicate the location of the dot as quickly as possible. Biased allocation of subliminal attention to negative emotional material in this task is indicated by faster reaction times to the dot when it appears in the location previously occupied by the negative stimulus. Using this task, Mathews et al. (1996) found no difference in reaction times between clinically depressed and non-depressed participants to anxiety-relevant words. Similarly, Mogg et al. (1995) found evidence for a negative attentional bias in participants diagnosed with an anxiety disorder, but not in participants diagnosed with depression.

These findings, which suggest that depression is not characterized by automatic biases in attention toward negative material, are consistent with results of studies using the subliminal version of the emotional Stroop. In this task, participants are presented with a series of masked emotional and neutral words, and the time participants take to name the non-semantic attributes of the words (most typically the ink color in which a word is presented) is used as a measure of attentional interference caused by the emotional content of the masked words; an increase in reaction time indicates an increase in attention to the emotional meaning of the word. Researchers have largely failed to find a difference between clinically depressed and non-depressed participants' latency to name the colors of subliminally presented negative words (Mogg et al., 1993; Bradley et al., 1995a; Lim and Kim, 2005). Similarly, Yovel and Mineka (2005) found no associations between biases for subliminally presented depression-relevant words and levels of self-reported depressive symptoms in a sample of undiagnosed undergraduate students.

Finally, a subliminal lexical decision task has been used to examine biases in the rapid orienting to negative material in depression. In this task, participants are presented with a subliminal prime emotional or neutral word, followed by a supraliminal string of letters that participants must judge as being a word or not. Increased attention toward negative material is indicated by shorter response latencies to supraliminal words that are negative in valence and that are identical, or semantically related, to the meaning of the subliminal prime. Using this task, Bradley et al. (1994) found that undiagnosed graduate students with higher levels of negative affect exhibited stronger priming effects for depression-relevant words, and further, that priming effects were more strongly associated with symptoms of depression than with symptoms of anxiety. However, Matthews and Southall (1991) and Dannlowski et al. (2006) failed to observe an effect of subliminal negative primes on reaction times to target words in a sample of clinically depressed individuals.

Although the available behavioral research suggests that major depression is not characterized by biases in the rapid orienting of attention toward negative material, investigators have begun to use neuroimaging methodologies to further explore whether there is neural evidence for biases to subliminally presented stimuli in the absence of observable group differences in behavior. Investigators in this area have focused primarily on patterns of activation in the amygdala, a region that is crucial to the perception of salient affective information and that can process emotional information on a subconscious level by virtue of direct connections from the retina via the superior colliculus and pulvinar (Pessoa, 2005). Results from these investigations are mixed. In one early study, Sheline et al. (2001) observed greater amygdala activation in clinically depressed, relative to non-disordered, participants during the passive viewing of emotional backward-masked faces; importantly, this pattern of hyper-reactivity was not found to be valence-specific. More recently, Dannlowski et al. (2008) found no difference in amygdala reactivity between clinically depressed and non-disordered participants during the viewing of masked sad and angry faces. In contrast, both Suslow et al. (2010) and Victor et al. (2010) found heightened amygdala activation in clinically depressed relative to non-depressed participants during the viewing of masked sad faces. It is important to note, however, that 20% of the depressed participants in Suslow's study and 50% of Victor's depressed sample met diagnostic criteria for comorbid anxiety. Therefore, it is not clear whether increased amygdala reactivity in depressed participants in these latter investigations was influenced by this comorbidity.

Considered collectively, there is only modest evidence to support an association between major depression and a subliminal attentional bias toward negative material. While two studies have reported that a neural processing bias may occur in the absence of observable differences in behavior, the influence of anxiety comorbidity clearly requires further investigation. Certainly, distinguishing effects of anxiety from depression on subliminal attention will help to clarify whether these biases are central to the onset and maintenance of depressed mood individuals vulnerable to MDD. Given the high prevalence of comorbid depression and anxiety (Sartorius et al., 1996), however, as well as data showing that the combined disorders are characterized by a more severe course of illness than is either disorder alone (Keller et al., 1983, 1984; Brown et al., 1996), it will be important for researchers to continue to assess patterns of cognitive and neural dysfunction that are associated with comorbid depression and anxiety.

Future research examining automatic processing biases in depression may also benefit from the use of techniques, such as electroencephalography (EEG), that yield high temporal precision. Event-related potentials, for instance, have been used successfully to document differences in the spatial and temporal patterning of neural activity occurring in response to emotional stimuli presented overtly and outside conscious awareness (Williams et al., 2007b). Neuroimaging approaches may also further elucidate the basis for other supraliminal biases in cognition. In a pair of studies, for example, Dannlowski et al. (2007a,b) found that both clinically depressed and non-depressed individuals who exhibited particularly high levels of amygdala activity in response to subliminally presented negative facial expressions, rated neutral material as more negative in a separate series of cognitive assessments conducted outside the scanner than did individuals with low levels of amygdala reactivity. Thus, rapid and automatic patterns of neural responding in the amygdala may contribute to other supraliminal biases in cognition.

LATER STAGES OF PROCESSING

In contrast to investigations of attention biases to subliminal stimuli in depression, findings from studies examining biases to negative stimuli that are presented at longer (supraliminal) durations are more consistent in suggesting the presence of a mood-congruent bias in attention. When the presentation of emotional facial expressions is extended in the dot-probe task from 14 to 1000 ms for example, clinically depressed participants, in comparison with non-disordered controls, exhibit longer reaction times to sad than to happy, angry, or fearful faces (Gotlib et al., 2004; Fritzsche et al., 2010). This bias has also been found in formerly depressed participants (Joormann and Gotlib, 2007), as well as in non-disordered girls at familial risk for depression (Joormann et al., 2007b; Kujawa et al., 2011), suggesting that attentional biases are involved in risk for the onset and recurrence of MDD (but see also Mogg et al., 1995; Koster et al., 2006). Based on the results of these and similar studies, researchers have posited that depression is not characterized by a rapid orienting to negative stimuli, but instead, involves difficulties in disengaging from this material once it captures an initial attention (e.g., Gotlib and Joormann, 2010). In line with this formulation, clinically depressed individuals are not found to generally differ from non-disordered controls in their likelihood of attending to negative stimuli, but once their attention is captured by such stimuli, they spend significantly more time looking at this material than do controls (Mathews and Antes, 1992; Eizenman et al., 2003; Caseras et al., 2007; Kellough et al., 2008).

Investigators have documented heightened amygdala activation in clinically depressed individuals during the passive viewing of negative emotional stimuli (Siegle et al., 2002, 2007b; Anand et al., 2005; Dichter et al., 2009; Peluso et al., 2009; but also see Davidson et al., 2003; Irwin et al., 2004), suggesting that attentional biases in the supraliminal processing negative material may be associated, at least in part, with functional abnormalities in this brain region. Moreover, it appears that increased amygdala activation in MDD is sustained beyond the presentation of the negative material itself. For example, Siegle et al. (2002) found that during a valence identification task, whereas non-disordered controls exhibited amygdala responses to all stimuli that decayed within 10 s, clinically depressed individuals were characterized by sustained amygdala responses to negative words that persisted through a subsequent non-emotional distracting task (25 s later) that was designed to induce activation in brain areas hypothesized to suppress activation in the amygdala (e.g., dorsolateral prefrontal cortex; dlPFC). Moreover, sustained amygdala activation to unpleasant words in this study was correlated in depressed participants with self-reported rumination, a hallmark feature of depression that has been posited to be closely linked to sustained processing of negative information. Results that are conceptually similar to findings of sustained amygdala activation in MDD have been obtained in studies examining EEG and pupillary dilation responses to affective material (Deldin et al., 2001; Siegle et al., 2001, 2003; Deveney and Deldin, 2004). Considered collectively, therefore, the available research suggests that depressed persons' affective experience of negative stimuli persists well beyond the direct exposure to the material and that this processing interferes with engagement in subsequent activities.

Biases in attention to negative stimuli in MDD have also been found in studies using the supraliminal version of the emotional Stroop. Similar to the subliminal version of this task, participants are asked to name the colors in which a series of emotional and neutral words are presented; delays in response times are interpreted as indicating interference caused by increased attention to, and processing of, the emotional meaning of the words. Investigators using the supraliminal emotional Stroop task have found that clinically depressed participants take longer than do non-disordered controls to name the color of negative, but not of positive words (Gotlib and McCann, 1984; Williams and Nulty, 1986; Gotlib and Cane, 1987; Gilboa and Gotlib, 1997). One neuroimaging study has examined patterns of activation occurring during the performance of this task and found that a bias for negative words in clinically depressed individuals was associated with increased activation in the rostral anterior cingulate cortex (rACC) and precuneus (Mitterschiffthaler et al., 2008). This pattern of the results, in the rACC in particular, appear relevant to the study of attentional biases in depression; a large body of research supports a role of this region in the top-down control of attention to emotional material (Bush et al., 2000; Elliott et al., 2000; Vuilleumier et al., 2001). Increased rACC activation in depressed individuals during the processing negative words, therefore, could indicate that these participants require additional activation in this area to be able to override the interference caused by the emotional meaning of these stimuli. The positive correlation that was observed in this study in depressed individuals between activation in the rACC and reaction time latencies to color naming of negative words supports this interpretation. It is also possible, however, that increased activation in the rACC of depressed participants is related more generally to a role of this region in the processing of salient emotional information; the rACC is activated by a variety of affective paradigms, including tasks that involve the generation of sad mood and attention to affective (versus non-affective) characteristics of a pictorial stimuli (Bush et al., 2000; Phan et al., 2004). Thus, it is difficult to determine whether depression-associated anomalies in behavior and brain function during the emotional Stroop are due to negative biases in attention, to negative biases in inhibitory function, or both. The question of whether depression is associated with valence-specific biases in inhibition and cognitive control is an important area of research that we discuss in greater detail below.

Other investigations of possible biases in supraliminal attention to negative material in depression have turned to the use of an emotional version of the Go/No-Go task. In this task, participants are presented with a series of words and are asked to initiate a button press to words that match a target valence and withhold a button press to words that do not. Faster reaction times are interpreted as indicating better detection and, therefore, increased attention to the emotional meaning of the word. Murphy et al. (1999) found that, compared with non-disordered controls, clinically depressed participants were faster during "Go" trials when responding to sad versus happy words. This MDD-related bias toward negative material on the emotional Go/No-Go task has since been replicated (Erickson et al., 2005; Kyte et al., 2005; Kaplan et al., 2006), and been associated in one neuroimaging study with abnormally elevated activation in the rACC (Elliott

et al., 2002). Thus, consistent with the neuroimaging literature on the emotional Stroop task, biases in attention toward negative words in the emotional Go/No-Go task appear to be directly related to dysfunction in this region.

One final paradigm that investigators have used to examine the influence of emotion on attention in depression is the emotional oddball task. In a typical oddball experiment, participants are presented with infrequent task-relevant (target) events, to which they initiate a button press, embedded within a continuous stream of frequent standard events. Other task-irrelevant (distractor) events that are equally infrequent are also presented, and the valence of these distractor events is manipulated to assess whether increased attention toward these events influences reaction times to subsequent task-relevant targets. Wang et al. (2008) recently found that, compared with non-disordered control participants, clinically depressed individuals exhibited significant slowing of responses to task-relevant targets when they were preceded by sad, but not by neutral, distractors. Thus, depressed participants appeared more easily distracted by task-irrelevant negative (but not neutral) stimuli than were non-disordered controls, and this distraction interferes with ongoing task performance.

Interestingly, in examining the neural aspects of performance on the emotional oddball task, Wang et al. (2008) found that whereas non-disordered participants' responses to targets that followed negative (relative to neutral) distractors were associated with activation in the rostral ACC and insula, depressed participants did not show these activations. This difference in activation is important not only in again implicating the rostral ACC in attentional processing biases in depression, but in suggesting more specifically that dysfunction in this region (and in the insula) is associated with, or contributes to, difficulties disengaging from the processing of irrelevant mood-congruent material. What is more, depressed participants in this study demonstrated abnormal elevations in activation of executive (dlPFC) and inhibitory (ventrolateral PFC; vlPFC) regions as they responded to target events that followed sad (but not neutral) distractors. Wang et al. interpreted this pattern of function as compensatory, making up for insufficient levels of activity in the rACC and insula (Harvey et al., 2005; Wagner et al., 2006), although it is also possible that depressed individuals require greater recruitment of the lateral PFC when trying to minimize interference from negative emotional stimuli. Such a formulation is consistent with results of another recent functional neuroimaging study conducted by Kerestes et al. (2012), who found that, compared with their non-depressed counterparts, formerly depressed participants exhibited increased activity in the dlPFC and vlPFC during the presentation of negative, but not of positive, emotional distractors in a working memory task.

Considered collectively, the results of these studies suggest that depression is not characterized a rapid automatic biasing toward negative information, but instead, by difficulties disengaging attention from negative material once it has captured initial attention. Increased processing of negative material by depressed individuals may result from dysfunction in the amygdala. In addition, findings from neuroimaging studies using the Go/No-Go, Stroop, and emotional oddball tasks support the involvement of dysfunctional executive and inhibitory centers in difficulties in attentional control in depression. As we noted above, however, because accurate performance on some of aforementioned tasks depends on intact inhibitory function, it is difficult to determine whether negative biases in attention or in inhibitory function drive neural and behavioral abnormalities. The question of whether depression is associated with valence-specific biases in inhibition and cognitive control is an important area of research that we discuss in greater detail below.

INTERPRETATION BIASES

Investigators have posited that biases in the interpretation of emotionally ambiguous material play a central role in the onset and maintenance of depressed mood. In one early study, Butler and Mathews (1983) examined whether clinically depressed individuals interpret ambiguous information more negatively than do non-disordered individuals. These researchers presented participants with ambiguous social scenarios and then asked them to select, from a set of provided options, which interpretation was the most likely to come to mind. Clinically depressed participants chose the more negative option more frequently than did controls, suggesting the presence of a negative interpretation bias. This finding has since been replicated (Nunn et al., 1997; Voncken et al., 2007). Also consistent with these reports, Mogg et al. (2006), found, using a homophone task in which participants listened to ambiguous words (e.g., die/dye, weak/week) and then wrote the word they heard, that clinically depressed participants tended to write more negative words than did their never-depressed counterparts.

Although informative to our understanding of cognitive functioning in depression, findings of these studies are limited by depression-associated biases in self-report. That is, rather than processing ambiguous material in a more negative manner, depressed persons may have a greater tendency than do their non-depressed peers to report a more negative meaning of scenarios when queried directly about their interpretations. To address this issue, investigators have turned to the use of tasks that involve indirect measures of bias, such as reaction time. Results from these studies, which have generally assessed dysphoric individuals (i.e., individuals experiencing subclinical levels of depression), are mixed. Lawson and MacLeod (1999) presented participants with a series of ambiguous sentences, each of which was followed by a target word that participants read aloud and that was related to either the negative or the neutral interpretation of the sentence. Reaction times to target words were used as an index of interpretation bias: shorter response latencies to negative words than to neutral words were interpreted as being primed by a negative interpretation of the sentence. Results of this study showed no difference between dysphoric and non-dysphoric individuals in reaction times to negative words. This finding was later replicated in a sample of dysphoric participants who received a negative mood induction (Bisson and Sears, 2007), suggesting that response biases were responsible for the negative biases in interpretation reported in previous studies. In another study of dysphoric individuals, however, Lawson et al. (2002) found that dysphoric individuals who exhibited greater severity of depressive symptoms, compared to individuals who were experiencing lower levels of depressive symptoms, showed increased magnitude of the eye blink reflex,

a physiological marker of negative emotional processing, during the presentation of ambiguous stimuli. Moreover, using a modified word sentence association paradigm (Beard and Amir, 2009), Hindash and Amir (2012) found that dysphoric individuals were significantly faster to endorse associations between an ambiguous sentence and a negative descriptor word than were non-dysphoric individuals, again supporting an association between depressive symptoms and negative interpretation biases.

Although potentially susceptible to response biases, evidence for a negative interpretation bias in depression also comes from studies using emotion recognition tasks; clinically depressed individuals have been found to be both slower (Leppänen et al., 2004) and less accurate (Leppänen et al., 2004; Gollan et al., 2008) than have non-disordered individuals in recognizing neutral emotions. Moreover, clinically depressed participants have been found to more often misinterpret neutral faces as sad, a bias that has been found to persist following symptom remission (Leppänen et al., 2004). Other investigators have observed that clinically depressed individuals exhibit difficulties in the identification of subtle positive emotion (but no difference in the identification of low-intensity sadness; Suslow et al., 2001; Surguladze et al., 2004; Joormann and Gotlib, 2006). Again, such difficulties have been documented in remitted depressed individuals (Lemoult et al., 2009), and have also been observed in individuals at high risk for depression (Joormann et al., 2010), suggesting that biases in the interpretation of facial emotion represent a risk factor for the onset of a depressive episode.

In summary, studies examining interpretation biases in depression have yielded inconsistent results. This variability in findings may be attributable to biases in self-report, or to the clinical heterogeneity of the participant samples (e.g., sampling from dysphoric versus clinically depressed participants). Certainly, additional studies that examine individuals who are experiencing moderate to severe depression, and that use indirect measures such as reaction time to circumvent potential confounds caused by biases in self-report, are needed to clarify the role of negative interpretation biases in MDD. Moreover, functional neuroimaging studies would help to elucidate the neural correlates of these biases.

MEMORY BIASES

ENHANCED MEMORY FOR NEGATIVE MATERIAL

One of the most robust and consistent findings regarding cognitive biases in depression involves the preferential recall of negative over positive material (Watkins et al., 1992; Bradley et al., 1995b; Ridout et al., 2003). In a meta-analysis of studies assessing recall performance in clinical depression, Matt et al. (1992) found that individuals with MDD remembered 10% more negative than positive words on explicit recall tasks. Other investigators have found that clinically depressed individuals do not exhibit a bias toward the encoding and recall of positive material that has been reported in non-depressed persons (Gilboa-Schechtman et al., 2002; Ellwart et al., 2003; Harmer et al., 2009b; Gotlib et al., 2011). It is important to point out, however, that these findings have been obtained on tasks of explicit memory; biases in memory for positive and negative stimuli in MDD are found less reliably in studies that assess the unintentional encoding and/or retrieval of valenced material (Matt et al., 1992). This pattern has led researchers to posit that memory biases in depression are due in large part to increased elaboration occurring at later stages of attentional processing (Watkins, 2002). Consistent with this formulation, Koster et al. (2004) found, in a sample of participants experiencing subclinical depression, that attentional biases toward negative words predicted the number of negative words that were subsequently recalled in conditions that allowed for elaborative processing, whereas no such bias was found for words that were presented in conditions that prevented elaborative processing.

Researchers conducting both lesion and functional neuroimaging studies of healthy individuals have found that the amygdala is centrally involved in the encoding and retrieval of emotional material (Cahill et al., 1995; Adolphs et al., 1997). This structure exerts a bottom-up influence on other brain regions, including the hippocampus, which subserve episodic memory formation and retrieval (Steinvorth et al., 2005). Given these findings, neuroimaging studies that have attempted to elucidate the neural underpinnings of negative biases for negative material in explicit memory tasks have focused largely on activations in this region. In the first such study, Ramel et al. (2007) found bilateral amygdala response during the encoding of emotional material predicted increased recall of negative (but not of positive) words in formerly depressed participants in whom a sad mood was induced. This pattern was not observed in non-disordered participants or in remitted depressed participants who did not receive a sad mood induction. In the second study, Hamilton and Gotlib (2008) found that increased memory sensitivity for negative material in clinically depressed individuals was associated with greater activity in the right amygdala during successful encoding of this material. Again, this pattern of activation was not present in healthy participants during the encoding of negative stimuli, or in depressed participants during the encoding of positive stimuli. Interestingly, Hamilton and Gotlib also found that increased activation of the amygdala in depressed individuals was accompanied by increased functional connectivity between the amygdala and the hippocampus, caudate, and putamen, suggesting that during the encoding of negative material, depressed individuals over-recruit a neural network that is involved more generally in enhancing memory for affective stimuli.

OVERGENERAL RECALL OF AUTOBIOGRAPHICAL MEMORIES

In addition to biases in explicit memory, individuals experiencing clinical depression have also been found to demonstrate overgeneral recall of autobiographical memories (see Williams et al., 2007a, for a review). Williams et al. (2007a) argue that reporting overgeneral memories in response to negative cues on the autobiographical memory test (AMT; Williams and Broadbent, 1986) may represent attempts by individuals to protect against the negative affective features that were encoded within the episodic memory system. By recalling overly general descriptions of events that is, one may minimize the experience of negative affect that is attached to distressing memories by blocking access to the details of such memories. Notably, previous studies have found that overgeneral memory in depression correlates with rumination, cognitive deficits, and with longer durations of depressive episodes (Watkins and Teasdale, 2001, 2004; Raes et al., 2005). Further, overgeneral positive memories have been found to predict both poorer

recovery from depression (Brittlebank et al., 1993) and a longer delay in recovery from affective disorders (Dalgleish et al., 2001).

Investigators are just beginning to understand the neural correlates of overgeneral autobiographical memory in major depression. In one recent study, Zhu et al. (2012) observed significant associations between patterns of connectivity within the default mode network (DMN) and clinically depressed participants' tendency to recall overgeneral (versus specific) autobiographical memories: depressed participants who recalled a greater number of overgeneral memories on the AMT exhibited significantly decreased connectivity in the posterior regions of the DMN [posterior cingulate cortex (PCC), precuneus, and angular gyrus]. Interestingly, posterior DMN regions, and in particular the PCC and precuneus, have been found to play a role in the successful retrieval of autobiographical and self-relevant information in non-disordered individuals (Cavanna, 2007; Spreng et al., 2009; Spreng and Grady, 2010). Thus, aberrant activity within, and connectivity between, these regions may contribute to the patterns of overgeneral recall that are observed in depression.

In a second study, Whalley et al. (2012) compared activation patterns between clinically depressed and non-disordered individuals as they viewed cue words referencing a past autobiographical event. Whalley et al. found that although both groups exhibited similar patterns of activation in regions associated with autobiographical memory retrieval (e.g., PCC), depressed individuals showed reduced activity in the vlPFC, an area that has been posited to be a central component to autobiographical networks (Gilboa, 2004; Svoboda et al., 2006). Thus, reduced function in this region could be associated, in addition posterior portions of the DMN, with poorer retrieval of personal memories.

DEFICITS IN THE COGNITIVE CONTROL OF PROCESSING NEGATIVE MATERIAL

Overriding prepotent responses and inhibiting the processing of irrelevant material that captures attention are core abilities that allow individuals to respond flexibly and to adjust their behavior and emotional responses to changing situations. Deficits in cognitive control and inhibition may be associated with the elaborative and memory biases that we described above that characterize depressed individuals. In this section, we focus on studies that have examined valence-specific abnormalities in cognition involving inhibition and working memory in MDD.

INHIBITION

The negative priming task is one of several experimental tasks that have been used effectively to assess difficulties in cognitive control and inhibition. In this task, participants are asked to respond to a target in the presence of a distractor. For example, on one trial, participants may be asked to name a word written in red ink (target) while ignoring a simultaneously presented word written in blue ink (distractor). Negative priming occurs when inhibition to the blue word remains activated, delaying the response to a target on a subsequent trial if that target is identical to or related to the previously ignored distractor. Thus, delays in responding can be used to assess inhibitory function. In the context of depression, an emotional version of this task, the negative affective priming (NAP) task, has been used to assess depressed individuals' ability to inhibit the processing of irrelevant negative material. In the NAP task, a negatively valenced distractor on one trial becomes the target on the subsequent trial, allowing investigators to test the hypothesis that if depressed individuals are unable to inhibit the processing of the distractor, they will be faster than non-disordered controls to name the subsequent target. Findings from these studies show that both clinically (Goeleven et al., 2006; Joormann and Gotlib, 2010) and subclinically (Joormann, 2004) depressed individuals respond more quickly than do their non-disordered peers when a negative target is presented following the presentation of a negative distractor. No group differences have been found, however, in reaction times for positive material, suggesting that depressed individuals exhibit difficulties in inhibiting the processing of irrelevant negative, but not of irrelevant positive, material. In addition, difficulties inhibiting negative distractors have been found to be significantly associated with the severity of rumination, even after controlling for level of depressive symptoms (Joormann, 2006; Joormann and Gotlib, 2010).

One functional neuroimaging study of clinically depressed participants has used the NAP task to examine the neural basis of these inhibitory difficulties (Eugène et al., 2010). Results of this investigation showed that problems inhibiting the processing of irrelevant negative material were associated with heightened activity in the rACC of depressed participants. Non-disordered individuals, in contrast, demonstrated heightened activity in this region during the inhibition of positive information. While these findings implicate aberrant functioning of the rACC in difficulties of depressed persons inhibiting the processing of irrelevant negative material, it is important to note that, as was the case in the emotional Stroop task, increased activation in the rACC to irrelevant negative material in depression could reflect either increased salience of this material for the depressed participants (leading to increased conflict when they are required to ignore negative material), and/or difficulties experienced by these participants when they attempt to override automatic responding to these salient stimuli. Indeed, as we discussed above, the latter possibility is consistent with previous work that has implicated the engagement of rACC in the monitoring of emotional conflict (Etkin et al., 2006). Future studies that attempt to tease apart the effects of attention from inhibition with respect to performance on these tasks are needed.

WORKING MEMORY

Efficient functioning of working memory systems depends on inhibition, not only to limit the access of information into working memory, but also to remove this information from working memory stores once it is no longer relevant (Hasher and Zacks, 1998). Understanding the biases of working memory systems in depression is important because dysfunctions in expelling negative material from working memory as it becomes irrelevant could lead to difficulties attending to and processing new information and, as a result, to rumination, thereby increasing the likelihood of the onset or maintenance of a depressive episode.

One task that has been used reliably to investigate the role of working memory processes in depression is the emotional Sternberg working memory task (Joormann and Gotlib, 2008). This paradigm requires participants to first memorize two simultaneously presented lists of words. A cue then appears that instructs

participants to forget one word list and maintain the other. Finally, a word recognition, or "probe," epoch is presented when participants must indicate whether the probe word came from the list they were previously cued to remember, from the list they were cued to forget (i.e., the no longer relevant list), or did not come from either list. The difference in reaction times to an intrusion probe (i.e., a probe from the irrelevant list) and reaction times to a new probe (i.e., a completely new word) reflects the strength of the residual activation of the contents of working memory that were declared to be no longer relevant and, therefore, assesses a person's ability to remove irrelevant information from working memory (Oberauer, 2001). By manipulating the valence of the relevant and irrelevant word lists, as is the case in the emotional Sternberg working memory task, investigators can assess participants' ability to remove negative and positive material from working memory.

Using this task, Joormann and Gotlib (2008) found that clinically depressed individuals exhibit longer decision latencies than do their non-disordered counterparts to negative (but not to positive or neutral) probe words from the no longer relevant word lists. This finding was subsequently replicated (Berman et al., 2011), and is consistent with the formulation that depression is associated with difficulties in disengaging from negative information that was once, but is no longer relevant. This valence-specific deficit in working memory may help to explain why depressed individuals respond to negative life events with recurring, uncontrollable, and unintentional negative thoughts. Consistent with this possibility, Joormann and Gotlib (2008) found that deficits in the removal of no longer relevant negative information from working memory were associated with the severity of rumination, a finding that remained significant even when controlling for depressive symptoms.

Our group recently adapted the emotional Sternberg task for use in a functional neuroimaging investigation to examine whether difficulties removing negative information from working memory in depression were associated with anomalous neural function (Foland-Ross et al., in press). Results from our investigation indicated that during the presentation of the instruction cue, when participants are required to forget one word list and maintain the other, clinically depressed individuals showed greater activation than did non-disordered control participants in the dorsal anterior cingulate cortex (dACC), superior parietal lobule (SPL), and insular cortices when expelling negative information. In contrast, control participants exhibited stronger activation in these regions when attempting to expel positive material. Interestingly, the dACC, SPL, and insular regions are important components of the task positive network (TPN), a collection of structures that has been postulated to subserve active cognitive processing (e.g., executive control and working memory; Fox et al., 2005). Moreover, activation in these structures has been documented to increase linearly with cognitive effort (Paus et al., 1998; Wager et al., 2005; Allen et al., 2007). Depressed individuals, therefore, may exert greater cognitive and neural effort than do their non-depressed counterparts in removing no longer relevant negative material from working memory.

While these studies demonstrate that depressed individuals are less able than are non-depressed persons to expel negative information from working memory, thereby exacerbating the effects of negative content on cognition, other investigators have examined whether depressed individuals are also impaired at selecting relevant positive material for processing in working memory. Difficulties in this area could limit depressed persons' ability to use positive material to ameliorate the adverse effects of processing negative information. Levens and Gotlib (2009) examined this possibility using an emotional version of the recency-probes task. In this task, participants are presented with a set of three target words, followed by a brief fixation, and then a probe display, in which a single word is presented. Participants are asked to indicate, using a button press, whether the probe word was previously presented as one of three words in the target set. Individuals' ability to successfully select material for processing in working memory is assessed using reaction times to probes during interference trials, in which the probe word is not a member of the target set for that trial, but was a member of previous target sets. Longer response times during these trials reflect impairments in the selection of that material for initial processing in working memory. Levens and Gotlib found that, compared to non-disordered controls, clinically depressed individuals exhibited longer response times during interference trials for positive (but not for negative or neutral) stimuli, indicating that depressed persons are impaired in selecting task-relevant positive stimuli for processing in working memory.

In sum, the results of research examining cognitive inhibitory functioning in depression suggest that depressed individuals experience problems both inhibiting the access of irrelevant negative material into working memory and disengaging from this material in working memory once it is no longer relevant. In addition, depressed individuals do not show the normative bias toward the selection and maintenance of positive material demonstrated by non-depressed individuals. Difficulties in the control of working memory contents, in turn, appear related to dysfunctioning of the rACC as well as components of the TPN. Below, we review research that has attempted to link cognitive difficulties and biases to the dysregulation of emotion that has been found to characterize individuals diagnosed with MDD.

EFFECTS OF COGNITIVE BIASES ON EMOTION REGULATION IN DEPRESSION

Cognitive deficits and biases in the processing of emotional information are likely to impair depressed individuals' ability to adaptively regulate their emotions. Below, we discuss how biases in attention and memory, and difficulties in cognitive control, might affect emotion regulation processes in depression, and contribute to persistent negative mood.

ATTENTION

Arguably one of the easiest ways to regulate emotion is to try to look away from or ignore an emotion-eliciting stimulus or situation. Individual differences in attention for emotional information, therefore, represent one important factor that may influence emotional states. As we have described earlier in this paper, depression does not appear to be characterized by a rapid automatic biasing toward negative information. Rather, once this material captures initial attention, individuals experiencing clinical depression have difficulty disengaging from this material. This

tendency of being "stuck" in attending to negative aspects of the situation may prevent depressed people from using effective emotion regulation strategies such as distraction and attentional avoidance when confronted with stressful events. Moreover, biases in attention may interfere with a person's ability to successfully reframe emotion-eliciting events and lead to the sustained processing of emotion-eliciting stimuli and prolonged negative affect.

Several studies of non-disordered samples have investigated whether difficulties disengaging from negative information can increase emotion reactivity and impair emotion regulation efforts. Compton et al. (2000) reported that decreased ability to disengage attention from negative stimuli was related to increased reactivity to an upsetting film. Similarly, Ellenbogen et al. (2006) found that problems disengaging attention from dysphoric images was associated with increased negative affective in response to a subsequent stressor. MacLeod and Hagan (1992) extended these findings by demonstrating that women with the strongest attentional biases toward negative material reported the greatest increases in distress following a diagnosis of cancer. Given this research, it will be important in future studies for investigators to examine, using causal experimental designs, whether attentional biases have deleterious effects on emotional reactivity in individuals with depression.

It will also be important to examine the neural relations between attention and emotional experience. Van Reekum et al. (2007) found that, when cognitively reappraising negative scenes, non-disordered participants tended to shift their gaze away from the extremities of an image, and that individual differences in gaze fixation accounted for a significant portion of variance in neural activation of the amygdala. These findings suggest not only that effortful forms of emotion regulation rely, at least in part, on attention, but further, that the ability to disengage attention from emotion-inducing aspects of a situation can directly influence activity in brain regions that work to mediate emotional responses. Whether there are similar relations among emotion, gaze, and neural function in depression is unknown.

INTERPRETATION OF EMOTIONALLY AMBIGUOUS INFORMATION

Individuals often impose meaning on ambiguous situations without intervening awareness of possible alternative interpretations. An increase in the tendency to interpret ambiguous situations as negative could influence vulnerability to experience negative mood. Evidence in support of this postulation comes from studies of non-clinical samples that have examined the relation between interpretation biases and prospective measures of mood symptoms and emotional reactivity. Rude et al. (2002) found that greater negative interpretation bias in non-disordered participants was significantly associated with an increase in depressive symptoms at a follow-up assessment. In a subsequent study, Holmes et al. (2009) observed that training positive biases in non-disordered individuals helped to alleviate the effects of an induced negative mood state. Training a negative interpretation bias, in turn, was found by Wilson et al. (2006) to predict heightened emotional reactivity to a subsequent stressful video clip. Thus, the tendency to interpret ambiguous scenarios in a negative or positive manner likely influences the generation and experience of an emotional response.

MEMORY

Biases in memory can also influence emotion regulation in significant ways. It is well documented, for example, that recalling positive autobiographical memories can repair negative mood in non-disordered individuals (Josephson et al., 1996; Rusting and Dehart, 2000; Joormann and Siemer, 2004). Increased memory sensitivity for negative material in depression, therefore, could contribute to the difficulties for depressed individuals to access mood-incongruent (i.e., positive) material, causing interference with the selection and use of positive memories to regulate emotion. Consistent with this formulation, Josephson et al. (1996) found that, whereas non-clinical samples of undergraduate students who scored low on measures of depression severity tended to retrieve positive memories following sad mood induction, individuals reporting more severe negative mood symptoms were more likely to retrieve mood-congruent memories. Students in this study, in turn, who engaged in mood-incongruent recall following a negative mood induction showed the greatest improvement in subsequent mood.

Other studies suggest that clinically depressed individuals are as able as their non-disordered peers to recall positive memories, but are less effective in using these memories to repair negative mood states. For example, Joormann et al. (2007a) had clinically depressed, remitted depressed, and never-depressed participants report levels of affect following the induction of a sad mood, and again after they wrote a list of positive autobiographical events. Joormann et al. found that, although the groups did not differ in the number, intensity, or specificity of positive autobiographical events that they recalled, whereas never-depressed participants' mood improved following the recall of positive memories, the sad mood of remitted and currently depressed participants remained unchanged or had worsened.

Reduced specificity of autobiographical memory may also influence emotion regulation in depression. As we note above, overgeneral memory represents one avoidance strategy that may be useful in minimizing distress in the short term (Raes et al., 2003). In the longer term, however, overgeneral memory places individuals at increased risk for developing depression (Gibbs and Rude, 2004). Although the precise reasons for this process are unclear, theorists have speculated that avoiding the recall of specific aspects of past events hinders the development of effective strategies for solving interpersonal problems (Evans et al., 1992). Poor problem-solving abilities, in turn, could lead to more negative social encounters in the future (Hermans et al., 2005), and contribute to increased negative mood.

COGNITIVE CONTROL

Biases in cognitive control may also contribute to emotion-regulatory difficulties in depression. One common type of emotion regulation strategy that is both highly dependent on cognitive control mechanisms and that is effective in altering the trajectory of an unfolding emotional response is cognitive reappraisal. This approach to emotion regulation involves cognitively reframing the meaning of a stimulus or event in a manner that makes the event less distressing. Individuals who more frequently use cognitive reappraisal have fewer depressive symptoms than do individuals who use other emotion regulation strategies, such

as emotion suppression and rumination (Gross and John, 2003; Campbell-Sills et al., 2006; Garnefski and Kraaij, 2006, 2007). Neuroimaging studies demonstrate that engagement in cognitive reappraisal strategies is associated with increases in activation of the dACC and ventro- and dorsolateral PFC, and with decreases in activation of areas that mediate emotional responding, such as the amygdala (Ochsner et al., 2002, 2004). This inverse coupling between frontal and subcortical limbic areas is consistent with the formulation that reappraisal triggers top-down cognitive control of emotion-generating systems. Moreover, the finding that reappraisal activates the same regions that are activated in working memory and inhibition – areas that are dysfunctional in depression (Elliott et al., 2002; Beauregard et al., 2006; Johnstone et al., 2007; Mitterschiffthaler et al., 2008; Erk et al., 2010; Eugène et al., 2010; Kerestes et al., 2012) – supports the position that emotion regulation depends on cognitive functioning in these areas, and that dysfunction in these regions, paired with difficulties in controlling negative, mood-congruent contents of working memory, may directly impair depressed individuals' ability to flexibly reappraise or reinterpret life events or situations (Siemer, 2005, 2007).

Investigators have just begun to examine neural correlates of effortful emotion regulation in depression. Beauregard et al. (2006) found that clinically depressed individuals experienced more difficulty in regulating emotional responses to a sad film clip than did never-depressed participants, and that this difficulty was related to increased activity in the dACC. Similarly, Johnstone et al. (2007) found that, during the cognitive reappraisal of negative images, non-disordered individuals exhibited an inverse correlation between activation in the amygdala and vmPFC. In contrast, clinically depressed participants demonstrated a positive correlation between these regions, as well as heightened activation in a separate, more dorsal, portion of the PFC, suggesting that effortful attempts to reappraise negative situations in depression are counterproductive. And finally, in a cognitive reappraisal study reported by Erk et al. (2010), clinically depressed individuals were found to be able to down-regulate amygdala responses; however, this effect was short-lived and was associated with decreased activation of the dlPFC. Taken together, although replication studies are certainly needed, a picture of neural dysfunction is beginning to emerge in depression indicating that emotion regulation in this disorder is associated with abnormalities in prefrontal function.

Importantly, negative biases in inhibitory and working memory function may contribute to the occurrence of rumination. Ruminative responding – or the recurrent, self-reflective, and unintentional focus on depressive symptoms and their possible causes and consequences (Nolen-Hoeksema, 1991) – has been significantly associated with difficulties in the ability of depressed persons to inhibit, expel or disengage from negative cognitions, and memories that were once, but are no longer, relevant (Joormann, 2006; Joormann and Gotlib, 2008, 2010). Rumination, in turn, may exacerbate negative emotional states; in a study of individuals experiencing subclinical depression, Williams and Moulds (2010) found that participants who were induced to ruminate reported more negative mood and rated intrusive memories as more distressing than did dysphoric participants who were distracted. Moreover, in a recent review, Nolen-Hoeksema et al. (2008) reported evidence suggesting that a greater tendency to ruminate, when combined with negative cognitive biases, predicts longer episodes of depression. Clearly, therefore, a vicious cycle can emerge between deficits in cognitive control and negative mood states, and represents an important area for further research.

TREATMENT IMPLICATIONS

The cognitive biases and deficits that have been found to characterize depression may represent important targets for intervention. Indeed, given findings demonstrating that biases in attention, memory, and cognitive control are associated with course of illness (e.g., Johnson et al., 2007), ameliorating dysfunction at the cognitive level may help to reduce depressive symptomatology, as well as other features of depression, such as rumination. As we review in this section, a small, but growing body of research has found that cognitive biases can be targeted directly by computer-based training paradigms, and that this training is effective in reducing depressive symptoms.

ATTENTION

Investigators attempting to manipulate attentional biases in depression have used a modified dot-probe task. In the training version of this paradigm, a pair of stimuli are presented to the participant, but the subsequent probe is presented more frequently in the location of the neutral or positive stimulus than in the location of the negative stimulus, thereby directing participants' attention away from the negative stimulus and toward the neutral or positive stimulus. This attentional training procedure has been found to reduce subsequent emotional reactivity to induced or to real-life stressors in undiagnosed participants (MacLeod et al., 2002; Dandeneau and Baldwin, 2004; Dandeneau et al., 2007). In two recent experiments of individuals experiencing clinical and subclinical depression, Baert et al. (2010) examined the effects of attentional bias modification on depressive symptomatology. Importantly, given that depression appears to be characterized by biases that occur in later stages of stimulus processing (see Teachman et al., 2012 for a review), Baert et al. had participants perform a dot-probe training task in which stimuli were presented at supraliminal durations (e.g., 1500 ms). Results of these investigations showed that 2 weeks of training away from negative and toward positive stimuli led to improvements in depressive symptomatology in mildly depressed participants; however, participants with more severe symptoms of depression did not show such improvement. The reasons for this latter finding are not clear, and it is important for investigators to examine more explicitly the mechanisms underlying the apparent differential effectiveness of attentional bias training.

In another study of mild to moderately depressed participants, Wells and Beevers (2010) examined the effects of four sessions of attention training away from negative and toward neutral stimuli, again using relatively longer stimulus durations to allow participants to more fully process the content of the stimuli. These investigators found that four sessions of training over a period of 2 weeks resulted in a significant and immediate decrease in depressive symptoms that was not present in participants who received sham training. Moreover, these reductions were found to persist in a 2-week follow-up assessment. Interestingly, path analyses showed

that symptom improvement was mediated by attention modification training, suggesting that the manipulation of this bias directly affected symptom levels.

INTERPRETATION OF EMOTIONALLY AMBIGUOUS INFORMATION

Few studies have examined whether modifying negative interpretation biases can have a significant impact on negative affect in depressed individuals, despite demonstrations that computerized cognitive bias modification (CBM) techniques that target interpretation (CBM-I) can cause a significant increase in the tendency for non-disordered participants to interpret new and emotionally ambiguous information in a positive manner (Holmes et al., 2006, 2009). In this training approach, individuals are repeatedly presented with potentially ambiguous scenarios whose interpretation is constrained in a particular direction (positive or negative). In non-disordered samples, repeated positive CBM-I training sessions have been found to reduce vulnerability to anxiety to a later stressor (MacKintosh et al., 2006). Further, positive CBM-I has been found to be effective in reducing negative interpretative biases in individuals who report high levels of anxiety (Mathews et al., 2007; Murphy et al., 2007; Salemink et al., 2009).

Only one study to date has examined the effects of positive CBM-I training in depression. Blackwell and Holmes (2010) had depressed individuals listen to a series of ambiguous situations in which ambiguity was resolved in a positive direction. Following daily sessions of positive CBM-I training for 1 week, four out of seven of the depressed participants demonstrated significant improvements in depressive symptoms. Moreover, these effects were maintained at follow-up, 2 weeks later. Although modest, such a response rate is comparable to that of studies examining efficacy of antidepressant medication or CBT (Hollon et al., 2002). Thus, more rigorous testing using larger samples with a sham control group is warranted.

MEMORY

Given studies showing that overgeneral memory influences the course of depression (Brittlebank et al., 1993; Dalgleish et al., 2001; Watkins and Teasdale, 2001, 2004; Raes et al., 2005), investigators have also begun to examine the effects of interventions designed to increase memory sensitivity. Watkins et al. (2009) found that training participants with subclinical depression to actively engage in generating concrete construals (e.g., focusing on specific details of an event) when thinking about autobiographical memories led to significant reductions in both depressive symptoms and frequency of rumination. In another study of more severely depressed participants, Raes et al. (2009) found that training clinically depressed inpatients to recall more specific memories generated improvements in their memory retrieval, level of rumination, and quality of problem-solving. Thus, overgeneral memory may represent another cognitive aspect of depression that, like attention, is amenable to successful modification.

Researchers have also examined whether biases in explicit memory are amenable to training. In a study investigating whether individuals could be trained to forget negative material using a modified "Think-No-Think" (TNT) paradigm (Anderson and Green, 2001), Joormann et al. (2009) presented clinically depressed and non-disordered participants with word pairs consisting of one neutral cue word and one positive or negative target word. In an initial learning phase, participants were asked to learn cue-target associations. Participants were then instructed not to think about the negative targets when shown their neutral cues, but instead, to either think of a new valenced word (substitute condition) or to refrain from thinking of another word (unaided condition). Joormann et al. found that, when asked to recall the original target words, depressed participants in the substitute, but not in the unaided condition showed successful forgetting of negative words. Moreover, the number of negative targets they forgot was directly related to length of training. Thus, although this study examined memory performance within a single session and did not assess symptom change, these findings are promising in suggesting that future training paradigms could be developed, using modified versions of the TNT task, to help depressed individuals suppress their enhanced retrieval of negative material.

COGNITIVE CONTROL

Although difficulties in controlling the access and manipulation of negative material into working memory represent clear features of cognitive disturbance in depression, few studies have examined whether modifying this domain of cognition can have beneficial effects on depressive symptomatology. Indeed, in the only study that has examined the effects of cognitive control training on depression, Siegle et al. (2007a) had clinically depressed and non-disordered participants undergo 2 weeks of training using a pair of tasks: a variant of the Paced Auditory Serial Attention Task (Gronwall, 1977), in which individuals continuously add serially presented digits in working memory, and an attention task (Wells, 2000) that requires participants to selectively attend to specific environmental auditory stimuli. Results of this study showed that mood symptoms decreased continuously in clinically depressed individuals throughout the two-weeks of intervention, as did rumination. Moreover, analyses of neural data from a subsample of the depressed participants in this study revealed that cognitive control training was associated with a reduction in amygdala reactivity to negative affective stimuli, as well as an increase in dlPFC activity during the performance of a working memory task. Given these initial findings, as well data from several studies of dementia indicating that cognitive control training has a significant, although unexpected, effect of lowering depressive symptoms (see Sitzer et al., 2006 for a review), the potential impact of cognitive control training on depressive symptoms and diagnosis, and on levels of ruminative thinking, is promising.

TREATMENT IMPLICATIONS: SUMMARY

The available research suggests that depression-associated biases in attention, memory, interpretation, and cognitive control may be targeted directly using computer-based training paradigms, and that attenuating these biases may effectively reduce severity of depressive symptoms. Such training approaches could serve as useful monotherapies, or alternatively, may be used as adjunctive tools for other pharmacologic and therapeutic interventions. Given evidence that information processing biases may be present prior to the initial onset of depression (Joormann et al., 2007b, 2010), future investigations should examine whether early interventions with cognitive training could prevent the onset of MDD

through inhibiting or reversing the development of dysfunctional schemas. At the same time, because some bias modification procedures have been found to be effective only in individuals who are experiencing mild symptoms of depression (e.g., Baert et al., 2010), investigations examining the parameters of effective training programs for specific types or severity of depression would be helpful to prevention efforts.

SUMMARY AND FUTURE DIRECTIONS

As we have documented in this review, the available research finds that a diagnosis of MDD is accompanied by increased elaboration of negative information, a tendency to interpret ambiguous information as negative, difficulties disengaging from negative material, and deficits in cognitive control when processing this material. Neuroimaging investigations of the neural bases of these difficulties find, in the context of biases in attention, that sustained processing of negative affective material in depression is associated both with prolonged activation of the amygdala and dysfunction in the rACC. Examinations of the neural underpinnings of enhanced memory for negative material in depression, in turn, appear to be associated with the over-recruitment of the amygdala, as well as other subcortical regions that are involved more generally in the encoding of affective material. And finally, problems in controlling and inhibiting the processing of negative material in depression relates to dysfunction in higher-order cognitive control regions, including the ACC, dlPFC, and vlPFC.

Several important goals for future research remain. One involves the more systematic mapping of links between cognitive and affective aspects of depression. It will be critical, for example, for researchers to elucidate the causal nature of the relation between depressed mood and cognition. This issue could be addressed through studies that continue to investigate the impact of cognitive retraining on emotion, or through longitudinal investigations that examine whether cognitive biases observed during a clinically significant episode of depression resolve following successful treatment with medication. Along these lines, it would be helpful for future studies to understand the mechanisms by which cognitive retraining improves mood; it is currently unclear, for example, whether retraining attention biases in depression alters symptom profiles through altering bottom-up processes involved in generation of affect, top-down processes involved in the regulation of affect, or through influencing other aspects of cognitive functioning (e.g., memory).

In addressing possible interactions between cognitive biases, investigators have begun discussions on the "near" and "far" transfer of training effects of CBM (Hertel and Mathews, 2011; MacLeod and Mathews, 2012). While bias modification training typically transfers to new stimulus materials presented in assessment versions of a task (near transfer), changes in emotional functioning or performance on tasks that are less closely related to the training task (far transfer) are particularly informative for our understanding of mechanisms. Findings from a small of collection of recent investigations indicate that far transfer effects occur with training that is focused on discrete aspects of cognition. One instance of this comes from a study by White et al. (2011), who found that attention bias training leads to changes in interpretive biases. Similarly, training of interpretation biases have been found to influence biases in both attention (Amir et al., 2010) and memory (Salemink et al., 2010; Tran et al., 2011). These findings suggest not only that the distinctions made by researchers among biases in attention, interpretation, and memory need to be reconsidered, but further, that at least some aspects of these biases share common mechanisms of action.

Future studies will also benefit from the integration of cognitive biases with other biological aspects of depression. A number of recent studies have found that reductions in serotonin levels, induced by tryptophan depletion, causes cognitive impairments in non-disordered individuals that are similar to those found in depression. This includes reduced autobiographical memory specificity (Alhaj et al., 2012), selective encoding of negative material (Wang et al., 2009), and attention toward negative stimuli (Murphy et al., 2002; Roiser et al., 2008). Moreover, similar to clinically depressed individuals, increased amygdala responses to negative material (Roiser et al., 2008), and altered activation in ventrolateral prefrontal regions during the processing of task-irrelevant negative distractors (Wang et al., 2009) are also found in participants treated using acute tryptophan depleting compounds. Further support for the involvement of serotonin in neural and cognitive abnormalities in depression comes from studies examining associations between these measures and polymorphisms of the serotonin transporter-linked polymorphic region (5-HTTLPR): compared to long-allele homozygotes, individuals who carry one or two 5-HTTLPR short alleles have been found to exhibit difficulties disengaging attention from emotional stimuli (Beevers et al., 2009) and to have greater amygdala reactivity to sad material (Hariri et al., 2005). Given these findings, it follows that cognitive biases in depression may be modulated, at least in part, by serotonergic systems, and that negative affective biases are amenable to treatment with medications that target this system (e.g., SSRIs; Clark et al., 2009; Harmer et al., 2009a). To date, however, investigators have not examined changes in cognitive biases in depressed individuals as a consequence of pharmacological treatment. Certainly, an investigation into the interaction between serotonin and cognition represents an area for promising research in depression. Along these lines, studies examining the relation between cognition and other aspects of neurobiological function implicated in depression and in the regulation of affective states (e.g., dopamine, cortisol) would be helpful in the developing a more complete understanding of the cognitive abnormalities that are associated with MDD.

Finally, a small, but growing body of literature is demonstrating that depression-related biases in cognition are not necessarily correlates or consequences of the experience of depression, but could reflect a pattern of dysfunction that precedes the initial onset of this disorder. Indeed, like depressed adults, young individuals who are not themselves depressed but are at high risk for developing depression by virtue of having a depressed parent have been found to demonstrate negative biases in the interpretation (Dearing and Gotlib, 2009) and identification (Joormann et al., 2010) of neutral and emotional material. Moreover, similar to depressed adults, never-disordered girls at familial risk for depression selectively attend to negative facial expressions on the dot-probe task (Joormann et al., 2007b). It is possible, therefore, that negative biases in cognition play a direct role in

placing children of depressed parents at increased risk for developing a depressive disorder. A necessary next step to addressing this question involves using longitudinal designs to examine whether specific cognitive biases can predict which high risk individuals are at greatest risk for developing depression. Similarly, given neuroimaging findings that familial risk for depression is associated with depression-related abnormalities in brain structure (Peterson et al., 2009; Chen et al., 2010; Rao et al., 2010; Huang et al., 2011) and function (Monk et al., 2008; Mannie et al., 2011), it would be helpful if future studies could examine whether abnormalities in neural measures are useful in predicting the onset of depression. Furthermore, and perhaps most importantly, given the initial promise of cognitive retraining procedures in altering cognitive biases in adults with depression, researchers need to develop a more comprehensive understanding of how cognitive retraining might be used in the prevention of major depression.

In reviewing the literature on cognitive biases in depression, we have described several sources of methodological variability that, if addressed, may increase the consistency in the results of future studies. First, despite recent estimates that up to 65% of depressed individuals experience clinically significant symptoms of anxiety (Brown et al., 2001), the effects of this comorbidity on the neural and behavioral measures of depression are not fully understood. Although current evidence suggests that trait levels of anxiety may account for biases in subliminal attention that have been reported in some studies of clinical depression (Gotlib and Joormann, 2010; Teachman et al., 2012), additional research is needed examining the effects of this comorbidity on automatic perception and other aspects of cognition and neural function. Second, cognitive biases in depression may be influenced by the duration of MDD; individuals who are experiencing a first episode of depression have been found to exhibit a different pattern of emotional responding than do individuals who have experienced recurrent episodes of depression (e.g., Nandrino et al., 2004). Related to this issue are findings showing that cognitive and neural processing biases in depression (Suslow et al., 2010) are affected by depression severity (e.g., Dannlowski et al., 2007a; Suslow et al., 2010). Third, there is evidence to suggest that task performance varies as a function of how depressed individuals process experimental stimuli. Some investigators, for example, have found depressed individuals to exhibit difficulties inhibiting the processing of mood-congruent material, but only when this material was processed in a self-referential manner (Segal et al., 1995; Power et al., 2000). Along these lines, there is also evidence showing that stimulus type (e.g., words versus images) influences task performance (Isaac et al., 2012). Fourth, future investigations of depression are likely to benefit from researchers controlling for trauma history. Childhood maltreatment is a significant predictor of both amygdala response (Dannlowski et al., in press), and biases in attention (Fani et al., 2010) in adult participants. Moreover, epidemiological studies show that trauma occurring during childhood is associated with the onset and severity of depressive symptoms during adulthood (see Heim et al., 2008 for a review). Fifth, the effects of gender on depression-related abnormalities in neural and cognitive is still unclear; investigators often combine men and women in their samples or sample exclusively from women. Given that men and women have different clinical manifestations of depression (Piccinelli and Wilkinson, 2000; Nolen-Hoeksema, 2001), studies examining how emotional material is processed in depressed females versus males would be helpful in elucidating the parameters of cognitive and neural biases in major depression. Such research could also help to explain the gender difference in the prevalence of MDD (e.g., Nolen-Hoeksema and Hilt, 2009). Finally, investigators should examine more closely and control for the effects of psychotropic medication on cognition and neural function. Given the findings we presented earlier showing that targeted manipulation of the serotonergic system using tryptophan depletion leads to cognitive and neural changes in non-disordered adults that resemble those found in major depression, the issue of exactly how SSRIs or medications targeting other neurotransmitter systems may affect neurocognitive profiles of depressed adults clearly warrants further research.

In closing, although there are several issues that require further study, the available research indicates that MDD is characterized by significant impairments in the processing of mood-congruent material in the context of attention, interpretation, memory, and cognitive control, and that these cognitive difficulties contribute to difficulties in emotion regulation and neural dysfunction. Investigators have also provided important new leads in the development of alternative treatments for depression in the form of computer-based cognitive bias retraining paradigms, which may be helpful as adjuncts to existing therapies or as prevention strategies in individuals at high risk for developing this disorder. It will be important to continue to integrate findings across different research modalities in order to inform etiological models of depression and advance the development of new approaches to the prevention and treatment of this debilitating disorder.

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Electrophysiological correlates of fearful and sad distraction on target processing in adolescents with attention deficit-hyperactivity symptoms and affective disorders

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In this study we used event-related brain potentials (ERP) as neural markers of cognitive operations to examine emotion and attentional processing in a population of high-risk adolescents with mental health problems that included attention deficit and hyperactivity disorder (ADHD), anxiety, and depression. We included a healthy control group for comparison purposes, and employed a modified version of the emotional oddball paradigm, consisting of frequent distracters (scrambled pictures), infrequent distracters (sad, fearful, and neutral pictures), and infrequent targets (circles). Participants were instructed to make a right hand button press to targets and a left hand button press to all other stimuli. EEG/ERP recordings were taken using a high-density 256-channel recording system. Behavioral data showed that for both clinical and non-clinical adolescents, reaction time (RT) was slowest in response to the fearful images. Electrophysiological data differentiated emotion and target processing between clinical and non-clinical adolescents. In the clinical group we observed a larger P100 and late positive potential (LPP) in response to fearful compared to sad or neutral pictures. There were no differences in these ERPs in the healthy sample. Emotional modulation of target processing was also identified in the clinical sample, where we observed an increase in P300 amplitude, and a larger sustained LPP in response to targets that followed emotional pictures (fear and sad) compared to targets that followed neutral pictures or other targets. There were no differences in these target ERPs for the healthy participants. Taken together, we suggest that these data provide important and novel evidence of affective and attention dysfunction in this clinical population of adolescents, and offer an example of the disruptive effects of emotional reactivity on basic cognition.

Keywords: ADHD, adolescents, anxiety, attention, depression, emotion, event-related potentials

INTRODUCTION

Emotion can both enhance and impair cognition and performance (Dolcos et al., 2011; Chan and Singhal, 2013). For instance, increased attention to emotional stimuli can also lead to distracting effects on cognitive performance if the emotional information is task-irrelevant (Dolcos and McCarthy, 2006; Shafer et al., 2012). These opposing effects of emotion are exacerbated in clinical conditions, such as depression and anxiety, where increased emotional distractibility is observed. This heightened susceptibility to emotional distraction may, in part, be due to faulty regulatory mechanisms that help individuals cope in the presence of unwanted emotional stimuli. The ability to regulate emotion is a complex phenomenon that begins to develop in infancy, and continues through the childhood and adulthood years. Moreover, a healthy set of emotional regulatory strategies are considered to be highly associated with overall positive health states and general wellbeing (Thompson and Calkins, 2006; Denkova et al., 2012). In recent years there have been important advances in the neuroscientific study of emotion and emotion regulation (see Dolcos et al., 2011). In particular, the neural basis of emotion regulation has received considerable research interest because of the compelling argument that certain types of psychopathology are linked to a fundamental *dys*regulation in emotion processing (Davidson, 2002; Phillips et al., 2008). This dysregulation has been described as involving an imbalance between basic affective processing and higher-level executive processes including top–down attentional control (Johnson et al., 2005). Moreover, in pediatric populations emotion regulation is likely of paramount

importance in the development of stable and normal cognitive function over time (Lewis et al., 2006). It is widely known that psychopathologies with a childhood onset are associated with a higher incidence of relapse, heightened resistance to therapy, and other long-term varied health problems (Snyder, 2001). It has been suggested that children at risk for depression may be vulnerable to other risks due to trouble with self-regulation of their own emotions as well as receiving inconsistent regulatory management from caregivers and peers due to their reactivity (Thompson and Calkins, 2006). That is, these children may be offered less support and help with alternate strategy formation that is critical for normal development. Similar evidence exists in the attention deficit and hyperactivity disorder (ADHD) literature. Where emotional dysregulation contributes to behavioral excess, impulsive responding, and delayed cognition that ultimately leads to the child's feelings of heightened frustration and interferes with normal development of socio-emotional skills (Walcott and Landau, 2004).

From a neuroimaging point of view, emotion regulation processes have been shown to correlate with activation in dorsal–lateral, medial prefrontal, and lateral parietal cortices associated with attentional control processes, as well as changes in activation in the amygdala, ventral–lateral, and ventral medial prefrontal regions associated with emotional re-appraisal and attenuated emotional reactivity (Beauregard et al., 2001; Yamasaki et al., 2002; Urry et al., 2006). Although much of the relevant cognitive neuroscience literature in this area has been provided by fMRI research, important contributions to this field have also been made through event-related potential (ERP) methods. ERP reflect synchronous post-synaptic neural activity that is time locked to the onset of an eliciting stimulus, and are typically characterized by their peak amplitude, time-to-peak latency, and scalp topography (Luck, 2005). This technique is highly valuable for the study of human cognitive phenomena because they are non-invasive and provide a reflection of neural activity with excellent temporal resolution in the order of milliseconds (Luck, 2005). Thus, they are useful for modeling near simultaneous neuronal activity, while at the same time are highly suitable for studying brain function in pediatric and clinical populations. The primary focus of the present study was to examine the ERP markers of emotion and emotional regulation in youth suffering from affective and attentional disorders while engaged in an emotional oddball task (modified from Wang et al., 2005) that allowed for the assessment of neural activity in response to both emotional stimuli and non-emotional stimuli requiring attentional control, as well as the interactions between them.

ERP studies of emotion processing employing stimuli from the International Affective Picture System (IAPS), a standardized set of photographs that vary along dimensions such as emotional valence and arousal (Lang et al., 2005), identified specific ERP components sensitive to emotion modulation. Using IAPS stimuli, research has shown that emotional images are often associated with an increase in early and sustained attention that presumably facilitates the processing of emotional information, and is reflected by a modulation of the amplitude of the ERPs. For example, both the P100 and the late positive potential (LPP) are well characterized ERP components that are sensitive to modulations by emotion [see Olofsson et al. (2008) for a review]. The P100 is a positively deflecting waveform that typically occurs between 80 and 200 ms post-stimulus onset and has been shown to be a marker of extrastriate activity (Clark et al., 1995). The P100 is the most consistently found early component that can be modified by fearful emotion (Eimer and Holmes, 2002; Smith et al., 2003; Carretie et al., 2004; Delplanque et al., 2004; Pourtois et al., 2005; Holmes et al., 2006). While the P100 is commonly modulated by emotion, the topography of the modulation has varied from occipital, to lateral-occipital, to parietal, to frontal locations. It has been suggested that this fluctuation in topography is largely due to methodological and task effects (Olofsson et al., 2008).

The LPP is a positive deflection that peaks over parietal electrode sites at latencies that are after 300 ms, and is evident throughout the presentation duration of the eliciting emotional picture or word. It has been shown to be larger in amplitude in response to aversive stimuli compared to neutral stimuli, as well as stimuli that are highly arousing (Dolcos and Cabeza, 2002; Schupp et al., 2004; Weinberg and Hajcak, 2010). Moreover, the larger LPP effect in response to emotional stimuli is not sensitive to habituation effects associated with repeated stimulus presentation (Olofsson and Polich, 2007) as is the case of galvanic skin conductance (GSR), electromyography (EMG), and amygdala activation in fMRI (Breiter et al., 1996; Codispoti et al., 2006, 2007). The LPP appears to require the conscious awareness of the eliciting stimulus (Williams et al., 2007), and shows consistent morphology over time within subjects (Codispoti et al., 2006). In terms of its functionality, it has been argued that the LPP reflects an increase in sustained attention in order to facilitate the extended processing of motivational information, including higher cognitive processes such as memory encoding and retention (Koenig and Mecklinger, 2008). The LPP has been linked to activity in the occipital, parietal, and inferior temporal lobes (Keil et al., 2002; Sabatinelli et al., 2007), perhaps also reflecting downstream activity due to initial emotional modulation of the amygdala (Hajcak et al., 2010). Despite relatively limited research examining the LPP in children and youth, it has been shown that a measurable LPP is evident in response to emotional face presentation in populations as young as 7 month old (Leppanen et al., 2007). More recently, Hajcak and Dennis (2009) showed that the LPP is larger in response to emotional compared to neutral content in IAPS stimuli in children, and it has been suggested that children who have suffered abuse elicit larger LPP waves to stimuli that portray threatening and anger situations (Shackman et al., 2007). Moreover, it has been argued that since the LPP is a viable marker of fear-based processing, it may be useful as an indicator of emotional dysregulation in clinical populations, including pediatric affect disorders (Solomon et al., 2012).

Another ERP component that has been shown to be strongly related to attention and also emotion processing is the P300, which is observed as a large positive waveform maximal over midline central and parietal electrode sites peaking between 300 and 500 ms after stimulus onset (Sutton et al., 1965). Extensive literature supports the idea that the P300 wave has multimodal generators (Kok, 2001) and peaks once a task relevant stimulus has been evaluated. It is typically observed when attention is paid to a stimulus train which has both frequent and infrequent

(oddball) trials. It has been shown that the peak latency of the P300 increases if the categorization of a target stimulus becomes more difficult suggesting it is also involved in low level perception (Kutas et al., 1977; Coles et al., 1995). There is an agreement that P300 amplitude reflects the intensity of processing (Donchin et al., 1986a,b) as well as perceptual-central resources (Donchin et al., 1986a; Kramer and Spinks, 1991) within a multiple capacity framework (Wickens, 1984; Singhal and Fowler, 2004, 2005). In a study co-registering ERP and fMRI data, the brain networks underlying the visual P300 (oddball P3b) were localized to both parietal cortex and inferior temporal cortex (Bledowski et al., 2004). It has also been long argued that the multimodal nature of P300 is likely due to significant frontal lobe contribution (Johnson, 1993). The P300 has been shown in some studies to be larger in response to affective images compared to neutral images (Carretie et al., 2004) and this effect has been attributed to the idea that emotion directs the allocation of attention and, it has been further argued that emotional stimuli are "natural targets" because of their strong salience and motivational relevance (Johnston et al., 1986; Sabatinelli et al., 2005). In the context of emotion regulation, it has been argued that the amplitude of P300 may reflect the amount of cognitive resources allocated to the processing of information that follows an emotional stimulus (Ellis and Ashbrook, 1988). Further, it has been suggested that this process may function to critically subserve regulatory processes (Deveney and Pizzagalli, 2008).

Previous research examining emotion regulation and attentional control in youth suggests that this population maybe less well equipped to properly inhibit unwanted allocation of their attentional resources toward distracting emotional information. Furthermore, youth suffering from mental health concerns including attentional and affective disorders may have more difficulty with this type of inhibition. However, to date the underlying neural mechanisms of this phenomenon have not been fully elucidated. The primary research purpose of this study was to examine the nature of these emotion and attention ERP markers (i.e., P100, LPP, and P300) in a population of youth with potential dysfunction in emotion regulation and attention because they had been diagnosed with symptoms related to affective disorders and ADHD. To that end, adolescents suffering with mental health problems and a healthy control group of participants performed a modified version of the emotional oddball paradigm (after Wang et al., 2005), that allowed for the assessment of emotion processing, goal directed attentional processing, and the interaction between the two. For distracter processing, we predicted differences in behavioral and ERP data such that reaction time (RT) would be delayed and early and late ERP components would be modified by emotional images compared to neutral distracter images. Specifically, the P100 and LPP amplitude would be enhanced by affective compared to non-affective distracters. For target processing, we predicted differences in behavioral and ERP data such that RT and P300 amplitude in response to targets would differ as a result of the preceding distracter type. Moreover, we predicted that the pattern of behavioral and neural responses for both distracters and targets would be different between our clinical and healthy control groups.

METHODS

PARTICIPANTS

Twenty-seven (10 male, 2 left-handed) adolescents (12–17 years; average age = 14.3; SD = 1.27) were recruited from a residential mental-health treatment facility in the City of Edmonton, Alberta, Canada. These individuals were clinically diagnosed with DSM-IV Axis-1 disorders including ADHD combined, predominantly inattentive type and predominantly hyperactive/impulsivity type, oppositional defiant disorder, conduct disorder, depressive disorders (major depression and dysthymia), and anxiety disorders (including generalized anxiety disorder; post-traumatic stress disorder; and anxiety disorder). Clinical characteristics of these participants were summarized in **Table 1**. For summary purpose, we grouped depressive disorders and anxiety disorders as distress disorders. As shown in **Table 1**, there were pre-existing or co-occurring co-morbidities. Six healthy control adolescents were recruited from the City of Edmonton (three male, 13–16 years, average age = 14.67; SD = 1.21). All participants had normal or corrected-to-normal vision. Informed consent and assent were obtained from parental guardians and participants before participating. The experimental protocol was approved for ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta. ERP data was assessed on a subset of 10 (5 male, 1 left-handed) clinically diagnosed adolescents (13–16 years; average age = 14.1 years; SD = 1.2). These 10 were chosen because they had the best ERP signal-to-noise ratio as determined by visual inspection. ERP data were assessed for all six healthy control (non-clinical) adolescents.

TASK AND STIMULI

Participants performed a modified version of the emotional oddball paradigm (Wang et al., 2005) which consisted of frequent stimuli serving as the baseline [scrambled pictures, 79% (465 trials)], infrequent distracters and oddball targets, 21% (124 trials). Infrequent distracters consisted of sad and fearful pictures (13 trials each), neutral pictures (26 trials), and positive pictures (4 trials). The oddball targets (circles) were sub-grouped according to their preceding infrequent stimulus type [i.e., target-after-sad (11 trials), target-after-fear (11 trials), target-after-target (24 trials), and target-after-neutral stimuli (22 trials)]. To ensure that sad and fear pictures were paired to a neutral picture that possessed similar visual qualities (e.g., sad picture, man sitting and crying; neutral picture, another man sitting with no overt emotional expression), the neutral pictures were originally subdivided into neutral paired with sad and neutral paired with fear. However, for analyses these separate neutral categories were collapsed resulting in one neutral picture and one target-after-neutral category. Positive pictures only served as emotional anchors, to provide a context for ratings, and were not included in the analyses. The infrequent distracter stimuli (sad, fearful, and neutral pictures) were selected from IAPS based on normative ratings for valence and arousal and were supplemented with in-house pictures used in previous studies (Wang et al., 2005, 2008). Participant's ratings of the distracter categories did not differ between the clinical and non-clinical groups, $F_{(4,\ 80)} = 0.3$, $p = 0.88$ for valence and $F_{(4,\ 80)} = 0.34$, $p = 0.85$ for arousal.

Table 1 | Diagnostic and medication information for the 27 clinical adolescents.

Diagnosis	Number (male/female)	Medication (number of patients)			
		None/unknown	Stimulants	Anti-depressants	Others
ADHD CO-MORBID WITH ONE OR MORE FOLLOWING DISORDERS					
ODD, OCD, PCRP, SRC, RAD, IED, conduct disorder, learning disorders	10 (5/5)	3/1	5	SSRI-2 NRI-1	Atypical antipsychotic-2 Benzodiazepine-1 β-adrenergic receptor agonist-1
Distress disorders (one or more of the following: major depression, dysthymia, anxiety GAD, PTSD, social phobia)	4 (2/2)	1/0	2	SSRI-2	Atypical antipsychotic-1
DISTRESS DISORDER					
Major depression	1 (0/1)	–	–	SSRI-1	Atypical antipsychotic-1
DISTRESS DISORDERS (MAJOR DEPRESSION, DYSTHYMIA, GAD, PTSD) CO-MORBID WITH ONE OR MORE FOLLOWING DISORDERS					
Distress disorder	1 (1/0)	–	–	NDRI-1	Atypical antipsychotic-1
ODD, PCRP, SRC, RAD, conduct disorder, substance abuse, sexual abuse	8 (1/7)	–	2	SSRI-7 NDRI-2 NRI-1	Atypical antipsychotic-4 Benzodiazepine-1
OTHERS: TWO OR MORE FOLLOWING DISORDERS					
ODD, PCRP, conduct disorder	3 (1/2)	3/0	–	–	–
Total	27 (10/17)	7/1	9	SSRI-12 NDRI-3 NRI-2	Atypical antipsychotic-9 Benzodiazepine-2 β-adrenergic receptor agonist-1

ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; OCD, obsessive-compulsive disorder; PCRP, parent-child relation problem; RAD, reactive attachment disorder of infancy or early childhood; SRC, sibling-relational conflict; IED, intermittent explosive disorder; SSRI, selective serotonin reuptake inhibitors; NRI, norepinephrine reuptake inhibitors; NDRI, norepinephrine-dopamine reuptake inhibitors.

There was main effect of valence, $F_{(2,\ 80)} = 129.55$, $E = 0.65$, $p < 0.001$, and a main effect of arousal $F_{(2,\ 80)} = 44.22$, $E = 0.79$, $p < 0.001$. The fear images were rated as most negative (fear > sad > neutral) and most arousing (fear > sad > neural). The mean valence/arousal scores for each distracter type rated by the 27 clinical adolescents (on a scale from 1 to 9) were as follows: 5.22/2.48 for neutral; 2.65/5.22 for fear; and 2.87/4.04 for sad. The mean valence/arousal scores rated by the 10 ERP clinical adolescents were as follows: 5.34/2.32 for neutral; 2.58/4.62 for fear; and 2.83/3.42 for sad. The mean valence/arousal scores as rated by the six non-clinical adolescents were as follows: 5.3/2.21 for neutral; 2.4/5.33 for fear; and 3.05/3.97 for sad. The infrequent circle targets varied in size and color so that each target stimuli was unique. The frequent distracter stimuli (scrambled pictures) were digitally scrambled versions of the picture stimuli and thus contained the same average spatial frequency and luminance as the emotional and non-emotional pictures. Participants made one button press to all frequent (i.e., scrambled pictures) and infrequent (i.e., neutral, sad, and fear pictures) stimuli, and they made another button press to all target stimuli.

EVENT-RELATED POTENTIAL (ERP) RECORDING AND ANALYSES

ERPs were recorded using a high-density 256-channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR), amplified at a gain of 1000 and recorded at a sampling rate of 250 Hz [impedance <50 KΩ and initially referenced to the vertex electrode (Cz)]. Using Netstation (Version 4.4.2, Electrical Geodesics Inc., Eugene, OR), data were bandpass filtered from 0.1 to 30 Hz, grand average re-referenced offline, and segments were constructed around events of interests from 300 ms pre-stimulus to 800 ms post-stimulus. Data were also baseline corrected (−300 to 0 ms), and corrected for eye-movement artifacts. A min of five epochs per condition were necessary for the participant to be included in ERP analyses. The individual waveforms were visually inspected, and clear components of interests (i.e., P100, P300, and LPP) were identified for each participant at or near electrodes sites shown in prior literature to display maximal amplitudes. More specifically, because our primary goal of the study is to investigate emotional dysregulation effects on cognition in a clinical population, we first investigated significant effects in the clinical group. A secondary analysis on the non-clinical group data was performed for confirmation. Thus, analyses were observation-driven with ERP inspection in the clinical group for distracter and target ERPs at cardinal electrode clusters. Significant effects that were identified in the clinical group were then compared to the corresponding electrode sites in the non-clinical control group. Mean amplitude data for late (LPP and P300) ERP components and maximum amplitude data for early (P100) ERP components were then extracted. Time windows for each component were determined from visual inspection and were 300–549 ms post-stimulus for the P300, 550–800 ms post-stimulus for LPP, and 100–200 ms post-stimulus for P100. Since data was acquired with a high-density net consisting of 256 electrodes, we also employed an extent threshold of three adjacent electrodes for all components of interests.

EXPERIMENTAL PROCEDURES

The oddball trials (i.e., infrequent distracters and target stimuli) were divided into 4 runs of 25 trials and 1 run of 24 trials. To avoid induction of mood states, the negative distracter oddball trials within each run were pseudorandomized so that no more than two trials of the same valence type were consecutively presented. The inter-trial interval was 2 s. Each trial started with the presentation of a stimulus (frequent, infrequent distracter, or a target) presented for 750 ms and was followed by a fixation screen for 1250 ms. To prevent the participants from anticipating the occurrence of a stimulus the interval between rare stimuli (i.e., the infrequent distracters and targets) was randomized on an exponential distribution with a median of 8 s and a range between 6 and 10 s (see **Figure 1**). The participants' task was to indicate whether the stimulus was a target or non-target by pressing a button. Participants were instructed to make a right hand button press any time they saw a target (circle) and a left hand button press to all other stimuli (i.e., frequent scrambled and infrequent sad, fearful, neutral, and positive distracters). Participants were also instructed to respond as soon as the image was presented and to respond as quickly and as accurately as possible, and to experience any feelings and thoughts the pictures might trigger.

STATISTICAL ANALYSES

For comparison of clinical and non-clinical groups, behavioral RT and ERP (P100 max amplitude; P300 and LPP mean amplitude) data in response to distracters and targets were analyzed via two separate mixed model analyses of variances (ANOVA) tests. For each ANOVA the between subject variable was group (clinical and non-clinical). For the distracter ANOVAs the within subjects variable was distracter type (neutral, fear, and sad), while for the target ANOVAs the within subject variable was target type (target-after-target, target-after-neutral, target-after-fear, and target-after-sad). These mixed model analyses were performed using the clinical group ($n = 10$) that had both behavioral and ERP data. For within group comparisons One-Way repeated measures ANOVA were performed for distracter and target data. The distracter ANOVA assessed responses to the infrequent sad, fearful, and neutral distracters. The target ANOVA assessed responses to the targets as a function of the preceding rare stimulus type (i.e., target-after-target; target-after-neutral; target-after-sad; and target-after-fear). For all analyses the p-value corresponding to the Greehouse-Geisser correction is reported. The epsilon values are reported only where significance was found. *Post-hoc* comparisons were performed where appropriate using the Fisher LSD test. The within group analyses were performed on all three groups (i.e., non-clinical, clinical with 10 participants, and clinical with 27 participants) separately. In the behavioral analyses trials were excluded if they were incorrect and if RT data were $\leq$175 ms or $\geq$2000 ms. While error rates were significantly greater for target ($M = 12.4\%$, SE $= 2.4\%$) compared to distracter ($M = 4.1\%$, SE $= 1.4\%$) stimuli, $F_{(1,\ 40)} = 8.84$, $p = 0.005$, they did not differ as a function of group, $F_{(2,\ 40)} = 0.91$, $p = 0.41$, nor did they differ within stimulus type (i.e., within

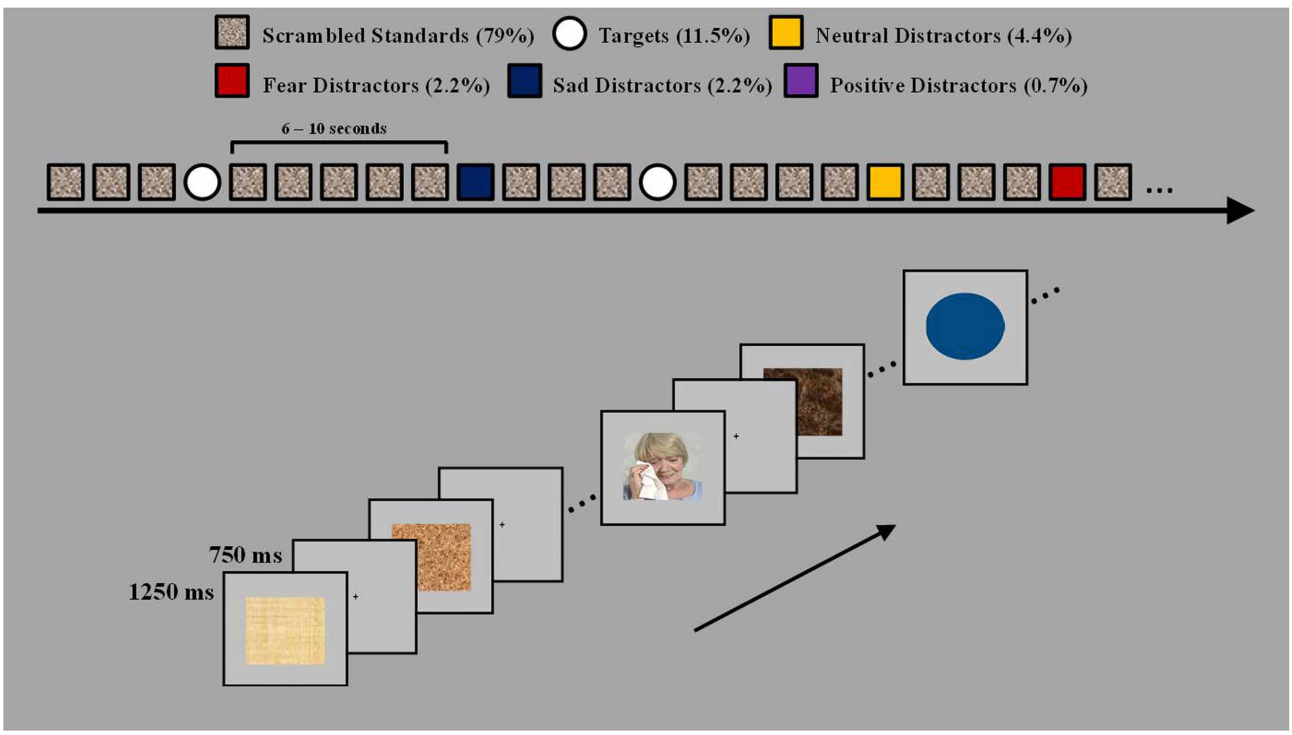

FIGURE 1 | Task design. The task used four types of rare events, fear, sad, neutral distracters, and target circles varying in size and color. The four types of rare events were presented pseudorandomly between the standard scrambled pictures and were separated by 6–10 s. Participants were instructed to make a left hand button press to all scrambled pictures and any picture with a person and to make a right hand button press to all target stimuli.

distracter and target stimuli), $F_{(2, 80)} = 0.93$, $p = 0.4$, for distracters, and $F_{(3, 120)} = 0.16$, $p = 0.93$, for targets. For the ERP analyses, all trials were included in the analyses as the number of trials usable after data processing was low.

RESULTS

INCREASED BEHAVIORAL IMPACT OF FEARFUL DISTRACTERS

Processing of fearful distracters was associated with longer RTs in both clinical and control groups. There were no differences between clinical ($n = 10$) and non-clinical adolescents ($n = 6$) in RT to distracters, $F_{(1, 14)} = 0.004$, $p = 0.95$, or the Distracter Type × Group interaction, $F_{(2, 28)} = 0.05$, $p = 0.86$. There was a main effect of Distracter Type, $F_{(2, 28)} = 8.35$, $E = 0.59$, $p = 0.008$, and *post-hoc* comparisons using Fisher LSD test showed RT to fear distracters was significantly longer than to neutral, $p = 0.006$, and sad, $p = 0.01$ distracters, where the later two type of distracters were not different from each another, $p = 0.48$. Assessing the effect of Distracter Type on RT for each group separately showed that the same pattern was present for both clinical, $F_{(2, 18)} = 4.11$, $E = 0.58$, $p = 0.065$, and non-clinical, $F_{(2, 10)} = 9.18$, $E = 0.66$, $p = 0.017$, adolescents. Similar to the above results for the clinical sub-sample of 10 and the non-clinical sample of six, the analysis on RT data for all 27 participants also showed a main effect of Distracter Type, $F_{(2, 52)} = 7.57$, $E = 0.071$, $p = 0.004$. *Post-hoc* comparisons using Fisher LSD test showed longer RT to the fearful distracters than to neutral ($p = 0.002$) or sad ($p = 0.009$) distracters, but the latter two were not significantly different from each another ($p = 0.45$) (see **Table 2** for mean and standard error RT data for each distracter category for clinical samples of 27 and 10 and the non-clinical sample of six).

ERP EVIDENCE OF INCREASED PROCESSING OF FEARFUL DISTRACTERS IN CLINICAL ADOLESCENTS

The ERP data revealed an impact of Distracter Type and Group for both early (P100) and late (LPP) components in response to the distracter images. First, the P100 amplitude at right hemisphere occipital-temporal electrodes (P10 in 10–10 topography) showed a significant interaction between Distracter Type and Group, $F_{(2, 28)} = 4.41$, $E = 0.88$, $p = 0.027$, but no main effect of Distracter Type [$F_{(2, 28)} = 0.92$, $p = 0.4$] or Group [$F_{(1, 14)} = 2$, $p = 0.2$] effect. There was a main effect of Distracter Type for the clinical sample, $F_{(2, 18)} = 3.83$, $E = 0.91$, $p = 0.047$, where replicating the observed behavioral pattern, *post-hoc* comparisons using Fisher LSD test showed overall the amplitude was larger for fearful images relative to both neutral ($p = 0.02$) and sad ($p = 0.05$), where the later two were not different from each another ($p = 0.82$), see **Figure 2**, left panel. Whereas, for the non-clinical sample there was no effect of Distracter Type on P100 amplitude, $F_{(2, 10)} = 1.99$, $p = 0.2$, see **Figure 2**, right panel, and **Table 3**.

There was no Distracter Type × Group interaction effect for the LPP at the left, midline, or right parietal electrodes (P3, Pz, and P4 in 10–10 topography), $F_{(2, 28)} = 1.78$, $p = 0.19$, nor was there a main effect of Group, $F_{(1, 14)} = 1.17$, $p = 0.3$. However, there was a significant effect of Distracter Type, $F_{(2, 28)} = 5.1$, $E = 0.81$, $p = 0.02$. Analyses examining the effect of Distracter Type on parietal LPP amplitude for clinical and non-clinical samples separately found a main effect of Distracter Type for clinical, $F_{(2, 18)} = 9.52$, $E = 0.94$, $p = 0.002$, but not non-clinical adolescents, $F_{(2, 10)} = 0.48$, $p = 0.55$, see **Figure 3**. *Post-hoc* comparisons for the clinical data using Fisher LSD test identified a pattern similar to the behavioral and P100 data with this main effect driven by larger mean amplitude in response to fearful distracters compared to neutral ($p = 0.001$) and sad ($p = 0.01$) distracters, again there were no difference between sad and neutral distracters ($p = 0.69$), see **Figure 3**, left panel, and **Table 3**. There was no effect of Distracter Type, $F_{(2, 28)} = 0.12$, $p = 0.84$, Group, $F_{(1, 14)} = 0$, $p = 1$, or Distracter Type × Group interaction, $F_{(2, 28)} = 0.5$, $p = 0.57$, on P300 amplitude measured at parietal electrodes.

Left temporal electrodes (TP7 in 10–10 topography) showed a main effect of Distracter Type, $F_{(2, 28)} = 10.57$, $E = 0.87$, $p = 0.001$, but no main effect of Group, $F_{(2, 14)} = 2.75$, $p = 0.12$, or Distracter Type × Group interaction, $F_{(2, 28)} = 0.19$, $p = 0.8$. Pairwise comparison using Fisher LSD test showed LPP mean amplitude was larger for fear compared to neutral distracters ($p = 0.009$) and the neutral distracters mean amplitude was larger compared to sad distracters ($p = 0.08$) (i.e., fear > neutral > sad). Investigation of the LPP for clinical and non-clinical samples separately revealed a main effect of Distracter Type for the clinical sample, $F_{(2, 18)} = 9.21$, $E = 0.96$, $p = 0.002$, and a trend effect for the non-clinical sample, $F_{(2, 10)} = 3.08$, $E = 0.58$, $p = 0.09$, see **Figure 4**. *Post-hoc* comparisons using Fisher LSD test showed for the clinical group the amplitude to fear distracters was larger

Table 2 | Mean reaction time (RT) and standard error (SE) data to distracters and targets for both the large sample of 27 participants and the small sample of 10 participants.

Distracter type	Group	Neutral	Fear	Sad	
RT (SE)	Clinical $n = 27$	578.49 (24.63)	629.43 (32.48)	568.59 (23.18)	
	Clinical $n = 10$	620.65 (47.08)	699.54 (64.24)	619.77 (47.92)	
	Non-clinical $n = 6$	633.38 (70.17)	704.65 (57.07)	617.95 (65.38)	
Target type	**Group**	**Target-after-neutral**	**Target-after-fear**	**Target-after-sad**	**Target-after-target**
RT (SE)	Clinical $n = 27$	527.91 (16.02)	536.98 (17.89)	538.31 (18.27)	526.45 (15.85)
	Clinical $n = 10$	555.94 (26.18)	557.61 (25.19)	548.62 (31.04)	544.5 (24.15)
	Non-clinical $n = 6$	502.81 (31.07)	499.11 (26.01)	515.9 (20.87)	498.88 (24.76)

than to neutral distracters ($p = 0.02$), which were no different from the amplitude to the sad distracters ($p = 0.14$) (i.e., fear > neutral = sad). *Post-hoc* comparisons for the non-clinical samples showed no significant differences between distracter types, even though the pattern was in the same direction as for the non-clinical sample (see **Table 3**).

ERP EVIDENCE FOR MODULATION OF TARGET PROCESSING BY EMOTIONAL DISTRACTION IN CLINICAL ADOLESCENTS

For RT data, there were no significant effects of Target Type, $F_{(3, 42)} = 0.7$, $p = 0.51$, or Group, $F_{(1, 14)} = 1.56$, $p = 0.23$, or an interaction between Target Type and Group, $F_{(3, 42)} = 0.25$, $p = 0.8$. Neither the clinical or non-clinical samples showed a main effect of Target Type on RT, $F_{(3, 27)} = 0.44$, $p = 0.66$ and $F_{(3, 15)} = 0.54$, $p = 0.54$, respectively. Analysis on the larger clinical sample using all 27 participants also did not show a main effect of Target Type on RT data, $F_{(3, 78)} = 1.38$, $p = 0.26$, although the larger analysis showed a trend level effect of sad distracter images on performance, where targets-after-sad had slower response times compared to targets-after-targets, $t_{(26)} = 1.89$, $p = 0.07$. See **Table 2** for mean and standard error RT data for each target category.

ERP data for the P300 at left parietal electrodes (P5 and P3 in 10–10 topography) showed no main effect of Target Type, $F_{(3, 42)} = 1.8$, $p = 0.18$, or Group, $F_{(1, 14)} = 0.11$, $p = 0.74$ nor a significant interaction between Target Type and Group, $F_{(2, 42)} = 1.8$, $p = 0.18$. While this overall model was not significant, examination of Target Type for clinical and non-clinical

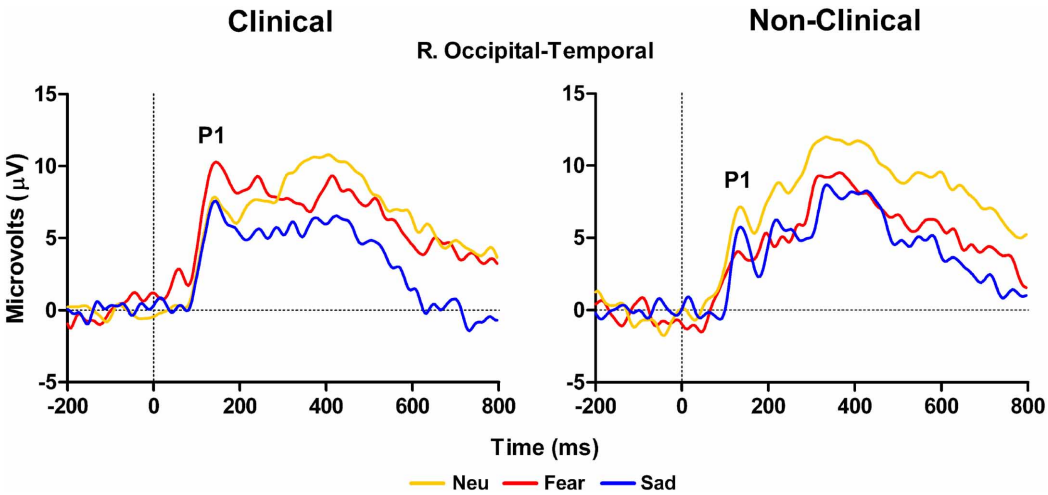

FIGURE 2 | Grand average waveforms in response to distracter stimuli over right temporal-occipital electrodes showing larger peak P100 amplitude to fearful distracters compared to neutral and sad distracters for clinical adolescents (left panel) compared to non-clinical adolescents (right panel). Neu, Neutral pictures; Fear, Fear Pictures; Sad, Sad Pictures.

Table 3 | Mean ERP amplitudes and standard error (SE) for the LPP, P100, and P300.

ERP component	Electrode cluster	Group	Distracter type		
			Neutral	Fear	Sad
P100	R. occipital-temporal	Clinical $n = 10$	8.76 (0.79)	11.37 (1.33)	8.48 (1.25)
		Non-clinical $n = 6$	9.03 (1.29)	6.22 (1.5)	7.02 (1.42)
LPP	Parietal	Clinical $n = 10$	3.36 (0.98)	6.34 (1.18)	3.92 (0.95)
		Non-clinical $n = 6$	6.34 (1.26)	6.8 (1.52)	5.76 (1.22)
	L. temporal	Clinical $n = 10$	1.02 (1.06)	3.75 (1.09)	−0.66 (0.87)
		Non-clinical $n = 6$	3.1 (1.37)	5.49 (1.42)	2.11 (1.13)

			Target type			
			Target-after-neutral	Target-after-fear	Target-after-sad	Target-after-target
P300	L. parietal	Clinical $n = 10$	4.12 (1.19)	5.68 (0.97)	5.5 (1.21)	3.23 (1.31)
		Non-clinical $n = 6$	4.44 (1.54)	5.5 (1.26)	5.2 (1.56)	5.71 (1.69)
LPP	L. occipital-temporal	Clinical $n = 10$	−0.81 (0.99)	1.85 (0.76)	2.04 (0.99)	−0.75 (0.82)
		Non-clinical $n = 6$	2.29 (1.28)	3.37 (0.98)	2.03 (1.28)	2.03 (1.28)

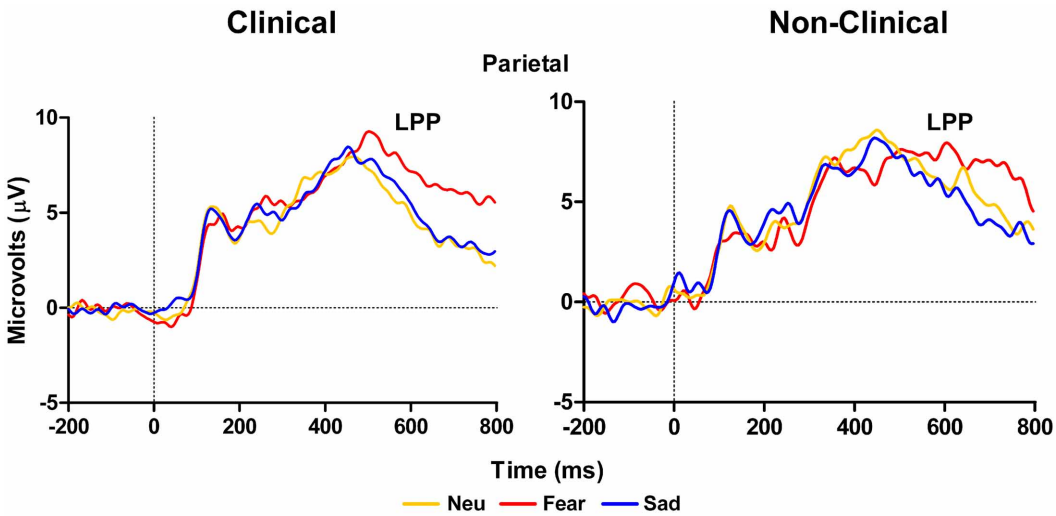

FIGURE 3 | Grand average waveforms in response to distracter stimuli. The late positive potential (LPP) over left, midline, and right parietal electrodes is larger for fearful distracters compared to neutral and sad distracters for clinical adolescents (left panel), but not non-clinical adolescents (right panel). Neu, Neutral pictures; Fear, Fear Pictures; Sad, Sad Pictures.

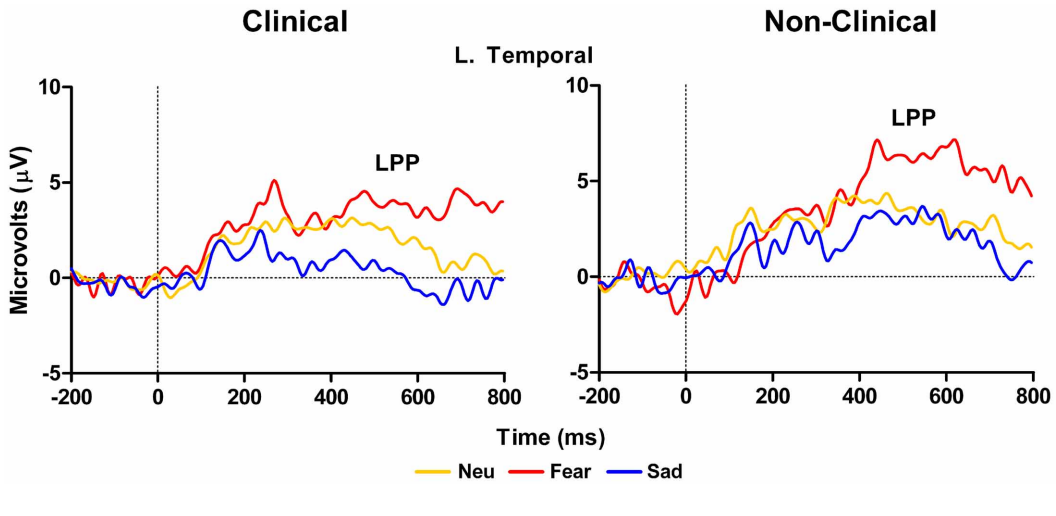

FIGURE 4 | Grand average waveforms from left temporal electrodes showing a larger LPP for clinical adolescents in response to high arousal negative fearful distracters compared to neutral distracters. The LPP did not differ between neutral and sad distracters (left panel). Non-clinical adolescents had no significant differences between distracter groups (right panel). Neu, Neutral pictures; Fear, Fear Pictures; Sad, Sad Pictures.

samples separately, showed a marginal effect of Target Type for the clinical sample, $F_{(3,\ 27)} = 2.86$, $E = 0.67$, $p = 0.08$, but not for the non-clinical sample, $F_{(3,\ 15)} = 1.68$, $p = 0.24$. For the clinical group, *post-hoc* comparisons using Fisher LSD test showed that P300 amplitude to target-after-sad was larger than target-after-target ($p = 0.03$), while the amplitude to target-after-fear was marginally larger than to target-after-target ($p = 0.07$), see **Figure 5** and **Table 3**.

In addition to the P300 results reported above, a main effect of Group, $F_{(1,\ 14)} = 4.48$, $p = 0.05$, with the clinical group having overall smaller amplitudes compared to the non-clinical group, and a marginal Target Type × Group interaction, $F_{(3,\ 42)} = 2.78$, $E = 0.74$, $p = 0.07$, was identified for LPP mean amplitude over left hemisphere temporal-occipital electrodes (TP7, P7, and P07 in 10–10 topography), see **Figure 6** and **Table 3**. There was no main effect of Target Type, $F_{(3,\ 42)} = 1.92$, $p = 0.16$. To determine the effects driving the interaction, separate ANOVAs were performed on the clinical and non-clinical groups. There was a main effect of Target Type for the clinical group, $F_{(3,\ 27)} = 3.69$, $E = 0.7$, $p = 0.04$, but not the non-clinical group, $F_{(3,\ 15)} = 2.09$, $p = 0.18$. Further investigation of the main effect of Target Type in the clinical group using Fisher LSD tests showed target-after-fear and target-after-sad mean amplitudes to be larger than target-after-target, $p = 0.05$ and $p = 0.02$, respectively.

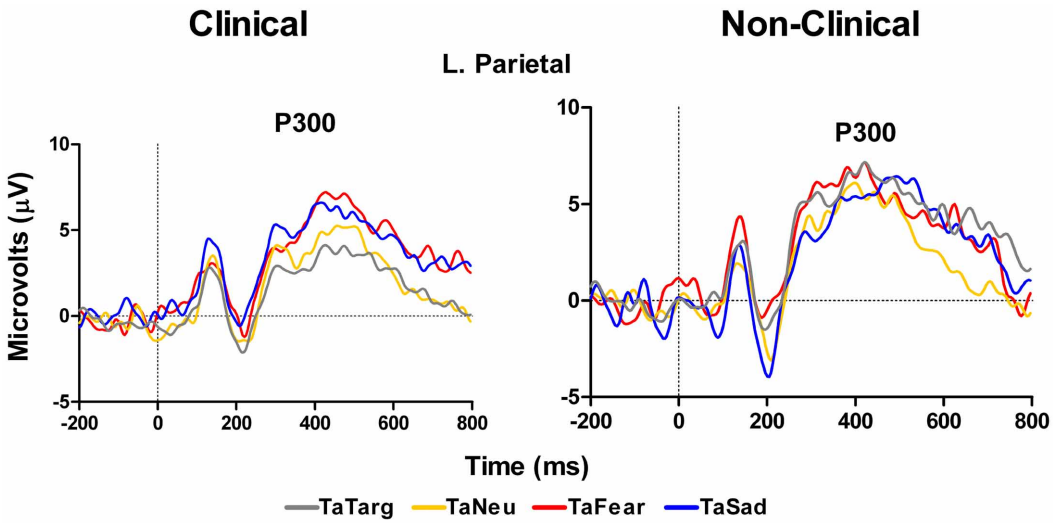

FIGURE 5 | Grand average waveforms in response to target stimuli over left hemisphere parietal electrodes. Figure shows increase in P300 amplitude in response to targets-after-sad and targets-after-fear compared to targets-after-targets for the clinical group (left panel), but not in the non-clinical group (right panel). TaTarg, target-after-target; TaNeu, target-after-neutral; TaFear, target-after-fear; TaSad, target-after-sad.

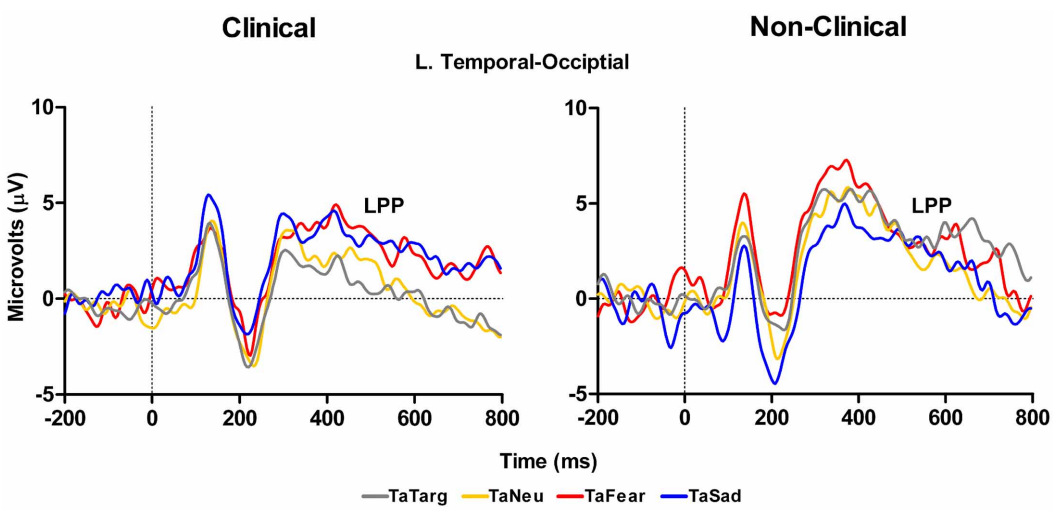

FIGURE 6 | Grand average waveforms to target stimuli from left-hemisphere temporal-occipital electrodes show an effect of valence on the LPP in response to target processing with both targets-after-sad and -fear having an increased amplitude compared to targets-after-targets for the clinical (left panel), but not non-clinical (right panel) group. TaTarg, target-after-target; TaNeu, target-after-neutral; TaFear, target-after-fear; TaSad, target-after-sad.

DISCUSSION

The main purpose of this study was to examine the morphology of ERP markers of emotion and attention in response to stimuli presented in an emotional oddball task with a group of youth primarily suffering from disorders of attention and emotion regulation. Analyses were performed on three sets of data: two from clinical samples (with or without ERP data), and one from the control sample. The task employed allowed for the comparison of behavioral and ERP responses to distracter pictures that were fearful, sad, or neutral, as well as target stimuli that were circles, which contained no emotional content. We performed analyses on the distracter events themselves (all picture types) as well as the target events that immediately followed distracters (fearful, sad, and neutral) or other targets. Our study yielded three main findings. First, we identified an increased impact of fearful distracters on behavioral performance and this difference was found for both clinical and non-clinical samples. Second, in clinical adolescents, this behavioral difference corresponded to an increase in the amplitude of early and late emotion ERP components in response to fearful relative to neutral distracters. Lastly, clinical adolescents exhibited difference in ERP morphology to targets following emotional distraction.

INCREASED BEHAVIORAL IMPACT OF FEARFUL DISTRACTERS

The behavioral finding in our study was that we observed longer RT in response to the fearful distracters compared to sad or neutral distracter images. We observed this fearful effect in all three of our samples, the large group of 27 participants the smaller group of 10 participants and the control group of 6 participants. This suggests that from a behavioral perspective, all three of our adolescent groups were similar and that our smaller subset clinical group is representative of the larger clinical cohort in our study. These findings show that all our participants were spending a longer time in the preparation and execution of a manual response to the fearful pictures. This delay can be interpreted as reflecting an increase in the capture of attention by the fearful images compared to sad or neutral (Ohman et al., 2001), even though they were not the main target stimuli in the task (Vuilleumier and Schwartz, 2001). Thus, the fearful images may have competed more for attention-related resources, which led to impaired performance (Dolcos and McCarthy, 2006; Zanto and Gazzaley, 2009; Denkova et al., 2010). The error rates were equivalent across all conditions, and so the differences in RT that we observed are not due to simple speed-accuracy trade-off effects. We also observed a trend in the target RT data for the large group of 27 clinical participants, where responses to targets that followed sad images were slightly slower than responses to targets that followed other targets. We are cautious to interpret this effect because our control sample is very small in comparison to the larger clinical sample, but in light of the P300 differences (discussed below), these findings are consistent with a carry-over-effect of the emotion from the affective pictures on the perception and decision making processes required for target response.

ERP EVIDENCE OF INCREASED PROCESSING OF FEARFUL DISTRACTERS IN CLINICAL ADOLESCENTS

In response to the distracter pictures, we observed early and late effects in the P100 and LPP waveforms, respectively. In the case of the P100 we unexpectedly observed larger amplitudes in response to the fearful images compared to the other image types at right hemisphere occipital-temporal electrodes. Importantly, this effect was only observed in the clinical sample, and was not present in the healthy control sample. It is well-known that the P100 reflects early spatial attention operations associated with activity in extra-striate brain regions (Martinez et al., 1999), and it is one of the earliest endogenous ERP components that is sensitive to top–down control mechanisms. Thus, on the face of it this pattern of data suggests that the clinical group participants were likely allocating more attention-based resources toward images that were fearful in nature compared to the other image types. Moreover, the healthy control sample did not show evidence of this attentional strategy.

In the case of the LPP at parietal and temporal electrodes we observed larger amplitudes in response to the fearful images compared to the other two image types in the clinical sample. This effect is consistent with the RT data in response to the fearful images. Again, as with the P100 results, this pattern of data was absent in the control sample data, as there were no differences in LPP amplitude across the image types in the healthy control group; also, this effect is inconsistent with the behavioral data. The LPP has been shown to be sensitive to the arousal level of eliciting pictures (Schupp et al., 2004) and this effect appears to be verified in our data. Our ratings clearly show that the fearful images were also the most arousing. Moreover, our fear-based LPP result in the clinical sample may reflect the conscious awareness and salience of the images (Williams et al., 2007) that results from downstream processing of emotional information perhaps associated with amygdala activity (Bradley et al., 2003). Taken together with research showing that LPP amplitude correlates with anxiety level in healthy adults (MacNamara et al., 2011) and in youth with anxious attachment styles (Zilber et al., 2007), we may have observed a unique signature of anxiety and arousal associated with fear processing in our clinical population of adolescents. That is, the salience of the fear images is perceptually and cognitively heightened in our special population possibly due to a pre-existing susceptibility for fear-based reactivity.

Critically, this pattern of data was not present in the healthy control sample, which further supports our argument that our clinical adolescent group has a unique processing style for emotional information. This is particularly evident for the fear-based stimuli. Also, in the case of the healthy sample, the ERP data did not follow the behavioral data as it did in the clinical data. This finding may be explained by the small sample size of our healthy control group that makes it difficult to identify reliable physiological differences in distracter processing between groups. It could also be due to individual differences in processing of fear-based stimuli in non-clinical individuals. One other possibility is that the unique mechanisms in fear processing we observed are not intimately linked with behavior in our task. Rather, the ERP effects may reflect processes unrelated to the conscious awareness of the stimulus that are reflected in the response selection and execution process. When the LPP data is considered in conjunction with our P100 data in response to the distracter images in the clinical sample, our ERP data may be a reflection of very early attention modulation in our clinical youth population that is associated with a heightened focus toward the fearful images. The P100 is known to have neural generator sources in similar occipital-temporal regions that also underlie the LPP generation (Bradley et al., 2003), and the similar fear-based effects we observed in these two waveforms may have been facilitated by a common neural substrate related to projections between sensory and affective brain regions in our special clinical sample.

ERP EVIDENCE FOR MODULATION OF TARGET PROCESSING BY EMOTIONAL DISTRACTION IN CLINICAL ADOLESCENTS

The ERP in response to the target stimuli that we analyzed were the P300 and the LPP. The P300 is a well-known marker of selective attention, perceptual processes, and working memory processes (Kok, 2001). In our clinical sample at left parietal sites, the P300 was larger to targets that followed sad images and slightly larger to targets that followed fearful images compared to when targets followed other targets. These differences were absent in the control sample data. Thus we observed a target processing effect related to the preceding emotional stimuli that presumably was related to some carryover effect. This does not follow the behavioral data that showed no differences in RTs to targets following

emotional images compared to targets that followed other targets. However, the P300 measure appears to be more sensitive to these putative carry-over effects than behavior, perhaps because P300 reflects perceptual processes rather than response-related processes (Kok, 2001), whereas the RT measures must reflect all operations that are engaged between stimulus presentation and response execution. Finally, the LPP data in response to targets showed a strong effect over left temporal sites where amplitudes were larger for targets following both fearful and sad images compared to targets that followed other targets. Again, this finding was only for the clinical sample, and this finding follows the P300 result over left parietal sites and may be a unique reflection of the sustained emotion processing that occurred and affected the target-related processes reflected by the P300. Thus, whereas P300 may reflect the increase in attention-related resources toward a stimulus following an emotional image in our clinical population, the LPP effect in response to targets may be more of a reflection of the sustained duration of the neural representation of the emotion itself (Hajcak et al., 2010). That is, a sustained downstream reflection of lower level processes in the amygdala and other affective structures. This sustained activity may result from the inability to disengage from processing emotional information triggered by the distracters (e.g., recollection of negative memories cued by the negative pictures), which continues after the cues disappear and affect the ability to focus on the following targets. This is consistent with mood congruent effects of emotion on memory and may be linked to emotion dysregulation as in the case of post-traumatic stress disorder (McFarlane, 2010). Importantly, this pattern of effects was absent in the control sample.

Caveats

Although the findings presented shed light on emotion-attention interactions in clinical compared to non-clinical adolescents, the present investigation also has limitations. First, the sample size in both the clinical and non-clinical ERP groups was relatively small. It should be under consideration that with a large sample these effects may slightly change. For example, a common finding in the emotion ERP literature is an enhanced LPP to high arousing emotional relative to neutral stimuli and even though we did not replicate this finding in our healthy control group, we clearly see a trend toward a significant LPP to fear stimuli (see **Figures 3** and **4**). However, in light of this, our findings are consistent with an exacerbated LPP response to high arousing emotional stimuli in clinical compared to non-clinical populations (Hajcak and Dennis, 2009). Furthermore, despite differences in the size of the behavioral only ($N = 27$), behavioral and ERP ($N = 10$), and control ($N = 6$) samples, the pattern of behavior was equivalent between all groups. We also acknowledge that our criterion of a min of five ERP trials per condition is low. A second limitation is co-morbid nature of the diagnoses in our clinical group. In fact, only one adolescent had been diagnosed with a single mental health disorder, and all others presented with two, sometimes three different disorders. Most undoubtedly the underlying neural mechanisms of these varied diagnoses differ from one another, however, and as shown here there may be some overarching abnormalities in processing that can be identified using electrophysiological measures. A third limitation of the study is the varied medication of the clinical adolescents and within our sample it is impossible to rule out the effects of medication on behavioral and ERP performance. It is possible that the behavioral measures in task performance were insensitive to group differences and those group differences observed with ERP measures were mitigated by the effects of these medications. Future studies using a similar experimental design and a larger number of subjects should further investigate these issues.

CONCLUSION

Our small scale but complex study is unique in that it has examined both behavioral and ERP responses to stimuli in an emotional oddball task with a sensitive population of adolescents suffering from Axis-1 disorders including ADHD, anxiety, and depression. Moreover, we included a small sample of healthy controls individuals for comparison purposes. Overall we observed an interesting pattern of behavioral (RT) and neural responses (P100, LPP, and P300) that showed similarities (i.e., behavioral data) and differences (i.e., ERP data) in emotion and attentional processing between clinical and non-clinical samples. Fearful images impacted behavioral performance for both clinical and non-clinical samples, showing a consistent behavioral effect of fearful emotion regardless of potential underlying alterations in the neural mechanisms of emotion processing between groups. Early (P100) and late (LPP) ERP components assessing emotion processing differentiated between groups as clinical adolescents showed augmented amplitudes to fearful relative to sad and neutral pictures. Furthermore, emotion modulation of attentional processing (P300) and a sustained emotion effect on target processing (LPP) were identified for the clinical sample only. Suggesting attentional control processes in our sample of clinical adolescents were more susceptible to emotion modulation through either an increase in the initial engagement of resources or the inability to disengage from the emotional information. Taken together, these data may reflect a pattern of emotion dysregulation in adolescents suffering from Axis-1 disorders that modulates certain aspects of emotion-attention interactions. These effects did not uniquely follow the behavioral responses and perhaps reflect emotion and cognition processes that are not part of the response selection and execution process. Moreover, our results provide an example of the impairing effects that emotion and emotional reactivity can have on very basic cognitive function in sensitive individuals, but not in more robustly healthy persons. Thus, we have provided a small window into potential dysfunction between emotion and cognition in this youth population with clinical disorders.

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Affective priming in major depressive disorder

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Research on cognitive biases in depression has provided considerable evidence for the impact of emotion on cognition. Individuals with depression tend to preferentially process mood-congruent material and to show deficits in the processing of positive material leading to biases in attention, memory, and judgments. More research is needed, however, to fully understand which cognitive processes are affected. The current study further examines the impact of emotion on cognition using a priming design with facial expressions of emotion. Specifically, this study tested whether the presentation of facial expressions of emotion affects subsequent processing of affective material in participants with major depressive disorder (MDD) and healthy controls (CTL). Facial expressions displaying happy, sad, angry, disgusted, or neutral expressions were presented as primes for 500 ms, and participants' speed to identify a subsequent target's emotional expression was assessed. All participants displayed greater interference from emotional vs. neutral primes, marked by slower response times to judge the emotion of the target face when it was preceded by an emotional prime. Importantly, the CTL group showed the strongest interference when happy emotional expressions served as primes whereas the MDD group failed to show this bias. These results add to a growing literature that shows that depression is associated with difficulties in the processing of positive material.

Keywords: affective priming, cognitive biases, depression

Cognitive theories of depression propose that individuals with Major Depressive Disorder (MDD) show mood-congruent cognitive biases, typically giving preference to the processing of negative vs. positive material. According to Beck (1967), negative biases in MDD stem from stable cognitive patterns, termed schemata, which serve as negative filters through which individuals view themselves, the world, and others. Cognitive theories further highlight the interconnectedness of negative schemata in depression, which leads to automatic and efficient processing of mood-congruent information (Ingram, 1984). Thus, the presence of a negative stimulus will easily activate other negative thoughts and memories in depression. It is this high degree of interconnectedness of negative vs. positive information that is believed to heighten risk for the onset and maintenance of depressive episodes (e.g., Ingram, 1984; Taylor and Ingram, 1999), highlighting the importance of examining the effect of emotion on cognition.

The interconnection of mood-congruent material has been tested using affective priming designs (e.g., Fazio et al., 1986; Murphy and Zajonc, 1993). In a typical affective priming experiment, two words (referred to as *prime* and *target*) are presented sequentially, and participants are asked to indicate the valence of the target as quickly as possible. The speed with which people respond to the target is believed to be dependent on the prime. People typically demonstrate a priming effect: they process the target faster when the prime is valence-congruent (e.g., both prime and target are positive) compared to when the prime valence-incongruent (e.g., prime is neutral but target is positive). Priming occurs because the prime activates other information of the same valence (e.g., Fazio et al., 1986). The more closely interconnected valence-congruent information, the faster people will respond to the target. Previous studies have shown that the presentation of a prime can affect feelings, thoughts, and action tendencies (e.g., Neely, 1991; Bargh et al., 1996).

Given that negative information is more closely interconnected in depression, cognitive theories propose that depressed compared to control participants will show stronger priming for negative stimuli; however, priming studies in depression have not yielded consistent results. Bradley et al. (1995), for example, used a lexical decision task with subliminal primes, and found greater priming for negative words in depressed vs. control participants. In contrast, Matthews and Southall (1991) did not find priming from negative words in depression despite using a similar design. Null findings have also been reported in several other studies using subliminal primes (Koschack et al., 2003; Dannlowski et al., 2006a). Interestingly, Dannlowski et al. (2006b) found evidence of reverse priming, or interference. The authors examined the impact of prime words on how quickly participants judged the valence (positive or negative) of the targets. Rather than responding faster on congruent prime-target trials, depressed participants were slower to judge the valence of negative target words following negative primes. Taken together, studies do not provide consistent evidence of enhanced priming of negative concepts in depression, which

stands contrary to predictions made by cognitive theories of depression.

Difficulties obtaining priming effects could be related to the length of time the prime is presented. Priming studies in depression traditionally have examined the automatic activation of schemata by presenting primes subliminally. Many studies on cognitive processing in depression, however, have reported that biases are more consistently found at later stages of processing (e.g., see Mathews and MacLeod, 2005, for a review). With this in mind, to better understand cognitive biases in MDD, stimuli may have to be presented for longer durations to allow more elaborative processing of the material. The current study, therefore, examined how emotional information presented for a prolonged period of time affected the processing of subsequent emotional targets.

In addition, the choice of stimuli may affect priming effects in depression. Thus far, the majority of studies have utilized word stimuli (e.g., Bradley et al., 1995; Dannlowski et al., 2006b). Given the importance of deficits in social functioning in the maintenance and recurrence of depression (Blair, 2003), facial expressions may provide stronger and more relevant stimuli than words. The ability to quickly and accurately identify facial expression of emotions is critical for successful interpersonal functioning (e.g., Hess et al., 1988). Increasing evidence suggests important differences in the way depressed and control participants process facial expressions. In fact, results from both behavioral and neuroimaging studies highlight that depressed individuals differ from healthy controls (CTL) in the processing of facial expressions. Some studies have reported that depressed participants exhibit global deficits when processing facial expressions of emotion (e.g., Feinberg et al., 1986), whereas others indicate that MDD is associated with difficulty identifying specific emotions (e.g., happy but not sad; Suslow et al., 2001). Moreover, results from neuroimaging studies indicate that, compared to healthy controls, depression is associated with a different pattern of neural responses to happy vs. sad expressions (e.g., Surguladze et al., 2005) as well as differential neural responses to facial expression of disgust (e.g., Surguladze et al., 2010). Given the substantial evidence suggesting the importance of facial processing in the severity, persistence, and relapse of depressive episodes (e.g., Hale, 1998; Bouhuys et al., 1999a,b), it might be particularly relevant to examine priming effects using facial expressions of emotion.

The current study used a priming design to test the impact of emotion on participants' speed to cognitively process subsequent information. Emotional primes were presented for a prolonged period of time to allow thorough processing, and we tested the impact of these primes on participants' speed to identify a subsequent congruent or incongruent target. We predicted that all individuals would show priming effects, evidenced by faster processing of targets when the prime is of congruent valence compared to a neutral prime. However, we expected depressed participants, compared to healthy controls, to show especially strong priming effects for negative vs. positive material, thereby highlighting the enhancing effect of negative emotions on processing speed for MDDs but not CTLs.

METHODS

PARTICIPANTS

Adults between the ages of 18 and 60 were recruited via newspaper advertisements and Internet postings. Potential participants were screened over the phone for initial inclusion and exclusion criteria. Two groups of individuals were included in the study: participants who met DSM-IV criteria for MDD and participants who did not meet criteria for a current or past Axis I disorder (CTL). Individuals were excluded if they had severe head trauma, a learning disability, or met DSM-IV criteria for bipolar disorder, alcohol abuse, or substance abuse with the past 6 months. After participants provided informed consent, diagnoses, and exclusion criteria were confirmed in the laboratory by trained and experienced interviewers using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Based on the SCID, 19 MDD and 30 CTL participants were deemed eligible and included in the study.

AFFECTIVE PRIMING TASK

Stimuli

Pictures were selected from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998), which consisted of black-and-white photographs of Caucasian individuals portraying a variety of facial expressions. For the current study, we selected 29 male and 28 female faces depicting neutral, happy, sad, angry, and disgusted expressions. Pictures of 11 additional models were used during the practice trials. All pictures were cropped just below the chin, above the hairline, and at the start of each ear. Pictures were approximately 8 cm × 10 cm in size and each pair was presented approximately 14 cm apart (measured from their centers).

Design

In the priming task (adapted from Yoon and Zinbarg, 2007), photograph pairs were presented sequentially on the computer screen using eprime software. Each trial began with "Ready" displayed for 500 ms in white text in the center of a black computer screen. Next, the first photograph (*the prime*) was presented in the center of the screen for 500 ms. Participants were asked to attend to the prime photograph, but they did not need to take any action. Immediately following the offset of the prime, a second photograph (*the target*) of a different actor was displayed in the center of the screen. The target photograph remained on the screen until participants judged the valence (positive or negative) of the facial expression using the 1 and 2 keys of a standard keyboard's number pad. Participants' reaction time to judge the valence of the target face was used to calculate the priming score (see below). The key 1 was partially covered with a sticker labeled N for negative valence, and the key 2 was partially covered with a sticker labeled P for positive valence. Participants were asked to use these keys to make their valence ratings as quickly and as accurately as possible. To test our hypothesis, it was critical to ensure that participants were consciously processing the prime and target facial expressions. For that reason, after both photographs went off the screen, participants saw a screen displaying the question, "Which picture was friendlier?" The accuracy of participants' response provided a check of their attention to both

photographs. Participants then judged whether the first or second face was friendlier. Participants used the 1 and 2 keys of the number pad to make their friendly judgment: 1 indicated the first face was friendlier, and 2 indicated the second face was friendlier. Participants completed 10 practice trials before going on to complete 240 task trials.

The target faces depicted happy, sad, angry, or disgusted emotional expressions. For each emotional category, 20 trials were emotion-emotion (the prime and target displayed the same emotional expression), 20 were neutral-emotion (the prime depicted a neutral expression but the target depicted an emotional expression), and 20 were fillers (the prime and target depicted two different emotional expressions). Filler trials were included in the design so that emotional primes would not lead to participants anticipating a target of congruent valence. Given that filler trials consisted of a different number of each prime-target pair type (e.g., angry-sad vs. angry-disgust, vs. angry-happy) for each participant and that we did not expect participants to respond to negative-negative and negative-positive pair types the same, we did not include filler trials in the analyses.

QUESTIONNAIRES

BDI

To measure depression severity at the time when the priming task was administered, participants completed the Beck Depression-Inventory-II (BDI-II, Beck et al., 1996). This 21-item self-report measure of the severity of depressive symptoms has shown excellent reliability and validity ($\alpha = 0.92$; Beck et al., 1996).

PROCEDURE

Participants first came into the laboratory to partake in the SCID, which took approximately 2 h. Eligible participants were scheduled for their second session, which took place typically within 2 weeks of the SCID. During the second session they completed the priming task and the BDI. The current study was approved by the University of Miami Internal Review Board (IRB).

RESULTS

PARTICIPANT CHARACTERISTICS

Clinical and demographic characteristics of the participant groups were examined (see **Table 1**). First, BDI scores were analyzed to confirm that MDD participants continued to exhibit high levels of depression at the time the priming task was completed. Given that two participants in the MDD group had BDI scores less than 10, these participants were excluded from further analysis. We analyzed data on the remaining 30 CTL and 17 MDD participants. Percent female did not differ between the CTL and MDD groups, $\chi^2(1, N = 47) = 0.64$. Race/ethnicity also did not differ across the two groups, $\chi^2(4, N = 45) = 4.85$. Ethnicity data are missing from two participants who elected not to provide this information. In addition, age did not differ in the CTL and MDD groups, $t_{(45)} = 0.86$, all $p > 0.05$. There was, however, the anticipated significant difference in participants' BDI scores, $t_{(45)} = 11.11$, $p < 0.001$, with CTL participants obtaining significantly lower BDI scores than MDD participants. Based on the SCID, 10 of the MDD participants also met criteria for one or more DSM-IV disorder, including panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, specific phobia, obsessive-compulsive disorder, posttaumatic stress disorder, and generalized anxiety disorder.

Table 1 | Participant characteristics.

Variable	Group	
	CTL	MDD
Percentage of women	46.67	58.82
Percentage of race/ethnicity	–	–
American Indian or Alaska native	3.45	0.00
Black or African American	31.03	6.25
White—Non Hispanic or Latino	17.24	31.25
White—Hispanic or Latino	41.38	50.00
Other	6.90	12.50
Age (SD)	37.17 (12.71)	40.59 (13.66)
BDI (SD)	3.13 (4.57)[a]	29.29 (11.46)[a]
# WITH COMORBID AXIS-I DISORDERS		
Panic disorder with or without agoraphobia	–	5
Agoraphobia without panic disorder	–	1
Social phobia	–	3
Specific phobia	–	6
Obsessive-compulsive disorder	–	1
Posttraumatic stress disorder	–	2
Generalized anxiety disorder	–	4

Note: CTL, control; MDD, major depressive disorder; BDI, Beck Depression Inventory-II; participants may have more than one comorbid diagnosis.

[a] $p < 0.001$.

ATTENTION CHECK

In order to adequately test our hypotheses, it was critical to ensure participants were consciously processing the prime and target facial expressions. To check for this, the accuracy with which participants judged the relative friendliness of facial expressions was examined on trials in which neutral facial expressions served as primes. The frequency that participants judged the emotional facial expression as more friendly was compared across happy, sad, angry, and disgusted trials. Friendly ratings are missing for five participants for whom there was a computer error. A two-way group (MDD, CTL) by emotion (happy, sad, angry, and disgusted) repeated-measures analysis of variance (ANOVA) was conducted on number of times the emotional face was judged friendlier than the neutral face. The main effect of group was not significant, $F_{(1, 40)} = 0.80$, $p > 0.05$, $\eta^2 = 0.02$. However, there was a significant main effect of emotion, $F_{(3, 120)} = 325.23$, $p < 0.001$, $\eta^2 = 0.89$, see **Table 2**. As expected, happy faces were judged friendlier more often than sad faces, $t_{(41)} = 23.64$, angry faces, $t_{(41)} = 24.81$, and disgusted faces, $t_{(41)} = 21.00$, all $p < 0.001$. In addition, sad faces were judged friendlier more often than angry faces, $t_{(41)} = 3.61$, and disgusted faces, $t_{(41)} = 4.84$, both $p < 0.01$. In contrast, there was no difference in the frequency with which participants judged angry vs. disgusted faces friendlier, $t_{(41)} = 1.90$, $p > 0.05$. The group by emotion interaction also did not reach significance, $F_{(3, 120)} = 0.37$, $p > 0.05$, $\eta^2 = 0.01$. Thus, the accuracy with which participants attended to both facial expressions did not differ by group.

Table 2 | Percent trials emotional face judged friendlier than neutral face as a function of emotion and group.

Emotion (%)	Group	
	CTL	MDD
Happy[a]	92.15 (12.90)	92.50 (14.55)
Sad[a,b]	18.35 (14.90)	22.50 (14.20)
Angry[a,b]	12.85 (10.80)	12.50 (17.90)
Disgusted[a,b]	8.00 (8.25)	12.90 (18.05)

[a] *Happy faces were judged friendlier more often than sad faces, angry faces, and disgusted faces, $p_s < 0.01$.*

[b] *Sad faces were judged friendlier more often than angry faces and disgusted faces, $p_s < 0.01$.*

Table 3 | Priming data by emotion and trial type.

Emotion	Reaction time (in ms)	
	Emotion–emotion	Neutral–emotion
HAPPY		
CTL	1,559.91 (468.26)	1,276.69 (308.09)
MDD	1,385.42 (415.96)	1,176.28 (381.25)
SAD		
CTL	1,657.47 (492.67)	1,628.20 (411.99)
MDD	1,466.51 (570.49)	1,434.44 (376.02)
ANGRY		
CTL	1,701.37 (469.24)	1,588.27 (402.61)
MDD	1,446.50 (426.11)	1,346.19 (398.14)
DISGUSTED		
CTL	1,618.84 (467.57)	1,567.35 (364.22)
MDD	1,492.42 (496.87)	1,282.10 (339.46)

Note: Standard deviations in parentheses. CTL, control participants; MDD, participants diagnosed with Major Depressive Disorder.

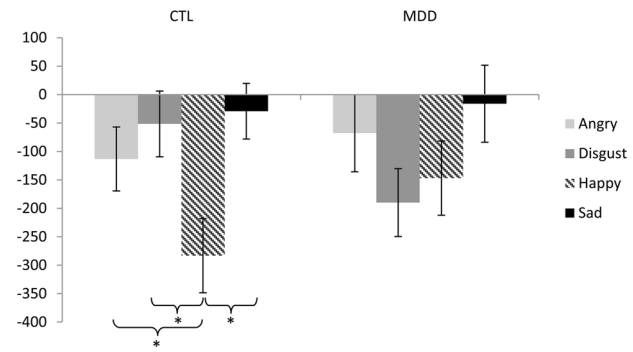

FIGURE 1 | Priming scores for each emotion (angry, disgust, happy, and sad) for both control (CTL) and depressed (MDD) participants. Negative priming scores reflect reverse priming or difficulty disengaging from the emotional compared to neutral primes. Error bars indicate ±1 SE. *$p < 0.02$.

PRIMING

To assess priming, reaction times to indicate the target face valence were examined depending on whether the prime displayed a congruent or neutral facial expression. A priming score was calculated for each emotional expression using the following equation (see **Table 3** for means by trial type):

$$\text{Priming Score} = \text{RT(neutral-emotion)} - \text{RT(emotion-emotion)}$$

Neutral-emotion indicates the prime displayed a neutral expression; emotion-emotion indicates the prime displayed the same emotional expression as the target. Therefore, RT (neutral-emotion) indicates the mean reaction time to indicate the valence of the target face when the prime is neutral. According to this formula, larger priming scores indicate people were faster when prime-target pairs had congruent facial expressions. Response times from only correct responses were examined. Error rates were low (less than 10% across all participants). To eliminate outliers, reaction times exceeding plus or minus one standard deviation from the mean were eliminated. Percent outlying trials did not differ in the CTL (10.82%) and MDD groups (8.87%), $t_{(45)} < 1, p > 0.05$.

To test our main hypothesis regarding depression and priming from emotional facial expressions, a two-way group (MDD, CTL) by emotion (happy, sad, angry, and disgusted) repeated-measures ANOVA was conducted on priming scores. The ANOVA yielded a significant main effect of emotion, $F_{(3,\ 135)} = 5.62$, $p < 0.001$, $\eta^2 = 0.11$, and a significant group by emotion interaction, $F_{(3,\ 135)} = 2.88$, $p < 0.04$, $\eta^2 = 0.06$; see **Figure 1**. The main effect of group was not significant, $F_{(1,\ 45)} = 0.04$, $p > 0.05$, $\eta^2 = 0.00$. Overall, participants displayed a *negative* priming score that suggests reverse priming. Reverse priming scores significantly differed from zero for happy, $t_{(46)} = 4.83$, angry, $t_{(46)} = 2.24$, and disgust faces, $t_{(46)} = 2.34$ $p < 0.05$; however, reverse priming scores did not significantly differ from zero for sad faces, $t_{(46)} < 1$, $p > 0.05$. Between-group follow-up analyses revealed no significant difference between the CTL and MDD groups' scores for happy, sad, angry, or disgusted faces [$t_{(45)} = 0.50$, 1.55, 1.37, and 0.16 respectively, all $p_s > 0.05$]. Within-group follow-up analyses revealed a significant main effect of emotion for the CTL group, $F_{(3,\ 87)} = 7.59$, $p < 0.001$, $\eta^2 = 0.21$. Specifically, CTLs demonstrated greater reverse priming for happy faces than angry $t_{(29)} = 2.50$, disgusted $t_{(29)} = 3.46$, or sad faces $t_{(29)} = 4.30$, all $p < 0.02$. There was no difference in priming scores for angry faces compared to disgusted $t_{(29)} = 0.99$, or sad faces $t_{(29)} = 1.71$, both $p > 0.05$. Nor was there a difference between priming scores for disgusted and sad faces, $t_{(29)} = 0.51$, $p > 0.05$. In contrast, follow-up analyses revealed no significant main effect of emotion for the MDD group, $F_{(3,\ 48)} = 2.35$, $p > 0.05$, $\eta^2 = 0.13$, suggesting that MDD participants did not experience differential priming for happy faces compared to negative faces.

DISCUSSION

The current study examined the effect of emotion on cognitive processing in MDD using an affective priming task with prolonged presentation of facial expressions of emotion. Participants

displayed *reverse* priming for angry, disgusted, and happy expressions: participants took longer to identify emotional faces when they were preceded by an emotional face of the same valence vs. preceded by a neutral face. In addition, our analysis yielded a significant valence by group interaction. CTLs showed greater reverse priming from happy compared to angry, disgusted, and sad facial expressions; however, no such valence effect was obtained in the MDD group. Results suggest that the emotionality of the prime affected cognition in the control group. More specifically, when CTL participants viewed a happy face first, it took them longer to process the subsequent happy face. Longer reaction times could be viewed as evidence of "impaired" cognition; however, when longer reaction times indicate more time is spent processing positive expressions, it might actually be functional. In fact, dwelling on positive facial expressions may enhance mood (e.g., Vrugt and Vet, 2009). With this in mind, the fact that positive expressions are not associated with prolonged cognition in the MDD group might impair their ability to use positive expressions to recover from negative mood states.

Although findings of reverse priming are not consistent with our hypotheses, reverse priming effects have been reported in several other studies (e.g., Dannlowski et al., 2006b; Klauer et al., 2009). When interpreting priming results, Bargh and Chartrand (2000) emphasize the importance of considering the delay between prime and target presentation. With brief delays between prime and target (i.e., less than 250 ms), Bargh and Chartrand suggest that only automatic effects should influence people's response to the target. The prime should therefore facilitate faster responses to congruent targets, as is traditionally observed in priming studies. As the delay between prime and target increases, however, strategic and elaborative processing of the prime is expected to override traditional priming effects. Thus, the more difficulty people have disengaging from the prime, the slower they will be to respond to the target. Supporting this, Klauer and colleagues documented reverse priming effects using a prime-target delay of 420 ms (Klauer et al., 2009), and they suggest similar reverse priming effects would also be observed for prime-target delays between 300 and 600 ms. In the current study, 500 ms separated the presentation of the prime and target, which could have allowed attentional capture and elaborative processing of the prime. Moreover, other studies note the contribution of affectively extreme primes to reverse priming effects (e.g., Glaser and Banaji, 1999; Dannlowski et al., 2006b). Our use of facial expressions displaying 100% emotional intensity may have further encouraged attentional capture. Reverse priming effects, therefore, likely reflect people's difficulty disengaging from angry, happy, and disgusted facial expressions captured by attention.

In addition, our findings demonstrate greater reverse priming for happy vs. negative facial expressions in the CTL group, suggesting that CTLs had particular difficulty disengaging from positive compared to negative facial expressions. In contrast, the MDD group showed no effect of prime valence. Our findings are in line with a growing literature showing that non-depressed participants show preferential processing of positive material that is not present in participants with depression (e.g., Deveney and Deldin, 2004; Gotlib et al., 2011). Attention capture by positive information and difficulties disengaging from positive material in the CTL group may contribute to resilience and to the ability to repair negative affect (Joormann et al., 2010) and may therefore represent an important "cognitive vaccine" against depressed mood (Holmes et al., 2009). In contrast, the lack of this "vaccine" in the MDD group might place individuals at increased vulnerability to experience prolonged negative mood states. Finding from the current study also dovetail with results from recent neuroimaging research. For example, Surguladze et al. (2005) found that CTL—but not participants with depression—demonstrated linear increases in limbic-subcortical and extrastriate visual object processing regions when processing happy facial expressions. The authors make important links between neural processing differences and attentional biases typical of depression (see Mathews and MacLeod, 2005, for a review). Similarly, whereas participants with depression showed greater amygdala response to implicitly presented sad faces, CTL showed greater amygdala response to implicitly presented happy faces (Victor et al., 2010), further highlighting that healthy but not depressed individuals show a processing bias toward positive stimuli. Research also has demonstrated associations between anhedonia and neural response to happy expressions (e.g., Keedwell et al., 2005). More specifically, anhedonia severity was associated with greater activity in the ventromedial prefrontal cortex and less activity in the amygdala/ventral striatal regions when processing happy expressions. Future research might therefore examine whether there is a similar correlation between anhedonia severity and degree of priming effects for happy faces.

Several limitations in the current study should be noted. Given the small sample size, it is possible that the follow-up tests were underpowered to detect differences between the CTL and MDD groups. Null findings should therefore be interpreted with caution and replication of the current findings within a larger clinical sample is warranted. That the group by emotion interaction was significant despite a potential lack of power, however, speaks to the strength of this finding. Second, some participants in the MDD group met criteria for a comorbid diagnosis. Because the sample size in the current study prevented us from examining the effects of comorbidity, future research might consider an a priori examination of the role of comorbid anxiety disorders.

Despite these limitations, the current study provides an important look at participants' disengagement from emotional facial expressions captured by attention. CTLs had difficulty disengaging from happy compared to negative facial expressions. Prolonged processing of positive affect might help people regulate negative emotions or "vaccinate" them against future negative mood (e.g., Holmes et al., 2009; Joormann et al., 2010). Moreover, the bias toward positive facial expressions could facilitate prolonged engagement in positive social interactions, which has also been shown to protect individuals against negative mood (e.g., Paykel, 2007). The fact that individuals with MDD failed to show this protective positive bias might therefore contribute to the onset and maintenance of depressive episodes.

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Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies

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Posttraumatic stress disorder (PTSD) is a psychiatric syndrome that develops after exposure to terrifying and life-threatening events including warfare, motor-vehicle accidents, and physical and sexual assault. The emotional experience of psychological trauma can have long-term cognitive effects. The hallmark symptoms of PTSD involve alterations to cognitive processes such as memory, attention, planning, and problem solving, underscoring the detrimental impact that negative emotionality has on cognitive functioning. As such, an important challenge for PTSD researchers and treatment providers is to understand the dynamic interplay between emotion and cognition. Contemporary cognitive models of PTSD theorize that a preponderance of information processing resources are allocated toward threat detection and interpretation of innocuous stimuli as threatening, narrowing one's attentional focus at the expense of other cognitive operations. Decades of research have shown support for these cognitive models of PTSD using a variety of tasks and methodological approaches. The primary goal of this review is to summarize the latest neurocognitive and neuroimaging research of emotion-cognition interactions in PTSD. To directly assess the influence of emotion on cognition and vice versa, the studies reviewed employed challenge tasks that included both cognitive and emotional components. The findings provide evidence for memory and attention deficits in PTSD that are often associated with changes in functional brain activity. The results are reviewed to provide future directions for research that may direct better and more effective treatments for PTSD.

Keywords: neuropsychology, fMRI, amygdala, threat bias, cognitive control, memory, anxiety, neuroimaging

INTRODUCTION

Stress and anxiety serve the important functions of preparing an individual to meet the demands of everyday life and increasing the chance for survival. It is therefore not surprising that arousing and emotionally salient stimuli readily capture attention and have a powerful influence on how information is processed, encoded, stored, and retrieved. However, extreme levels of stress can have a devastating effect on healthy functioning. Nowhere is this demonstrated more clearly than in psychiatric disorders such as posttraumatic stress disorder (PTSD). PTSD develops after exposure to terrifying and life threatening events and is characterized by intense reliving of the traumatic event through disruptive memories and nightmares, avoidance of reminders of the event, and hypervigilance toward potential threats in the environment. These hallmark symptoms involve alterations to cognitive processes such as memory, attention, planning, and problem solving, underscoring the impact that emotion has on cognitive functioning.

Influential cognitive theories of PTSD emphasize the interaction between emotion and cognition in contributing to the symptoms of PTSD. These theories contend that psychopathology arises when emotional stress alters cognitive networks that process information about perception, meaning, and action responses toward executing goals (Lang, 1977; Foa and Kozak, 1986; Chemtob et al., 1988). In PTSD, networks representing information about fear become highly elaborated and accessible, which has implications for encoding and retrieval of information. For instance, an elaborated fear structure may lower one's capacity to process non-threat related information, leading to attentional bias toward potential threats in the environment (Chemtob et al., 1988). Furthermore, nodes of the fear network representing threat arousal may predispose an individual to interpret even innocuous stimuli as threatening. Intrusive memories result from spreading activation of the threat arousal node to related threat nodes, while nodes representing opposing alternatives become inhibited.

In this review, we summarize the latest research examining the dynamic interplay between emotions and cognitive processes in PTSD. We begin with an overview of the criteria that must be met for a PTSD diagnosis. Next, we separately review studies that examine the effect of emotion on cognitive functions and those that examine the effect of top-down cognitive control processes on emotion, following this useful distinction put forth by Dolcos et al. (2011). Finally, we provide a summary

of the reviewed literature and discuss open questions in the field. To directly assess emotion-cognition interactions in PTSD, we focus our review on studies employing a challenge task in which both emotional and neutral stimuli were presented. Such studies may lend themselves to better reproduce conditions in everyday life in which emotions influence task performance. Other recent papers have comprehensively reviewed studies that employed only neutral stimuli (i.e., Aupperle et al., 2012b) or have examined the brain under task-free conditions in PTSD (i.e., Engdahl et al., 2010; Georgopoulos et al., 2010; Daniels et al., 2012).

CLINICAL DEFINITION OF PTSD

As outlined in the current Diagnostic and Statistical Manual (DSM-IV-TR), PTSD develops after exposure to a Criterion A1 event, defined as involving actual or threatened death, serious injury, or threat to one's physical integrity (American Psychiatric Association, 2000). To meet Criterion A1, the individual must have been directly involved in the traumatic event, witnessed the event, or learned about the death or serious injury of a family member or close friend. The individual must have responded to the traumatic event with intense fear, helplessness, or horror (referred to as Criterion A2) although future conceptualizations of PTSD may omit this criterion (Friedman et al., 2011). The symptoms of PTSD can be broadly divided into three symptom clusters, B, C, and D. Symptom cluster B involves persistent and unwanted recollections of the traumatic event, intrusive memories of the event, and dissociative flashbacks. The individual re-experiences the event despite being removed from the traumatic situation and context. These symptoms can be frightening and highly disruptive of activities of daily living. Cluster C involves persistent avoidance of people, places, and activities that serve as reminders of the traumatic event, emotional numbing, difficulty experiencing a full range of emotions, and diminished expectations of one's ability to lead a long, fulfilling life. Finally, symptom cluster D involves symptoms of hyperarousal including difficulty with sleep, irritability and anger, poor concentration, hypervigilance, and exaggerated startle response. The symptoms of PTSD must be present for more than one month and cause significant distress or impairment in social and occupational functioning in order to differentiate the disorder from transient and acute stress reactions. The typical course of PTSD begins with the development of symptoms within 6 months of the onset of the traumatic event, although delays in symptom occurrence can occur. Individuals whose symptoms persist for more than 3 months are diagnosed with chronic PTSD, which is associated with a host of poor health outcomes, including heart disease, obesity, alcohol abuse, and lowered perceptions of general health (Dobie et al., 2004; Hoge et al., 2007; Boscarino, 2008).

The prevalence rate of PTSD is estimated to be 7–8% in the general population (Kessler et al., 1995) although prevalence estimates have varied depending on the type of trauma exposure and demographic characteristics. For instance, prevalence rates are higher among individuals exposed to military combat, ranging between 12–20% (Hoge et al., 2004; Dohrenwend et al., 2006; Tanielian and Jaycox, 2008).

EMOTIONAL EFFECTS ON COGNITIVE FUNCTION

MEMORY AND LEARNING

Explicit memory

Decades of emotional memory research in healthy individuals suggests that emotional information tends to be remembered better than neutral information (Christianson, 1992; Kensinger, 2007). However, the extent to which emotion provides a facilitating effect on memory encoding and retrieval in PTSD is unclear. Cognitive models of PTSD predict that patients remember emotional information better due to a bias toward (Chemtob et al., 1988) or difficulty disengaging from (Chemtob et al., 1999) threat-related information, which may lead to greater resources applied to processing and encoding emotional information. A variety of behavioral and neuroimaging memory paradigms have been employed to examine the extent to which patients with PTSD remember emotional information better than neutral information in comparison to healthy or trauma-exposed controls. Consistent with the notion that emotion enhances memory, there is evidence for a memory advantage in patients vs. controls for negative threat information (Vrana et al., 1995; McNally et al., 1998; Golier et al., 2002; Paunovic et al., 2002). In these studies, word lists were presented with either incidental or intentional encoding instructions and participants were subsequently instructed to recall as many words as they could from the lists. Results showed that patients either remembered more emotional words than controls or that memory performance for emotional vs. neutral words improved to a greater extent than controls.

However, memories are often subject to a wide range of distortions and biases that impact accurate recollection (Schacter, 1999). One of the most controversial topics in the field of traumatic stress is that of the accuracy of recovered memories, prompting PTSD researchers to examine how memory for negative and traumatic information fares in false memory paradigms such as the Deese–Roediger–McDermott (DRM) paradigm (Roediger and McDermott, 1995). In the DRM paradigm, participants are presented with a list of words that are semantically related to a critical non-presented word (lure). The critical lure is often falsely remembered as being previously presented on subsequent recall and recognition tests and may reflect gist-based encoding rather than encoding of specific details (Brainerd and Reyna, 2002). In PTSD, two of the three DRM studies employing verbal lists indeed reported greater false alarms to critical lures in patients with PTSD than control participants (Bremner et al., 2000; Brennen et al., 2007). However, a third study employing the DRM paradigm did not report greater false alarms in patients (Zoellner et al., 2000). It is unclear why these studies found differential effects, although it is possible that the false memory effect is more likely to be elicited when trauma-specific material, as opposed to generally negative material, is presented. Studies employing paradigms other than the DRM but including trauma-specific material have reported greater false alarms in PTSD (Hayes et al., 2011) or a bias in making memory decisions about trauma-specific information (Litz et al., 1996).

Negative arousal can alter the type of information that is encoded and retrieved. Neurohormones including norepinephrine and cortisol play a critical role in the fear and stress response by mobilizing the body's response to the stressor via

the hypothalamus-pituitary-adrenal axis (HPA) and amygdala, among several other key regions. Norepinephrine has been shown to facilitate emotional memory (for a review see Ferry et al., 1999). However, emotional memory may not be uniformly enhanced during high levels of arousal. For example, individuals exposed to highly arousing negative material show a narrowing of attention (Easterbrook, 1959), referred to as "tunnel memory," in which the central objects and features of a scene are better remembered than peripheral background (Christianson and Loftus, 1991). A recent study examined the extent to which patients with PTSD showed this memory trade-off effect (i.e., greater memory for negative items vs. backgrounds) in comparison to a trauma-exposed control group and a healthy unexposed group (Mickley Steinmetz et al., 2012). The findings showed that the PTSD and the healthy non-trauma exposed group exhibited a greater memory trade-off effect for emotional items than the trauma-exposed-no-PTSD group. Although further research is required, these results suggest that patients with PTSD do not exhibit greater tunnel memory than healthy control participants.

Distortions in memory have been observed during autobiographical retrieval in PTSD. Autobiographical memories represent personally experienced recollections and knowledge about oneself (Conway and Pleydell-Pearce, 2000) and may be key in understanding the accessibility and completeness of traumatic memories (McNally et al., 1994). Two experimental studies have shown that during the recollection of personal past events, individuals with PTSD tend to recall personal memories with very few details and very little specificity (McNally et al., 1994, 1995). This "overgeneral memory" effect is thought to result from inadequate search of memory during retrieval, perhaps due to rumination, avoidance, and impairment in executive capacity (Williams et al., 2007). However, the difficulty with retrieving detailed personal information does not appear to be specific to traumatic memories but extends to neutral and positive events.

Research on the neural underpinnings emotion and memory suggests that the benefit of emotion on memory occurs in part via interactions between the amygdala and hippocampus. According to the *modulation hypothesis*, emotional events are remembered better than neutral events due to the amygdala's influence on other medial temporal lobe structures including the hippocampus (McGaugh et al., 1996). Support for the modulation hypothesis has been reported in humans using fMRI, showing greater activity in the amygdala and hippocampus for successfully remembered vs. forgotten emotional memories (Dolcos et al., 2004). However, a key question is whether medial temporal lobe structures interact in PTSD as the modulation hypothesis would predict. Whereas the majority of imaging studies have shown increased amygdala activity in PTSD (Pissiota et al., 2002; Shin et al., 2004a, 2005), studies of hippocampal activity have been mixed, showing either an increase (Shin et al., 2004b; Thomaes et al., 2009) or decrease in PTSD (Bremner et al., 2003; Astur et al., 2006). To examine the role of the amygdala and hippocampus in emotional memory formation in PTSD, researchers have employed the subsequent memory paradigm, in which neural activity is measured at encoding for items that are probed for memory success after a delay. Differences in encoding activity for successfully remembered and forgotten material is evaluated to identify brain regions subserving successful memory operations (Paller and Wagner, 2002). Hayes et al. (2011) reported reduced amygdala and hippocampal activity during successful memory encoding of trauma-related material in patients with PTSD. In this study, patients with PTSD produced greater false alarms for trauma-specific negative information, suggesting that the reduced medial temporal lobe activity may underlie memory distortions. However, Brohawn et al. (2010) reported enhanced hippocampal activity in patients with PTSD during encoding of emotional items relative to controls and Dickie et al. (2008) reported greater activity in both the amygdala and hippocampus for remembered vs. forgotten stimuli (a control group was not included in this study and therefore comparisons were made within the PTSD group). Two major differences may explain the discrepant results among studies. In the latter two studies, there were no behavioral differences in memory performance between patients and controls or between emotional and neutral information, and general negative stimuli were used whereas Hayes and colleagues used trauma-specific combat stimuli in recent war veterans. Therefore, although these studies report mixed results, the findings may provide more support for the notion that false memory, and associated decreases in neural signal in the amygdala and hippocampus, is elicited primarily for trauma-specific information in PTSD.

In summary, the research findings of explicit memory performance in PTSD are decidedly complex. The evidence suggests that recall of gist-based negative information may be enhanced in PTSD, whereas information about specific details and contextual information appears to be diminished. This is consistent with the notion that cognitive resources may be preferentially allocated to process threat information at the expense of neutral or non-threat related information. An important consideration is whether memory alterations occur for all types of emotional information or only for trauma-specific information. Although there are mixed findings in this regard, overall there is stronger evidence that false memories are elicited mainly for trauma-specific information. Research regarding the neural correlates of memory in PTSD is still in its infancy, but the abnormalities observed in the amygdala and hippocampus suggests that the symptoms of PTSD are associated with disturbances in memory encoding and retrieval.

Fear conditioning

Pavlovian fear conditioning and extinction has been a fruitful model of fear memory in PTSD. Fear conditioning paradigms involve the repeated presentation of a neutral conditioned stimulus (CS) such as an auditory tone or a colored light, followed immediately by an aversive unconditioned stimulus (US) such as a finger shock. Extinction of the fear memory occurs when the CS is subsequently and repeatedly presented in the absence of the US. This experimental paradigm models a crucial aspect of emotion-cognition interactions in PTSD: individuals with PTSD repeatedly show elevated fear responses to trauma reminders, even when those reminders occur in a safe context (i.e., a film portraying combat). Some researchers see a parallel between this clinical phenomenon and a failure of fear extinction or fear extinction recall (e.g., Pitman, 1988).

Early in the PTSD fear conditioning and extinction literature, fear responsivity was quantified as physiological responses such as skin conductance responsivity and heart rate. In line with the enhanced effect of emotion on explicit declarative memory discussed above, physiological studies have demonstrated that, relative to controls, individuals with PTSD show evidence of enhanced fear conditioning (Orr et al., 2000). This may represent a pre-existing vulnerability. Severity of PTSD symptoms and the PTSD-linked personality trait of behavioral inhibition have been correlated with facilitated eyeblink conditioning (Myers et al., 2012). Furthermore, fear extinction studies have demonstrated impaired safety signal learning (Orr et al., 2000; Peri et al., 2000), a possible mechanism for the intractability of fear responses to reminders of a trauma decades past. A more recent study measuring skin conductance responses in identical twins discordant for Vietnam combat exposure provided evidence that deficits in fear extinction recall are an acquired characteristic of PTSD and not a familial risk factor (Milad et al., 2008).

In general, neuroimaging studies of healthy individuals have found activation of amygdala and dorsal anterior cingulate cortex (dACC) during fear conditioning, and activation of ventral medial prefrontal cortex (vmPFC) structures during fear extinction and extinction recall (reviewed in VanElzakker et al., 2012). The first imaging study of fear conditioning in PTSD compared a fear acquisition condition, in which a picture of a blue square was paired with shock, to a control condition, in which participants were shocked randomly without a CS, and found that women with childhood sexual abuse-related PTSD had greater dACC and left amygdala activation than healthy women with no history of abuse (Bremner et al., 2005). During extinction of the blue square-shock association, the PTSD group had less activation in vmPFC structures than the comparison group.

More recently, a series of studies compared fMRI responses between individuals with PTSD and trauma-exposed healthy control participants at each stage of a two-day fear conditioning and extinction paradigm. The authors reported that the PTSD group had increased amygdala responsivity to the UC (shock) relative to trauma-exposed control group (Linnman et al., 2011). During late conditioning and early extinction, after the CS had been associated with the US and still signaled threat, the PTSD group showed increased dACC activation, relative to the control group. Presentation of the CS during late extinction learning, when the CS should no longer have signaled danger, also led to relatively increased amygdala and dACC responses and relatively decreased vmPFC activation in the PTSD group. Furthermore, on the second day of the paradigm, during early extinction recall, the PTSD group showed vmPFC hypoactivation and dACC hyperactivation (Milad et al., 2009; Rougemont-Bücking et al., 2011) (**Figure 1**).

These results provide a neurobiological basis to the characteristic unrelenting strength of trauma memories in PTSD patients (re-experiencing) and the mechanisms of associative learning between trauma and the environmental cues that later serve as triggers for intrusive memories. The simple fear conditioning model of PTSD does not explain aspects of the disorder such as emotional responses other than fear, neuroendocrine dysfunction, or many of the more complex cognitive deficits discussed elsewhere in this review. However, it has been a valuable model of PTSD in that the functional neurocircuitry abnormalities in this disorder point to enhanced conditioning responses during trauma, as well as deficits in fear extinction and extinction recall after the trauma has passed.

Implicit memory

Implicit memory refers to memory for encoded items that are not associated with conscious recollection. Perceptual priming is a type of implicit memory in which prior exposure to a stimulus leads to subsequent facilitated perception of this stimulus. Intrusive memories in PTSD are often triggered by sensory cues that individuals experienced right before or during their traumatic event. Thus, several studies have examined the hypothesis that there is enhanced perceptual priming for trauma-related cues. Early PTSD priming studies used word-stem completion tasks and either failed to find evidence that individuals with PTSD have enhanced priming for trauma-related words (McNally and Amir, 1996) or found only weak evidence (Amir et al., 1996). Using a more sensitive word-stem completion protocol, Michael et al. (2005) found that participants with assault-related PTSD showed preferential priming for assault-related words more than general threat or neutral words, relative to the control group who had experienced assault but did not have PTSD. However, there may be an important reason for the inconsistent findings in word-stem priming studies: words prime conceptual or semantic trauma reminders while the cues that trigger re-experiencing in PTSD tend to be perceptual or sensory. Therefore, perceptual stimuli such as pictures may be more appropriate priming stimuli than conceptual stimuli such as words.

A two-part study utilizing a blurred picture paradigm reported that individuals with PTSD and acute stress disorder (ASD) identified more blurred trauma-related pictures than blurred neutral pictures (see **Figure 2**), and that this processing advantage for trauma-related pictures correlated positively with severity of PTSD symptoms, dissociative symptoms, and re-experiencing symptoms, as well as with self-reports of fear levels and perceptual processing during the actual traumatic experience (Kleim et al., 2012). A follow-up study of the individuals with ASD demonstrated that the initial processing advantage for trauma-related pictures predicted a diagnosis of PTSD 6 months post-trauma.

Blurred picture paradigms have also been used to demonstrate enhanced perceptual priming in healthy, trauma-unexposed individuals for neutral pictures that were associated with violent stories, and an association between enhanced perceptual priming and trait dissociation (Ehlers et al., 2006; Michael and Ehlers, 2007). In addition, "re-experiencing" (operationalized as sensory memories imbued with a sense of immediacy) was associated with greater priming, and that re-experiencing was reduced by asking participants to write about the stories and relate them to their personal lives, which the authors argued was a model of elaboration of traumatic memories during clinical therapy. Future studies may replicate these findings in participants with PTSD.

In a recent fMRI study of trauma-unrelated emotional priming, Mazza et al. (2012) administered a subliminal affective priming task to 10 individuals with earthquake-related PTSD and to 10 healthy controls. In this task, the subliminal (150 ms) presentation of emotional faces was immediately followed by the

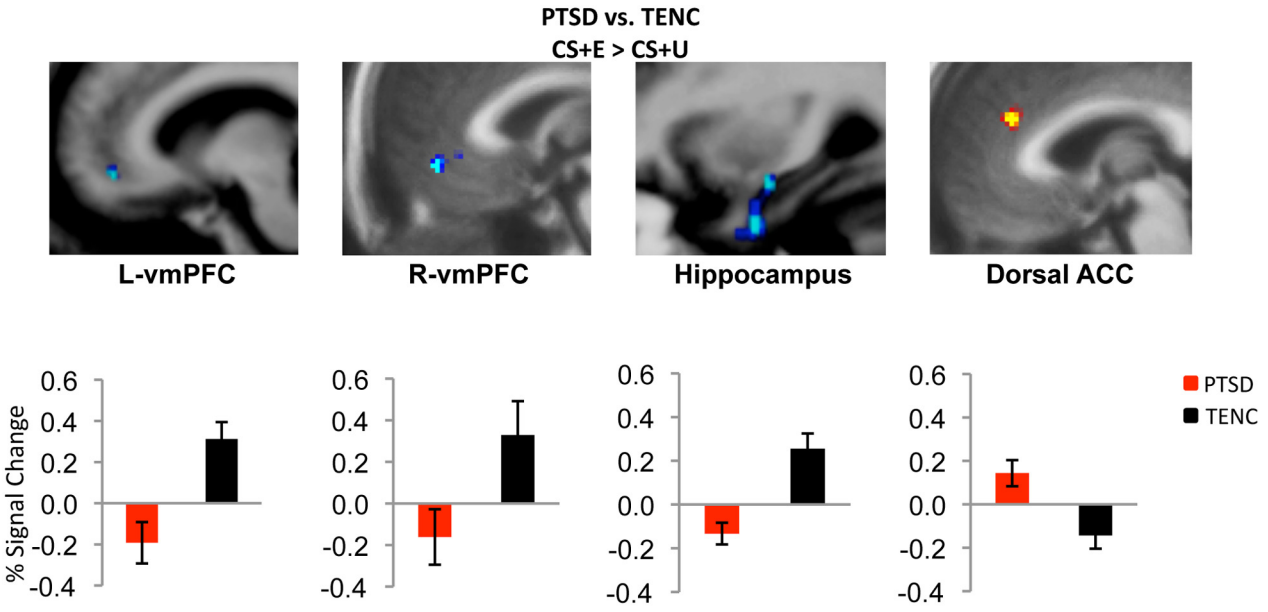

FIGURE 1 | Neural correlates of extinction recall in PTSD. During early extinction recall, participants with PTSD showed hypoactivation in bilateral ventromedial prefrontal cortex (vmPFC) and hippocampus and hyperactivation in dorsal anterior cingulate cortex (ACC) relative to the trauma-exposed normal control (TENC) group. CS + E = stimulus that was extinguished; CS + U = stimulus that was not extinguished. Adapted with permission from Figure 3; Milad et al. (2009).

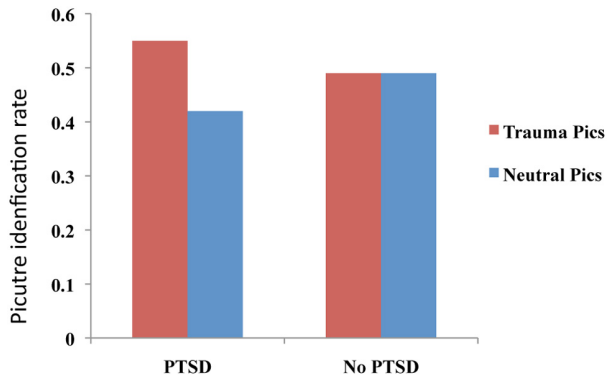

FIGURE 2 | Performance on an implicit memory task (blurred picture paradigm). Patients with PTSD identified more trauma-related blurred images than neutral images. No difference between trauma-related and neutral pictures was observed for the No PTSD group. This figure was created from the data supplied in Table 3; Kleim et al. (2012).

supraliminal (1850 ms) presentation of neutral pictures (Chinese ideographs), which were later rated as pleasant or unpleasant. Individuals with PTSD were more likely than controls to rate the ideographs that followed negative facial expressions as negative, and less likely than controls to rate the ideographs that followed positive facial expressions as pleasant, suggesting a propensity in PTSD for priming of threat-related cues. Furthermore, during the contrast between negative facial expression primes and the baseline fixation dot, individuals with PTSD had significantly greater BOLD responses in left amygdala and right insular cortex, relative to controls.

In summary, some priming studies demonstrate enhanced perceptual priming for threat-associated cues in both individuals with PTSD and in healthy populations. The enhanced priming for threat cues may be associated with hyperactivity of amygdala and insular cortex in PTSD. Future studies should more systematically investigate differences in conceptual vs. perceptual priming. The propensity for enhanced perceptual priming of these cues, combined with the facilitated conditioning and attenuated fear extinction recall discussed previously, may be a powerful combination in both the etiology and maintenance of PTSD.

ATTENTION AND WORKING MEMORY

Attention bias

In individuals with PTSD, trauma-related memories intrude into consciousness and are difficult to ignore. In addition, reminders of traumatic events can capture attention and evoke distress and anxiety. Some researchers have hypothesized that in PTSD, attention is involuntarily biased toward stimuli that are threatening, leading to a disruption of ongoing cognitive activities. Researchers have attempted to study attention biases in the laboratory using several different paradigms: the emotional Stroop (also known as the "modified Stroop"), the dot probe paradigm, and the emotional oddball paradigm.

In the emotional Stroop, researchers ask participants to view (on a computer screen or on printed cards) words of varying emotional salience and to name the color of the words while ignoring their meaning. The researchers record the time it takes for participants to name the colors of different types of words (e.g., trauma-related words, neutral words, positive words). Delays in

color naming (i.e., Stroop interference) occur when the meaning of a particular category of words is closely related to the participants' psychopathology and thus attracts attention despite efforts to the contrary.

Several studies in the literature have reported increased response times for trauma-related words relative to neutral words (and/or other types of words) in individuals with PTSD compared to trauma-exposed comparison participants without PTSD (e.g., McNally et al., 1990; Foa et al., 1991; Cassiday et al., 1992; Thrasher et al., 1994; Bryant and Harvey, 1995; Kaspi et al., 1995; Vrana et al., 1995; Beck et al., 2001; El Khoury-Malhame et al., 2011a). Furthermore, measures of trauma-related Stroop interference have been shown to positively correlate with PTSD symptom severity (McNally et al., 1990; Cassiday et al., 1992; Paunovic et al., 2002; Fleurkens et al., 2011). Stroop interference in PTSD appears to be specific to trauma-related material, although some studies have reported interference to other types of emotional stimuli (Litz et al., 1996; Paunovic et al., 2002). Increased interference for trauma-related words in PTSD may not occur outside of conscious awareness, as this effect has not been consistently demonstrated with masked stimulus presentations (McNally et al., 1996; Paunovic et al., 2002) but see also (Harvey et al., 1996). Importantly, however, some studies have failed to replicate the finding of greater interference for trauma-related words in PTSD (e.g., Freeman and Beck, 2000; Devineni et al., 2004; Wittekind et al., 2010) see also (Kimble et al., 2009).

Two functional neuroimaging studies have attempted to examine the brain circuits that may mediate emotional Stroop interference in PTSD (Shin et al., 2001; Bremner et al., 2004). Both studies reported that the rostral anterior cingulate cortex (rACC) was less activated during trauma-related vs. control Stroop conditions in individuals with PTSD compared to trauma-exposed individuals without PTSD. One of the studies also found greater activation in the dACC in PTSD during trauma-related vs. generally negative Stroop conditions (Shin et al., 2001). Rostral ACC activation may be required to effectively ignore the trauma-related information in the service of completing the color-naming (or word-counting) task at hand. When the rACC is not functioning normally, increased activation of the dACC may be required in order to facilitate task performance. Interpretation of these imaging findings within the framework of earlier behavioral findings in the literature is somewhat limited by the fact that response times in the neuroimaging studies were either not measured (Bremner et al., 2004) or did not show significant group differences (Shin et al., 2001) probably due to small sample sizes.

Although a useful tool for investigating the nature of intrusive cognitions in PTSD, the emotional Stroop is limited in that it cannot be used to determine whether individuals with PTSD have increased attentional engagement to trauma-related stimuli or delayed disengagement from them. The dot probe task (sometimes called the attentional deployment task, the visual probe task, or the probe detection task) represents an improvement over the Stroop task in that it can measure the direction of attentional bias (e.g., toward or away from trauma-related stimuli) as opposed to merely assessing the existence of interference, and can also use pictorial stimuli, reducing the need for semantic processing (MacLeod et al., 1986). In the dot probe task, two stimuli (e.g., one trauma-related and one neutral) are briefly shown on either side of a screen. The participant responds when a target probe then appears in the location previously occupied by one of the stimuli. Attentional bias toward trauma-related stimuli would result in faster reaction time during those trials in which the probe replaces the trauma-related stimulus.

Dot probe studies in PTSD have reported mixed findings. Some studies have found bias toward trauma or threat-related stimuli in PTSD (Bryant and Harvey, 1997; Dalgleish et al., 2001, 2003; Fani et al., 2012), while others reported an association between PTSD and a bias away from trauma or threat (Pine et al., 2005; Fani et al., 2011). Still others have failed to find significant attentional bias differences between PTSD and two control groups, consisting of healthy individuals and a group of recent trauma survivors that included both individuals with and without ASD (Elsesser et al., 2004, 2005).

A recent fMRI study of the dot probe task presented angry (threat-related) and happy and neutral (threat-unrelated) faces to female survivors of multiple traumas who either did or did not have PTSD (Fani et al., 2012). Within the PTSD group but not within the control group, bias toward threatening faces correlated positively with activation in the dACC and insula, as well as the parietal lobe, caudate and the medial frontal, precentral and parahippocampal gyri. However, there were no response time differences between the two groups, indicating no consistent bias toward or away from threat.

Time since trauma may be an important factor in these inconsistencies. There is evidence that, under immediate acute stress conditions, individuals under threat have a bias away from threat-related stimuli, which predicts later PTSD symptoms (Wald et al., 2011). One series of studies tested this explicitly, under unique circumstances. During the Israeli military operation against Gaza (Operation Cast Lead) Israeli civilians near the border experienced a predictable increase in danger from retaliatory rocket attacks. The immediacy of danger increased as a function of proximity to border areas, allowing for quantification of threat. Using a dot probe task adapted for Hebrew, researchers found that individuals under greatest imminent threat had an attentional bias away from threat-related words (e.g., DEAD) compared to neutral words (e.g., DATA) (Bar-Haim et al., 2010). Individuals who were more than 40 km from the border and not within rocket range showed attention bias toward threat-related words. PTSD and depression symptoms also increased as a function of threat, and state anxiety was highest among individuals who lived within 10 km of the border and thus had 15 s or less to seek shelter when they heard warning sirens. One year after the conflict, attentional bias away from threat during the acute stressor predicted PTSD symptoms (Wald et al., 2011). The process by which attentional bias away from threat during an acute stressor putatively transforms to attentional bias toward threat in PTSD may be related to the "rebound effect" discussed below in the section concerning thought suppression.

Attentional bias toward threat in PTSD could reflect either difficulty disengaging from threat-related stimuli or facilitated engagement of such stimuli. A study of healthy individuals that related attentional mechanisms to subclinical PTSD symptoms provided indirect evidence that attentional bias toward threat

in PTSD reflects difficulty disengaging as opposed to facilitated engagement (Bardeen and Orcutt, 2011). Interestingly, difficulty disengaging from threatening stimuli has been associated with the 5-HTTLPR serotonin transporter gene polymorphism (Beevers et al., 2009). Children's 5-HTTLPR short allele significantly moderated the relationship between maternal criticism and the children's attentional bias for angry faces, but not happy or sad faces, in a dot probe task (Gibb et al., 2011). This same polymorphism may predict poor response to cognitive-behavioral therapy in PTSD (Bryant et al., 2010). Furthermore, an fMRI study of a related attentional task called the detection of target (DOT) paradigm demonstrated that amygdala activation in PTSD patients, but not in healthy controls, correlated with attentional bias toward threatening faces and words (El Khoury-Malhame et al., 2011b). Future studies can better elucidate the relationships among time since trauma, serotonin function in the amygdala, and attentional processes in PTSD.

The emotional oddball paradigm has proved to be useful in demonstrating attention bias in PTSD. In this task, infrequent target stimuli are interspersed with frequent standard stimuli and infrequent distractor emotional stimuli. The task requires participants to inhibit their prepotent response to frequent standard and distractor stimuli in order to identify the target stimuli accurately. Patients with PTSD are impaired in identifying neutral targets, which may be a consequence of attention bias to distracting, potentially threat-related information (Pannu Hayes et al., 2009). Furthermore, event-related potential (ERP) studies have shown that during processing of threat stimuli, an enhanced P3 amplitude response is observed in patients with PTSD, which is thought to reflect heightened attention toward those stimuli (Attias et al., 1996; Stanford et al., 2001). More recently, fMRI studies using the emotional oddball paradigm demonstrated that PTSD symptomatology was associated with greater activity in the dorsolateral prefrontal cortex and vmPFC for threat stimuli (Pannu Hayes et al., 2009), accompanied by a reduction in dorsolateral prefrontal cortex activity for target, non-threat stimuli (Morey et al., 2008; Pannu Hayes et al., 2009). These studies provide a neural marker for threat bias in PTSD that is characterized by heightened activity in putative attention and emotion circuitry for potentially threatening information and dysfunction in attention circuitry during goal-relevant target identification.

Anticipation of an impending negative stimulus may influence attention allocation and subsequent cognitive performance. Researchers have examined whether women exposed to intimate partner violence show alterations in attention performance and neural circuitry while anticipating a negative visual stimulus (Simmons et al., 2008; Aupperle et al., 2012a). One particular study with a large sample size (41 women with PTSD and 34 healthy controls) examined the neural correlates of negative and positive anticipation embedded within a continuous performance task (Aupperle et al., 2012a). Results indicated that patients with PTSD showed greater activity in the insula and less activity in the dorsolateral prefrontal cortex than controls during anticipation of negative events. Furthermore, greater activity in the dorsolateral and ventrolateral prefrontal cortex was associated with better performance on an attention switching task (i.e., the Color–Word Interference Inhibition/Switching subtest of the Delis–Kaplan Executive Function System) and a digit symbol test. These intriguing results may suggest that engaging the lateral prefrontal cortex in the face of anticipatory threat supports cognitive performance, possibly through an inhibitory mechanism.

In summary, a majority of studies have found evidence for attentional bias effects in PTSD. Although the findings are mixed, there appears to be growing evidence that the attentional bias reflects difficulty disengaging from, rather than facilitated detection of, negative stimuli. Collectively, the brain regions consistently active during tasks of negative attention in PTSD include the dACC, amygdala, insula, with mixed findings of the vmPFC. The aforementioned regions have previously been associated with emotional reactivity, perhaps underlying privileged processing of negative images in PTSD.

Working memory

Working memory is often defined as the maintenance and manipulation of information in a temporary memory store (Baddeley, 1992). Importantly, working memory has a limited capacity, suggesting that individuals can track and work with a small amount of information at a given time. An implication of this limited capacity store is that interference from distracting stimuli can reduce an individual's ability to maintain goal-relevant information. The interference of distracting stimuli, such as intrusive thoughts and trauma memories seems to be a particular difficulty in PTSD and may underlie the hallmark symptom of difficulty with concentration. Working memory deficits in patients with PTSD have been demonstrated using both verbal and visual stimuli. Schweizer and Dalgleish (2011) reported poorer working memory performance in patients vs. trauma-exposed controls on a verbal sentence task, in which participants were instructed to remember words presented following trauma-related or neutral sentences. Consistent with the idea that trauma-related material is particularly disruptive to working memory performance, memory was worse for words presented after trauma vs. neutral sentences. Working memory difficulty was observed in both participants with a current diagnosis of PTSD and individuals with a lifetime history of PTSD.

Neuroimaging studies investigating the impact of emotional distraction on working memory have suggested that hyperactivity in an emotional processing network (including regions such as the amygdala, ventrolateral prefrontal cortex, and medial prefrontal cortex) and hypoactivity in a dorsal executive function processing network (including regions such as the dorsolateral prefrontal cortex and parietal cortex) underlies impaired maintenance of information in working memory as a result of emotional distraction (Dolcos and McCarthy, 2006). This model was supported in an fMRI studying examining working memory in PTSD. Morey et al. (2009) showed that patients with PTSD had poorer memory performance when both neutral and trauma-specific distracters were presented during the working memory delay in comparison to a trauma-exposed control group. Furthermore, this fMRI study showed disrupted activity in the dorsal executive function network during the working memory delay in PTSD that could explain the diminished performance. An interesting outcome of this study is that performance was

disrupted for both trauma-specific and neutral distracters, perhaps providing evidence for generalized hypervigilance.

DECISION-MAKING AND REWARD PROCESSING

Individuals make decisions in part based on motivational influences, weighing the rewards and costs that may result from each option. On one end of the spectrum, seeking immediate positive rewards is associated with the psychopathology of addiction disorders (Bechara et al., 2002) while on the other end of the spectrum, lack of reward seeking is associated with depressive disorders (Pizzagalli et al., 2008). In PTSD, numbing symptoms including loss of pleasure in activities and loss of the ability to experience positive emotions may suggest altered processing of positive rewards. Consistent with this notion, patients with PTSD are less satisfied with rewards than controls (Hopper et al., 2008) and expend less effort to obtain positive rewards (Elman et al., 2005). Thus, it follows that patients with PTSD may have altered decision-making capacity if the drive to achieve positive rewards is reduced.

Neuroimaging studies in healthy individuals have supported the notion of a putative reward circuit that includes the ventral striatum, ventral pallidum, orbital frontal cortex, and anterior cingulate. Two studies have examined the neural correlates of decision-making and reward in PTSD, both providing evidence for reduced capacity for positive reward in PTSD. Sailer et al. (2008) showed that the nucleus accumbens (part of the ventral striatum) was less active in patients with PTSD than controls during processing of positive gains. Behaviorally, patients with PTSD were slower in learning how to maximize their gains in a monetary gain/loss paradigm. Although speculative, it is possible that reduced reward processing in PTSD may have negatively influenced patients' motivation in learning the task. Similarly, PTSD patients showed reduced activity in the striatum during gains vs. losses of a monetary task in another study (Elman et al., 2009). Interestingly, striatal activity for gains vs. losses was negatively correlated with CAPS items "loss of interest in significant activities" and "feelings of detachment/estrangement."

COGNITIVE CONTROL OF EMOTION AND TREATMENT EFFECTS

When distressing events occur during the course of the lifespan, individuals often engage in various strategies to manage and cope with negative emotions. In doing so, they can change their emotional experience of the stimulus, and also change how the emotional stimulus affects their cognitive performance. Individuals can exercise control of emotion for the desired effect; they can engage in cognitive reappraisal to improve affect, or conversely, amplify negative affect (Dillon et al., 2007). Furthermore, cognitive control strategies can be used to improve memory performance (Hayes et al., 2010) or suppress unwanted memories (Depue et al., 2007). Such deliberate modulation of emotion serves to manage distractions in the face of otherwise debilitating affect and helps individuals to remain focused on goal-directed behaviors. In treating psychopathology, cognitive-behavioral interventions often instruct patients to exercise greater control of emotion through thought challenging exercises and promoting alternative ways of thinking about a negative situation (Resick and Schnicke, 1993). Preliminary evidence suggests that these types of interventions not only reduce symptoms, but also improve cognitive performance (Sutherland and Bryant, 2007).

In PTSD, experimental work investigating the cognitive control of emotion has examined whether patients can purposely forget negative information. Some researchers have suggested that patients with PTSD have an enhanced ability to forget information, which may explain amnesia for important details of their traumatic event. This idea, mainly evolving out of the child sexual abuse literature, suggests that repeat trauma survivors with PTSD cope during their trauma by dissociating from their surroundings and disengaging attention from the event, sometimes leading to amnesia for large stretches of time (Terr, 1991). This avoidant coping style may manifest in adulthood by increased ability to forget new information presented in an experimental setting (McNally et al., 1998). Alternatively, others have suggested that intrusive memories arise from the failure of inhibitory processes to curb distracting and aversive memories (Zwissler et al., 2011).

One frequently used paradigm to examine this issue is the directed forgetting task, which examines deliberate attempts to control memory performance. In this task, participants are instructed to either remember or forget words presented in a list. Subsequently, participants attempt to recall and/or recognize all the words that were presented in the list regardless of whether they were to-be-remembered or to-be-forgotten. The "standard directed forgetting effect" refers to the behavioral outcome showing greater remembering for items presented during the remember condition than the forget condition. The task is often adapted for study of PTSD by including general emotional or trauma-specific words. Two studies that examined directed forgetting of trauma-relevant information in PTSD failed to show between group differences among PTSD and control participants (McNally et al., 1998; Zoellner et al., 2003). However, these studies and others have demonstrated differences between groups for non-trauma emotional and/or neutral stimuli. Specifically, patients fail to show the standard directed forgetting effect either due to difficulty forgetting to-be-forgotten items (Zoellner et al., 2003; Cottencin et al., 2006) or decreased performance in the remember condition (McNally et al., 1998; Zwissler et al., 2011). Taken together, the directed forgetting literature provides little evidence that patients with PTSD adopt an avoidant coping style that results in enhanced forgetting of negative information. Rather, a general inhibitory control mechanism may be impaired evidenced by poorer performance for non-threat related items.

A separate literature has emerged examining the effects of actively suppressing one particular thought. Unlike directed forgetting paradigms, thought suppression is less concerned with recall and recognition memory performance but rather the frequency with which thoughts arise following instructions to suppress them. Wegner and colleagues demonstrated that when participants were instructed to initially suppress a thought, they went on to think about it to a greater extent than if they were initially allowed to let the thought enter consciousness, referred to as a "rebound effect" (Wegner et al., 1987). Two studies have shown that patients with PTSD have more trauma-related thoughts after a thought suppression period than trauma-exposed controls

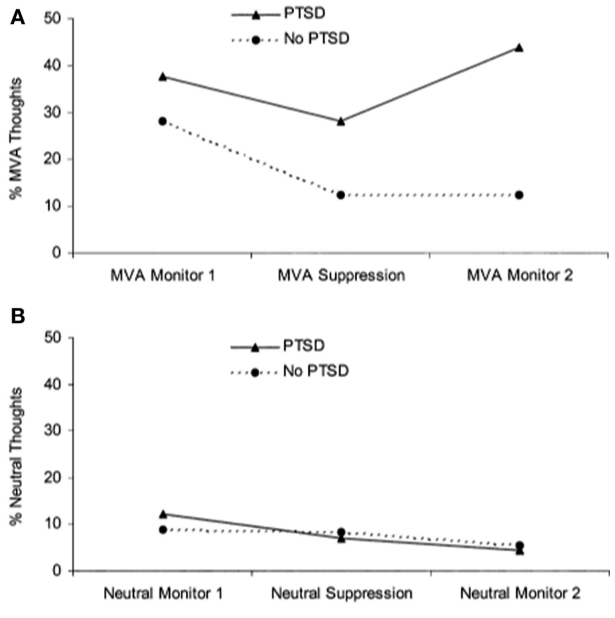

FIGURE 3 | Performance on a thought suppression task. (A) Patients with PTSD reported more trauma-related (i.e., motor vehicle accident, MVA) thoughts after engaging in thought suppression, showing a "rebound" effect. (**B**) Participants did not show a rebound effect for neutral thoughts. Reproduced with permission from Shipherd and Beck (2005).

(Shipherd and Beck, 1999, 2005) (see **Figure 3**). In another study that instructed participants to suppress neutral information, combat veterans with PTSD had greater combat-trauma related intrusions during attempts to suppress thoughts about a "white bear" than combat veterans without PTSD (Aikins et al., 2009). These studies suggest that attempts at thought suppression might in fact be associated with greater frequency of trauma-related cognitions in PTSD.

Other forms of cognitive control include emotion regulation strategies, in which participants are instructed to change their natural response to a stimulus. Gross and colleagues have shown that individuals can engage in thought-change strategies, such as cognitive reappraisal, to deliberately reduce negative affect (Gross, 1998). Most studies examining emotion regulation in PTSD have used self-report measures to examine the frequency with which these different strategies are used and whether they are associated with greater or reduced frequency of trauma symptoms. However, there appears to be only one paper to date that has directly manipulated emotion regulation strategies in PTSD (New et al., 2009). This fMRI study compared sexual assault victims with and without PTSD on an emotion regulation task. Participants were shown negative photos and instructed to down-regulate their emotional response to the picture (diminish condition), enhance their negative response, or maintain their current response to the picture. Behavioral results showed that the healthy control group was able to diminish negative affect to a greater extent than the PTSD group whereas no group difference was observed in the enhance condition. Imaging results showed that the control group recruited greater prefrontal cortex activity across superior and middle frontal gyri for both the diminish and enhance conditions, which may suggest that controls engage in cognitive control to a greater extent than patients with PTSD.

Psychosocial treatment interventions may benefit patients by teaching them the cognitive control skills necessary to manage their symptoms, thereby reducing the detrimental effect of strong negative emotion on cognitive performance. Alternatively, drug therapies may directly affect neural circuitry and consequently blunt the effect of emotion on cognitive function. A few studies have examined the extent to which therapy improves cognitive function in PTSD. Although the evidence is limited, there is a small body of data that supports the effectiveness of therapy on normalizing cognitive function in certain domains in patients. Sutherland and Bryant (2007) reported improved autobiographical memory specificity in PTSD after treatment. Two studies have reported improved emotional Stroop performance in patients relative to controls after psychosocial intervention (El Khoury-Malhame et al., 2011a; Thomaes et al., 2012). Finally, Putman et al. (2007) reported a reduction in color naming response times to masked fearful vs. neutral facial expressions after a 40 mg dose of hydrocortisone (vs. placebo) in highly anxious men. Although this study did not include individuals with PTSD, its findings seem to call for examining the effect of glucocorticoids on emotional Stroop interference in PTSD, especially given that the administration of glucocorticoids has been associated with symptomatic improvement (e.g., Surís et al., 2010) and a reduction of fear responses in this disorder (e.g., Jovanovic et al., 2011; Miller et al., 2011), but see also (Grossman et al., 2006). Other studies, however, have not found effects of treatment on emotional Stroop measures in PTSD (Devineni et al., 2004; Taylor et al., 2006). Clearly, additional research is necessary to examine what types of treatments may confer benefits in cognitive function to individuals with PTSD.

SUMMARY AND FUTURE DIRECTIONS

The literature summarized here provides strong support for the privileged processing of emotionally charged information in PTSD. A key question is whether emotional information facilitates or interferes with cognitive processing. In other words, does PTSD confer advantages in cognitive performance given that emotional stimuli are often processed with greater efficiency than neutral stimuli? Over the span of different study paradigms, there appears to be a trade-off in cognitive performance as cognitive models of PTSD predict; although fear learning, perceptual priming, and recall memory for negative items are sometimes enhanced in PTSD, this advantage comes at the expense of processing other types of information. For example, task-irrelevant emotional information slows processing of goal-directed activity and interferes with memory and learning of neutral information. Furthermore, extinction learning and learning of safety cues is often impaired, memory for specific, detailed information is often poor, and patients with PTSD may be more prone to falsely remembering novel information. Deficits in cognitive control and emotion regulation may be exacerbated by the impact of emotion on cognitive function.

Neuroimaging studies have uncovered several key brain regions that may underlie the emotional bias effects observed in PTSD. Across studies, activity appears to be altered in

the anterior cingulate cortex, vmPFC, amygdala, hippocampus, insula, and lateral prefrontal cortex. Findings from quantitative meta-analyses of the neural correlates of PTSD have confirmed the importance of these regions in PTSD (Etkin and Wager, 2007; Hayes et al., 2012; Simmons and Matthews, 2012). A recent meta-analysis of imaging studies in PTSD showed that the amygdala and mid-ACC is hyperactive, whereas lateral and medial prefrontal cortex is hypoactive in PTSD for negative emotional stimuli vs. neutral and positive stimuli (**Figure 4**). A neurocircuitry model of PTSD posits that dysfunction of the vmPFC prefrontal cortex results in failure to inhibit an overactive amygdala, leading to an exaggerated fear response and impaired fear extinction learning (Rauch et al., 2006). Hippocampal dysfunction may be related to impairment in processing contextual information (Rauch et al., 2006; Hayes et al., 2011). The dACC, anterior insula, and amygdala, among other regions, comprise a putative "salience network" that processes information of personal relevance and is hyperresponsive in individuals with anxiety (Seeley et al., 2007). Researchers have posited that, in PTSD, hyperresponsivity of salience network regions and hyporesponsivity in putative regions important for cognitive control and working memory underlie greater distribution of processing resources in favor of potentially threatening stimuli even when neutral information is goal-relevant (Morey et al., 2009; Pannu Hayes et al., 2009; Hayes et al., 2012).

As reviewed in this paper, our understanding of emotion-cognition interactions in PTSD has progressed tremendously over the last two decades and neuroimaging research has identified pathways involved in the effect of emotion on cognition.

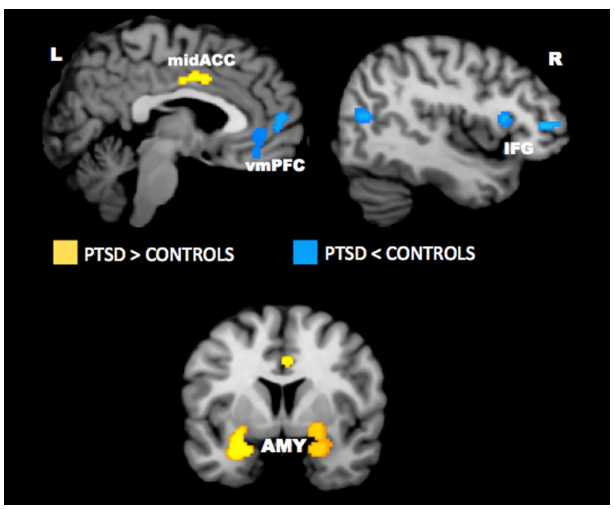

FIGURE 4 | Meta-analysis of functional neuroimaging studies in PTSD. Across various task designs, the amygdala and mid-ACC are hyperactive in PTSD whereas the lateral and medial prefrontal cortex are hypoactive for negative emotional stimuli vs. neutral and positive stimuli. Areas of hyperactivation in PTSD (PTSD > Control) are shown in yellow and areas of hypoactivation in PTSD (Control > PTSD) are shown in blue. AMY = amygdala, IFG = inferior frontal gyrus, L = left, mid-ACC = mid anterior cingulate cortex, R = right, vmPFC = ventromedial prefrontal cortex. Reproduced from Hayes et al. (2012).

However, a number of key questions need to be further examined to gain a better understanding of how emotion affects cognitive function in PTSD. An important consideration is the extent to which individual differences and moderating factors impact the development of PTSD. There is some evidence that deficits in configural cue processing and lower IQ precede the development of PTSD (Gilbertson et al., 2007; Vasterling et al., 2002). Further research is necessary to determine whether impairment in other cognitive processes precede trauma exposure and, conversely, the extent to which cognitive control and emotion regulation capacity prior to trauma exposure can offer resilience.

Currently, little is known regarding the neurobiology of cognitive control in PTSD. Surprisingly few studies have examined the neural correlates of deliberate attempts to control emotions. As reviewed above, there is presently only one neuroimaging study investigating emotion regulation in PTSD (New et al., 2009). This area needs to be developed to further examine whether impairment in the cognitive control of emotions is a PTSD symptom-maintaining factor and whether neural abnormalities during top-down regulation of emotion represents a useful biomarker for the diagnosis of PTSD. Moreover, further examination of the interplay between medial temporal lobe structures and the prefrontal cortex is necessary to better understand control processes during emotional memory encoding and retrieval. In healthy individuals, prefrontal cortex activity is associated with deep semantic encoding that supports improved recall of emotional memories (Ritchey et al., 2011), as well as suppression of aversive memories that reduces recall (Depue et al., 2007). However, less is known regarding the extent to which patients with PTSD can engage critical prefrontal cortex regions to influence the memorability of emotional stimuli.

Another emerging area of research is using drug therapies to manipulate emotion-cognition interactions. Norepinephrine has been shown to enhance emotional memory whereas adrenergic receptor blockers such as propranolol compromise the enhancing effect that emotional arousal has on memory (Cahill et al., 1994). Cerebrospinal norepinephrine levels are elevated in chronic PTSD (Geracioti et al., 2001) and research regarding the effectiveness of adrenergic blockers in preventing PTSD is underway. Although preliminary results have not yielded strong evidence to recommend the use of propronolol for the prevention of PTSD (Pitman et al., 2002; Vaiva et al., 2003; Hoge et al., 2012), further research is necessary to determine the precise time window in which such drug therapies may be useful (Cain et al., 2012). Furthermore, additional research is required to examine whether these drugs impact specific types of memory (e.g., explicit vs. implicit memory, autobiographical vs. memory for general negative events, central vs. peripheral details).

Finally, a very important area that is understudied is the commonalities or specificity of cognitive alterations in PTSD vs. other comorbidities such as depression, traumatic brain injury, and attention deficit and hyperactivity disorder. In many cases, cognitive abnormalities are observed across different mood and anxiety disorders. For example, overgeneral autobiographical memory is also a characteristic of individuals diagnosed with depression. Although many studies of PTSD focus on the fear and

anxiety based symptoms such as hypervigilance, it is possible that many of these cognitive deficits are related to the dysphoria and maladaptive appraisals that are often observed in PTSD. In fact, in recognition of these common symptoms, the proposed changes to the current diagnosis of PTSD for DSM-V may add a fourth symptom cluster of "negative alterations in cognitions and mood" (Friedman et al., 2011). Furthermore, a movement toward dimensional classification of symptoms that are shared among disorders is gaining momentum (Ofrat and Krueger, 2012). It is therefore important to understand the similarities and differences in emotion-cognition interactions between PTSD and other comorbidities to better determine the origin of and potential treatments for PTSD.

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Neural systems for cognitive and emotional processing in posttraumatic stress disorder

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Individuals with posttraumatic stress disorder (PTSD) show altered cognition when trauma-related material is present. PTSD may lead to enhanced processing of trauma-related material, or it may cause impaired processing of trauma-unrelated information. However, other forms of emotional information may also alter cognition in PTSD. In this review, we discuss the behavioral and neural effects of emotion processing on cognition in PTSD, with a focus on neuroimaging results. We propose a model of emotion-cognition interaction based on evidence of two network models of altered brain activation in PTSD. The first is a *trauma-disrupted network* made up of ventrolateral PFC, dorsal anterior cingulate cortex (ACC), hippocampus, insula, and dorsomedial PFC that are differentially modulated by trauma content relative to emotional trauma-unrelated information. The *trauma-disrupted network* forms a subnetwork of regions within a larger, widely recognized network organized into ventral and dorsal streams for processing emotional and cognitive information that converge in the medial PFC and cingulate cortex. Models of fear learning, while not a cognitive process in the conventional sense, provide important insights into the maintenance of the core symptom clusters of PTSD such as re-experiencing and hypervigilance. Fear processing takes place within the limbic corticostriatal loop composed of *threat-alerting* and *threat-assessing* components. Understanding the disruptions in these two networks, and their effect on individuals with PTSD, will lead to an improved knowledge of the etiopathogenesis of PTSD and potential targets for both psychotherapeutic and pharmacotherapeutic interventions.

Keywords: PTSD, emotion processing, cognitive control, neuroimaging, emotion-cognition interactions

INTRODUCTION

Posttraumatic stress disorder (PTSD) is triggered by trauma and characterized by intrusive memories, hypervigilance, and difficulties with concentration and memory. The dysfunctions in PTSD suggest an inability of cognitive control areas in the brain to regulate affective areas, particularly in the context of trauma-related information. In this review, we examine the effects of PTSD on neural substrates of cognitive processes, with a specific focus on the interaction of cognition and emotion. We will extend an established neural model describing cognitive-emotional interactions to understand how specific regions of this network are involved in emotion processing are dissociated in response to trauma-related information. Meanwhile, understanding the neural processes underlying major symptom clusters of PTSD that also involve emotion-cognition interactions, require disease-specific models. Emotion can have opposing effects on cognition. On one hand, *emotional facilitation* of cognition occurs when emotional processing enhances cognitive speed or accuracy. On the other hand, impairment of cognitive processes may result from *emotional interference*. In PTSD, an emotional facilitation effect would permit trauma-related information to be processed faster and/or more accurately than trauma-unrelated information. Conversely, emotional interference would impair cognition when processing trauma-related information. However, emotional interference or facilitation of cognition in PTSD may extend beyond trauma-related material to trauma-unrelated emotional material. The effects of emotion on cognition will be examined to explain how attending to emotional information influences cognitive processes in individuals with PTSD. We will explore whether trauma information influences cognitive processes in the same way as emotional non-trauma information or whether trauma information is a special case of emotional information that holds privileged status vis-à-vis cognitive processes.

High intensity acute stress, as experienced during a traumatic event, sets off a cascade of neurobiological changes which initially help the body respond to acute threat. In PTSD, however, the stress response is maintained and becomes maladaptive. Changes in hypothalamic-pituitary-adrenal (HPA) axis and catecholamine function reflect the long-term effects of this stress response (Yehuda, 2006; Yehuda and Seckl, 2011). Initially, experiencing trauma increases production of norepinephrine and HPA hormones, including corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. With long-term elevated activity, such as in PTSD, homeostatic

feedback loops are disrupted. Although our understanding of HPA axis dysfunction in PTSD is far from complete (Yehuda, 2006), PTSD is associated with altered cortisol levels, greater reactivity to cortisol, and greater CRH concentration (Charney, 2004; de Kloet et al., 2006). Levels of norephinephrine are elevated in individuals with PTSD without cormorbid major depression (Krystal et al., 1989). Disruptions in HPA axis and catecholamine function cause subsequent alterations in other neurotransmitter systems, including serotonin (Charney et al., 1993), which precipitate large-scale modifications of brain function and structure. Several brain areas, including the hippocampus, amygdala, and anterior cingulate cortex (ACC), show reduced volume in PTSD (Bremner et al., 1995; Yamasue et al., 2003; Abe et al., 2006; Karl et al., 2006; Kitayama et al., 2006; Morey et al., 2012). Whether these changes represent a pre-existing vulnerability to PTSD or develop as a consequence of the disorder remains unclear (Gilbertson et al., 2002). These brain regions also show increased serotonin and dopamine release and turnover under stress, with accompanying decreases in cognitive ability (Murphy et al., 1996; Arnsten and Li, 2005), and may show long-term alterations in neurotransmitter function in PTSD (Krystal and Neumeister, 2009). Although current neuroimaging methodologies are limited in their ability to precisely assess neurotransmitter function, measuring the resulting alterations in brain function are useful for understanding the regional and network disruptions in PTSD.

Earlier neurobiological models of PTSD based on neuroimaging findings, hypothesized a hypoactive hippocampus and prefrontal cortex (PFC) that are unable to fully regulate a hyperactive amygdalar response to trauma (Brewin, 2001; Rauch et al., 2006). However, these early models reflect an understanding of neuranatomical connections with the amygdala that were elucidated primarily in rodents. Further research that elaborated amygdalar connections with the prefrontal cortical organization found in higher primates has revealed multiple, divergent roles for various regions within the PFC (Price and Amaral, 1981; Amunts et al., 2005) that process emotional information differently depending on its valence and relation to the trauma experience and memory. Our model of cognition-emotion processing put forth in this review (see **Figure 1**) distinguishes among multiple prefrontal areas and clarifies the roles of other brain regions based on their responses to various kinds of external information. First, we propose that specific brain regions experience unique disruptions when processing trauma-related material in PTSD. These disruptions occur within specific nodes of a more

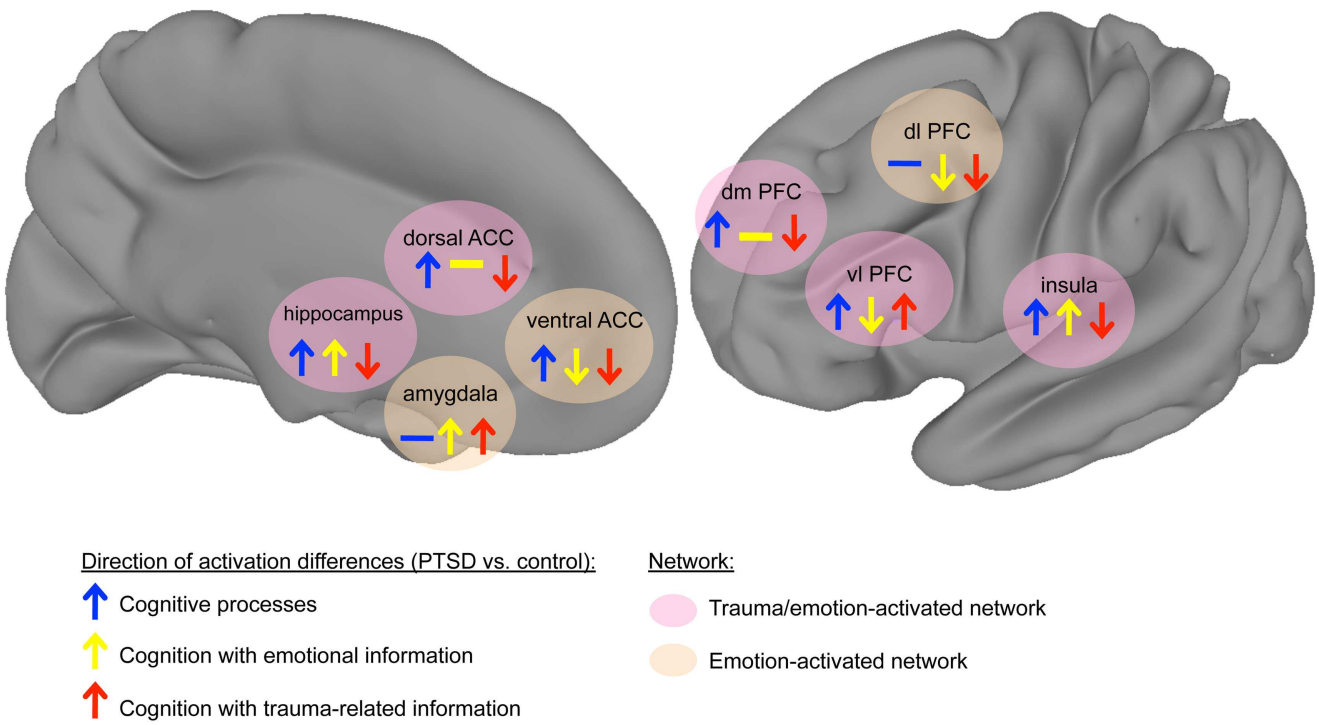

FIGURE 1 | Model of cognition-emotion interaction in PTSD. The *trauma-disrupted* regions show differential responses to trauma-related information, reflecting attentional biases to trauma-related information in PTSD. These *trauma-disrupted network* includes the ventrolateral PFC, dorsal anterior cingulate cortex (ACC), hippocampus, insula, and dorsomedial PFC, whereas other emotion-processing regions such as the amygdala, insula, and ventral ACC appear not to be uniquely affected by trauma-related information. Arrows signify direction of activation differences in contrasting the PTSD group to the comparison group (upward arrow: PTSD > control, downward arrow: control > PTSD). Arrow colors indicate stimulus category (blue: cognition, yellow: cognition with emotional information, red: cognition with trauma-related information). Background colors of areas signify network (pink: regions differentially modulated by trauma-related information, tan: regions affected by emotion but not differentially modulated by trauma-related information). (Note: network connections are not specified because of a lack of published data describing changes in connectivity strength between nodes. Thus network connections are not explicitly shown, but implied to be consistent with known human neuroanatomy.)

generalized emotion-processing network and an interconnected cognitive processing network. This broader emotion-processing network and its relationship to cognitive processing network has previously been described in healthy normal subjects (Yamasaki et al., 2002; Dolcos and McCarthy, 2006) as well as in major depressive disorder (Mayberg, 1997; Mayberg et al., 1999; Drevets, 2000, 2001). These models segregate attentional and emotional operations into constituent dorsal and ventral processing streams that extend into the PFC and integrate in the ACC (Yamasaki et al., 2002). In depression, the model predicts dorsal neocortical decrease in activity and ventral paralimbic increases (Mayberg et al., 1999). Our model extends the basic ventral/affective and dorsal/executive organization to specific points at which the processing of trauma-related information dissociates from emotional (trauma-unrelated) information, particularly in relation to cognitive processing.

During cognitive processes, the dorsal anterior cingulate and ventral prefrontal areas, including orbital frontal cortex, inferior frontal gyrus, and ventromedial PFC, show greater activation in trauma-related contexts (Morey et al., 2008b; Hayes et al., 2009; Fonzo et al., 2010). This hyperactivation is accompanied by hypoactivation in dorsal prefrontal areas, including the dorsolateral and dorsomedial PFC, as well as the hippocampus (Shin et al., 2001; Bremner and Vermetten, 2004). This model dissociates the role of specific regions to trauma-related information from their response to emotional (trauma-unrelated) material. However, other areas show alterations in their response that depend on emotional valence, not trauma content. The amygdala and insula show hyperactive responses to emotional information, but their responses to non-emotional information in PTSD have not been found to differ (Simmons et al., 2008, 2011a; Fonzo et al., 2010). The rostral/ventral ACC shows greater activation in PTSD during cognitively demanding, emotionally neutral processes and diminished activation with emotional information (Bryant et al., 2005; Kim et al., 2008; Felmingham et al., 2009a; Shin et al., 2011). For clarity, we subdivide the ACC into the dorsal ACC (red area in **Figure 2**) and the ventral ACC (blue area in **Figure 2**), which can be further subdivided into the pregenual ACC (anterior to the genu of the corpus callosum) and subgenual ACC (inferior to the genu). We propose a subnetwork within a larger emotion-processing network that exhibits altered neural responses in PTSD. These *trauma-disrupted* regions include the ventral PFC, dorsal PFC, dorsal ACC, and hippocampus, whereas other emotion-processing regions such as the amygdala, insula, and ventral ACC appear not to be uniquely affected by trauma-related information. The *trauma-disrupted regions* show

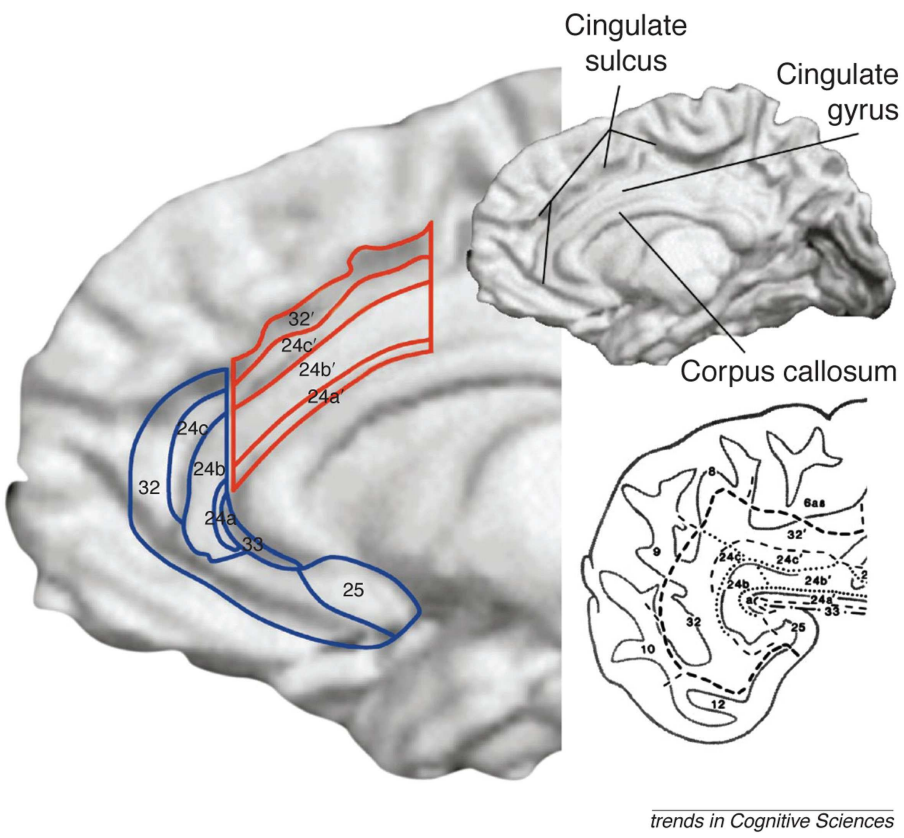

FIGURE 2 | The anterior cingulate cortex (ACC) is subdivided into the dorsal ACC (outlined in red), sometimes referred to as the mid-cingulate and the ventral ACC (outlined in blue), which can be further subdivided into the pregenual ACC (anterior to the genu of the corpus callosum) and subgenual ACC (inferior to the genu; Shackman et al., 2011). Ventral and dorsal streams for processing emotional and cognitive information, respectively, converge in the medial PFC and cingulate cortex. Figure from Bush et al. (2000) with permission.

differential responses to trauma-related information, reflecting attentional biases to trauma-related information in PTSD. The remaining emotion-processing regions show activation differences based on the emotional content of information rather than its relevance to trauma. This organization reflects two related dysfunctions of cognition in PTSD: difficulties processing trauma-related information and problems with processing emotional information more generally. Understanding how these two networks are altered, and how the alterations affect individuals with PTSD, will lead to an improved knowledge of the etiopathogenesis of PTSD and potential targets for therapeutic interventions.

COGNITION-EMOTION PARADIGMS IN PTSD

We have partitioned studies on cognition and emotion in PTSD into three broad categories: cognitive processing of information without emotional content, cognitive processing of information with emotional content, and cognitive processing of information with trauma-related content. The emotional or trauma information can be relevant to the cognitive process or incidental to the cognitive process, i.e., purely serving as a distractor. Specific task designs have been utilized in neuroimaging studies to probe cognition in these three broad categories. Although these tasks do not measure the same cognitive processes, they may tap into common cognitive dysfunctions in PTSD. Stimuli in purely cognitive processing consist of words, pictures, or sounds that are designed to be absent of emotion. Effects of emotional information are assessed by contrasting neutral stimuli to emotional stimuli, such as fearful faces and positive or negative pictures. In PTSD, trauma-related information is generally contrasted to neutral information. The exact content of trauma-related stimuli depends on the trauma experienced by the study subjects, but may include combat pictures or sounds for combat-traumatized subjects or angry faces for survivors of intimate partner violence. Nevertheless, a limitation of trauma-related stimuli is that stimulus-relevance cannot be exquisitely matched to individual participants' trauma histories and results in variability of neural responses (Liberzon and Garfinkel, 2009). Contrasting the findings from these three kinds of paradigms clarifies the role of cognitive processing of neutral and emotional information in PTSD.

We review a variety of paradigms designed to assess different domains of cognition (see **Table 1**). This includes studies using neuroimaging methods, such as EEG or fMRI, to assess overt cognition in PTSD, including those with an emotional or trauma-related component. Behavioral studies were not included, nor were studies that involved emotional processing without explicit cognitive demands, such as fear conditioning, passive viewing or listening, symptom provocation, and script-driven imagery. While an important focus of PTSD research, these experimental designs are outside the scope of this review (for reviews see Lanius et al., 2006; McNally, 2006; Rauch et al., 2006; Francati et al., 2007; Liberzon and Sripada, 2007; Aupperle et al., 2012).

COGNITIVE PROCESSING OF NON-EMOTIONAL INFORMATION

Individuals with PTSD show preserved cognition in many domains, but poorer performance during sustained attention as well as memory encoding and retrieval (Vasterling et al., 2002; Aupperle et al., 2012). During cognitive processing, our model (see **Figure 1**) highlights hyperactivation of ventral PFC and hippocampus and hypoactivation of dorsal PFC. The model is consistent with neuroimaging studies investigating the effects of PTSD on working memory, response inhibition, and sustained attention (see **Table 1**) that have established elevated activation in ventral PFC (Yamasaki et al., 2002; Bremner et al., 2004a; Bryant et al., 2005; Werner et al., 2009; although see Falconer et al., 2008 for less inferior frontal gyrus activation in PTSD). These regions are involved in emotion regulation and executive control.

Memory encoding and retrieval in PTSD is associated with greater activation in the hippocampus and parahippocampal gyrus, which also show activation in non-clinical populations during episodic memory encoding and retrieval (Shallice et al., 1994; Nyberg et al., 1996; Cabeza and Nyberg, 2000). Attention and working memory tasks that require response inhibition and monitoring show that PTSD is associated with greater activation in the pre- and postcentral gyri, which are areas typically involved in motor responses (Bryant et al., 2005; Falconer et al., 2008; Felmingham et al., 2009b; Werner et al., 2009). When processing neutral information, the downregulation of ventral PFC areas and upregulation of task-related areas in PTSD may reflect reallocation of processing resources on these task-related areas of the brain. However, results in other task-related areas are less clear. Beyond motor response areas, attention and working memory paradigms engage dorsolateral prefrontal-inferior parietal networks (Cabeza and Nyberg, 2000), which show both greater (Bremner et al., 2004a; Bryant et al., 2005; Felmingham et al., 2009b; Werner et al., 2009) and lesser (Clark et al., 2003; Falconer et al., 2008; Moores et al., 2008) activation in PTSD. Working memory has also been associated with greater activation in PTSD in the hippocampus and parahippocampal gyrus (Felmingham et al., 2009b; Werner et al., 2009), rendering the effects of PTSD on activation in these areas during cognition as inconclusive.

Cognitive processing of neutral information in the amygdala does not differ in most studies of PTSD whereas the anterior insula generally reveals increased activation (Shin et al., 2007; Werner et al., 2009; see also reduced activation in Falconer et al., 2008). Given the amygdala's important role in emotional attention, a lack of activation for neutral information is expected. Bryant et al. (2005), found higher amygdala activation in PTSD during an auditory oddball task. This finding may have been due to a lenient region of interest analysis (criteria of $p < 0.05$, uncorrected, and three contiguous voxels), or it may reflect amygdala engagement in oddball tasks, unlike other emotionally neutral paradigms (Kiehl et al., 2005). The ACC reveals greater ventral ACC activation (Bremner and Vermetten, 2004; Bryant et al., 2005; Morey et al., 2008a; Werner et al., 2009; but see Felmingham et al., 2009b), and dorsal ACC activation (Bryant et al., 2005; Shin et al., 2007, 2011; Felmingham et al., 2009b) in PTSD. However, dorsal and ventral ACC have distinct functional roles in normative subjects, with ventral ACC active during emotion suppression and emotional conflict and dorsal ACC involved in emotional appraisal and cognitive conflict (Bush et al., 2000; Yamasaki et al., 2002; Polli et al., 2005; Etkin et al., 2011). Increased ventral ACC and decreased dorsal ACC may reflect emotional intrusion on cognitive tasks, especially when emotional distractors are intermingled

Table 1 | Functional neuroimaging studies of cognition-emotion interaction in PTSD.

First author	Pub. year	Pt	TE	HC	Stimulus type	Modality	Challenge task	Amyg	vACC	Ins.	vlPFC	dACC	Hippo	dlPFC	dm-PFC
Morey	2009	22	20	–	Trauma	fMRI	Working memory retrieval	↑			↑			↓	↑
Bremner	2004	12	9	–	Trauma	PET	Stroop (emotional vs. color)			↓	↓	↓	↓	↓	
Shin	2001	8	8	–	Trauma	fMRI	Stroop (emotional vs. counting)		↓	↓	↑	↓	↑	↓	
Landre	2011	16	–	16	Trauma	fMRI	Lexical *n*-back							↑	
Morey	2008	18	21	–	Trauma/ neutral	fMRI	Visual oddball		↑	↓	↑	↓		↓	
Hayes	2011	15	14	–	Trauma	fMRI	Subsequent memory	↓					↓		
Fonzo	2010	12	–	12	trauma/ emotional	fMRI	Face matching	↑	↓			↑			
Summary								↑	↓	↓	↑	↓	↓	↓	↑
Fonzo Handwerger	2010	12	–	12	Trauma/ emotional	fMRI	Face matching	↑	↑	↑				↓	
Simmons	2011	12	12	12	Emotional	fMRI	Face matching	↑	↓	↑					
Dickie	2008	27	–	–	Emotional	fMRI	Subsequent memory	↑					↑		
Kim	2008	12	–	12	Emotional	fMRI	Face matching with distractor		↓						
Simmons	2008	15	–	15	Emotional	fMRI	Cued anticipation			↑					
Hayes	2009	14	12	–	Trauma	fMRI	Visual oddball		↓		↓			↓	
Summary								↑	↓	↑	↓	Unch.	↑	↓	Unch.
Shin	2011	12	14	26	Neutral	fMRI	Motor interference					↑			
Bremner	2004	12	9	–	Trauma	PET	Stroop (emotional vs. color)		↑		↑			↑	
Shin	2007	13	13	–	Neutral	fMRI	Counting Stroop			↑		↑			
Werner	2009	12	–	12	Neutral	fMRI	Associative learning		↑	↑	↑		↑	↑	↑
Clark	2003	10	–	10	Neutral	PET	Working memory updating							↓	↑
Morey	2008	18	21	–	Trauma/ neutral	fMRI	Visual oddball								
Moores	2008	13	–	12	Neutral	fMRI	Working memory updating					↓	↓	↓	
Falconer	2008	23	17	23	Neutral	fMRI	Go/NoGo			↓	↓			↓	↓
Bryant	2005	14	–	14	Neutral	fMRI	Auditory oddball	↑	↑		↑	↑		↑	
Felmingham	2009	11	–	11	Neutral	fMRI	Auditory oddball		↓			↑	↑	↑	
Sailer	2008	14	13	–	Neutral	fMRI	Decision making								↓
Summary								Unch.	↑	↑	↑	↑	↑	Incon.	Incon.

TC, trauma-exposed controls; NC, non-trauma-exposed controls; Unch, unchanged; Incon, inconsistent.

with task-relevant stimuli (e.g., Morey et al., 2008b), or it may result from a disruption of normal network activity in PTSD. Dorsal ACC activation increases in PTSD resulted from Stroop and attentional tasks, whereas decreases or no differences were primarily seen in working memory or associative learning tasks, suggesting a process-specific dysfunction during attention in the dorsal ACC in PTSD; see review of Stroop findings (Hayes et al., 2012) in present issue.

A major drawback of these results is that most studies used trauma naive control participants, although a few studies (Shin et al., 2007, 2011; Falconer et al., 2008; Morey et al., 2008b) used trauma-exposed control groups. Therefore, the role of PTSD relative to trauma exposure is unclear. In general, though, these results suggest a downregulation of dorsal executive areas and an accompanying increase in activation of ventral affective areas in PTSD while performing cognitive tasks that are emotionally neutral. Thus, there is suggestion that ventral areas are tonically upregulated in PTSD even in the absence of trauma cues or other emotional information that is not trauma-relevant.

COGNITIVE PROCESSING OF EMOTIONAL INFORMATION

Behavioral performance on cognitive tasks that involve emotional information (either task-relevant or task-irrelevant) has either demonstrated lack of differences in patients with PTSD (Kim et al., 2008; Fonzo et al., 2010; Simmons et al., 2011a), or lower performance with PTSD (Dickie et al., 2008; New et al., 2009). Generally, the evidence does not demonstrate a diagnosis by condition interaction where participants with PTSD perform differently only on emotional items, which would lend credence to a facilitation or interference effect. However, a behavioral study by Mueller-Pfeiffer et al. (2010) found evidence of emotional interference in PTSD. During a Stroop task, subjects with PTSD performed worse when emotional, but not neutral, pictures were shown before each trial. The findings from this study reflect intrusion of irrelevant emotional information on task performance, while most of the neuroimaging studies used stimuli with emotional content as task-relevant stimuli (Dickie et al., 2008; Simmons et al., 2008, 2011a; Fonzo et al., 2010). One neuroimaging study (Kim et al., 2008) included distracting emotional information and neutral task-relevant information, but did not find behavioral evidence of facilitation or interference.

Examining the neural differences in PTSD for emotional information shows hypoactivity in vlPFC (Hayes et al., 2009) and dlPFC (Hayes et al., 2009; Fonzo et al., 2010). In contrast, neutral material revealed dlPFC to show inconsistent and conflicting findings (see above). Our model (see **Figure 1**) consists of an emotion-disrupted network, comprising amygdala, dlPFC, and ventral ACC. Emotional stimuli consistently elicit greater amygdala and insula activation in PTSD (Simmons et al., 2008, 2011a; Fonzo et al., 2010). The pattern of ACC activation also differs in PTSD. The ventral ACC shows less activation (Kim et al., 2008; Hayes et al., 2009; Simmons et al., 2011a) whereas the dorsal ACC typically displays null findings (**Table 1**). However, increased activation was reported in a subsequent memory paradigm (Dickie et al., 2008; Fonzo et al., 2010). As with studies using neutral information, many of these studies used a non-traumatized control group, although one study used two control groups of trauma-exposed and trauma-unexposed participants (Simmons et al., 2011a).

COGNITIVE PROCESSING OF TRAUMA-RELATED INFORMATION

Mirroring the findings for emotional material, neuroimaging studies using trauma-related information have rarely found that behavioral performance showed an interaction of PTSD diagnosis and stimulus type. A few behavioral studies have found such an interaction with tasks measuring attentional interference (Pineles et al., 2009) or target detection with visual, trauma-related distractors (Chemtob et al., 1999). These findings are similar to the interference effect found with emotional distractors during the Stroop task summarized above (Mueller-Pfeiffer et al., 2010). These results suggest that, if PTSD is associated with trauma-related interference, it applies to only specific cognitive processes. Specifically, the ability to disengage from task-irrelevant trauma information seems to be affected in PTSD (Chemtob et al., 1999; Pineles et al., 2009; Mueller-Pfeiffer et al., 2010; Aupperle et al., 2012), although poorer performance in PTSD may be due to the greater overall cognitive demands of interference tasks rather than an effect of interference itself. Otherwise, performance differences between trauma-related and trauma-unrelated trials have not been observed in PTSD. Contrary to the notion that PTSD facilitates performance when stimuli are interpreted as threatening, there is little evidence of better performance in PTSD with trauma-related material. In general, trauma-related information has shown either a main effect of stimulus type, with participants performing either worse (Hayes et al., 2009) or better (Hayes et al., 2011) regardless of group, or a main effect of diagnosis, with poorer performance across stimulus types in the PTSD group (Shin et al., 2001; Bremner and Vermetten, 2004; Morey et al., 2009).

Despite the paucity of behavioral findings, neuroimaging research has demonstrated that activation in a number of areas is predicted by the interaction of stimulus type and PTSD diagnosis, thus supporting the idea of a trauma-disrupted network. In our model (see **Figure 1**), trauma-related cognitive processing involves select trauma-disrupted regions (showing a unique response to trauma stimuli) among a generalized emotion-processing network (regions responding trauma-unrelated emotional stimuli). Generally, when processing trauma-related versus trauma-unrelated material, PTSD is associated with hyperactivity in the ventrolateral PFC, ventromedial PFC, and orbitofrontal cortex and amygdala (Morey et al., 2008b, 2009; Hayes et al., 2009; Fonzo et al., 2010), although see reports of less ventrolateral PFC activation (Bremner and Vermetten, 2004) and for less amygdala activation (Hayes et al., 2011) in PTSD. A hypoactive dorsal network, which includes the dorsolateral PFC (Shin et al., 2001; Bremner et al., 2004b), as well as lower hippocampal activation (Hayes et al., 2011). The insula, which is involved in interoceptive and affective processing, shows variable but generally greater activation with trauma-related information (Shin et al., 2001; Bremner and Vermetten, 2004; Morey et al., 2008b, 2009). These findings are concordant with studies of emotional information, which suggests the amygdala shows more activity in PTSD for emotional information regardless of the relevance to trauma. The ACC displays mixed, but generally lower ventral ACC activation (Shin et al., 2001; Fonzo et al., 2010, but

see Morey et al., 2008b) and lower dorsal ACC activation (Shin et al., 2001; Bremner and Vermetten, 2004; Morey et al., 2008a) in PTSD. Compared to cognition in the absence of emotional information, studies with trauma-related information show nearly opposite patterns of activation, particularly in prefrontal regions. Specifically, when processing trauma-related information PTSD is associated with greater ventral prefrontal, lower dorsal prefrontal, greater amygdala, lower ventral ACC, and greater dorsal ACC activation. Most studies using trauma-related information have used control groups with levels of trauma similar to the PTSD subjects. The use of mostly trauma-unexposed control groups in studies with neutral information limits comparisons between these types of studies.

COMPARISON OF FINDINGS ACROSS INFORMATION CATEGORIES

Across studies using neutral, emotional, and trauma-related material, a network of brain areas shows functional differences in PTSD. The direction of effects in each area, however, depends on the type of information used. The ventral PFC, which includes medial PFC, orbital frontal cortex, and ventrolateral PFC, shows greater activation when performing cognitive processes with trauma-related material but less activation with trauma-unrelated material with emotional content. These areas are involved in a diverse array of processes, including decision making, extinction learning, and cognitive control of emotion (Bechara et al., 2000; Gray et al., 2002; Milad et al., 2007; Wager et al., 2008), but have a role in regulating affect and integrating emotional and cognitive information, and maintaining executive processes while coping with distracting affective content. Similarly, the hippocampal region shows more activation for trauma-unrelated and less for trauma-related material. These findings suggest that processing trauma-related information has a unique pattern where access to memories is modulated by connections with the amygdala (Dickie et al., 2008; Brohawn et al., 2010; Hayes et al., 2011). Conversely in the lateral PFC, trauma-related material biases the ventrolateral PFC response while reducing activation in dorsolateral areas. This pattern of activation may be related to an inability to effectively regulate trauma-induced affective responses in PTSD. In fact, individuals with PTSD show less dorsal PFC activation in PTSD when consciously up- or down-regulating responses to emotional material, suggesting that they do not recruit those areas to the same extent during emotion regulation of trauma-related material (New et al., 2009). Learning how this shift in neural processing can be corrected, either by learning cognitive strategies as in cognitive-behavioral therapy (CBT) or through guided remembering of trauma in prolonged-exposure therapy, may be a goal of research on psychotherapy for PTSD. In addition, understanding the relationships among nodes in these networks, which have been under-investigated (Gilboa et al., 2004; Fonzo et al., 2010), will explain how activation changes occur in PTSD. Examining whether these areas form connected networks or comprise parts of different networks that show similar activation patterns is an area of active research.

In contrast, the amygdala shows reduced activation in PTSD for trauma-related and trauma-unrelated emotional information. Meanwhile, studies of cognitive processing (without emotional information) have failed to demonstrate amygdala response in PTSD, suggesting that amygdala dysfunction is specific to emotional information, despite evidence from normative groups implicating the amygdala in decision making (Morrison and Salzman, 2010). It is well known that the amygdala shows activation in response to a variety of emotionally salient information, including fear, reward, and surprise (Phelps, 2006; Pessoa and Adolphs, 2010). After repeated presentations of similar stimuli, however, amygdala responsiveness decreases (Wright et al., 2001). Amygdalar habituation to emotional stimuli is attenuated in PTSD (Shin et al., 2005), leading to a sustained amygdala response even to familiar emotional stimuli. Increased amygdala activation in PTSD may reflect heightened activation to emotional content in the amygdala, lessened habituation, or both. The relationship of structural changes in the amygdala associated with PTSD to processing of emotional and trauma-related information as well as fear processing is an area that remains largely unexplored (Morey et al., 2012).

The insula is an area of interest in anxiety disorders and specifically in PTSD. The insula responds to potential threat (Simmons et al., 2008) by assigning value to incoming stimuli. In PTSD, the insula showed greater activation with emotional material and reduced activation for trauma-related material but mixed findings for neutral material. The insula is responsible for representing internal states and is involved in the anticipation of negative events (Singer et al., 2009); non-psychiatric subjects who are anxiety-prone (Simmons et al., 2006) or who exhibit faster avoidance learning (Samanez-Larkin et al., 2008) have greater insula activation. In their meta-analysis of emotion processing in anxiety disorders, Etkin and Wager (2007) found insular and amygdalar hyperactivation during fear processing. Activation in these areas represents a "final common pathway" for processing of anxiety and fear. Overactivity in the insula and amygdala to trauma-unrelated emotional material suggests that emotional information is preferentially processed through fear and anxiety networks in PTSD.

The ventral and dorsal prefrontal processing streams converge in the ACC to mediate these and other information streams from ventral limbic structures (Yamasaki et al., 2002; Dolcos et al., 2011). The dorsal and ventral portions of the ACC show similar activation patterns except for emotional trauma-unrelated stimuli. The dorsal ACC shows lower activation for trauma-related information and increased activation during cognitive processing. Meanwhile, the ventral ACC shows diminished activation for trauma related and unrelated emotional material and greater activation during cognitive processing of neutral information. Activation in the dorsal ACC, an area that may play a role in hypervigilance in PTSD (Fonzo et al., 2010), could reflect a state of high arousal and attention in PTSD that is specifically caused by trauma-related information. This finding is similar to the pattern in other trauma-disrupted areas of the brain in PTSD. Activation in the ventral ACC may exhibit greater reliance on the emotional valence of the material, rather than its relevance to trauma, although this hypothesis remains to be directly tested. The ventral ACC has connections to the amygdala and other limbic areas as well as the PFC, suggesting that this area mediates communication among emotion-related areas in the PFC and limbic system. Although

the precise function of the ventral ACC is unclear, it is involved in emotional interference resolution (Whalen et al., 1998; Etkin et al., 2006) and feedback learning (Quilodran et al., 2008). In addition, increased activation in the ventral ACC correlates with symptom improvement following successful treatment of PTSD with CBT (Bryant et al., 2008) and the therapeutic response to CBT in PTSD is predicted by larger ventral ACC volume (Bryant et al., 2008). After trauma exposure, successful recruitment of the ventral ACC may mediate the attention bias for emotional information; an inability of ventral ACC to resolve emotional conflict may be involved in the onset of PTSD (Shin et al., 2001). Targeting the subgenual ACC (see **Figure 2**), the most ventral aspect of the ACC, with deep brain stimulation may treat refractory depression (Mayberg et al., 2005; Lozano et al., 2008), suggesting dysfunction in this region may be common to mood and anxiety disorders. Therefore, understanding and normalizing anterior cingulate dysfunction should be a vital goal in PTSD research.

Neuroimaging studies in PTSD show that patterns of brain activation differ in response to cognitive processing alone, with emotional material, and with trauma-related material. As expected by the nature of the disorder, individuals with PTSD show differences in brain activation to trauma-related information. However, their responses to other forms of emotional information also differ from people without PTSD, but only in partially overlapping ways. PTSD-related differences in brain activation during cognitive processing of trauma-related information is dissociated from processing of trauma-unrelated emotional information in *trauma-disrupted* regions including the ventrolateral PFC, insula, hippocampus, dorsal ACC, and dorsomedial PFC. Meanwhile, other regions including the amygdala, dorsolateral PFC, and ventral ACC manifest consistent differences associated with trauma-related and trauma-unrelated emotional material.

In reviewing the neuroimaging literature on PTSD that involves emotion-cognition interactions, we have enumerated empirical evidence that is largely consistent with a ventral-dorsal organization. We have highlighted regions that are dissociated based on their response to trauma-related information, into a so-called *trauma-disrupted network* as a distinct subnetwork of a larger emotion-cognition processing network. The model of interacting cognitive and emotion-processing systems elaborated by Mayberg (1997) and Drevets (2001) in depression and later in healthy normals (Yamasaki et al., 2002; Dolcos and McCarthy, 2006) is also of value in PTSD. Functional MRI studies in normative groups have established that tasks of sustained attention activate medial PFC and ACC as well as inferior parietal cortex (McCarthy et al., 1997; Kirino et al., 2000; Yamasaki et al., 2002), while those involving inhibitory behavior activate parts of the ventrolateral PFC, dorsolateral PFC, ventromedial PFC, and orbitofrontal cortex (Garavan et al., 1999; Menon et al., 2001; Aron et al., 2004). The ventrolateral PFC has been implicated in response inhibition for emotional and non-emotional settings (Compton et al., 2003; Bledowski et al., 2010). In this regard, the ACC plays a specialized role as more ventral regions are primarily involved in inhibition of responses to emotional stimuli, while dorsal regions are associated with the inhibition of neutral information (Bush et al., 1998; Whalen et al., 1998; Yamasaki et al., 2002).

The model proposed by Mayberg (1997) and Drevets (2001) provides an important foundation for understanding functional brain changes in depression (Mayberg, 1997). Mayberg's model provides a framework for understanding the entire gamut of clinical symptoms of depression that includes cognition and attention impairments, vegetative-somatic changes (sleep, eating, and activity), and diminished mood/affect. The model segregates dorsal brain regions and ventral areas. Vegetative-somatic functions are associated with subgenual ACC (see **Figure 2**), anterior insula, hypothalamus, hippocampus, and brainstem. Attention-cognition functions are associated with dorsal regions including dorsalateral PFC, dorsal ACC, inferior parietal, and posterior cingulate cortex. Mood and affect changes are associated with the ventral (pregenual) ACC. As Mayberg points out, "depression is not simply dysfunction of one or another of these components, but is the failure of the coordinated interactions between the subcomponents of either compartment and between the two compartments." Overall, the model predicts dorsal neocortical decrease in activity and ventral paralimbic increases in depression (Mayberg et al., 1999).

While there are specific aspects of this model that are clearly relevant to PTSD, particularly understanding cognitive-emotional interactions, the model does not adequately comprehend the effect of traumatic events and trauma-related information as distinct from emotional (trauma-unrelated) information. Moreover, this comparatively narrow treatment of cognitive-emotional processing does not encompass major symptom clusters of PTSD such as re-experiencing (frequent memories and thoughts of the trauma, reliving the trauma), hyperarousal (being frequently on guard, hyperalert, suddenly startled), and avoidance of persons and places that trigger reminders of the trauma (reviewed in Davidson et al., 1997; McDonald et al., 2008, 2009; Hayes et al., 2012). A traumatic experience is classified as Citerion-A of DSM-IV but is not a required diagnostic feature of depression, which makes it unique to PTSD (First et al., 1997). While depression may be precipitated by life stressor(s) (e.g., job loss, divorce, etc.), these stressful events are fundamentally different from a traumatic events. Moreover, onset of a depressive episode is common even in the absence of any environmental precipitant (Kessler, 1997).

The model put forth by Drevets (2001) postulates abnormal activity in the amygdala, ventral ACC, the orbitofrontal cortex, ventrolateral PFC, dorsomedial PFC, dlPFC, anterior insula, ventral striatum, posterior cingulate cortex, and thalamus where activity in regions that mediate emotion and stress respond with elevated activity and regions mediating attention and sensory processing respond with reduced activation. Our model simply extends the basic ventral/affective and dorsal/executive organization to include the processing of trauma-related information processing, which occupies a privileged position that is neurally dissociated from emotional (trauma-unrelated) information, particularly in relation to cognitive processing. To put the present information on cognitive-affective processes into the larger context of a model that reflects the neural alterations associated with the full syndrome of PTSD, we review a network model that explains key PTSD symptom features, particularly re-experiencing and hypervigilance.

COGNITION-EMOTION INTERACTIONS IN FEAR LEARNING AND EXTINCTION

Associative fear learning, while not a cognitive process in the traditional sense, provides important insights into the maintenance of the core symptom clusters of PTSD such as re-experiencing and hypervigilance (Jovanovic et al., 2009; Jovanovic and Ressler, 2010; Norrholm et al., 2011; Mahan and Ressler, 2012). Fear learning is typically adaptive in that danger is signaled by the similarity of current threat cues with previously encountered conditions predictive of aversive outcomes (Blechert et al., 2007). However, the transfer of fear to innocuous stimuli following a traumatic experience can lead to maladaptive consequences and marked impairment of functioning in occupational and social domains (Amaya-Jackson et al., 1999). For instance, trauma-exposed individuals who widely cast defensive behaviors toward a broad range of stimuli are at risk of wasting energy resources that compromise cognitive functions and promote anxiety (Dunsmoor et al., 2011).

Extensive psychophysiological and neurobiological research in both humans and non-human animals has established several key regions involved in fear learning processes, including the amygdala, insula, cingulate gyrus, striatum, sensory cortex, and PFC (Phelps and LeDoux, 2005). Pavlovian fear conditioning and extinction of an acquired fear response has been the focus of several behavioral experiments in PTSD (Debiec and LeDoux, 2006; Blechert et al., 2007; Milad et al., 2008; Shin and Handwerger, 2009; Norrholm et al., 2011). However, extremely few studies to date have examined fear processing in the neuroimaging setting (Bremner et al., 2005; Milad et al., 2009; Rougemont-Bücking et al., 2011; van Well et al., 2012; reviewed in Hayes et al., 2012). Therefore, much of our review on the network organization of fear learning systems is extrapolated from neural models derived from healthy subjects as well as non-human primates and rodents. Pavlovian fear conditioning is a relevant model for PTSD where learned fear may persist for years and sometimes a lifetime after trauma exposure(s). Purportedly, the exaggerated and persistent fear responses to reminders of the initial psychological trauma in PTSD are associated with impairment in the extinction recall memory (Milad et al., 2009).

A basic neural circuit model that is at the basis of re-experiencing and hyperarousal symptoms of PTSD can be partitioned into two main circuits that include the temporo-striatal and corticostriatal circuits, sometimes considered together as the limbic corticostriatal loop (Cardinal et al., 2002). The general organization of the loops has been worked out in the context of Pavlovian conditioning in animal models and to some extent in humans as well (Cardinal et al., 2002). The system can be visualized as concentric loops passing through the striatum and the multiple cortical association regions. The major components of this loop are the (i) medial temporal lobe structures, including the hippocampus, amygdala, and extended amygdala regions such as the bed nucleus of the stria terminalis; (ii) striatal structures, including the caudate nucleus; (iii) medial frontal regions, including the ventromedial PFC, ACC, dorsomedial PFC, and precuneus; and (iv) lateral prefrontal structures, including the insula and ventrolateral PFC.

To understand this model in the context of PTSD, a logical starting point is hippocampal function which is necessary to access episodic memory for comparing current information to past experiences (Iordanova et al., 2009). The hippocampus can construct an encoded memory that is the conjunction of spatial and contextual information and other details about threat-related cues when functioning effectively. On the other hand, partial encoding may result in fractured memory that is inaccurate and lacking detail (see Mickley Steinmetz et al., 2012 in present issue). In PTSD, there is inadequate input from the hippocampus or a predilection toward gist based information (Brewin et al., 2010; Hayes et al., 2011). Consistent with this, PTSD patients have pronounced volume loss of the hippocampus (Karl et al., 2006; Morey et al., 2012) particularly in the dentate gyrus (CA3; Wang et al., 2010), which is essential for intact contextual memory (Nakashiba et al., 2008). Hippocampal dysfunction can bias learning strategies toward discrete associations between environmental features and the traumatic event, which in PTSD may bias fear learning and recall toward simple discrete item associations over contextual associations (Iordanova et al., 2009; Rudy, 2009). The medial temporal lobe provides inputs to the striatum and the ACC for computing an error signal between a predicted and observed outcome to indicate the need for deployment of attentional resources in order to adjust behavior or cognition (Botvinick et al., 2004). This information is resolved against potentially conflicting information and is selectively attended by the ACC (Shin et al., 2001; Hayes et al., 2009) and striatum. The striatum is strongly implicated in learning reinforced by both rewarding and aversive outcomes (LaBar et al., 1998; Phelps et al., 2004). Likewise, this information is placed in the appropriate semantic and autobiographical context through connections to dorsomedial PFC and the precuneus, which contribute the extent of self-relevance and self-reference. Striatal and medial PFC structures inform the ventrolateral PFC to maintain cognitive control over emotional distraction while assessing potential threat relevance.

In parallel, the amygdala and vmPFC are responding to potential threat and ensuing fear. The vmPFC is critical in learning about fear and safety cues, and lesions in this region produce impairment in extinction retention (Milad and Quirk, 2002; Phelps et al., 2004). The insula also responds to potential threat (Simmons et al., 2008) by assigning value to the input stimulus. The insula has been studied intensively in relation to anticipatory reward processing but there is growing evidence that it plays an analogous role in anticipatory signals important for learning about aversive outcomes (Paulus et al., 2003; Paulus and Stein, 2006; Delgado et al., 2008; Somerville et al., 2010). The inputs from the insula to the striatum may be important for responding to stimuli that share properties with a learned threat in order to adaptively react to potential threats from the environment (Delgado et al., 2008). Finally, inputs from the medial PFC, striatum, and insula are being integrated in the ventrolateral PFC to facilitate cognitive control and subsequently in the dorsolateral PFC to place information within the context of current priorities and plans.

In summary, this neural model can be conceptualized as having a *threat-alerting* component that consists of the amygdala, insula, and vmPFC, and a *threat-assessing* component that

consists of hippocampus, anterior cingulate, striatum, dorsomedial PFC, precuneus, and ventrolateral PFC. A functional balance between the threat-alerting and the threat-assessing systems following trauma exposure facilitates a highly resilient response, whereas as an imbalance can result in PTSD symptoms. In PTSD the neural system is biased in favor of activation in the *threat-alerting* system over the *threat-assessing* system.

FUTURE DIRECTIONS

Examining both trauma-related and emotional trauma-unrelated emotional material within a single study design are uncommon (Morey et al., 2008b; Fonzo et al., 2010). Furthermore, these categories have not been compared directly even when contained within the same study. Understanding how individuals with PTSD react to emotional material with or without trauma reminders is necessary to develop an accurate model of cognition and emotion in PTSD that will inform the design of more effective treatments. Future studies should directly contrast these stimulus categories. Most neuroimaging studies included emotional or trauma-related stimuli in the cognitive process of interest, instead of using such stimuli as distractors. A comparison of task-relevant and distracting information may clarify the mechanisms of emotion or trauma-related interference or facilitation in PTSD.

The emotional and trauma-related information from some studies was relevant to the ongoing task whereas in other studies it was irrelevant to the ongoing task (served only as a distractor). For instance studies of Stroop tasks (Shin et al., 2001; Bremner et al., 2004b) or episodic memory (Dickie et al., 2008; Brohawn et al., 2010; Hayes et al., 2011) that examined neural response to encoding necessarily employed task-relevant stimuli (reviewed in Hayes et al., 2012). On the other hand other types of tasks such as working memory (Morey et al., 2009) or the oddball task (Hayes et al., 2009) utilized task-irrelevant information to distract participant from the cognitive demand of the ongoing task. It is unclear how these types of differences might modulate the response in cognitive, emotion, or trauma processing networks until specific comparison studies are performed.

Few studies have examined connections among different areas in the networks. Among the studies we reviewed, two studies that explored network connectivity found amygdala connectivity differences in PTSD with the insula, ventral ACC, and ventrolateral PFC (Fonzo et al., 2010; Simmons et al., 2011a). A few additional studies that lack cognitive processing have examined connectivity relationships in response to symptom provocation (Gilboa et al., 2004) and rest (Rabinak et al., 2011; Sripada et al., 2012). More studies assessing connectivity across cognitive, emotion, and trauma processing networks are required to determine how these brain networks are related.

By incorporating recent findings, our model provides a finer-grained survey of brain areas involved in PTSD that move beyond previous models consisting of ventromedial PFC amygdala, and hippocampus. However, activation patterns in this model for regions such as ventrolateral PFC and insula, are composed of several regions that differ anatomically and functionally. Areas such as the amygdala and hippocampus also contain a number of functionally heterogeneous subregions (Amunts et al., 2005). Studies that successfully dissociate these areas will offer a more nuanced view of neural dysfunctions in PTSD.

A handful of studies on cognition-emotion interactions have begun to apply findings to improve understanding of the etiology and treatment of PTSD. Behavioral and neural performance on a motor interference task in twins discordant for combat exposure revealed that trauma-unexposed twins performed similarly to their co-twins with PTSD, despite the lack of a PTSD diagnosis (Shin et al., 2011). This finding, combined with higher pre-trauma IQ as a resilience factor (Buckley et al., 2000; McNally, 2006), suggests that the deficits reviewed above may be due to pre-existing vulnerabilities. Further research examining cognition-emotion interactions before and after developing PTSD or in twin pairs will clarify deficits reported as pre-existing vulnerabilities versus deficits that develop because of PTSD. Neuroimaging of cognitive-emotional processing tasks may hold value in improving and tailoring treatments for PTSD (Bryant et al., 2008).

Existing studies on the interaction of cognition and emotion in PTSD are beginning to coalesce on the roles of specific brain areas, but findings are still inconsistent and unclear. Improving a few key methodological considerations will clarify the neural disruptions in PTSD. First, attributing the differences to PTSD rather than trauma exposure will be simplified by using control groups matched for level of trauma exposure. Alternatively, including two control groups, trauma-exposed and -unexposed, will dissociate the differential effects of trauma and PTSD. This study design will also enable investigation of resilience factors in trauma survivors who do not develop PTSD. Second, many of the studies we reviewed had small sample sizes, a frequent limitation of neuroimaging studies. Better planned, coordinated, and analyzed studies with larger sample sizes will improve statistical validity and provide more definitive results that are less prone to false positive results (Palmer, 2000; Simmons et al., 2011b; Yong, 2012).

Conventional task-based fMRI analyses in patient populations are usually conducted by examining the interaction of stimulus type and diagnosis (e.g., trauma-related versus neutral information in PTSD versus control subjects). Although this approach addresses many methodological issues in fMRI analysis, concordant behavioral findings were not reached in many of the studies we reviewed. Indeed, most studies lacked evidence that behavioral performance showed interaction of stimulus type by diagnosis, yet they reported an interaction for the corresponding neuroimaging findings. Another issue with this analysis setup is the necessity of relative, rather than absolute, baselines in fMRI. The conventional approach of contrasting emotional with neutral stimuli, first within and then between subjects, may not capture the nature of the neural differences. As an example, an emotionally neutral attention task may find less activation in ventral ACC in PTSD when contrasting attentional tasks with a non-attentional baseline. When examining emotion processing, the same neutral attentional task may be contrasted with an emotional attentional task, and a greater difference in ventral ACC activation is found in PTSD. However, it is unclear if this larger activation difference is due to lower activation during the neutral attention task or to greater activation during the emotional task. A focus on correlating behavioral effects with differences in neural activations, more sensitive task paradigms such as parametric modulation studies, and the use

of neuroimaging techniques that go beyond cognitive subtraction to study network-based connectivity, will improve the relevance of neuroimaging findings to behavioral dysfunction in PTSD.

Despite finding significant neural differences in PTSD while processing information with emotional or trauma-related content, few studies found corresponding behavioral differences. The behavioral components of these generally found a main effect of stimulus type or a main effect of PTSD diagnosis, but failed to find an interaction effect. However, a significant interaction of stimulus type by PTSD diagnosis has generally been reported by purely behavioral studies (lacking a neuroimaging component). Several reasons for this discrepancy are possible. First, the addition of neuroimaging may impose restrictions on the complexity and sensitivity of task design and/or analysis methods; the lack of behavioral findings may reflect the difficulties of teasing apart small behavioral effects in paradigms ill suited for the fMRI, PET, or EEG environment. Second, the lack of behavioral differences in the setting of corresponding neural findings indicates that the task is insufficiently sensitive to detect differences between groups that become evident only when probing the underlying neural processes. Third, the neural effects may reflect successful compensatory efforts by participants with PTSD who are able overcome behavioral deficits.

In conclusion, behavioral evidence of emotional facilitation or interference of cognition is sparse in PTSD. However, individuals with PTSD have difficulty withdrawing attention or shifting attention away from emotional information, particularly when the information is trauma-related. During emotion-related cognitive processes, individuals with PTSD show altered neural responses in a number of brain regions, which can be grouped into a trauma-disrupted and an emotion-disrupted network. These networks show that although trauma-related material has unique effects on brain activation in PTSD, the effects of emotion processing on cognition are not limited to trauma-related information. Elucidating how these areas differ through direct comparison and how the neural differences in PTSD can be addressed by psychotherapy and pharmacotherapy will improve our understanding and treatment of PTSD.

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Linking enhancing and impairing effects of emotion—the case of PTSD

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INTRODUCTION

As illustrated by the present Research Topic, emotion that can either enhance or hinder various aspects of our cognition and behavior. For instance, the emotional charge of an event can increase attention to and memory for that event (Dolcos et al., 2012), whereas task-irrelevant emotional information may lead to increased distraction away from goal-relevant tasks (Iordan et al., 2013; see also Dolcos et al., 2011). Interestingly, sometimes these opposing effects of emotion co-occur. For example, hearing a gunshot may enhance memory for central aspects of what was happening at the time, while impairing memory for peripheral details (Christianson, 1992). It is also possible that increased distraction from ongoing goals produced by task-irrelevant emotional stimuli may lead to better memory for the distracting information itself. The co-occurrence of enhancing and impairing effects of emotion is probably most evident in affective disorders, where both of these opposing effects are exacerbated. Specifically, uncontrolled recollection of and rumination on distressing memories observed in depression and post-traumatic stress disorder (PTSD) may also lead to impaired cognition due to enhanced emotional distraction. Here, we illustrate an example based on evidence from studies of PTSD, pointing to the importance of investigating both enhancing and impairing effects of emotion, in elucidating the nature of alterations in the way emotion interacts with cognition in clinical conditions.

BACKGROUND: EMOTIONAL AND COGNITIVE PROCESSING IN PTSD

Changes in emotional and cognitive processing are critical features in PTSD patients, typically reflected in increased emotional reactivity and recollection of traumatic memories, along with impaired cognitive/executive control (Rauch et al., 2006; Shin and Liberzon, 2009; see also in this issue Brown and Morey, 2012; Hayes et al., 2012). Of particular note is emerging evidence concerning the neural correlates of alterations associated with the encoding of emotional memories (Hayes et al., 2011) and with the responses to task-irrelevant emotional distraction (Morey et al., 2009). These changes are reflected in regions associated with functions that may be enhanced (episodic memory) or impaired (working memory) by emotion—i.e., the medial temporal lobe (MTL) and dorsolateral prefrontal cortex (dlPFC), respectively. Here, we illustrate how understanding the changes associated with the way traumatic memories are formed and retrieved in PTSD (involving MTL areas) may clarify their impact on ongoing cognitive/executive processes (reflected in changes of dlPFC activity), when potential cues for traumatic memories are presented as task irrelevant distracters.

THE ENHANCING EFFECT OF EMOTION

Studies investigating the memory-enhancing effect of emotion in healthy participants point to the role of basic MTL mechanisms involving interactions between emotion-based regions (amygdala—AMY) and memory-related regions (hippocampus and associated parahippocampal cortices—HC, PHC) in the formation and retrieval of emotional memories (Dolcos et al., 2012). Neurobiological models of PTSD (Layton and Krikorian, 2002) propose that the development and maintenance of the disorder is linked to altered activity in the MTL during encoding of traumatic memories. Hence, intrusive recollection of traumatic memories observed in PTSD may be linked to dysfunction of the basic MTL mechanism identified in healthy participants as being responsible for the memory-enhancing effect of emotion (Dolcos et al., 2004). Specifically, processing of cues related to traumatic events may trigger recollection of traumatic memories, which due to dysfunctional interactions between AMY and the MTL memory system may engage a self-sustaining functional loop in which emotion processing in AMY may enhance recollection by increasing activity in HC; this, in turn, may intensify AMY activity as a result of re-experiencing the emotions associated with the recollected memories (Dolcos et al., 2005; McNally, 2006). On the other hand, there is also evidence suggesting a disconnect between the effects observed in AMY and their link to emotional or cognitive aspects of processing in PTSD patients. Specifically, while greater AMY activation is identified in studies of symptom provocation (Rauch et al., 2000; Hendler et al., 2003; Shin et al., 2004, 2005; Williams et al., 2006), such an effect is not observed in studies of cognitive processing (Shin et al., 2001; Clark et al., 2003; Bremner et al., 2004; Morey et al., 2008).

An important observation that has emerged in the PTSD literature may reconcile this apparent discrepancy. Specifically, there is evidence that memories for negative events in PTSD patients may be non-specific, gist-based, rather than detailed, context-based (McNally et al., 1994; Kaspi et al., 1995; Harvey et al., 1998). Gist refers to familiarity-based retrieval of memories for the general meaning of a situation or event, rather than recollection of specific contextual details (Tulving, 1985). Given that gist-based memories are often

inaccurate (Roediger and McDermott, 1995; Wright and Loftus, 1998) and susceptible to enhanced rate of false alarms that may diminish or cancel an actual enhancing impact of emotion on memory (Dolcos et al., 2005), it may be the case that the basic AMY-MTL mechanisms typically responsible for the memory-enhancing effect of emotion are in fact attenuated in PTSD. Hence, this could explain the non-specific, gist-based, memories observed in these patients. This idea is supported by recent findings from a fMRI study using the subsequent memory paradigm with emotional stimuli in PTSD patients (Hayes et al., 2011), which showed reduced memory-related activity in the AMY-MTL system during memory encoding, and higher false alarm rates during retrieval, compared to a trauma exposed control (TEC) participants (**Figure 1A**). Moreover, the PTSD patients also lacked the anterior posterior dissociation along the longitudinal axis of the MTL, with respect to its involvement during successful encoding of emotional memories, which was initially identified in healthy participants (Dolcos et al., 2004), but such dissociation was preserved in the TEC group (Hayes et al., 2011). Together, these findings suggest a disorganization of the MTL mechanisms involved in the memory-enhancing effect of emotion in PTSD, which leads to inefficient encoding of information for trauma-related stimuli and subsequent non-specific gist-based retrieval.

THE IMPAIRING EFFECT OF EMOTION

Studies investigating the neural correlates of the impairing effect of task-irrelevant emotional distraction on cognitive performance identified distinct patterns of responses in emotion and cognitive control brain regions (i.e., increased activity in AMY and reduced activity in dlPFC, respectively), which are specific to emotional distraction (Dolcos et al., 2011). On the one hand, based on this evidence, increased emotional reactivity linked to changes in the AMY function in PTSD may lead to increased specific disruption of dlPFC activity by emotional distraction. On the other hand, there is evidence for a non-specific heightened sensitivity to both threatening and non-threatening stimuli in PTSD (Grillon and Morgan, 1999; Peri et al., 2000), which may explain increased distractibility to trauma related and unrelated stimuli alike.

The fact that information unrelated to the trauma may also be highly distracting in PTSD patients is consistent with the clinically observed symptom of *hypervigilance* in these patients (American Psychiatric Association, 2000), and with the evidence for non-specific encoding of trauma-related material discussed above (Hayes et al., 2011). Specifically, it is reasonable to expect that seemingly neutral stimuli that may remind of trauma could act as cues for non-specific retrieval of trauma-related information, which in turn may be as distracting as the trauma-related stimuli themselves. Evidence from a recent study of WM with trauma-related and non-related distraction is consistent with this idea (Morey et al., 2009). Using an adaptation of our WM task with emotional distraction (Dolcos and McCarthy, 2006), the study by Morey and colleagues investigated how trauma-related task-irrelevant emotional information modulates WM networks in PTSD. Similar to the study on memory encoding discussed above, recent post-9/11 war veterans were divided into a PTSD group and a TEC group. Functional MRI results showed that the PTSD group had greater trauma-specific activation than the control group in main emotion processing brain regions, including the AMY and ventrolateral PFC (vlPFC), as well as in brain regions susceptible to emotion modulation (e.g., fusiform gyrus—FG). However, the PTSD group also showed greater non-specific disruption of activity to combat-related and neutral task-irrelevant distracters in brain regions that subserve the ability to maintain focus on goal-relevant information, including the dlPFC. This suggests a more generalized dlPFC disruption in the PTSD group than in the control group, which showed disruption specific to the trauma-related distraction. The undifferentiated dlPFC response to combat and non-combat distracters in PTSD is consistent with the *hypervigilance* hypothesis that may explain enhanced response to and distracting effect of neutral stimuli (**Figure 1C**). This neural-level finding was complemented by the behavioral results, which showed lower overall working memory performance for task-irrelevant distracters scenes in the PTSD group, in the absence of a differential impact between combat-related and neutral distracters.

THE LINK BETWEEN ENHANCING AND IMPAIRING EFFECTS OF EMOTION

Overall, the evidence from separate lines of investigations discussed above, regarding the neural changes in PTSD linked to dysfunctions in the recollection of traumatic events and the response to emotional distraction, converge toward the idea that non-specific response to emotional and neutral distraction may reflect retrieval distortions linked to inefficient initial encoding of trauma-related information. Namely, it is possible that the non-specific disruption of the dlPFC activity by trauma-related and neutral distraction is linked to the retrieval of the traumatic memories triggered by non-specific cues, which may also contribute to the perpetuation of the state of *hyperarousal* observed in these patients (**Figure 1D**). Moreover, it is also possible that the source of these effects may be linked to elevated arousal during the initial exposure to traumatic events. Consistent with this idea, in addition to showing non-specific activity to subsequently remembered items in AMY and MTL memory system in PTSD, the study by Hayes and colleagues discussed above (Hayes et al., 2011) also identified a negative co-variation of memory-related hippocampal activity for trauma-related items with scores of hyperarousal symptoms, as measured with the Clinician-Administered PTSD Scale (**Figure 1B**). In other words, participants who had greater hyperarousal scores also had reduced memory-related activity during the encoding of trauma-related pictures. This finding is consistent with evidence for an inverted U-shaped function in the hippocampus as a function of stress (Nadel and Jacobs, 1998) and provides a possible explanation for the non-specific effects observed in the tasks assessing emotional memory for trauma-related cues and their undifferentiated impact on goal-relevant processing when presented as task-irrelevant distraction. Consistent with the role of the initial arousal in these effects, PTSD patients also showed relatively greater activity for forgotten items, which may be linked to AMY hyperactivity leading to later forgetting of those items (Hayes et al., 2011).

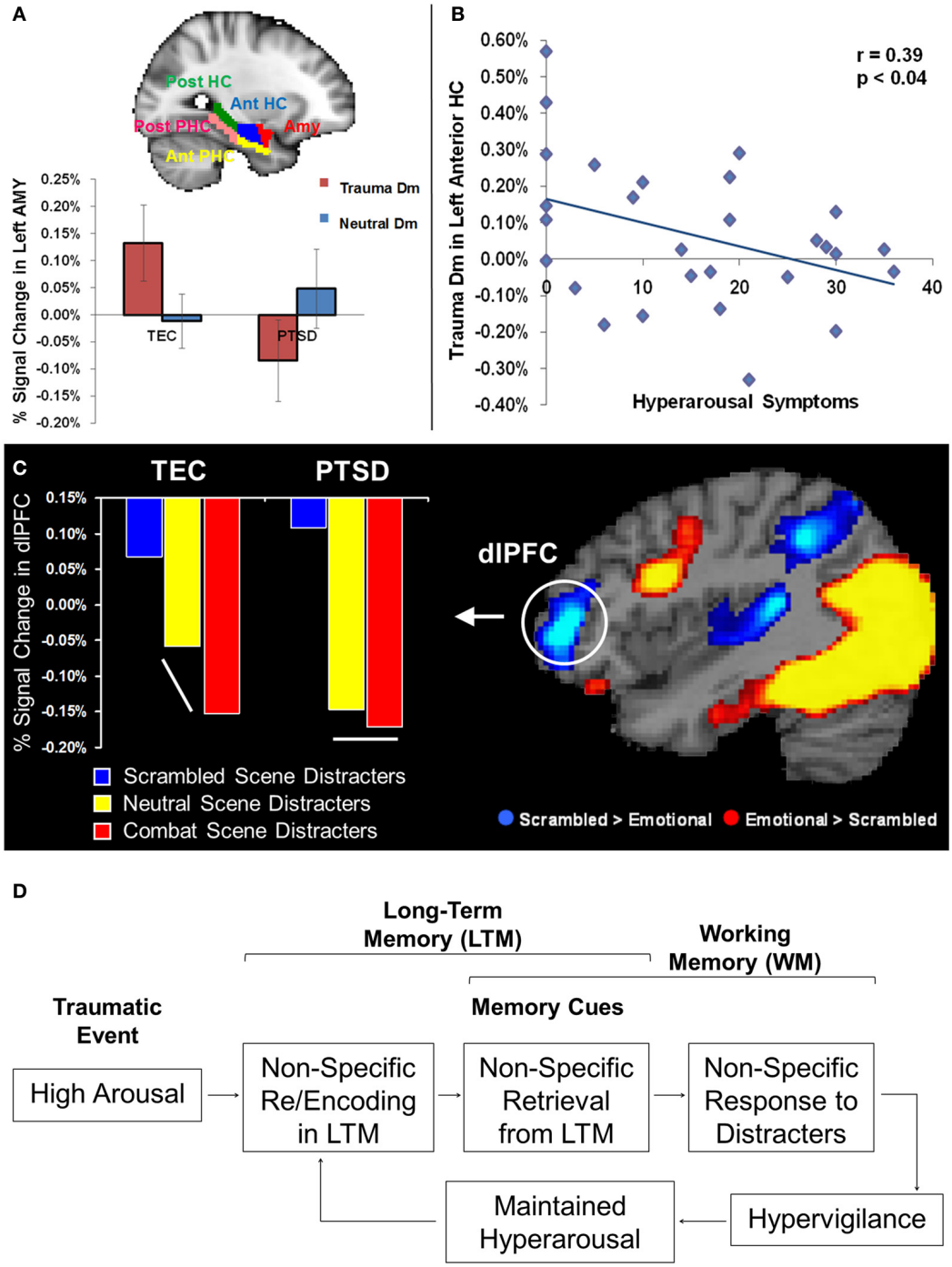

FIGURE 1 | (A–B) Memory-Related Changes in the Medial Temporal Lobe Activity in PTSD. Reduced memory-related activity (Dm) in AMY for trauma-related pictures, in the PTSD group **(A)**; a similar effect was also observed in the HC (not shown). Reduced Dm for trauma-related pictures in the anterior HC linked to increased symptoms of arousal **(B)**. Dm, Difference due to Memory effect (brain activity for Remembered minus Forgotten items); PTSD, post-traumatic stress disorder; TEC, Trauma-Exposed Control group; AMY, Amygdala; HC, Hippocampus; PHC, Parahippocampal Cortex; Ant, Anterior; Post, Posterior. Error bars represent the standard error of means. Adapted from Hayes et al. (2011), with permission. **(C)** Evidence for Non-specific Response in dlPFC to Trauma-Related and Neutral Distracters in PTSD. Comparison of mean percentage signal change in dlPFC during the active maintenance period of a working memory task in the PTSD and Trauma-Exposed Control (TEC) groups point to a generalized dlPFC disruption of activation for salient task-irrelevant distracter scenes in the PTSD group, which showed an undifferentiated response in the dlPFC to combat and neutral distracters. The TEC group showed disruption in the same area, but specific to combat-related distraction. dlPFC, dorsolateral prefrontal cortex. Adapted from Morey et al. (2009), with permission. **(D)** Diagram illustrating a possible link between the impact of emotion on long-term memory and working memory in PTSD.

CONCLUSION

In summary, available evidence from investigations of PTSD patients points to general and specific emotional and cognitive disturbances that are linked to alterations in the neural circuitry underlying emotion-cognition interactions. This evidence suggests that reduction of AMY and HC signals for trauma-related cues may underlie non-specific encoding of gist-based representations instead of specific and detailed contextual details of the trauma-related memories. This, in turn, may be linked to symptoms of *hypervigilance* and non-specific responses to trauma-related distraction, which contributes to the maintenance of a *hyperarousal* state (**Figure 1D**). This evidence also highlights the importance of investigating both the enhancing and the impairing effects of emotion, in understanding the changes associated with affective disorders, where both effects are intensified. Collectively, these findings point to the importance of investigating both of these opposing effects of emotion within the same clinical group, to complement similar approaches in healthy participant concomitantly investigating the enhancing and impairing effects of emotion on cognitive processes (Shafer and Dolcos, 2012; Dolcos et al., 2013).

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The effects of trauma exposure and posttraumatic stress disorder (PTSD) on the emotion-induced memory trade-off

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Many past examinations of memory changes in individuals with posttraumatic stress disorder (PTSD) have focused on changes in memory for trauma. However, it is unclear if these mnemonic differences extend beyond the memory of the trauma to memory for other positive and negative information and if they are specific to individuals with PTSD or extend to other individuals who have experienced trauma. The present study examined the influences of trauma exposure and PTSD on an effect that may parallel tunnel memory in PTSD: the emotion-induced memory trade-off, whereby emotional aspects of an experience are remembered at the expense of the nonemotional context. Three groups of participants (25 with current PTSD, 27 who had experienced trauma but did not have current PTSD, and 25 controls who had neither experienced significant trauma nor met criteria for current PTSD) were shown complex visual scenes that included an item (positive, negative, or neutral) placed on a neutral background. Forty-five minutes later, participants underwent a recognition memory test for the items and backgrounds separately. An emotion-induced memory trade-off was said to occur when there was a significant difference in item and background memory for emotional scenes, but not for neutral scenes. Results indicated that people with PTSD, like the other groups, were more likely to remember positive and negative items than neutral items. Moreover, people with PTSD exhibited a memory trade-off comparable in magnitude to that exhibited by the non-trauma control group. In contrast, trauma-exposed people without a current diagnosis of PTSD did not show a trade-off, because they remembered items within scenes better than their accompanying contexts not only for emotional but also for neutral scenes. These results suggest that (1) the effect of emotion on memory for visual scenes is similar in people with PTSD and control participants, and (2) people who have experienced trauma, but do not have PTSD, may have a different way of attending to and remembering visual scenes, exhibiting less of a memory trade-off than either control participants or people with PTSD.

Keywords: emotion, memory, PTSD, trauma

INTRODUCTION

Exposure to trauma may induce cognitive changes in the memory system (see Vasterling and Brewin, 2005). These mnemonic changes may be especially pronounced when posttraumatic stress disorder (PTSD; Breslau, 2002) develops. PTSD is characterized by abnormalities in memory and attention (American Psychiatric Association, 2000). Individuals with PTSD have difficulty concentrating on or attending to neutral stimuli, while at the same time exhibiting hypervigilance, or increased sensitivity to detecting threat (see Vasterling and Brewin, 2005). People with PTSD also exhibit involuntary re-experiencing of their trauma (e.g., flashbacks) despite intentionally avoiding stimuli associated with the trauma (American Psychiatric Association, 2000).

Although PTSD is defined by cognitive changes in *involuntary* memory for a traumatic incident (American Psychiatric Association, 2000), there is also interest in understanding how PTSD may affect the *voluntary* retrieval of emotional experiences. Studies assessing memory for trauma-related information have yielded mixed results as to whether people with PTSD remember stimuli that are related to their trauma better than people who have experienced trauma but do not have PTSD. Some studies have found that when participants are asked to freely recall trauma-related and non-trauma-related words embedded in an attentional task (such as an emotional Stroop task), people with PTSD remember proportionally more traumatic words than do non-patient controls (Kaspi et al., 1995; Vrana et al., 1995; Chemtob et al., 1999). Yet other studies have suggested that PTSD patients may show a response bias to endorse any trauma-related stimulus (Litz et al., 1996) or may have particularly bad memory for non-trauma stimuli rather than particularly good memory for trauma-relevant stimuli (McNally et al., 1998; Paunovic et al., 2002; Golier et al., 2003).

While no consensus has been reached regarding the effect of PTSD on voluntary retrieval of trauma-related information, even less is known about the effect of PTSD on memory for emotional information that is not related to the trauma. The findings

for negative stimuli have been mixed, with some studies finding no exaggerated enhancement in memory in people with PTSD (Bremner, 2003; Dickie et al., 2008; Brohawn et al., 2010) and others showing that PTSD patients may be biased to endorse negative stimuli (Thomaes et al., 2011) or to claim to vividly recollect negative stimuli (Tapia et al., 2012).

Fewer studies have investigated memory for positive information. Because one of the symptoms of PTSD is emotional numbness to positive stimuli, it is possible that people with PTSD may experience changes in memory for positive information (Jatzko et al., 2006). However, the existing studies examining memory for positive stimuli did not find group differences in memory for positive images when comparing individuals with and without PTSD (Brohawn et al., 2010; Tapia et al., 2012), and when comparing those with and without acute stress disorder (Paunovic et al., 2002). However, in the studies conducted by Brohawn et al. (2010) and Paunovic et al. (2002), the positive stimuli were significantly less arousing than the negative stimuli. So although these studies suggest that memory for positively valenced information is preserved in PTSD, the results cannot speak to potential effects of PTSD on memory for positive images that are also high in arousal. Thus, the impact of PTSD on memory for positive or negative stimuli is still an open question. The first goal of the present study, then, is to examine whether PTSD affects the ability to remember emotional items—positive or negative.

Despite the lack of consensus about the effect of PTSD on the *quantity* of emotional information retained, there may be differences in the *quality* of the trauma memory. Trauma narratives in PTSD have been described as exhibiting "tunnel memory," or a detailed memory for the emotional element or gist of the scene without much memory for the surrounding elements or contextual details (Safer et al., 1998; LaBar, 2007). For example, an individual with PTSD might have a vivid memory of a body in combat but not remember the details of where the body was found. However, it is unclear if tunnel memory in PTSD is qualitatively different from tunnel memory in people without PTSD.

The concept of tunnel memory—characterized by differential memory for central and peripheral elements of a scene, as well as missing pieces of information—is notably similar to a now well-established phenomenon of memory in individuals without a history of trauma or PTSD: the emotion-induced memory trade-off. The trade-off refers to the retention of emotional information at the expense of surrounding nonemotional information (see Reisberg and Heuer, 2004; Levine and Edelstein, 2009). For instance, after viewing a scene that contains an emotional element—such as a snake in the forest—people will often remember the snake well but have poor memory for the forest.

There is reason to believe that tunnel memory in individuals with PTSD is supported by mechanisms similar to those that evoke the emotion-induced memory trade-off in individuals without PTSD. Higher anxiety levels and lower levels of cognitive control (e.g., lower ability to manage other cognitive processes, leading to poorer ability to plan, think abstractly, etc.) have been correlated with a stronger memory trade-off (Waring et al., 2010). Because those who develop PTSD tend to have higher levels of anxiety and lower levels of cognitive control than those who do not develop PTSD (see van der Kolk, 2004), people with PTSD might be expected to show more of a trade-off. However, the magnitude of the trade-off effect has not been systematically tested in a population with PTSD, and so the validity of this hypothesis is unknown. The second goal of the present study is to examine whether individuals with PTSD might show an enhanced trade-off as compared to control participants. In other words, would the tunnel memory reported for trauma memory extend to a memory trade-off in voluntary recall of other types of emotional information?

Lastly, despite the research that has been done specifically looking at individuals with PTSD, it is often not clear if these changes in memory are unique to PTSD or if they are a consequence of extreme stress. Many of the studies that have examined emotional memory in PTSD have not included a trauma-exposed control group without current PTSD. Thus, these studies show that people with PTSD exhibit differences in emotional and cognitive processing compared to non-traumatized individuals but cannot determine if these processes are caused by PTSD specifically or trauma exposure itself.

There is reason to believe that exposure to trauma—or extreme or repeated stress—can cause changes in memory (see Kim and Diamond, 2002 for review). It has been fairly well established that exposure to chronic and severe stress can decrease hippocampal connectivity and impair memory (see McEwen, 1999; Starkman et al., 2001). However, much less work has been done on the effects of stress exposure on the retention of emotional information. The few existing studies have revealed that chronic stress may enhance amygdala functioning (Vyas et al., 2002, 2003) and enhance fear conditioning in rats (Conrad et al., 1999). Because the amygdala has been shown to enhance memory for emotional items, but not for their contexts (Kensinger and Schacter, 2006; Waring and Kensinger, 2011), there is reason to believe that exposure to stress may enhance emotional memory but decrease memory for surrounding neutral information.

This pattern of results has been found when stress is induced in a laboratory setting. Payne et al. (2006) found that acute psychosocial stress may enhance thematically induced trade-offs in emotional memory. In this study participants were exposed to a psychosocial stressor before watching a slide show with an emotional narrative. During a later memory test, participants who had undergone this stressor (as opposed to those who were not stressed at encoding) were more likely to remember emotional aspects of the slide show and were more likely to forget the neutral aspects. This finding indicates that stress at encoding may play a role in trade-offs between emotional and neutral aspects—at least in the instance of a thematically induced emotional narrative (as opposed to an emotional visual scene). However, it is unclear if a previously experienced stress in trauma-exposed individuals would also have similar trade-off-inducing effect. Thus, the third goal of this study is to investigate the effects of trauma-exposure, without current PTSD, on the emotion-induced memory trade-off.

To summarize, the purpose of this study is to investigate these three questions: (1) What is the effect of PTSD on memory for positive, negative, and neutral items? (2) What is the effect of PTSD on an emotion-induced memory trade-off? (3) What is

the effect of trauma-exposure on an emotion-induced memory trade-off? In the current study, these questions were addressed by testing people with PTSD, people who experienced trauma but do not currently have PTSD, and a control group who reported no experience of trauma. All participants studied scenes that included a positive, negative, or neutral item placed on a neutral background. Memory was then tested separately for emotional and neutral items and their accompanying backgrounds. In this way, we can compare memory for emotional versus neutral items in the three participant groups (addressing question 1), as well as the relation between memory for the emotional item and memory for the surrounding information in the background (addressing questions 2 and 3).

METHODS

PARTICIPANTS

Eighty-six individuals were recruited via postings on the Internet, throughout the community, and at a local trauma center. Presence of PTSD was determined by diagnosis on the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1995) by a qualified clinician. Trauma exposure was determined by the SCID and according to DSM-IV criteria. Of the 86 individuals recruited for the study, 77 were used in the analysis. Two participants were excluded from analysis because they had high PTSD Checklist and Depression scores although they reported that they had never experienced trauma. Two were excluded due to psychotic disorders and one was excluded for current alcohol dependence. One was excluded for refusing to answer questions on the PTSD portion of the SCID, and three were excluded for failure to complete the second part of the study. Of the remaining 77 participants, 25 met criteria for current PTSD (PTSD group, 8 Males); 27 had undergone trauma but did not meet criteria for current PTSD (Trauma-Exposed group, 14 Males); and 25 neither had experienced significant trauma nor met criteria for current PTSD (Non-Trauma Exposed group, 12 Males; See **Table 1**). In the Non-trauma Exposed Group, there were no comorbidities. None of these 77 participants had a psychotic disorder or current alcohol or substance dependence. The groups did not differ on age or education level (See **Table 2**).

STIMULI

Stimuli consisted of complex visual scenes that were created by placing images of positive, negative and neutral items onto neutral background scenes (see **Figure 1**). The stimulus set included objects and backgrounds used in prior studies (Kensinger et al., 2007a; Waring and Kensinger, 2009; Waring et al., 2010; Steinberger et al., 2011). Composite images were created by placing an item onto a plausible background scene. Care was taken to make sure that positive, negative, and neutral items were of comparable size and were placed in the same approximate location across scenes. Across emotion categories, scenes were also matched for visual complexity, congruency between item and background, and number of people, animals and buildings. Each picture was approximately 10 × 13 in. and 700 × 550 pixels.

Items were 180 nameable, photographic-quality, color images that were taken from photo clip art packages (Hemera Technologies, Quebec, Canada), from the International Affective Picture System (Lang et al., 1999) and from other online databases of images. There were 60 positive images (mean valence = 6.02, SE = 0.81), 60 negative images (mean valence = 3.80, SE = 0.82) and 60 neutral images (mean valence = 5.29, SE = 0.75). Arousal (rated on a five point scale, with low numbers indicating soothing or subduing images and high numbers indicating exciting or agitating images) ratings were as follows: mean (SD): Positive = 3.02 (0.57); Negative = 3.19 (0.66); Neutral = 2.35 (0.61). The positive and negative images were matched on arousal and absolute valence (all $p > 0.30$), and neutral images were considered less arousing than both positive and negative images (all $p < 0.05$).

Stimuli were randomized to create two different study lists with 90 items per list (30 negative, 30 positive and 30 neutral). Those lists were then also presented in reverse order, yielding four total study lists that were counterbalanced across participants. It was never the case that more than three of the same emotion category appeared in a row.

At test, composite scenes from the study sessions were broken down into the isolated item and background components and these two elements were shown independently in the recognition memory test. The recognition memory test was also randomized for a total of four test lists to ensure that there were not effects of placement of a certain picture in context to another picture. These test lists were counterbalanced across participants. In addition, which items and backgrounds were "old" versus "new" were counterbalanced across participants based on the study list that they viewed.

PROCEDURE

Participants first filled out the consent form, a demographics questionnaire, an assessment of their state and trait anxiety [BAI (Beck et al., 1988); STAI-S and STAI-T (Spielberger et al., 1983)] and an assessment of their depressive symptoms (BDI-II; Beck et al., 1961).

Participants then took part in an incidental encoding session. They were told that this first part of the study was designed to measure their reactions to emotional images. During this session, 90 scenes (30 from each emotion category) were shown on a white computer screen for 5 s each. While viewing the scene, participants were asked to rate the valence of the picture on a nine-point scale, nine being the most intensely positive and one being the most intensely negative. After 5 s, a screen appeared that required the participant to press the space bar to move on to the next picture. Each participant completed a short practice version of the task before performing the actual task.

After participants completed the encoding session, a variety of standardized cognitive tasks were administered, creating a retention delay of approximately 45 min: Rey–Osterrieth Complex Figure Test (Rey–O; Rey, 1941; Osterrieth, 1944), Stroop Test (Stroop, 1935), Wechsler Backward Digit Span (Wechsler, 1997), FAS test of verbal fluency (Spreen and Benton, 1977), Shipley Vocabulary (Shipley, 1986), The Wechsler Adult Intelligence Scale Digit Symbol Test (Wechsler, 1997), Short Michigan Alcoholism Screening Test (SMAST, Selzer et al., 1975). At this point participants were also given a 5–10 min break.

During the unanticipated recognition testing phase, participants viewed 90 items and 90 backgrounds extracted separately

Table 1 | Type of trauma and comorbidities for the PTSD and the Trauma-Exposed Groups.

Sex	Trauma	Comorbidity	Past PTSD?
PTSD GROUP			
F	Arrest	None	
F	Captivity	None	
M	Family tragedy	None	
F	Family tragedy	Pho	
F	Family tragedy	None	
F	Family tragedy	None	
F	Physical abuse	None	
M	Physical and psychological abuse	None	
F	Physical and psychological abuse	Epi	
M	Physical and psychological abuse	BPD, BED	
F	Physical and sexual assault	MDD, Pho, OCD	
F	Physical and sexual assault	None	
M	Physical assault	GAD	
M	Physical assault	None	
F	Physical assault	MDD, PD, OCD	
F	Physical, sexual, psychological abuse	None	
F	Physical and psychological abuse	MS, MDD, PD, Pho	
M	Physical and psychological abuse	MDD	
F	Sexual assault	MDD, GAD, BED	
M	Sexual assault	MDD, GAD	
F	Sexual assault	MDD, PD	
F	Sexual assault	Epi, MDD	
F	Sexual assault	None	
M	Sexual assault	MDD	
F	Sexual assault	None	
TRAUMA-EXPOSED GROUP			
M	Arrest	None	No
M	Arrest	GAD	No
M	Captivity	None	Yes
M	Family tragedy	Pho	No
M	Family tragedy	GAD	No
F	Family tragedy	None	No
F	Family tragedy	None	Yes
M	Motor vehicle accident	BPD, Pho, OCD	No
M	Motor vehicle accident	Epi	No
M	Motor vehicle accident	None	No
M	Motor vehicle accident	None	No
F	Motor vehicle accident	None	No
F	Motor vehicle accident	None	Yes
F	Physical and psychological abuse	MDD, Dys	Yes
F	Physical and psychological abuse	Dys	Yes
F	Physical assault	Pho	Yes
M	Physical assault	Pho	Yes
F	Physical assault	PD	Yes
M	Physical assault	None	No
M	Physical assault	BPD	Yes
F	Physical assault	None	Yes
M	Physical assault	GAD	Yes
F	Sexual abuse	None	Yes
F	Sexual abuse, captivity	MDD, Pho	Yes
F	Sexual assault	None	No
M	Witnessed death	Pho, BED	No
F	Witnessed death	Dys	Yes

MDD, major depressive disorder; GAD, generalized anxiety disorder; BED, binge eating disorder; PD, panic disorder; Pho, phobia; OCD, obsessive compulsive disorder; Epi, epilepsy; BPD, bipolar disorder; Alc, alcohol dependence; Dys, dysthymic disorder.

Table 2 | Demographic, cognitive, and psychopathological characteristics of the samples.

	PTSD $N = 25$	Trauma-exposed $N = 27$	Non-trauma-exposed $N = 25$	Statistics
Sex (male/female)	(8/17)	(14/13)	(12/13)	$\chi^2(1) = 1.05$, ns
Age	39.68 (14.28)	42.0 (15.22)	36.2 (15.11)	$F_{(2,74)} = 0.99$, ns
Years of education	14.52 (3.12)	14.44 (2.38)	14.84 (2.51)	$F_{(2,74)} = 0.16$, ns
Age of trauma	20.76 (12.99)	26.0 (13.99)	n/a	$t_{(47)} = 1.36$, ns
Years since trauma	17.04 (14.4)	16.0 (13.53)	n/a	$t_{(47)} = 0.26$, ns
PCL	55.78 (13.04)	36.74 (13.62)	21.88 (6.27)	$F_{(2,74)} = 54.27$, $p < 0.001$
BDI	20.24 (10.61)	11.89 (8.34)	4.32 (4.67)	$F_{(2,74)} = 23.32$, $p < 0.001$
BAI	28.24 (10.72)	18.78 (14.39)	6.92 (7.6)	$F_{(2,74)} = 22.17$, $p < 0.001$
STAI-T	53.26 (10.83)	42.33 (10.21)	31.56 (7.02)	$F_{(2,74)} = 32.49$, $p < 0.001$
STAI-S	43.56 (11.78)	37.93 (12.84)	29.36 (8.37)	$F_{(2,74)} = 10.18$, $p < 0.001$
FAS	45.28 (10.83)	39.59 (12.64)	44.48 (11.69)	$F_{(2,74)} = 1.80$, ns
FAS perseverations	0.92 (1.29)	1.56 (2.98)	1.56 (1.78)	$F_{(2,74)} = 0.73$, ns
Stroop_word	96.4 (23.2)	97.07 (18.32)	100.8 (17.13)	$F_{(2,74)} = 0.37$, ns
Stroop_X	68.88 (17.0)	65.7 (12.76)	72.72 (12.96)	$F_{(2,74)} = 1.56$, ns
Stroop_color	43.04 (14.46)	38.81 (9.34)	48.68 (7.92)	$F_{(2,74)} = 5.39$, $p < 0.01$
Stroop_interference	102.44 (10.29)	99.76 (7.72)	106.67 (6.73)	$F_{(2,73)} = 4.51$, $p < 0.05$
Digit symbol	36.16 (10.96)	34.15 (8.09)	40.52 (8.45)	$F_{(2,74)} = 3.21$, $p < 0.05$
Digit span backward	7.24 (2.83)	6.26 (2.19)	8.44 (2.77)	$F_{(2,74)} = 4.56$, $p < 0.05$
Shipley	31.04 (7.07)	28.33 (7.06)	31.68 (4.61)	$F_{(2,74)} = 2.04$, ns
Rey–O copy	34.4 (3.65)	33.56 (3.03)	34.64 (3.17)	$F_{(2,74)} = 0.79$, ns
Rey–O immediate	20.78 (7.09)	17.33 (6.3)	20.8 (9.21)	$F_{(2,74)} = 1.81$, ns
Rey–O delayed	21.54 (6.55)	16.35 (6.5)	21.38 (9.39)	$F_{(2,74)} = 3.99$, $p < 0.05$
Rey–O recognition	19.92 (1.74)	19.07 (1.75)	20.04 (2.03)	$F_{(2,73)} = 2.12$, ns
SMAST	1.84 (2.51)	1.74 (2.6)	0.56 (1.12)	$F_{(2,74)} = 2.66$, ns
CAPS frequency	1.34 (1.25)	0.74 (1.29)	n/a	$t_{(43)} = 1.59$, ns
CAPS intensity	2.0 (1.8)	0.86 (1.55)	n/a	$t_{(42)} = 2.24$, $p < 0.05$

ns, not significant; M (SD).

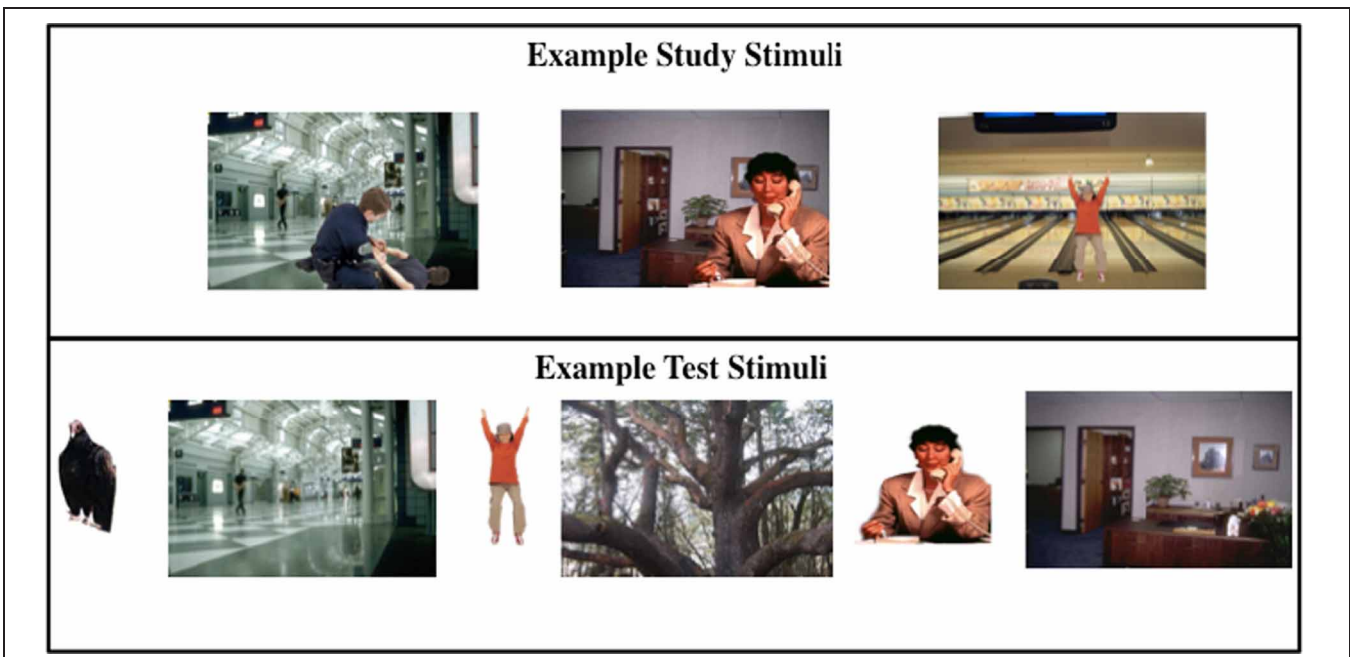

FIGURE 1 | Example stimuli from the study and test session.

from the studied composite scenes (30 from each emotion category), as well as 90 new items (30 from each emotion category) and 90 new backgrounds (note that all new backgrounds were by definition neutral; for the studied backgrounds, the emotionality was defined by the type of item that had been placed onto the background). For each item or background, participants were asked to indicate whether they believed the picture was new, whether they "remembered" it (recollected specific details of its presentation during the encoding session) or "knew" it (felt a sense of familiarity with the picture, without remembering details from the encoding session). Participants underwent an extensive practice and instruction phase to ensure their understanding of remember versus know ratings. This test was self-paced and the next picture appeared after participants made their response. There were no group differences in reaction time for the test responses.

After the test phase, participants were asked to fill out the PTSD checklist (PCL; Weathers et al., 1993) and the Life Events Checklist (Gray et al., 2004). For the PTSD and the Trauma-exposed groups, the presence of PTSD, as well as other comorbid disorders, was assessed using the SCID in a separate session. The severity of memory problems surrounding the trauma was also assessed using selected questions from the clinician-administered PTSD scale (CAPS).

DATA ANALYSIS

For all of the results presented here, "remember" and "know" responses were collapsed into all "old" responses (When the "remember" and "know" responses were analyzed separately, no main effect of group or interactions with group were found).

For behavioral memory data, corrected memory scores are first reported. For these corrected scores, the proportion of false alarms (new pictures that were incorrectly cited as being old) were subtracted from the proportion of hits (pictures that were correctly recognized as being old) in order to correct for a response bias to call a picture "old." These corrected recognition scores were computed separately for each item type (positive, negative, neutral) and for backgrounds. Note that only one false alarm rate could be ascertained for backgrounds: by definition new backgrounds are neutral because the emotionality of a background relates to the type of item with which it had been studied. In later analyses, the hit rates and false alarm rates were analyzed separately, to clarify whether differences in corrected recognition stemmed from differences in the hit rate or the false alarm rate.

Analyses of covariance (ANCOVAs) were run in order to compare the memory based on valence and group while controlling for scores on the Beck Depression Inventory (BDI) and Rey–O Complex Figure Test Delayed. A Bonferroni correction was used for the estimated marginal means in the *post hoc* tests. These scores were used as covariates because there were significant group differences in mood and in cognition. Because the various mood measures were intercorrelated, as were the various cognitive measures, we selected the BDI and Rey–O tasks as the covariates because we felt that they were the most representative of the co-morbidities and visuo-spatial cognitive abilities for which we should control.

RESULTS

PARTICIPANT DEMOGRAPHICS AND COGNITIVE TEST SCORES

Groups did not differ on any socio-demographic level (see **Table 2**). However, the groups did differ significantly on the scales measuring the severity of PTSD [PCL; ($F_{(2, 74)} = 54.27$, $p < 0.001$)], level of depression [BDI-II ($F_{(2, 74)} = 23.32$, $p < 0.001$)], and level of anxiety [BAI ($F_{(2, 74)} = 22.17$, $p < 0.001$); STAI-T ($F_{(2, 74)} = 32.49$, $p < 0.001$); STAI-S ($F_{(2, 74)} = 10.18$, $p < 0.001$)]. The groups also differed significantly on several cognitive tasks: Stroop Color [$F_{(2, 74)} = 5.39$, $p < 0.01$]; Stroop Interference [$F_{(2, 73)} = 4.51$, $p < 0.05$]; Digit-Symbol [$F_{(2, 74)} = 3.21$, $p < 0.05$]; Digit Span Backwards [$F_{(2, 74)} = 4.56$, $p < 0.05$]; Rey–O delayed [$F_{(2, 74)} = 3.99$, $p < 0.05$].

There also were some significant sex differences. Overall, males had higher Shipley vocabulary scores, [$t_{(71.7)} = 2.011$, $p < 0.05$], than females. Males were also older ("Age") at the time of test than females, [$t_{(75)} = 2.29$, $p < 0.05$], and had a higher age of trauma, [$t_{(27.1)} = 2.09$, $p < 0.05$], than females. Overall, females had higher Beck Anxiety scores, [$t_{(75)} = 3.06$, $p < 0.01$], than males. Females also scored higher than males on both the Rey–O Immediate, [$t_{(75)} = 2.56$, $p < 0.05$], and the Rey–O Delayed, [$t_{(75)} = 2.59$, $p < 0.05$], visual memory tasks.

PICTURE RATINGS

An analysis was conducted on the picture ratings at encoding in order to make sure that there were not differences in the way that the pictures were rated by the three different groups. These ratings were made on a nine-point scale, one being intensely negative and nine being intensely positive. A valence (positive, negative, neutral images) × group (PTSD, Trauma-Exposed, Non-Trauma Exposed) ANOVA was conducted. This analysis revealed a main effect of valence on the ratings, [$F_{(2, 74)} = 148.82$, $p < 0.001$], but no group effect or valence × group interactions (all $F < 1.0$, $p > 0.45$). As expected, all valence types differed significantly from each other: positive greater than negative, [$t_{(76)} = 13.93$, $p < 0.001$]; positive greater than neutral, [$t_{(76)} = 9.80$, $p < 0.001$]; neutral greater than negative, [$t_{(76)} = 10.57$, $p < 0.001$]. Arousal scores for each participant were calculated as the mean absolute distance from the neutral rating of five. An arousal (positive, negative, neutral images) × group (PTSD, Trauma-Exposed, Non-Trauma Exposed) ANOVA was also conducted. This analysis revealed a main effect of arousal on the ratings, [$F_{(2, 74)} = 10.34$, $p < 0.001$], but no group effect or arousal × group interactions (all $F < 1.0$, $p > 0.50$). As expected, neutral images were less arousing than both positive images, [$t_{(76)} = 6.74$, $p < 0.001$], and negative images, [$t_{(76)} = 2.93$, $p < 0.01$]; there was no significant difference in arousal between positive and negative images, [$t_{(76)} = 1.12$, $p > 0.25$].

EMOTION-INDUCED MEMORY TRADE-OFF SCORE

The memory data were first analyzed to determine the difference in memory for emotional items and backgrounds as compared to neutral. The emotion-induced memory trade-off has been defined as the combined increase in memory for emotional items as compared to neutral items and decrease in memory for backgrounds accompanying emotional items compared to neutral items. Thus, to calculate a memory trade-off score, corrected

recognition scores (hits—false alarms) for neutral items were subtracted from corrected recognition scores for positive or negative items, and corrected recognition scores for backgrounds paired with neutral items were subtracted from corrected recognition scores for backgrounds paired with positive or negative backgrounds (see Leclerc and Kensinger, 2008; Waring and Kensinger, 2009, for use of these types of difference scores).

To then calculate the magnitude of the trade-off effect (e.g., the discrepancy between item and background memory), these corrected scores for the backgrounds were subtracted from the corrected scores for the items. The overall formula was: (memory for emotional item–memory for neutral item)—(memory for background paired with emotional item–memory for background paired with neutral item). Thus, the largest trade-off occurs when there is both better memory for the emotional item and worse memory for the accompanying background as compared to neutral.

For the analyses using this memory trade-off score, a Group (PTSD, Trauma, Non-Trauma) × Valence (positive, negative) ANCOVA was conducted with the Beck Depression Inventory and Rey–O Complex Figure Test Delayed score used as covariates. The pattern of results remained the same when no covariates were used or when other mood and cognitive scores were used as covariates. This ANCOVA revealed a main effect of group [$F_{(2, 72)} = 4.48$, $p < 0.05$, PES $= 0.111$; see **Figure 2**]. As indicated by Bonferroni *post hoc* tests and adjusted marginal means, for both positive and negative items there was a smaller trade-off score for the trauma group (mean $= 0.10$, SE $= 0.03$) as compared to the PTSD group (mean $= 0.23$, SE $= 0.04$), and a marginally smaller trade-off for the trauma group as compared to the Non-trauma group (mean $= 0.20$, SE $= 0.04$). There was not a significant difference between trade-off scores for positive or negative scenes and there were no interactions (all $F < 0.5$, $p > 0.4$). There were also no interactions with any of the covariates.

To confirm that depression was not driving this group difference, a multiple regression was conducted with the emotional trade-off score as the dependent measure and the predictors as PTSD Group, Trauma Group (both dummy coded), and depression. The model was significant overall [$F_{(3, 76)} = 3.886$, $p < 0.05$]. The analysis revealed only a main effect of the Trauma Group ($\beta = 0.314$, $t = 2.32$, $p = 0.02$), suggesting that the trauma group, and not depression, was the significant predictor of the trade-off score.

MEMORY ANALYSES BY COMPONENT

In order to investigate the basis for this difference in the memory trade-off score, we next conducted an analysis of corrected recognition scores that considered all scene valences and scene component types separately. This was a Type (item, background) × Valence (positive, negative, neutral) × Group (PTSD, Trauma, Non-Trauma) ANCOVA with the Beck Depression Inventory and Rey–O Complex Figure Test Delayed score used as covariates (see **Figure 3**). This analysis revealed a main effect of type [$F_{(1, 72)} = 25.66$, $p < 0.001$, PES $= 0.263$]. This main effect was qualified by a type × valence interaction [$F_{(2, 72)} = 4.80$, $p < 0.05$; PES $= 0.063$], and a marginal type × valence × group interaction [$F_{(2, 72)} = 2.25$, $p < 0.07$; PES $= 0.059$]. This marginal three-way interaction remained present when other mood and cognitive scores were used as covariates, and it reached significance ($p < 0.05$) when no covariates were used. As indicated by the Bonferroni *post hoc* tests, the PTSD group and the Non-trauma Exposed group showed a similar pattern of results such that there was better memory for items than backgrounds for positive and negative pictures, while there was not a significant item-background discrepancy for neutral pictures. In contrast, the Trauma group exhibited a significant difference in memory for items as compared to backgrounds for positive, negative, *and* neutral pictures. When comparing each

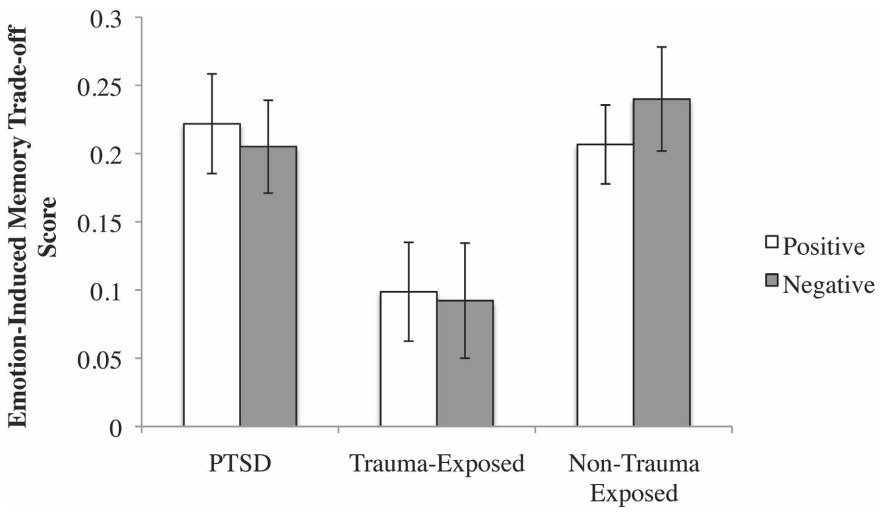

FIGURE 2 | The emotion-induced memory trade-off score ([memory for emotional item–memory for neutral item]—[memory for background paired with emotional item–memory for background paired with neutral item]) for the three groups. White bars indicate memory for scenes that included positive (pleasant) items. Gray bars indicate memory for scenes that included negative (unpleasant) items. There was a larger memory trade-off for both the PTSD and the Non-Trauma Exposed group as compared to the Trauma-Exposed group.

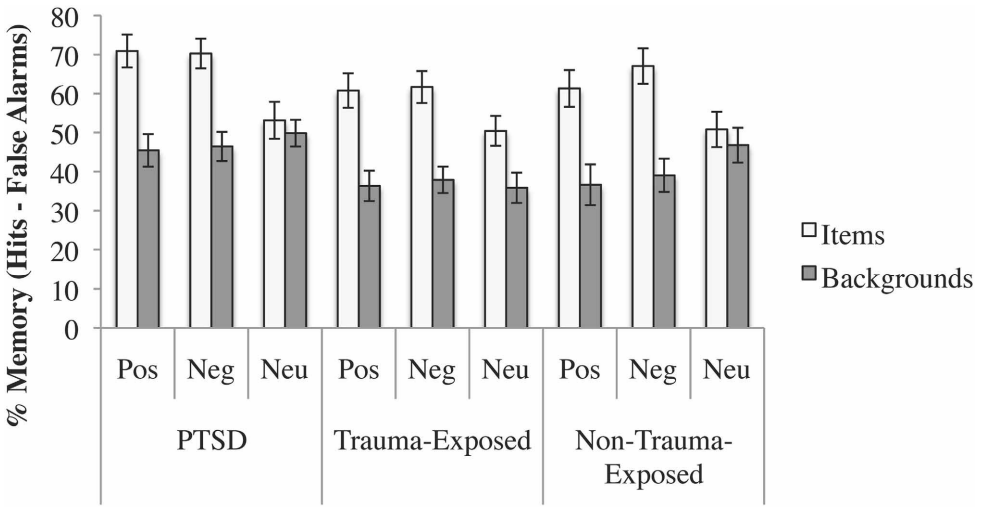

FIGURE 3 | Item and background memory for scenes that included a positive, negative, or neutral item.

valence there were no group differences in item memory. There was only one group difference in background memory, with better memory in the PTSD group and the Non-trauma Exposed group as compared to the Trauma group for backgrounds that had been paired with neutral items (see **Figure 3**). There were no interactions with any of the covariates.

In order to make sure that the pattern of results for the Trauma group were not driven by the presence of a prior history of PTSD, two subsequent Type (item, background) × Valence (positive, negative, neutral) ANCOVAs were run with just the participants in the Trauma group. These analyses also included the Beck Depression Inventory and Rey–O Complex Figure Test Delayed score as covariates. The first analysis included only those who previously had PTSD ($N = 14$). This analysis revealed no main effects or interactions (all $F < 1.4$, $p > 0.2$). The second analysis included those who never had PTSD ($N = 13$). This analysis revealed only a main effect of type [$F_{(1, 10)} = 5.17$, $p < 0.05$, PES $= 0.341$] such that there was greater item memory than background memory. Critically, there was no valence × type interaction for either group. Similarly, when past PTSD was run as a between subjects factor in a valence × type × past PTSD ANCOVA, there were no interactions with past PTSD (all $F < 1.2$, $p > 0.2$) and no interaction between valence and item type ($F < 0.25$, $p > 0.6$); the only significant effect was that of type [$F_{(1, 23)} = 6.924$, $p < 0.05$, PES $= 0.231$].

The prior analyses were run with the corrected memory data (hits—false alarms). However, hits and false alarms are listed separately in **Table 3**. When a Type (item, background) × Valence (positive, negative, neutral) × Group (PTSD, Trauma, Non-trauma) ANCOVA (with the Beck Depression Inventory and Rey–O Complex Figure Test Delayed score used as covariates) was run on the hit rates, there was the same pattern as when the corrected scores were used: a main effect of type [$F_{(1, 72)} = 37.19$, $p < 0.001$, PES $= 0.107$] qualified by a type × valence interaction [$F_{(2, 72)} = 8.67$, $p < 0.001$; PES $= 0.063$], and a type × valence × group interaction [$F_{(2, 72)} = 2.80$, $p < 0.05$; PES $= 0.072$]. When this ANCOVA was run for the false alarms, there was only a marginal effect of group [$F_{(2, 72)} = 2.76$, $p < 0.07$; PES $= 0.072$] such that there were fewer false alarms for the PTSD group than for the trauma-exposed and non-trauma exposed groups.

DISCUSSION

The current study sought to examine changes in memory for emotional information in individuals who currently meet diagnostic criteria for PTSD and trauma-exposed individuals who do not currently have PTSD. Looking at both item and background memory in the emotion-induced memory trade-off paradigm, this investigation focused on three central questions: (1) What is the effect of PTSD on memory for positive, negative, and neutral items? (2) What is the effect of PTSD on the emotion-induced memory trade-off? (3) What is the effect of trauma-exposure on the emotion-induced memory trade-off? First, we found that there are no group differences in memory for emotional items. For all groups emotional items (positive and negative) are better remembered than neutral items. Second, we found that people with PTSD did not have a larger memory trade-off when compared with control participants who had not experienced trauma; however, people with PTSD did have a larger memory trade-off when compared to trauma-exposed controls. A closer examination of the differences in item and background memory revealed that while the PTSD and non-trauma exposed control group had significant differences in item memory as compared to background memory for emotional items, there was no difference between item and background memory for neutral items. The decreased memory trade-off in the trauma-exposed controls was driven by a significant item-background difference between both the emotional and the neutral items. Thus, in answer to the third question, trauma exposure in the absence of PTSD does seem to change the memory trade-off, resulting in a mnemonic focus on the item within a scene regardless of whether that item is emotional or neutral. We expand on each of these points below.

Table 3 | Hits and false alarms for item and background memory for each group and each valence.

		Group	Mean	SD
ITEMS				
Hits	Positive	PTSD	0.79	0.19
		Trauma-exposed	0.78	0.18
		Non-trauma-exposed	0.79	0.17
	Negative	PTSD	0.80	0.17
		Trauma-exposed	0.81	0.16
		Non-trauma-exposed	0.82	0.16
	Neutral	PTSD	0.61	0.22
		Trauma-exposed	0.66	0.22
		Non-trauma-exposed	0.65	0.21
False alarms	Positive	PTSD	0.08	0.09
		Trauma-exposed	0.17	0.17
		Non-trauma-exposed	0.18	0.22
	Negative	PTSD	0.10	0.11
		Trauma-exposed	0.20	0.18
		Non-trauma-exposed	0.15	0.21
	Neutral	PTSD	0.08	0.08
		Trauma-exposed	0.16	0.18
		Non-trauma-exposed	0.14	0.20
BACKGROUNDS				
Hits	Positive	PTSD	0.58	0.21
		Trauma-exposed	0.58	0.23
		Non-trauma-exposed	0.55	0.23
	Negative	PTSD	0.59	0.19
		Trauma-exposed	0.60	0.21
		Non-trauma-exposed	0.58	0.19
	Neutral	PTSD	0.62	0.19
		Trauma-exposed	0.58	0.24
		Non-trauma-exposed	0.66	0.20
False alarms	Positive	PTSD	0.12	0.10
		Trauma-exposed	0.22	0.19
		Non-trauma-exposed	0.19	0.21
	Negative	PTSD	0.12	0.10
		Trauma-exposed	0.22	0.19
		Non-trauma-exposed	0.19	0.21
	Neutral	PTSD	0.12	0.10
		Trauma-exposed	0.22	0.19
		Non-trauma-exposed	0.19	0.21

WHAT IS THE EFFECT OF PTSD ON MEMORY FOR POSITIVE, NEGATIVE, AND NEUTRAL ITEMS?

There were not significant item memory differences between groups. All groups remembered positive and negative items better than neutral items. The current study found no evidence that PTSD patients remember non-trauma-related negative items particularly well or that they remember positive items particularly poorly. This suggests that for individuals with PTSD, though the memory for information related to the trauma may be enhanced, this does not translate to differences in the general emotion-memory system.

The results revealed no evidence of an effect of PTSD on the bias to endorse emotional items as studied: the item recognition performance of the PTSD group remained similar to the performance of the other groups even when recognition responses were corrected for incorrect endorsements of unstudied items, and if anything the PTSD group showed *lower* false alarm rates than the other participant groups. Although at least one study found that PTSD may lead to an enhanced response bias for negative information when verbal stimuli are used (Thomaes et al., 2011), this biasing effect has not been found in other studies using verbal stimuli (Thomaes et al., 2009; Tapia et al., 2012). The few studies that have assessed recognition memory using non-traumatic pictorial stimuli have not reported hits and false alarms separately (Dickie et al., 2008; Brohawn et al., 2010), but the present results suggest that PTSD does not always lead to a more liberal response bias for negative stimuli.

WHAT IS THE EFFECT OF PTSD ON THE EMOTION-INDUCED MEMORY TRADE-OFF?

The memory trade-off exhibited in PTSD patients did not differ in magnitude from the trade-off exhibited by the control participants who had never experienced trauma. Thus, in some ways, the memory pattern that the PTSD patients experienced in this study can be considered "normal," because, just as in the Control group, background memory was traded in favor of item memory only when an emotional item was present and not when a neutral item was present. As mentioned previously, memories of trauma in individuals with PTSD have been described as possessing "tunnel memory." However, it is still unknown if this effect is enhanced in individuals with PTSD as compared to those without PTSD. The current study cannot speak to "tunnel memory" in the trauma memory. However, the current data suggest that non-trauma memories are not remembered in a unique manner for individuals with PTSD. Though they do exhibit a "tunnel memory" of sorts (e.g., worse memory for backgrounds that are paired with emotional information than neutral information), this is not uniquely exaggerated in PTSD. By contrast, and as we will elaborate upon next, the trauma-exposed individuals without current PTSD consistently showed selective item memory, regardless of the emotionality of the item.

It will be interesting for future studies to examine whether a different pattern is revealed when verbal stimuli are used rather than visual stimuli. Prior studies have shown that participants are more likely to remember neutral words from sentences that include an emotional word as opposed to those same words from sentences that contain only neutral words (Kensinger et al., 2002; Medford et al., 2005). Thus, it seems that control participants process the sentence as one entity (rather than as the discrete words that make up the sentence) and thus show a memory benefit for all words within an emotional sentence rather than showing a trade-off. It would be interesting for future research to examine whether PTSD patients would show a memory pattern like control participants or instead would show a trade-off even for these sentence stimuli.

WHAT IS THE EFFECT OF TRAUMA-EXPOSURE IN INDIVIDUALS WITHOUT PTSD ON THE EMOTION-INDUCED MEMORY TRADE-OFF?

Our data suggest that the trauma-exposed group stands apart from the other groups tested, in that these individuals remember

both emotional and neutral items better than their backgrounds. This effect could either be seen as a positive coping mechanism or a negative reaction to stress. Because the trauma-exposed group had a discrepancy in item and background memory for both emotional and neutral information, this may indicate that emotional and neutral stimuli are processed in a similar manner. Perhaps participants who were exposed to trauma but do not currently have PTSD have managed to avoid developing PTSD or were able to recover from it because of an ability to process emotional events in a similar fashion as processing neutral information. On the other hand, this exaggerated trade-off may mirror the effects of stress on memory for contextual information. There is evidence that individuals who are under stress at the time of encoding (via the Trier Social Stress Test manipulation; Kirschbaum et al., 1993) trade off background memory in favor of item memory for neutral as well as emotional scenes (Mattingly et al., 2012). Further, individuals who are stressed exhibit increased amygdala activity for both high and low arousal information (Marle et al., 2009), suggesting that stressed individuals enter a state of "indiscriminate hypervigilance." Although the trauma-exposed individuals did not report higher state anxiety or rate the scenes differently than the other groups, it is nevertheless possible that they have more global changes in scene processing, such as seen under these stress manipulations, which lead them to exhibit a more focused attentional and mnemonic pattern for both emotional and neutral scenes. In addition, because both of these groups had trauma-exposure, this effect is specific to those who had experienced trauma and do not currently have PTSD. Though it is difficult to know from the current study how the presence of trauma with and without PTSD may change emotional processing, it may be that the PTSD group would be more likely to focus the stress response particularly on their traumatic experience as opposed to a more diffuse focus in the trauma-exposed group. In other words, perhaps those who both have experienced stress/trauma and who have PTSD would mostly show narrowed focus for things related to their trauma specifically, whereas those with stress/trauma but without current PTSD may more generally show a narrowed focus, even to neutral stimuli.

One thing of note is that the trauma-exposed group is impaired on many of the cognitive tests. This could suggest that these individuals' attention is more narrowed—regardless of valence—due to limited processing capacity. However, older adults, who have more limited processing capacities than young adults, still show the memory trade-off (Kensinger et al., 2007b; Waring and Kensinger, 2011). In addition, in the current study, lower performance on cognitive tests did not relate to the magnitude of the memory trade-off, and when the cognitive tests were used as covariates, there were no interactions with the covariates. Thus, it is likely not solely a deficit in cognitive capacity which leads to the selective retention of all items (emotional or neutral) in this trauma-exposed group.

SUMMARY OF FINDINGS

The current study provides insight into the pattern of emotional memory in individuals with PTSD and in those who have experienced trauma but do not have PTSD. When only emotional items are considered, there is no difference between any of the groups. Across the board, emotional items (positive and negative) are better remembered than neutral ones. The PTSD group showed no difference in the emotional memory trade-off when compared to the non-trauma-exposed control group. However, the PTSD group did show a larger emotional memory trade-off than the trauma-exposed individuals. The trauma-exposed individuals showed a pattern distinct from the other groups, in that they traded background memory in favor of item memory for all item types, emotional and neutral. This pattern of results suggests that the memory trade-off may be differentially exhibited depending on both the experience of trauma and the presence of PTSD.

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Cognition-emotion dysinteraction in schizophrenia

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Evolving theories of schizophrenia emphasize a "disconnection" in distributed fronto-striatal-limbic neural systems, which may give rise to breakdowns in cognition and emotional function. We discuss these diverse domains of function from the perspective of disrupted neural circuits involved in "cold" cognitive vs. "hot" affective operations and the interplay between these processes. We focus on three research areas that highlight cognition-emotion *dysinteractions* in schizophrenia: First, we discuss the role of cognitive deficits in the "maintenance" of emotional information. We review recent evidence suggesting that motivational abnormalities in schizophrenia may in part arise due to a disrupted ability to "maintain" affective information over time. Here, dysfunction in a prototypical "cold" cognitive operation may result in "affective" deficits in schizophrenia. Second, we discuss abnormalities in the detection and ascription of salience, manifest as excessive processing of non-emotional stimuli and inappropriate distractibility. We review emerging evidence suggesting deficits in some, but not other, specific emotional processes in schizophrenia – namely an intact ability to perceive emotion "in-the-moment" but poor prospective valuation of stimuli and heightened reactivity to stimuli that ought to be filtered. Third, we discuss abnormalities in learning mechanisms that may give rise to delusions, the fixed, false, and often emotionally charged beliefs that accompany psychosis. We highlight the role of affect in aberrant belief formation, mostly ignored by current theoretical models. Together, we attempt to provide a consilient overview for how breakdowns in neural systems underlying affect and cognition in psychosis interact across symptom domains. We conclude with a brief treatment of the neurobiology of schizophrenia and the need to close our explanatory gap between cellular-level hypotheses and complex behavioral symptoms observed in this illness.

Keywords: schizophrenia, emotion, cognition, working memory, delusions, fronto-striatal circuits, amygdala, cortical disinhibition

INTRODUCTION

Schizophrenia is perhaps one of the most complex neuropsychiatric illnesses (Walker et al., 2004) with a remarkably heterogeneous presentation (Peralta and Cuesta, 2001; Dutta et al., 2007). After more than 100 years of continuous research effort (Insel, 2010), it largely remains a puzzle and presents a major challenge for clinical neuroscience (Ross et al., 2006; Heckers and Konradi, 2010). Patients suffering from schizophrenia face a lifetime of disability across virtually all known higher cognitive functions (Reichenberg and Harvey, 2007) and specific affective processes (Aleman and Kahn, 2005; Kring and Moran, 2008) vital to social interaction (Ochsner, 2008), vocational function, and overall life outcome (Kee et al., 2003; Green, 2006). The earliest conceptualizations of schizophrenia emphasized fragmented thinking exhibited by patients and a "disconnect" between affective and cognitive functions (Bleuler, 1911). Modern diagnostic classifications typically conceptualize schizophrenia as a complex dimensional syndrome (Barch and Keefe, 2010) thought to arise from disturbances in distinct, but interacting neurotransmitter systems such as gamma-aminobutyric acid (GABA), glutamate, and dopamine (Krystal et al., 2003; Goldman-Rakic et al., 2004; Lewis and Hashimoto, 2007; Lewis et al., 2012), which compromise the function of distributed brain networks (Stephan et al., 2006). Dysregulation in such distributed neural systems is thought to give rise to diverse symptoms such as disturbances in perception (hallucinations), belief (delusions), emotional dysfunction (amotivation and anhedonia), as well as severe deficits in complex cognitive operations such as working memory, long-term memory, and executive functioning (Barch and Ceaser, 2012). Perhaps what is so puzzling about schizophrenia is that it affects broad and seemingly independent functions, producing neurocognitive disturbances that are far outside the realm of normal human experience (e.g., severe delusions). However, conceptualizing these emergent behavioral phenomena as "separate" often ignores how they may actually interact – a dichotomy particularly obvious in research on affect and cognition (Pessoa, 2008). Although we base our clinical diagnosis on the overt behavioral deficits in these seemingly "independent" processes, we have a growing understanding that the human brain is not simply carved into modules that give rise to "emotional" vs. "cognitive" deficits in mental illness (Pessoa, 2008), as might be argued by lesion accounts. Thus, examining how these vital and complementary processes interact is critical for

our complete characterization of the emerging symptom profile in schizophrenia.

Only in recent decades has our understanding of basic brain function evolved to elucidate the critical interplay of brain computations involved in "hot" affective processes (e.g., fear) and traditionally "cold" cognition (e.g., reasoning; Dolcos et al., 2004). That is, if we step beyond the study of mental illness, there is a long tradition in cognitive science largely devoid of any consideration for the role of affect (e.g., decades of research in memory, Tulving, 1972). Similarly, affective science has evolved in parallel, without a full integration into the emerging framework of cognitive science, until recently through the development of fields such as social, cognitive, and affective neuroscience. However, our academic divisions in research and the clinic do not always accurately cleave nature at its joints. Indeed, it has become widely accepted that brain regions involved in performing computations in the service of emotional and cognitive functions may be in a constant state of interaction depending on ongoing environmental and organismal demands (Pessoa, 2008). For instance, we now know that computations in the brain that give rise to fear responses are critically interwoven in the formation of memories (LeDoux, 2000).

Before we continue, we will briefly articulate some basic concepts and terminology that we will employ throughout the review. We will discuss findings related to the interaction of two traditionally independent, broad domains of function: emotion and cognition. Therefore it is important to briefly examine what we mean by "cognition" and "emotion." Cognition typically refers to an ensemble of complex higher-level functions that are implemented across distributed brain networks involving mainly cortical regions; these include memory (Tulving, 1972), attention (Posner and Petersen, 1990), language (Petersen et al., 1990), and cognitive control (Miller and Cohen, 2001; Miller and D'Esposito, 2005). These higher-order functions are typically considered to be largely under volitional conscious control and are invoked in the service of some action or goal (Miller and Cohen, 2001; Miller and D'Esposito, 2005; Braver, 2012). On the other hand, it has been difficult to reach a universal consensus regarding the true definition of "emotion" (Lang, 2010) as this domain of function encompasses more elusive and diverse processes (reviewed in more detail below) taking place at vastly different temporal scales (Phillips, 2003; Phillips et al., 2003; e.g., from millisecond perception of fear-inducing stimuli to year-long mood states). Despite these challenges, some authors have attempted to define emotion as a set of computations originally implemented to motivate and mobilize action in the service of optimal survival (Lang and Davis, 2006; Lang, 2010; Lang and Bradley, 2010). From this conceptualization, emotion has been traditionally viewed as a broad set of evolutionary older functions, largely supported by subcortical and limbic structures (LeDoux, 2000), that perform computations mainly in the service of approach (in response to appetitive stimuli) or avoidance (in response to aversive stimuli) dispositions and actions, with more complex elaborations on these basic functions in higher-level organisms. This is not to say that emotion does not involve volitional and more complex processes in humans (e.g., guilt, jealousy, empathy Harvey et al., 2012). Indeed there are remarkable and complex elaborations on these evolutionarily older neural functions in humans (for a more comprehensive theoretical treatment of the functional utility and complexity of human emotion we refer the reader to prior reviews on this topic; Salzman and Fusi, 2010; Niedenthal and Brauer, 2012).

Nonetheless, here we conceptualize both emotion and cognition to represent broad functional domains with specific "sub-processes" implemented by select brain regions and/or networks of brain regions. Thus, it is important to note that it is less likely that there really is an interaction between "domains" of function (as a brain region does not "know" whether a computation being performed is specifically emotional or cognitive in nature), but rather between "sub-processes" (e.g., memory consolidation and detection of fear stimuli) that may be classified into one of these broader domains based on the functions they subserve. Furthermore, even specific "components" of cognition (such as working memory) are likely to encompass a complex interaction of lower-level processes that act in concert to orchestrate a set of computations in support of that aspect of cognition. For instance, computations within regions maintaining fidelity of memory traces, interacting with regions involved in suppressing external interference, could be considered as processes implemented by specific brain areas; however, they could both be considered as components of the general rubric of working memory (Jonides et al., 2008). Henceforth, when discussing processes, we will mainly be referring to a more specific set of computations implemented at the level of brain systems and/or network of regions. In contrast, when referring to domains of function (e.g., emotion and/or cognition or rather broad rubrics of cognition/emotion such as memory or mood) we will be referring to a higher level of analysis, which emerges as a result of the brain implementing and orchestrating specific processes.

Despite the different theoretical and empirical traditions giving rise to "affective" and "cognitive" neuroscience, we cannot continue to de-emphasize how emotion and cognition computations are intricately intertwined (Pessoa, 2008; Pessoa and Adolphs, 2010). For instance, affective information influences neural computations as early as basic visual processing (Bradley et al., 2003; Padmala and Pessoa, 2008). We contend that these interactions are particularly relevant for mental illness, which does not obey our, perhaps arbitrary, way of carving up emotion and cognition. In fact, we argue that serious mental illness such as psychosis involves deficits across both affective and cognitive operations, highlighting the need to understand their interactions not only in healthy human function, but how their breakdowns impact upon one another to affect behavioral deficits observed in mental illness. Nevertheless, despite evidence for severe emotional abnormalities in schizophrenia, research to date has investigated emotion in this illness largely in isolation from cognitive abnormalities (Aleman and Kahn, 2005), and emotional-cognitive interactions have yet to be explored systematically in patients suffering from schizophrenia (Kring, 2011). Of note, throughout the review we will use the term dysinteraction to emphasize that the relationships between cognition and emotion and their disruption in schizophrenia are not simply a unidirectional loss of function in a particular domain, but likely represent a dynamic interplay between functions.

In the present review we discuss three emerging research domains relevant to our understanding of schizophrenia that highlight this critical interplay of affective and cognitive operations and their breakdown. We will approach these topics from an affective

and cognitive neuroscience perspective – that is we will highlight findings at the behavioral level and how they may relate to neural system-level findings that can be assayed with neuroimaging. First, we discuss the role of cognitive deficits and disruptions in neural systems responsible for context maintenance as in part contributing to motivational deficits in schizophrenia. Here we highlight findings suggesting that motivational abnormalities in schizophrenia may arise from the disrupted ability to "maintain" affective context over time to guide behavior. Through this perspective, we offer an example where a prototypical "cold" cognitive operation, namely working memory, may result in "affective" deficits in schizophrenia. Second, we review abnormalities in detection of salience that can manifest as heightened processing of non-emotional stimuli and inappropriate distractibility. Here we discuss emerging affective neuroscience findings in psychosis, which posit deficits in specific emotional processes, but not others – namely intact ability to perceive emotion "in-the-moment" but heightened reactivity to stimuli that ought to be filtered or ignored. Third, we highlight how breakdowns in learning mechanisms give rise to delusions, the fixed, false, and often emotionally charged beliefs that accompany psychosis. We offer an account for the role of affect in aberrant belief formation, mostly ignored by current theoretical models of delusions. Furthermore, we discuss how our continued understanding of schizophrenia and other mental illnesses depends on bridging our basic theoretical advances across affective and cognitive neuroscience to understand and ultimately treat complex neuropsychiatric disease. In turn, we argue that our evolving understanding of mental illness from this multidisciplinary perspective has the potential to cross-fertilize our basic understanding of human brain function. Finally, we will also attempt to link system and symptom-level findings to emerging cellular-level theories of neuropathology in schizophrenia (Krystal et al., 2003; Lewis et al., 2012; Marin, 2012). We argue that linking our cellular-level hypotheses with systems neuroscience findings and ultimately behavior is critical to close the explanatory gap that currently exists between our cognitive neuroscience evidence and hypotheses detailing synaptic pathology in schizophrenia research.

THE ROLE OF WORKING MEMORY IN EMOTIONAL CONTEXT MAINTENANCE

Emotional deficits in schizophrenia are prominent. Since the seminal work of Bleuler (1911) and Kraeplin (1950), affective abnormalities have been considered a central component of schizophrenia symptomatology. However, the precise profile of emotional deficits in schizophrenia is complex. In fact, fully describing the range of affective abnormalities in this illness deserves a comprehensive treatment in itself and is beyond the scope of the present review (see Trémeau, 2006; Kring and Moran, 2008 for detailed discussion). Briefly, there is emerging evidence that patients with schizophrenia exhibit deficits in their expression of emotion (Krause et al., 1989; Berenbaum and Oltmanns, 1992; Kring et al., 1993, 1994; Mattes et al., 1995; Sison et al., 1996; Iwase et al., 1999; Cedro et al., 2001; Trémeau et al., 2005), recognition of emotional facial expressions and emotional classification (Mandal et al., 1998; Habel et al., 2000; Edwards et al., 2002; Kohler et al., 2003; Scholten et al., 2005), as well as anticipating hedonic experience (Gard et al., 2007). While all of these deficits are incapacitating and deserve research attention, here we focus on the third specific area of emotional dysfunction – namely the ability to guide behavior based on anticipated future rewards – a deficit which may, in part, underlie the negative syndrome and anhedonia (Barch and Dowd, 2010). A prominent feature of the negative syndrome in schizophrenia is the lack of motivation and inability to initiate appetitive goal-driven behaviors. Here we argue that this cardinal "emotional" symptom of psychosis can, at least in part, be conceptualized as a breakdown in the interaction of emotion and cognition – specifically as a deficit in representation of emotional context over time.

However, before we continue it is important to highlight one paradoxical finding that needs to be explained in the current framework: patients with schizophrenia seem to exhibit intact "in-the-moment" responses to emotional stimuli (Herbener et al., 2008). That is, when presented with emotionally laden stimuli, patients rate (Herbener et al., 2008; Kring and Moran, 2008), experience (Burbridge and Barch, 2002; Mathews and Barch, 2004), and activate neural structures (such as the amygdala) similarly to healthy controls (Anticevic et al., 2012b,c). This is further highlighted by a recent meta-analysis of the emotional neuroimaging literature in schizophrenia demonstrating little difference in amygdala signals in response to emotional probes relative to healthy controls (Anticevic et al., 2012c; but see a recent meta-analysis for a more extensive examination of other emotional tasks (Taylor et al., 2011)). Consistently, behavioral studies find that when presented with actual physical stimuli, patients tend to rate affective valence and arousal dimensions similarly as healthy controls (Herbener et al., 2008; Anticevic et al., 2012b). For instance, Herbener et al. (2008) asked that both patients diagnosed with schizophrenia and matched healthy controls provide "in-the-moment" ratings of arousal and valence dimensions of complex images that were preselected from the International Affective Picture System (IAPS). This study reported a very similar profile of arousal and valence ratings across both groups of subjects, an effect subsequently replicated in our own work (Anticevic et al., 2012b). These findings highlight that, when an affectively charged stimulus is readily available for sensory processing, the quality and the intensity of the emotional experience in patients seems comparable to that found in healthy populations (although more work is needed to fully rule out experimenter demand characteristics). As noted, this is somewhat paradoxical, because representations of those stimuli seem to break down over time and hence patients may not be able to use the affective information to guide behavior in a goal-directed fashion (Barch and Dowd, 2010).

Consistent with this hypothesis, Heerey and Gold (2007) demonstrated that patients diagnosed with schizophrenia exhibit deficits in their ability to translate subjective emotional experience into motivated behavior, particularly when relying on internal representations. These findings offer one source of support for the notion that motivated reward-driven behavior may be compromised in schizophrenia, even in the face of seemingly intact in-the-moment effects of positive and negative stimuli on behavior. This may occur due to a number of factors, one of which may involve a breakdown in context representations over time. Indeed, this is a thesis proposed by the authors (Heerey and Gold, 2007; p. 269): "Cognitive factors may also undercut the ability to couple

motivational salience and behavior (Barch, 2005). For example, the degree to which an individual can activate a stimulus representation in working memory and use that representation to motivate behavior may prove important in understanding motivational deficits." However, there is an important nuance – Heery and Gold did not observe a significant interaction between *Evoked* vs. *Representational* conditions across patients and control groups, suggesting that there may not be a substantial difference in these two processes. Nevertheless, there was a correspondence between *Representational/Evoked* behavior and emotional ratings, suggesting a larger discrepancy between the *Representational* condition behavior and ratings (as opposed to Evoked). The authors postulate this second effect may imply that (p. 273): ". . .patients have more difficulty generating behavior on the basis of internal representations than in the direct presence of an evocative stimulus." The hypothesis that such affective deficits may be associated with problems in working memory was further bolstered by a significant relationship between both verbal and non-verbal working memory measures and the aforementioned effects. Together, these findings are in line with the proposal that guiding future reward-related actions may be compromised in part due to working memory deficits in schizophrenia.

Building on these insights, consider the following scenario: While patients may report that they enjoy a chocolate cake when they are consuming it, it seems that engaging in behaviors necessary to obtain the experience of the cake are compromised (Kring and Moran, 2008). Planning, purchasing, preparing, or baking the cake requires ongoing maintenance of contextual information regarding the food's rewarding properties, which will ultimately guide the volitional pursuits over time that may lead to such a reward (in this case intake of appetitive food). While it is clear that an intact reward valuation system is necessary for this set of behaviors to take place (O'Doherty et al., 2002; Berridge, 2003, 2004; Barbas, 2007), this function in large part also depends on the intact ability to maintain an appetitive context over time – a process reliant on working memory (Barch et al., 2003) and cognitive control (Barch and Ceaser, 2012). This is where emotion and cognition may "dysinteract" in schizophrenia. This is not to say that deficits are completely absent in basic reward processing in schizophrenia, as evidence suggests this may be the case (Dowd and Barch, 2010; Nielsen et al., 2012). However, such a deficit in basic reward processing may be exacerbated via the inability to actively maintain rewarding information in working memory. In that sense, there may exist a "tension" in the transition from initial learning (perhaps reliant on basic reward processing) and using what is learned to guide complex behavioral routines (perhaps more reliant on working memory) that ultimately may become more ritualized and habitual (and hence freed from working memory demands). Breakdowns in this process have yet to be systematically explored.

There is strong evidence suggesting that patients with schizophrenia exhibit both behavioral and neural deficits in their ability to represent context over time (as demonstrated by findings from continuous performance tasks; Braver et al., 1999) as well as in their working memory operation (Lee and Park, 2005; Van Snellenberg et al., 2006). Some researchers would argue that these cognitive deficits are at the "core" of the illness because they emerge prior to the full syndrome (Cornblatt et al., 1999; Niendam et al., 2003), remain present across the life-span (Heaton et al., 2001; Irani et al., 2011), and are even observed in first-degree relatives of patients (Delawalla et al., 2006). They may pre-date the emotional deficits or perhaps contribute to their emergence. One possibility is that inability to maintain and update information in working memory in the service of guiding goal-directed behavior may in part contribute to and/or interact with motivational problems observed in this illness. In line with this hypothesis, using an elegant design, a recent fMRI study by Ursu and colleagues found an effect consistent with this possibility (Ursu et al., 2011). While in the scanner, Ursu and colleagues exposed subjects to affective or neutral pictures for a brief period followed by a delay interval during which subjects "maintained" the affective state. Following this delay all subjects were instructed to provide ratings of their emotional experience of the previously presented stimulus. Interestingly, during the initial stimulus presentation phase (i.e., while the physical stimulus was presented on screen), patients and healthy comparison subjects showed little difference in neural activity, as revealed by a direct contrast. In fact, both groups activated a distributed network of regions previously associated with processing affective stimuli, including the visual cortex, insula, thalamus, midbrain structures, and other regions (Kober et al., 2008). However, when required to "maintain" the affective content over the delay, individuals with schizophrenia exhibited marked reductions in signal levels across regions previously linked to cognitive control (e.g., dorso-lateral PFC; Wager and Smith, 2003; Owen et al., 2005). The lack of maintenance signals correlated with negative symptom severity in their sample. It is important to note that Ursu and colleagues found an association with negative and not positive stimuli – this limits the generalizability of their findings somewhat. Nevertheless, this general pattern of reduced prefrontal signal in the context of maintaining affective information is in correspondence with a body of evidence showing that schizophrenia is associated with reduced DLPFC signals during cognitive control and working memory tasks (Van Snellenberg et al., 2006). Indeed, in a recent investigation we demonstrated clear loss of prefrontal signal during the delay phase of working memory in a task context devoid of affect (Anticevic et al., 2011a), replicating and extending a large body of evidence suggesting lateral prefrontal abnormalities during working memory in schizophrenia (Glahn et al., 2005). It may be possible that the same deficit in the maintenance of context is at play irrespective of the type of information maintained in working memory. In other words, a deficit in a primarily "cold" cognitive operation may give rise to problems in maintaining affective representations.

If breakdowns in context maintenance indeed produce some affective abnormalities in this illness, then understanding and treating cognitive deficits may in part "rescue" some of the abnormalities we would traditionally consider as purely affective (e.g., lack of motivation). Indeed, there is evidence that suggests that patients with more superior cognitive performance on a working memory task manifest less of a difference between in-the-moment and delayed reports of emotion (Burbridge and Barch, 2002), suggesting that the deficit could be explained, at least to some extent, by breakdowns in cognitive control. However, there are still unresolved questions that future research may need to address:

First, there may be unique deficits in representing and maintaining affective information, stemming from breakdown in initial representations of context and information (e.g., encoding deficits) vs. deficits in representing and shielding such representations over time. In other words, forming accurate internal representations of an appetitive context (e.g., encoding novel stimuli) vs. actually representing and retrieving this context (e.g., maintenance of activity over a delay period) may constitute unique sources of deficits in schizophrenia (Lee and Park, 2005). It remains unclear what aspect of this emotion-cognition "dysinteraction" may be more severe. Recent work in working memory devoid of affect suggests that these abnormalities may be present across both formation and maintenance of active representations (Anticevic et al., 2011a).

Second, to what extent do such deficits in cognitive control, which may in part drive abnormalities in maintenance of emotional context, interact with reward learning mechanism? Patients may exhibit additional disruption in more basic reward processing/learning deficits (Barch and Dowd, 2010; Dowd and Barch, 2010). Together, these abnormalities may combine to exacerbate negative symptoms. In that sense, at the stage of the illness where anhedonia is already severe, we may be observing a confluence of problems in learning the rewarding properties of stimuli and the ability to represent those stimuli in mind over time to drive purposeful goal-driven behavior. We return to this question in more detail in the final section, where we argue that at least some symptoms of psychosis are associated with deficits in learning and interaction of learning mechanisms with affect. Nevertheless, it will be critical to further characterize the interplay and possible breakdown of reward responsiveness, learning, and cognitive control in schizophrenia. One target at the neural system level may be the interplay of prefrontal cortex and the ventral striatum, whose responsiveness to positive stimuli has been linked to levels of anhedonia symptoms in prior research (Dowd and Barch, 2010).

Third, no study has directly and systematically compared both cognitive and affective maintenance deficits in the same sample of patients. Prospective studies may want to examine whether the same pattern of results emerges: that is, are patients with the most severe loss of signal during "cold" cognitive operations such as working memory maintenance also exhibiting the most degradation of signal during maintenance of affective/reward-related representations, and whether this pattern relates to individual differences in symptoms. Similarly, it will be important to determine whether the loss of prefrontal signals during "affective" maintenance is predictive of subsequent behavior. For instance, one could envisage a cognitive-emotional fMRI paradigm that requires a given precision of affective context representation to guide subsequent task performance such as loss or gain of a reward. In doing so, future work could further link the lack of "maintenance" signals following affective/reward cues to deficits in future goal-directed behavior and negative symptoms.

Fourth, future research should also address why such a breakdown may be more manifest for approach-related (i.e., positive) stimuli vs. avoidance-related (i.e., negative) stimuli (Barch and Dowd, 2010). Ursu and colleagues found that the degree of DLPFC signal loss specifically in the positive condition was predictive of negative symptom severity. If the source of the deficit was in cognitive control regions, which may not be specific to any one valence in particular, then the specificity of the breakdown in reward-related behavior (rather than defensive ones) needs to be explained and linked to possible striatal deficits. Perhaps, as Ursu and colleagues argue, converting active affective representations into motivated behavioral pursuits requires a different dynamic interplay between PFC and reward-related neural circuits (e.g., ventral striatum and orbitofrontal cortex). Future studies should further elucidate these possibilities using convergent task-based activation and functional connectivity methods that probe disruptions in distributed fronto-striatal circuits as a function of valence.

Fifth, prior work suggests that some of the observed differences in reward responsiveness and representation are related to individual differences in symptom severity (Dowd and Barch, 2010; Ursu et al., 2011; Nielsen et al., 2012). These findings highlight that observed deficits may not constitute a stable trait of the schizophrenia "diagnosis," but instead suggest that the level of the state (i.e., negative symptoms) may be related to the severity of regional disturbance and the dysinteraction between the aforementioned distributed prefrontal-striatal systems. Given this clinical heterogeneity, we suggest that emotion-cognition dysinteraction in this case may arise due to inadequate striatal reward representation and/or abnormal context representation in areas such as DLPFC. That is, these may be dissociable processes, at least to a certain extent. One way to test this possibility is to examine both striatal and cortical function across reward and executive tasks in the same well-powered sample. Indeed, as suggested by Dowd and Barch (2010), it will be critical for future studies to employ adequately powered samples to take into account possible individual differences. The importance of such a "dimensional" approach is further highlighted by recent National Institute of Mental Health efforts to link severity of system-level disturbances to emergent behavioral symptoms and underlying genetic risks (Insel and Cuthbert, 2009; Insel, 2010).

Finally, it remains to be determined whether the same hypothesized underlying neurotransmitter and cellular-level neuropathology is indeed producing deficits observed in the maintenance of "affective" vs. "cold" representations over time. There is evidence for striatal dysfunction in schizophrenia contributing to reward representation abnormalities, which may in part be driven by dopaminergic disruption (Laruelle et al., 1995, 1999). In turn, cognitive control deficits in schizophrenia are also associated with dopamine imbalance (Abi-Dargham et al., 2002), but may also arise due to NMDA and/or GABA pathology (Krystal et al., 2003; Lewis et al., 2012). Future work will need to characterize the role of complex system-level neurotransmitter interactions in these co-occurring processes. One technique that may help us understand the source of these neurochemical deficits mechanistically involves pharmacological manipulations in healthy adults (Krystal et al., 1994). These manipulations impact upon different neurotransmitter systems thought to be implicated in cognitive/affective disturbances in this illness (Corlett et al., 2006), which can be elegantly combined with human functional neuroimaging (Honey and Bullmore, 2004). For instance, a recent study successfully combined two convergent pharmacological challenges thought

to impact on dopamine vs. NMDA neurotransmitter systems through the combined use of amphetamine and ketamine administration (Krystal et al., 2005). Krystal and colleagues showed that ketamine induced cognitive and negative symptoms, whereas this effect was ameliorated by amphetamine. In contrast, both manipulations exacerbated positive psychotic symptoms, but the effects were not interactive. This study highlights how pharmacological approaches can begin to elucidate and dissociate the role of complex and interacting neurotransmitter systems in the formation of behavioral symptoms such as emotional (e.g., negative) and cognitive deficits. Furthermore, as noted, such pharmacological manipulations can be successfully combined with human functional neuroimaging to experimentally probe whether a common neurotransmitter pathway may be involved in these seemingly distinct manifest symptoms (Honey and Bullmore, 2004). Through this approach, we may be able to mechanistically examine neurotransmitter sources of observed deficits across affective and cognitive domains in a controlled experimental setting in healthy volunteers. The challenge facing the field is to elucidate how breakdowns in cognitive/emotional processes interact in schizophrenia, but also to move toward a final common neurobiological pathway that explains deficits across processes in such a way that treatment of both deficits can be applied, perhaps concurrently. Dowd and Barch (2010) have hypothesized that neuropathology in prefrontal-striatal signaling may in part underlie these deficits. We further discuss the need for such translation in the final section.

In summary, in the proceeding section we highlighted how a dysfunction in a "cold" cognitive process may in some ways give rise to deficits that compromise affective/reward processing. In the following section we focus on a similar possibility in the domain of immediate perception of salient and non-salient stimuli in the environment – particularly from the perspective of sensory filtering.

ABERRANT SALIENCE IN PSYCHOSIS – OVER-RESPONSIVENESS TO "NEUTRAL" STIMULI

Another seemingly paradoxical finding in the study of emotion, cognition, and their interaction in schizophrenia relates to patients' perception of "neutral" stimuli (i.e., stimuli that are not perceived as salient by healthy participants). A number of different lines of evidence suggest that patients with schizophrenia experience a state of "aberrant salience" marked by a blurred distinction between relevant and irrelevant stimuli in the environment (Gray et al., 1995; Gray, 1998; Kapur, 2003; Corlett et al., 2009a). Preclinically, this state has been captured as a weakening of the phenomenon of latent inhibition; normally, stimuli that have repeatedly been experienced as inconsequent receive less attention and do not enter as readily into associative relationships compared to non-pre-exposed stimuli. However, in the context of psychotomimetic drugs (O'Tuathaigh et al., 2003) and endogenous psychosis (Gray et al., 1991) the phenomenon of latent inhibition is weakened and irrelevant stimuli garner attention. This state of "aberrant salience" is a complex phenomenon, possibly mediated by breakdowns in glutamatergic (Corlett et al., 2010a) and dopaminergic signaling (Howes and Kapur, 2009) (see **Box 1**), and a number of models have postulated neurobiological mechanisms that may explain this effect (Kapur, 2003; Corlett et al., 2009a; Howes and Kapur, 2009). In this context, it is important to briefly distinguish between psychosis and schizophrenia: the former being a set of symptoms describing a state and the latter representing the syndrome or a theoretic construct used to label the constellation of manifest symptoms (Walker et al., 2004). While we argue that this deficit of aberrant salience is present in schizophrenia patients, it is proposed that it might be particularly exaggerated during acute psychosis (Gray, 1995, 1998; Gray et al., 1995; Kapur, 2003). An influential model originally proposed by Jeffrey Gray, David Hemsley and colleagues (Gray, 1995, 1998; Gray et al., 1995) and reiterated by Kapur more recently (Kapur, 2003; Kapur et al., 2005) suggests that a primary disruption in dopaminergic signaling in the mesolimbic pathway may result in exaggerated dopaminergic tone, which impacts upon prefrontal-striatal circuits. Indeed, Kapur states "...dopamine mediates the conversion of the neural representation of an external stimulus from a neutral and cold bit of information into an attractive or aversive entity." By assigning salience, via elevated ventral striatal dopamine, patients may imbue "emotionality" and meaning to random and/or typically irrelevant events.

A recent framework proposed by Corlett and colleagues argues for a disruption in prediction error mechanisms, mediated by NMDA and AMPA currents, that may operate during learning and belief formation – we discuss this framework extensively in the final section. The latter model argues that healthy perception and belief proceed via the generation of expectations, which are compared to incoming experiences. If expectations are not properly specified or sensory inputs misprocessed, prediction errors result. These prediction error signals guide learning and update future expectations or regulate the cancellation of sensory inputs (Corlett et al., 2009a,b, 2010a). Prediction errors impact learning directly, forging the formation and strengthening of associations (Rescorla and Wagner, 1972), and indirectly, through the reallocation of attention toward potentially explanatory stimuli (Pearce and Hall, 1980). Aberrant prediction error signals, registered independent of cue or context, drive the assignment of salience to random or otherwise ignored internal and external events, a state which may ultimately result in development of delusions. We will return to the commonalities and differences between these accounts as well as the empirical data on dopamine function in patients and the potential effects of antipsychotic medication on salience, emotions, and learning.

We highlight patterns of findings from apparently disparate lines of work that offer evidence consistent with this aberrant salience effect. We present the results from four separate experimental domains: studies of fear conditioning, learning, and reward processing, as well as the filtering of distracting information during working memory. Findings across these domains could be conceptualized broadly under this rubric of abnormal assignment of salience and/or deficits in suppressing salient stimuli. Moreover, these effects may result in an experience of neutral or irrelevant stimuli as meaningful and affectively laden, possibly manifest ultimately as an acute state of psychosis. If this indeed is the case, then during states of elevated psychosis, patients may by definition exhibit abnormalities in their emotional function driven by exaggerated responsiveness to events/stimuli that are typically not perceived as such by healthy individuals (Kapur, 2003).

Box 1 | Dopamine, salience, and psychosis.

As noted, multiple neurotransmitter systems have been implicated in schizophrenia, with dopamine playing a central role in aberrant salience. Therefore, it is critical to briefly consider dopamine in the present account and in particular medication targeting dopamine neurotransmission. The influential aberrant salience model was developed as a means of explaining to patients why, when they take their D_2 dopamine receptor blocking medication, do their delusions resolve (Kapur, 2003). Here we briefly consider the intersection between D_2 receptor blocking drugs, cognition, emotion, and symptoms. Certain negative symptoms like anhedonia and apathy may pre-date illness onset and are present in unaffected and un-medicated relatives (Chen et al., 2009), hence not all emotional deficits in schizophrenia are iatrogenic. However, attenuating dopamine transmission can curtail some motivated behaviors (Dickinson et al., 2000). While D_2 receptor antagonists ameliorate positive symptoms, their site of action may contribute to some of the anhedonia and amotivation observed in schizophrenia, because blocking dopamine transmission (particularly in the limbic striatum/nucleus accumbens (Beninger, 1983) can decrease motivation (Dickinson et al., 2000), perhaps explaining some side effects of D_2 blockers like loss of libido. Future work should continue to explore effects of D_2 blockers on emotional/cognitive processes in schizophrenia.

In terms of the underlying functional neuroanatomy, the site at which D_2-blocking antipsychotic drugs exert their effects was always assumed to be the nucleus accumbens or ventral striatum, a key region implicated in the ascription of aberrant salience (Kapur, 2003; because accumbens dopamine release was related to the ascription of motivational significance or salience to drug-related cues in preclinical models of addiction (Robinson and Berridge, 2001)). However, the Positron Emission Tomography (PET) data in patients with psychosis and individuals in the prodromal stages of psychosis point instead to the associative striatum or head of the caudate nucleus as a possible site of dopamine pathophysiology that may relate to psychosis, as well as a key target for D_2 medication effects (Howes et al., 2009). Hence, D_2 abnormalities in associative striatum (as opposed to ventral striatum) may be associated with positive symptoms whereas pathophysiology in the accumbens coupled with iatrogenic effects might underpin the negative symptoms (Kegeles et al., 2010). In support of the latter point, Juckel and colleagues employed a monetary incentive delay task in which a visual cue signals the requirement to emit a speeded instrumental response to gain (or avoid losing) money (Knutson et al., 2000). They found aberrant striatal signaling in patients with schizophrenia, indicative of a "blurring" of the distinction between salient and non-salient events in the striatum. This effect was significantly related to negative but not positive symptoms (Juckel et al., 2006a). A follow-up study suggested an iatrogenic origin for the effect (Juckel et al., 2006b); when patients were switched from typical D_2-binding drugs to atypical antipsychotics with significantly less D_2 receptor affinity, the striatal aberrations appeared to normalize (Schlagenhauf et al., 2008). Together, these findings highlight that carefully considering the site, source, and symptom relevance of D_2 antagonist effects is crucial to discerning their role in this illness as well as contributions to cognitive/affective dysfunction. Nevertheless, it is important to consider alternative mechanisms to D_2 dysfunction in psychosis: D_2 receptors and dopamine dysfunction may not be the only neural mechanism with relevance to psychotic symptom formation. In the context of a transient and reversible psychotomimetic ketamine infusion in healthy volunteers, inappropriate prediction error signals have been observed in cortex and these signals were associated with aberrant salience experiences and delusion-like ideation (Corlett et al., 2006). Indeed, dopamine does not appear to play a significant role in the acute effects of psychotomimetic compounds that impact the NMDA receptor. For instance, effects of ketamine (an NMDA antagonist) are not blocked by haloperidol (Krystal et al., 1999) and the PET data on raclopiride binding under ketamine are mixed (Kegeles et al., 2000). On the other hand, the psychotomimetic effects of ketamine are attenuated by lamotrigine, a drug that blocks presynaptic glutamate release (Anand et al., 2000). Hence, unregulated glutamate release may be another mechanism driving aberrant prediction error and psychosis. In contrast, dopamine may be more relevant for the longer lasting effects of repeated ketamine exposure and the emergence and maintenance of positive symptoms (Corlett et al., 2011). These hypotheses should be the focus of future empirical investigation to more fully characterize dopaminergic/glutamatergic mechanisms in psychotic symptoms.

The first study we highlight as reporting this effect was conducted by Corlett et al. (2007a). The authors studied the process of aberrant association formation in first-episode psychosis. They examined brain responses, using fMRI, during learning of associations and violation of those associations in patients compared with matched control subjects. Behaviorally, both groups of subjects acquired the associative relationships presented to them. This was critical as any demonstration of brain or behavioral differences during violation of expectation hinge upon both groups being able to learn the basic associations. In the context of associative learning it is possible to "violate" a learned expectation – this generates a prediction error, which can be conceptualized as a signal of salience or novelty (i.e., something in the environment does not match the organism's prior expectancy). Corlett and colleagues compared brain responses to such surprising events to those that occurred in response to events that confirmed predictions. Healthy subjects showed a robust difference in right lateral PFC response between the two conditions (Corlett et al., 2007a). However, there were group differences between patients and controls in right lateral PFC response (see **Figure 1A**). The pattern observed in patients can be best described as a "blurring" in the distinctiveness of responses to events that violate the expected association and events that confirmed expectations. Crucially, those patients in whom this effect was most pronounced reported the most severe delusions.

Murray et al. (2008) illustrated a highly similar phenomenon in the context of reward learning (as opposed to the relatively "cold" association process highlighted above) in a case-control design with first-episode psychosis patients. Subjects were asked to select one of two visually presented stimuli and observe the outcome of their choice: either a financial reward or no reward (neutral feedback). A computational analysis estimated prediction error from subjects' behavioral choices and aligned these estimates with subjects' brain responses to rewarding and neutral events. Comparing these two conditions in control subjects revealed a canonical set of brain regions associated with reward processing including the midbrain and ventral striatum. Patients with psychosis showed prediction error brain responses in the midbrain and striatum to neutral events that should not be salient. Again, this pattern of experimental findings highlights a blurring of the distinction between responses to events that should be important and those that were relatively unimportant (**Figure 1B**). This pattern of results was also replicated during aversive learning about

cues that predicted the delivery of mild transcutaneous shocks whereby inappropriate midbrain prediction error signals in a psychotic patient group correlated with delusion severity (Romaniuk et al., 2010). Inappropriate striatal prediction error signals to neutral cues that do not predict electric shock have also been observed (Jensen et al., 2008), however, these signals did not predict delusion severity.

The pattern of over-responsiveness to relatively neutral events compared to truly salient cues has been seen not only in brain signals but also in the peripheral physiological responses to those cues that predicted aversive electrical stimuli. Aversive events and the stimuli that predict them induce a sweating response that changes the skin conductance, which can be measured with electrodes. This skin conductance response is reflective of aversive learning or fear conditioning, as well as its subsequent correlation with previously neutral stimuli (arising through learning) when those neutral stimuli predict the aversive events. Patients with schizophrenia show a noisy skin conductance response consistent with an aberrant salience response (Gruzelier, 1976; Holt et al., 2009), which again correlates with delusion severity (Holt et al., 2009). Holt and colleagues used this response to explore extinction learning. In brief, extinction involves new learning such that a once salient stimulus, which was predictive of an important outcome (in this case transcutaneous electrical shock), is no longer predictive. Patients with schizophrenia can engage in extinction learning – their skin conductance responses to extinguished stimuli indeed

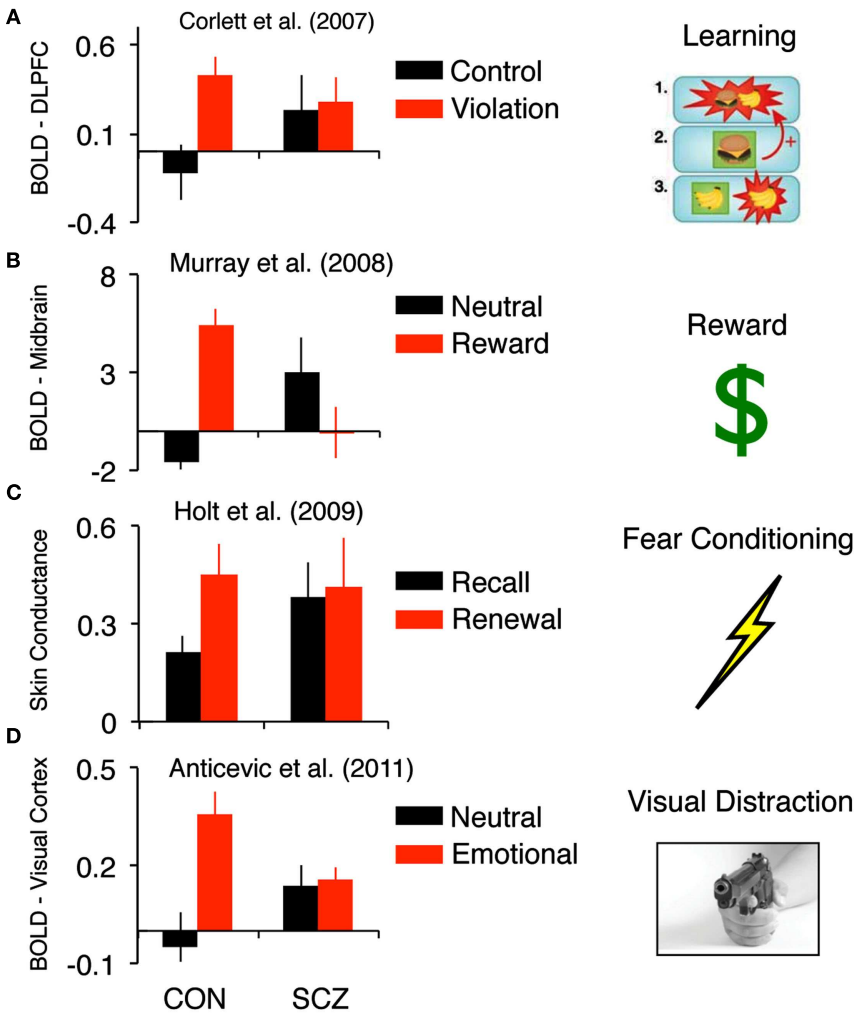

FIGURE 1 | Findings across different experimental contexts that highlight inappropriate responsiveness to "neutral" information in schizophrenia. (A) Corlett et al. (2007a) showed, in the context of "cold" associative learning, that events that did not violate expectation were associated with increased DLPFC signals in schizophrenia patients relative to healthy controls. **(B)** Murray et al.'s (2008) findings highlight, in the context of reward learning, that non-rewarding events were associated with increased striatal signals in schizophrenia patients relative to healthy controls. **(C)** Holt et al.'s (2009) results show aberrant skin conductance fear responses to cues that should be neutral (extinguished), in line with the pattern of responses observed in the brain during causal learning and learning about monetary rewards. **(D)** In a delayed working memory study faced with distraction, Anticevic et al. (2011b) found that patients were distracted by non-salient distraction, which was also associated with increased signals in basic visual regions in patients, particularly when distracted. Together, these findings suggest, across different experimental contexts and measures, that there may be evidence for increased responsiveness to "neutral" stimuli for which healthy controls respond to as less salient

decrease (Holt et al., 2009). However, that learning does not consolidate, such that when tested 24 h later, patients with schizophrenia showed fear responses to the cue that should now be neutral, in line with the pattern of responses observed in the brain during causal learning and learning about monetary rewards described above (Corlett et al., 2007a; Murray et al., 2008; **Figure 1C**).

In the final example we discuss a study by Anticevic et al. (2011b) examining the effects of interference during a delayed visual working memory task in patients with schizophrenia and matched healthy control subjects. While in the scanner, subjects performed a 2 h task that contained trials with no distraction or a distracter presented during the working memory delay phase. Of note, the distracter intensities were manipulated to examine the effects of different levels and types of interference on the maintenance of information in working memory in schizophrenia (i.e., they were either a complex neutral picture, complex emotionally negative picture, or a task-relevant distracter matched to the original memory set). The behavioral results demonstrated that patients were distracted irrespective of distracter type. Importantly, this effect was present even though the two groups were matched for performance when no distraction occurred (Anticevic et al., 2011b). Second, fMRI results showed that patients failed to recruit a region of the right dorso-lateral prefrontal cortex (DLPFC) specifically in response to distraction (again irrespective of distracter type). The degree of DLPFC recruitment correlated significantly with working memory accuracy for controls, specifically during the distracter condition – illustrating the functional relevance of this DLPFC response, in line with prior work implicating this region in filtering of distraction (Postle, 2005). No such relationship was observed for patients, supporting the hypothesis of a failure in distracter filtering. Together these findings show that even stimuli that are perceived as less salient and successfully "filtered" by healthy controls present a source of interference for patients. Furthermore, in complement to the observed prefrontal deficits, we identified a set of regions in primary visual and association cortices for which patients exhibited elevated responses, particularly when distracted by neutral information (**Figure 1D**). In other words, when both patients and controls were distracted (by examining incorrect trials specifically) we found an fMRI pattern in line with those described above – namely patients showing over-responsiveness in sensory regions when controls exhibited no such response.

These convergent findings suggest that patients respond abnormally to stimuli that are not perceived as salient by healthy controls. Aberrant salience experiences are inherently anxiogenic and hence demand explanation. Next, we focus on that explanatory process and how it might culminate in delusion formation.

THE POSSIBLE ROLE OF AFFECT IN FORMATION AND MAINTENANCE OF DELUSIONS

Delusions, the fixed, false beliefs present in schizophrenia, have been considered intractable to scientific inquiry (Jaspers, 1963). Recently, via cognitive neuroscience we have made strides in our empirical understanding of aberrant belief formation (McKay et al., 2007a; Fletcher and Frith, 2009; Coltheart, 2010; Corlett et al., 2010a; Coltheart et al., 2011). Theoretical models grounded in translational cognitive neuroscience suggest that delusions could result from disrupted brain mechanisms of predictive learning (Corlett et al., 2007b, 2010a; Fletcher and Frith, 2009). However, these accounts have mostly ignored the potential role of affective contribution to the process of belief formation and maintenance (Fotopoulou, 2010). Here we briefly expand existing theoretical accounts of delusion formation to incorporate the role of affective signals.

What role might affect play in delusion formation? As suggested, aberrant salience experiences are anxiogenic, since they are surprising and therefore demand explanation (Kapur, 2003). For instance, in uncertain conditions and stressful situations, people are likely to experience apophenia (Conrad, 1958) – perceiving structured meaning in meaningless noise (i.e., seeing and hearing things that are not actually there; Whitson and Galinsky, 2008). Furthermore, according to two-factor theories of delusions (Coltheart et al., 2011; see below), the Capgras delusion (believing that one's relatives have been replaced by impostors) and Fregoli delusion (the belief that strangers on the street are one's relatives in disguise) may be in part driven by a lack of predicted emotional response and an excessive emotional response, respectively. This possibility is supported by studies of the galvanic skin response (GSR) in Capgras sufferers who adopt the belief following head injury – they do not show normative skin conductance increase (sweating) when confronted by a close family member (Ellis and Young, 1990). This lack of familiarity response could be surprising and thus may demand explanation. In turn, such aberrant emotional responses could result in the impostor belief being formed (Corlett et al., 2010a,b). Based on this account, the Cotard delusion (the belief that one is dead) may be associated with an attenuated affective response to otherwise salient cues (Ramachandran and Blakeslee, 1998). Further supportive data for the role of affect have yet to be acquired for individuals suffering the Cotard or Fregoli delusions. Nevertheless, the noted finding in the context of the Capgras syndrome (Hagen, 2008) supports the hypothesis that emotional processes play a role in at least some delusions. In the following sections, we discuss how such processes could interplay with established models of aberrant belief formation.

We consider the learning model in the context of prior accounts that explain delusions in terms of aberrations of emotion, motivation, and desire (McKay et al., 2007a,b; Fotopoulou, 2010). Central to these accounts is the notion of self-deception (Trivers, 1985; Hagen, 2008; Mijovic-Prelec and Prelec, 2010), whereby patients with delusions hold their beliefs to maintain a model of the world that is not veridical but rather conforms to internally held views and thus avoids the negative emotions associated with discrepant perceptions (McKay et al., 2007a,b; Fotopoulou, 2010). These theories argue for a multi-agent conception of self (Mijovic-Prelec and Prelec, 2010), postulating an actor that supports self-deceiving beliefs, and a more objective critic that infers the appropriateness of those beliefs. We argue that such multi-controller models in the context of delusions are highly consistent with multi-controller models of instrumental learning from formal animal learning theory, which has been linked to delusion formation (Sutton and Barto, 1998; Daw et al., 2005). Later, we discuss how motivational processes may interact with the actor and critic.

Multi-controller models are accounts of instrumental learning (learning the consequences of one's actions in the environment)

from the psychology literature (Dickinson and Balleine, 1990) and the computational reinforcement learning literature (Daw et al., 2005). Such models posit more than one system (controller) that can guide instrumental action and choice. Each controller is hypothesized to use a different representation or metric to guide behavior. For example, psychologists have defined a goal-directed controller of instrumental action that is driven by the value of the outcome being learned about and mediated by stimulus-response-outcome associations. In contrast, they also postulate a more habitual controller that employs stimulus-response associations (and is hence insensitive to the value of the outcome being worked for) may also control instrumental behavior. With over-training, habitual control takes over such that, even when the outcome is devalued (e.g., by poisoning or satisfying the subject by free-feeding), animals continue to respond for the outcome (Adams and Dickinson, 1981). Functional neuroimaging data have demonstrated consistent effects in humans and linked habitual control with dorsal striatal signals (Tricomi et al., 2009). Some theorists posit that both controllers are present simultaneously and compete to guide behavior (Daw et al., 2005), which seems to be the case since manipulations can be made to switch habitual animals back toward goal-directed responding (Hitchcott et al., 2007). One possibility is that the competition is based on whose predictions are least uncertain (Daw et al., 2005). Therefore, prediction error (and the uncertainty with which it is associated) can bias toward a particular controller of behavior (Butts, 1998). If such signals are generated inappropriately and internally, they could contribute to development of aberrant beliefs, which are then maintained as cognitive habits. In schizophrenia, due to abnormal distractibility, cognitive impairment, and susceptibility to stress, corrective mechanisms that involve computationally intensive reasoning and evaluation may not be able to ameliorate fallible maladaptive beliefs (delusions; Mishara and Corlett, 2009). Furthermore, with excessive ruminative self-reinforcement (Eisenhardt and Menzel, 2007) the inflexible, self-deceptive habitual system may gain control despite corrective feedback (Corlett et al., 2009b). Critically, motivational factors may play a key role in this process.

Specifically, motivational processes could be considered in the domain of paranoid and persecutory beliefs (Kaney and Bentall, 1989, 1992; Kinderman and Bentall, 1996; Bentall et al., 2001) that defend against low self-esteem (McKay et al., 2007a,c). One possibility is that individuals with persecutory delusions have high overt self-esteem and relatively low unconscious, covert self-esteem (Kinderman, 1994; Kinderman and Bentall, 1996), which seems to be the case in patients with delusions (McKay et al., 2007c). Kinderman (1994) showed that individuals with persecutory delusions (a cardinal example of paranoia) exhibited attentional bias toward words related to low self-esteem while simultaneously reporting high self-esteem on an explicit self-rating task. Using the Emotional Stroop task (in which there is a response cost for naming the color of emotionally salient words), Kinderman found that individuals with persecutory delusions showed slowing to name the colors of negative self-descriptors. In contrast, on an overt measure of self-esteem, the same individuals exhibited higher self-esteem, explicitly rating themselves more highly on positive vs. negative adjectives. Kinderman concluded that this discrepancy between covert and overt self-esteem might reflect the impact of a defensive process that culminated in the formation of persecutory delusions. We acknowledge this is indirect evidence, but it offers some support for the role for self-esteem and motivational factors in persecutory delusion.

To further investigate the role of self-esteem in persecutory delusions, McKay et al. (2007c) used the implicit association test (IAT), demonstrating a link between implicit self-concepts, covert self-esteem, and persecutory delusions. The IAT measures automatic associations between concepts (Greenwald et al., 1998). Typically participants need to give two different responses to words from pairs of categories (e.g., press right hand button for words that fall into *flower* or *pleasant* categories and the left button for words that fall into the *insect* or *unpleasant* category). The association between the concepts that are paired together is hypothesized to be stronger the faster the subject responds. McKay and colleagues used *self*, *other*, *pleasant*, and *unpleasant* categories. As shown previously, the ease of making judgments when the *self* and *pleasant* categories are combined under one response rule can be used as a measure of implicit self-esteem (Greenwald and Farnham, 2000). Subjects also completed a number of overt self-relevance rating measures. Patients with current persecutory delusions showed a weaker implicit association between self and positive compared with depressed and remitted control groups, even when covarying for depressive symptoms. In contrast, when accounting for depression there were no differences between groups on overt self-esteem. The difference between implicit and overt self-esteem measures in paranoid patients is consistent with a possible defensive function – paranoid delusions may in part be related with the motivation to maintain self-esteem. One emphasis of both motivational/self-protective processes and learning accounts is the *need for closure* (Kruglanski et al., 1993; Kruglanski and Webster, 1996) – a motivational construct, associated with a preference for certainty and predictability (McKay et al., 2007a,c). Patients with persecutory delusions have higher need for closure (Bentall and Swarbrick, 2003). In the learning account, need for closure represents the drive to minimize prediction error and infer a model of the internal/external world that, although maladaptive and self-deceptive, reduces uncertainty (Mishara and Corlett, 2009). Across both accounts, such self-deception may be adaptive in that it allows the individual to engage in the world despite contradictory experiences (McKay and Dennett, 2009).

Another intersection of learning-based models of belief formation and emotion is fear. Most reinforcement learning models relevant to delusions center on reward processing, and the neuroimaging experiments using predictions derived from these models involve learning about appetitive outcomes (juice, monetary rewards). However, fear conditioning is also prediction error driven (Laviolette and Grace, 2006; McNally and Westbrook, 2006; Cole and McNally, 2007, 2009; McNally et al., 2011), involving a circuit incorporating the ventral tegmental area (VTA), amygdala and hippocampus as well as the striatum and prefrontal cortex (Schiller et al., 2008) – all implicated in aberrant prediction error (see Corlett et al., 2007a for more detail). Descending opioids and NMDA receptors are also critically involved in predictive fear learning (McNally and Westbrook, 2006; Cole and McNally,

2007, 2009; McNally et al., 2011), neurotransmitters that may be compromised in schizophrenia (see below). NMDA receptor antagonism (itself a pharmacological model of psychosis; Krystal et al., 1994) modulates the degree to which prediction error signals contribute to belief updating, possibly through aberrant predictive learning (Corlett et al., 2010a). In contrast, the opioid antagonist naloxone modulates the actual prediction error signals during fear conditioning (McNally and Westbrook, 2006; Cole and McNally, 2007, 2009; McNally et al., 2011), perhaps through an interaction with VTA dopamine cells. Aberrations of these neurotransmitter processes could induce inappropriate fear following perceived cues, resulting in a subsequent elevation of uncertainty, both of which may contribute to delusion formation (Corlett et al., 2010a). Furthermore, individuals with a low tolerance for ambiguity are more prone to paranormal beliefs and odd experiences (Houran and Houran, 1998). One possibility is that intense emotional states and learning dysfunction contribute to a vicious circle in which fear and aberrant perception are mutually reinforcing and demand explanation (Pally, 2005, 2007), ultimately contributing to aberrant beliefs (Corlett et al., 2010a). Moreover, such processes could contribute to aberrant belief maintenance (see **Box 2**).

In considering how affect may contribute to delusion formation and maintenance through interaction with learning mechanisms, we highlight how overlapping and interactive neural processes may engender aberrant beliefs, similarly to other processes reviewed above. For instance, a failure of top-down regulation of the amygdala by prefrontal cortex may contribute to excessive and inappropriate fear responses (Corlett et al., 2011). One specific prediction of this interactive emotion-cognition model is that anxious individuals may become more paranoid in context of pharmacological manipulations that may exacerbate aberrant beliefs (i.e., NMDA receptor antagonists), which would derange the specification and incorporation of prediction error signals in a system that was already sensitized. Future work should explore this possibility. Furthermore, by taking a more reductionist approach grounded in formal animal learning theory, we attempt to provide a translational framework, linking psychological/cognitive accounts with basic neuroscience findings (e.g., fear-learning mechanisms in animals). We hope that future studies continue to delineate the interactive role of affect with learning and motivational mechanisms that may operate in the formation of aberrant beliefs.

Next, we discuss how emotion-cognition dysinteraction across described processes in schizophrenia might arise from hypothesized downstream disruptions in cellular-level computations and in turn impact large-scale inter-correlated brain systems that have been linked to symptoms.

UNDERSTANDING AFFECTIVE AND COGNITIVE DEFICITS IN SCHIZOPHRENIA ACROSS LEVELS OF ANALYSES

Thus far we have discussed the complexity of cognitive and emotional processes affected in schizophrenia. We have focused on evidence and theoretical understanding at the level of neural systems and behavior – levels of analyses typically examined using cognitive neuroscience approaches.

As reviewed, cognitive neuroscience has established the tools to probe the underlying circuitry that may be affected in schizophrenia, as well as its relationship to cognition and emotion. By studying pathological states using these tools, we gain

Box 2 | Delusions, emotions, and memory.

It is adaptive for an organism to be able to remember salient events for extended periods without the necessity for repeat experiences (Dickinson, 2001). Reactivation of a memory trace for a salient event may increase the stabilization of that trace (Lee, 2008). Based on this hypothesis, our most salient memories would be reactivated most frequently and would therefore undergo greatest reconsolidation-based stabilization, increasing their fixity. Reconsolidation may facilitate the automation of behavior (Stickgold and Walker, 2007) – the transition from knowledge to belief (Eichenbaum and Bodkin, 2000) – shifting the representation that mediates behavior from declarative to procedural and thus reducing the demand for executive control. Further, reconsolidation is held to aid the extraction of important details from complex episodic memories and to permit the integration of those details in support of adaptive and efficient behaviors, possibly through the construction of habits or schemas (Bartlett, 1932). Our hypothesis is that delusions form under the influence of aberrant prediction errors, whose salience is anxiogenic and may demand explanation. Once delusions form, there may be relief from forming an explanation (Chouinard and Miller, 1999). In this proposal, subsequent aberrant salient experiences could reactivate the "explanation" and are interpreted in light of it and therefore strengthened via memory reconsolidation (Lee, 2008). Future work will be needed to further verify the role of stress, motivation and other emotional factors in this putative process.

We discussed the evidence regarding aberrant belief formation, but what about its maintenance? The state of a memory after consolidation may depend on the context in which it is recalled. Specifically, surprising information can update the memory trace or engage extinction learning, which competes with and overrides original traces (Pedreira et al., 2004). There is clinical phenomenological evidence consistent with the presence of competing representations, such as the duality of belief and disbelief during treatment (Stanton and David, 2000). Furthermore, delusions are elastic in the face of contradictory evidence (i.e., patients will incorporate contradictory evidence quite readily, strengthening the belief; Milton et al., 1978). The prognosis and response to cognitive behavioral therapy are worse for individuals engaging in this elasticity (Garety, 1991). There is further clinical evidence from a study involving the erasure of delusions following their engagement, administering electro-convulsive therapy following delusion reactivation (Rubin, 1976). More recently, there is cognitive behavioral evidence showing enhanced illusory truth effect in psychotic patients – when merely exposed to delusion congruent information, individuals with delusions will subsequently be more convinced of its truth when re-exposed to that information (Moritz et al., 2012). To summarize, patients may formulate an explanation for their aberrantly salient experiences. Once such a delusional scheme is formed it may be deployed in future contexts to explain subsequent aberrant experiences, strengthening the delusional association in the process. We recently discussed how the increasingly influential Bayesian brain account might help us to understand the role of prediction error in perception, belief, and delusion formation and maintenance (Corlett et al., 2009a; Fletcher and Frith, 2009). It will be key for future studies and theories to consider stress and emotional/motivational factors in the ongoing process of reconsolidation that may operate in delusion maintenance.

insights about the neurobiological and psychological mechanisms through which impairments in cognition and emotion might contribute to psychiatric illness. However, such approaches have more difficulty identifying underlying cellular mechanisms (in humans, and therefore patients suffering from mental illness, at least). Such a step is crucial to identify effective pharmacological therapies. We believe it will be critical to close the existing gaps in our understanding of emotion and cognition in schizophrenia across levels of explanation: from synaptic signaling at the micro-circuit level, to system-level disruptions, and ultimately behavior. We acknowledge that a comprehensive review of the neurobiology and neurochemical alterations in schizophrenia is beyond the scope of this manuscript. However, we briefly highlight how evolving cellular-level hypotheses of mirco-circuit disruptions offer a possible foundation for understanding higher-order emergent neural system and behavioral deficits in schizophrenia that demand mechanistic explanations.

The clinical neuroscience approach to schizophrenia has identified region-level abnormalities in both function and anatomy across areas such as DLPFC, hippocampus, amygdala, thalamus, and striatum (Csernansky et al., 1998, 2004, 2008; Laruelle et al., 1999; Harms et al., 2007, 2010, 2012; Reichenberg and Harvey, 2007; Dowd and Barch, 2010; Mamah et al., 2010; **Figure 2A**). This is not to say that other regions are not affected – we simply use these as an illustrative example for how to link levels of understanding. However, regions such as DLPFC, striatum, amygdala, and thalamus comprise a set of cortical-subcortical networks and loops, which function in concert and are influenced by multiple neuromodulatory signaling pathways (Carlsson and Carlsson, 1990; Carlsson et al., 2001). It is likely that such network-level interaction in cortico-thalamo-striatal circuits are crucial for organizing computations that support complex cognitive processes such as working memory and motivation (Barch and Dowd, 2010), likely impacted by interactive neurotransmitter systems such as glutamate and dopamine (Laruelle et al., 2003; **Figure 2B**). Indeed, disruptions in numerous interacting neurotransmitter systems, including dopamine, GABA, and glutamate have been implicated in schizophrenia (Kegeles et al., 2000; Abi-Dargham et al., 2002; Krystal et al., 2003; Lewis et al., 2012). As noted, there is mounting evidence for dopaminergic alterations in the striatum of patients with schizophrenia which result in hyperactivity (Laruelle et al., 1999; Howes et al., 2012; for review see Laruelle et al., 2003). Patients also present with reduced prefrontal dopamine tone (Howes et al., 2012; in particular hypo-stimulation of D1 receptors in PFC; Abi-Dargham et al., 2002). Patients may also exhibit disruptions in glutamateric signaling at the NMDA receptor (Krystal et al., 2003), as well as disruptions in GABA synthesis and signaling from interneurons onto pyramidal cells (Lewis et al., 2004, 2005, 2012; Gonzalez-Burgos and Lewis, 2012; Nakazawa et al., 2012; **Figure 2B**). There is still an ongoing *chicken*

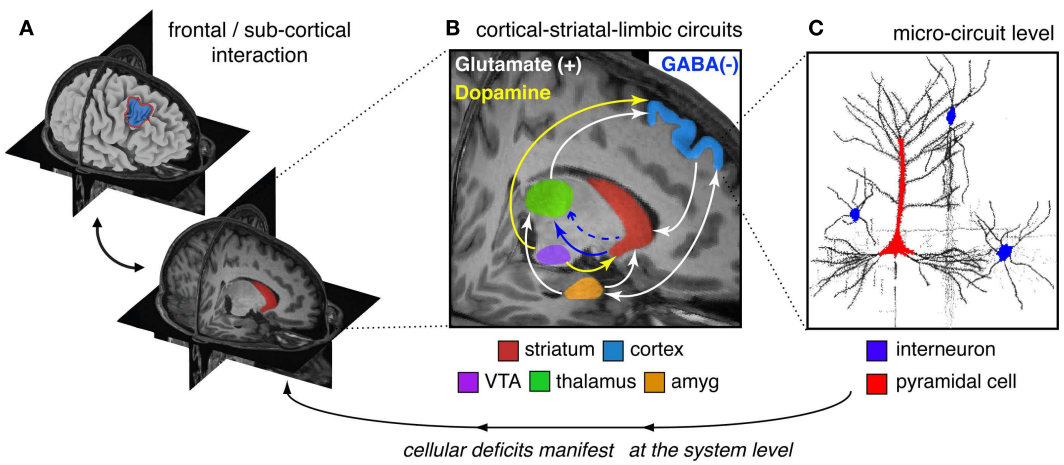

FIGURE 2 | Conceptual illustration of neural circuitry across levels of computation that may be involved in affective and cognitive disturbances in schizophrenia. The figure highlights how, in order to explain deficits at the phenomenological/behavioral level, we need to bridge observations across multiple levels of analysis in schizophrenia. **(A)** At the regional level there is clear evidence for both structural and functional abnormalities in cortical (Csernansky et al., 1998, 2004, 2008; Harms et al., 2010, 2012) and striatal/thalamic circuits in schizophrenia (Csernansky et al., 1998, 2004, 2008; Laruelle et al., 1999; Harms et al., 2007; Reichenberg and Harvey, 2007; Dowd and Barch, 2010; Mamah et al., 2010). **(B)** However, less is known about how some of these regional deficits manifest in possible system-level disruptions in functional loops between prefrontal, striatal, limbic, and thalamic nodes in schizophrenia (Lisman, 2012). Deficits in these interacting functional systems need to be considered when interpreting abnormalities between affective/hot and cognitive/cold operations in schizophrenia. Furthermore, there is known interplay between interacting neurotransmitter systems in cortico-striatal-thalamic loops that may be compromised in schizophrenia (Carlsson et al., 2001; Coyle, 2006). **(C)** Based on emerging findings from basic animal (Lewis et al., 2004; Yizhar et al., 2011), post-mortem (Lewis et al., 2005, 2012), and pharmacological studies (Krystal et al., 2003), there is an increasing understanding of micro-circuit abnormalities that may be at play in schizophrenia (Marin, 2012). It may be possible that abnormalities in the balance of excitation/inhibition in cortical microcircuitry contribute to downstream system-level disturbances that encompass distributed circuits and neurotransmitter systems. One leading hypothesis postulates an imbalance between cortical excitation and inhibition between pyramidal cells (red) and interneurons (blue), producing a state of "disinhibition," which may in turn affect regional and system-level function (Yizhar et al., 2011). Considering effects across all of these levels will be critical to mechanistically understand complex schizophrenia phenomenology and symptom-level interactions.

or the egg debate as to which one of these disruptions may be the proximal cause of downstream symptoms (Coyle, 2006), yet considering these complex interactions will be vital as we move toward a more complete understanding of this illness.

One way to organize these multiple, interactive dysfunctions across levels of analysis is to consider how they may be impacted by pathology at the level of cortical microcircuitry (**Figure 2C**; Lisman, 2012; Lewis et al., 2012; Marin, 2012). That is, perhaps if we were to start from cellular-level hypotheses of disrupted cortical computations in schizophrenia, we may ultimately be able to better understand complex dynamics that emerge at higher levels of observation (Loh et al., 2007; Rolls and Deco, 2011; Lisman, 2012). Optimal cortical function depends on the balanced interaction of pyramidal excitatory (glutamatergic) and inhibitory (GABAergic) neurons (Shadlen and Newsome, 1994). Disruptions of this balance can have drastic behavioral consequences (Yizhar et al., 2011; Marin, 2012). In schizophrenia there may be a functional deficit in the interaction between excitatory and inhibitory cortical neurons (Benes et al., 1991; Lewis et al., 2004, 2005, 2012; Lewis and Moghaddam, 2006; Marin, 2012). This may arise from a disruption in cortical inhibition; stemming perhaps from reduced inhibitory drive via GABA interneurons onto pyramidal cells and ultimately resulting in *disinhibition* of pyramidal cells (Lewis et al., 2012; Marin, 2012). Post-mortem studies of patients with schizophrenia consistently show reduced levels of the mRNA for the 67-kD isoform of glutamic acid decarboxylase (GAD67, encoded by *GAD1*), a key factor in optimal GABA levels, in the DLPFC of patients with schizophrenia (for review see Lewis et al., 2005). Furthermore, GABA's role in exerting lateral inhibition and synchronizing persistent firing of pyramidal cells in DLPFC (Rao et al., 2000) provides one potential mechanism for the tuning of representations of information. That is, lateral inhibition might enhance the processing and maintenance of salient information relative to less behaviorally relevant representations. Disruption of excitation/inhibitory (E/I) balance between pyramidal and GABA neurons may be one crucial pathophysiological mechanism operating in schizophrenia, relevant to the patterns of neural and behavioral responses that we discuss presently.

Therefore, perhaps a way of reconciling abnormalities in cognition/emotion and circuit-level disruptions is to consider a common computational motif: "attractor states." Attractor states represent reverberating patterns of neural activity that are candidate mechanisms for working memory (outlined above Wang, 1999), perception (Braun and Mattia, 2010), and emotion (Rolls and Stringer, 2001). Attractor states and their sustaining recurrent neural activity are also crucial to some models of predictive coding in perception (Kiebel et al., 2009) and prediction error driven reinforcement learning in the basal ganglia (providing the reward expectation in a given situation; Morita et al., 2012). Neural evidence across species suggests that such attractor mechanisms exist. However, rather than remaining in a steady state, populations of neurons can jump from one attractor state to another (Hopfield, 1982), driven by intrinsic neural activity. Such intrinsic neural activity can actually contain meaningful spatial and temporal information and may encourage transitions across the attractor landscape (Braun and Mattia, 2010) – for example the prior expectations that constrain current perception (Berkes et al., 2011), which if mis-specified might result in psychotic symptoms (Corlett et al., 2009a). We argue that while cognitive, emotional, and delusional symptoms may appear "distinct," they not only interact, but at a neural level, their pathophysiology may share important common features such that disruptions can affect all processes and the interaction between such processes. Thus, examples discussed above, where response patterns may be exaggerated following a "neutral" cue, could be considered in terms of the inappropriate establishment of an attractor state for that cue, possibly due to inappropriate function within a region (e.g., GABAergic disinhibition) or between regions (e.g., glutamate spillover and increased noise in message passing between regions; Yamashita and Tani, 2012).

We appreciate that, at present, it is unknown how these cellular disruptions in E/I balance may manifest at the level of neural systems and ultimately diverse psychological processes compromised in this illness (Yizhar et al., 2011). The challenge facing the field is to close this gap. There are paths forward: (i) one approach is to start at the level of cells and make predictions regarding the higher levels of analysis. A way to accomplish this goal could involve computational modeling (Montague et al., 2012), particularly models that are rooted in neurophysiologic data and that build on assumptions based on molecular and systems neuroscience (Wang, 2006, 2008, 2010; Anticevic et al., 2012a); (ii) another approach is to test hypotheses regarding neural dysfunction in schizophrenia via pharmacological manipulations in healthy adults (Corlett et al., 2007b). This is accomplished through perturbations of the underlying circuitry thought to be compromised in individuals suffering from the illness (Honey and Bullmore, 2004), via relatively well-understood neurochemical mechanisms. Furthermore, attempts have been made to unite the pharmacological and psychological levels of analysis to explain why these interventions are psychotomimetic (Corlett et al., 2007b; Anticevic et al., 2012a). In turn, such manipulations may reveal clues regarding specific links between disruptions in neurotransmitter systems, which can be connected to system-level deficits and ultimately behavior (Anticevic et al., 2012a); (iii) continued development of more sophisticated animal models of the neural pathology that may be present in this illness that are well-linked to both intermediate and behavioral phenotypic markers should also be pursued (Yizhar et al., 2011). For instance, primate physiology experiments of working memory, in combination with targeted neurochemical and optogenetic manipulations (Tye and Diesseroth, 2012), provide this framework (Simen et al., 2009; Arnsten, 2011; Arnsten and Rubia, 2012); (iv) and lastly, large-scale imaging genomic studies as well as detailed spatial and temporal genetic transcriptomics approaches (Johnson et al., 2009; Kang et al., 2011) could hone our search for genes that influence cortical development, that may ultimately disrupt the cortical microcircuitry detailed above. We argue that these and other complementary neuroscientific approaches will be critical to close our vast explanatory gaps in clinical neuroscience of schizophrenia and ultimately move toward ameliorating dysfunction in neural systems affecting cognition, emotion, and belief.

CONCLUSION

To summarize, we discussed the interplay of cognition and emotion in schizophrenia across different processes – namely motivation and anhedonia, perceiving and filtering sensory stimuli, and how affective responses may interplay with learning mechanisms in the context of belief formation. We argue that, while some affective responses may be seemingly intact in schizophrenia, it is vital to consider how emotion and cognition impact upon one another across contexts to achieve a full understanding of emergent symptom-level disturbances in this illness. Finally, we discuss the evolving understanding of the underlying pathophysiology in schizophrenia. Here we argue that a translational perspective across levels of analyses – from cellular to system-level phenomena, and in turn behavioral deficits – will be critical to fully characterize the complex and debilitating symptoms observed in schizophrenia.

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The interplay between emotion and cognition in autism spectrum disorder: implications for developmental theory

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is clinically defined by abnormalities in reciprocal social and communicative behaviors and an inflexible adherence to routinised patterns of thought and behavior. Laboratory studies repeatedly demonstrate that autistic individuals experience difficulties in recognizing and understanding the emotional expressions of others and naturalistic observations show that they use such expressions infrequently and inappropriately to regulate social exchanges. Dominant theories attribute this facet of the ASD phenotype to abnormalities in a social brain network that mediates social-motivational and social-cognitive processes such as face processing, mental state understanding, and empathy. Such theories imply that only emotion related processes relevant to social cognition are compromised in ASD but accumulating evidence suggests that the disorder may be characterized by more widespread anomalies in the domain of emotions. In this review I summarize the relevant literature and argue that the social-emotional characteristics of ASD may be better understood in terms of a disruption in the domain-general interplay between emotion and cognition. More specifically I will suggest that ASD is the developmental consequence of early emerging anomalies in how emotional responses to the environment modulate a wide range of cognitive processes including those that are relevant to navigating the social world.

Keywords: autism, emotion, social-motivation, social brain, social cognition

INTRODUCTION

Ever since the behavioral syndrome now recognized under the rubric of the Autism Spectrum was first described more than six decades ago, it has been noted that atypicalities in reciprocal emotion related behaviors constitute a hallmark feature of its clinical presentation. Both Kanner (1943) and Asperger (1944) identified difficulties in this domain as a unifying characteristic amongst the cases they described, and to this day diagnostic instruments and screening tools consider anomalies in emotional reciprocity as a clinically significant indicator of the disorder (Schopler et al., 1980; Lord et al., 1989, 1994; Robins et al., 2001). For as long as disturbances in affective processes have been considered central to the clinical phenotype of *Autism Spectrum Disorder* (ASD), however, their significance in the development of the disorder has remained a matter of debate. Kanner (1943) and Asperger (1944) originally disagreed over whether they had identified a biologically determined disorder of interpersonal affect or a particular personality trait. During the 1950s and 1960s views diverged over the misguided concern of whether the primary caretakers might be to blame for their child's emotional withdrawal or not, and most recently the dispute has turned to the question of whether early emerging impairments in social-cognitive processes are responsible (e.g., Baron-Cohen, 1995, 2005; Frith, 2003; Schultz, 2005), or whether Kanner's (1943) original emphasis on innately specified interpersonal affective processes may have been correct after all (e.g., Hobson, 2002; Loveland, 2005; Chevallier et al., 2012). As diverse as the ideas have been over the decades, they have all shared the view that emotion related difficulties in ASD are to be understood with reference to atypicalities in social processes. In this review I will question this position and suggest instead that the social-emotional characteristics of the disorder are more fruitfully conceptualized in terms of domain-general anomalies in how the influences of emotions on cognition, that sometimes augment and at other times attenuate experiences of the world, organize what an infant learns about salient events in a complex and dynamically changing environment. In the context of the broader issues under consideration in this Special Topic, the study of ASD is therefore of considerable interest as it sheds light on a critical developmental function of the interplay between emotion and cognition.

The Autism Spectrum comprises a set of related pervasive developmental disorders (PDDs) that are all characterized by atypicalities in the domains of communication and socialization and by a restricted and repetitive pattern of interests and activities (Wing and Gould, 1979; American Psychiatric Association, 2000). The disorders subsumed under this spectrum include *Autistic Disorder*, *Asperger's Disorder*, and PDD-*Not Otherwise Specified* (PDD-NOS), which together affect approximately 1% of the population and are around three to four times more common in males than females (Bertrand et al., 2001; Baird et al., 2006). All subtypes of ASD share a uniquely patterned cognitive profile that includes difficulties in understanding behaviour in terms of mental states, such as beliefs and desires (Baron-Cohen et al., 1985; Baron-Cohen, 1995; Frith, 2003), difficulties in deploying cognitive resources flexibly in order to plan and execute goal directed

behaviors (Ozonoff et al., 1991a; Hill, 2004), a tendency to process information in a piecemeal and perceptually driven rather than holistic and conceptually driven fashion (Shah and Frith, 1993; Mottron and Burack, 2001; Frith, 2003; Mottron et al., 2006) and a characteristic profile of memory strengths and weaknesses that parallels that seen in neuropathologies of the frontal and/or medial-temporal lobes (Boucher and Bowler, 2008; Boucher et al., 2012). Since there is little evidence to support a nosological differentiation of subtypes of autistic pathologies (see Wing and Gould, 1979; Wing, 1993; Prior et al., 1998; Volkmar et al., 2004; Bowler, 2007 for discussion), the forthcoming edition of the Diagnostic and Statistical Manual of Mental Disorders 5[1] will include only the single category of "ASD," which will be the preferred term used throughout this review. I will describe individuals who have received a diagnosis of an ASD as *autistic individuals* rather than *individuals with autism* to reflect the preferred terminology of those who are on the spectrum (see Pellicano et al., 2011).

In relation to emotions, the view I adopt in this review is informed by several influential authorities in the field (e.g., James, 1890; Cannon, 1927; Schachter and Singer, 1962; Reisenzein, 1983; Lazarus, 1984; Zajonc, 1984; Ekman, 1992; Levenson, 1992; Damasio, 1994, 1999, 2003; LeDoux, 1996, 2002; Lane and Nadel, 2000; Russell, 2003; Lane, 2006; Barrett et al., 2007). I will use the words "*emotion(al)*" and "*affect(ive)*" in a theoretically neutral sense to describe the phenomena that accompany situations that tend to elicit approach and avoidance behaviors. The term "*arousal*" will denote automatic changes in physiological parameters such as heart rate, skin conductance, or pupil dilation that occur during (but are not specific to) emotional episodes. Although arousal is also often used to describe changes in brain activity (e.g., cortical arousal), I will restrict my discussion here to changes in peripheral nervous system activity that are, broadly speaking, open to conscious awareness. The word "*feeling*" will be used to describe the subjective experience that people report when they are asked about their emotional state. It does not comprise "feelings" of mere physical sensations (e.g., I feel cold) or homeostatic imbalances (e.g., I feel sick) although the two are closely related. The critical difference is that emotional feelings necessarily involve an *evaluation* (often termed appraisal) of arousing events whilst physical feelings are primarily conscious perceptions of the body's internal milieu. The nature of the *evaluative* process in question in this context remains the matter of debate but most authors agree that it is intricately linked to self-awareness and consciousness on the one hand and self-preservation on the other (e.g., LeDoux, 2002; Damasio, 2003; Lane, 2006). More specifically, stimulus induced arousal is thought to shape (or elicit) perceptions of arousing objects or events in terms of their *value* (innately specified or learned) to the wellbeing (physical or psychological) of the Self, which modifies how the Self is expressed in consciousness (e.g., as feeling afraid). Finally, it is important to note that this review will not deal with the topic of mood. Although moods and emotions are closely related, only emotions are intentional in the philosophical sense of being about something and the focus of this paper is on how autistic individuals experience, understand, and relate to the objects and events in the world that emotions are about.

THE SOCIAL-EMOTIONAL DIFFICULTIES ASSOCIATED WITH ASD

Although emotion related processes have been of interest in relation to ASD since Kanner (1943) first described the syndrome, work in this area has almost exclusively focused on the processes and behaviors that serve to regulate interpersonal conduct. Within this narrow focus, the literature is vast, covering more than 100 empirical papers and a broad theoretical literature. Doing justice to this work in the space available is difficult and I must therefore apologize to all authors whose views I have caricatured in the service of brevity. Fortunately, the three points I want to make in this section are relatively uncontroversial. The first is, that it is widely accepted that ASD is characterized by difficulties in multiple facets of interpersonal emotional communication. The second, that dominant explanations of these difficulties attribute them to anomalies in the development of broader reciprocal social competences. And the third, that these reciprocal social competences are mediated by a network of cortical and sub-cortical regions that collectively constitute what has often been called the "social brain."

THE EVIDENCE

Amongst the earliest studies to systematically assess emotion related behaviors in ASD was a series of experiments by Hobson and colleagues who showed that autistic children were limited in understanding the emotional expressions of others. Such children experienced difficulties in matching emotional expressions across facial, vocal, and gestural modalities (Hobson, 1986a,b; Hobson et al., 1988a) and they appeared not to take notice of emotional expressions when asked to sort photographs of faces in whatever way they wished (Weeks and Hobson, 1987). When they were instructed to sort faces according to their expressions, autistic children were able to do so but through a more piecemeal perceptual processing style (Hobson et al., 1988b).

The pioneering work by Hobson and colleagues remains exemplary in terms of methodological rigor and ingenuity and it also remains representative of the observations of the 100 or so studies that followed. This last conclusion may come as a surprise because brief summaries of the relevant literature in empirical papers often give the impression that it is not entirely clear whether or not autistic individuals perceive and identify emotional expressions differently. Fortunately, a recent review of the facial emotion recognition literature in ASD by Harms et al. (2010) clarifies this issue. Following their systematic scrutiny of over 40 behavioral, 7 eye-tracking, and 22 brain imaging and electrophysiological studies up to 2010, Harms et al. (2010) conclude that, despite inconsistencies in behavioral observations, there is little doubt that autistic individuals extract emotions from faces differently than comparison groups. **Tables 1** and **2** below are an attempt to complement Harms et al. (2010) by summarizing emotion perception studies in ASD across modes of expression. **Table 1** provides a brief description of behavioral studies up to April 2012 with studies failing to demonstrate convincing group differences listed first. **Table 2** summarizes

[1]A draft version of the DSM-V can be found here http://www.dsm5.org/proposedrevisions/pages/proposedrevision.aspx?rid=94

Table 1 | Studies examining emotion perception in ASD.

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
STUDIES FAILING TO NOTE ASD SPECIFIC ATYPICALITIES											
Ozonoff et al. (1990, Exp. 1)	ASD; TD	14; 14	VA	Sort static photographs of faces according to emotional expression	x	x	x				
Prior et al. (1990)	ASD; TD; DD	20; 20	VA	Match static schematic facial expressions with vocalizations, gestures, and contexts	x	x	x	x			
Loveland et al. (1997)	ASD; TD; DD	35; 23; 18	VA	Identify expressions from prosodic verbal and non-verbal vocal stimuli	x	x	x		x		
Serra et al. (1999)	PDD-NOS; TD	31; 31	CA; FSA	Explain how situational contexts influence a protagonist's actual and displayed emotions				Not specified			
Buitelaar et al. (1999)	ASD; TD; DD	40; 20; 20	CA; FSA; VA; NVA	Match static facial expressions with one another and with situational contexts	x	x	x	x	x	x	x
Adolphs et al. (2001, Exp. 1)	ASD; TD; Amyg lesion	6; 28; 3	FSA	Discriminate static facial expressions of various intensities	x	x	x	x	x	x	
Adolphs et al. (2001, Exp. 2)	ASD; TD; Amyg lesion	7; 18; 8	Not specified	Identify static facial expressions	x	x	x	x	x	x	
Gepner et al. (2001)	ASD; TD	13; 13	≠CA; FSA	Identify facial expressions from static, smooth dynamic, or strobe dynamic displays (ASD performance differently modulated by experimental manipulations)	x	x			x	x	
Hillier and Allison (2002)	ASD; TD; DD	10; 20; 10	CA; VA; NVA	Influence of audience on judgments of embarrassment of a protagonist							x
Robel et al. (2004)	ASD; TD	20; 20	CA	Identify and match static facial expressions with one another	x	x		x	x		
Castelli (2005)	ASD; TD	20; 20	VA	Identify and match static facial expressions with one another	x	x	x	x	x	x	
Ashwin et al. (2006a)	ASD; TD	18; 18	CA; FSA	Visual search for static schematic facial expressions	x		x				
Begeer et al. (2006, Test 2)	ASD; TD	28; 32	CA	Select photographs of faces according to what person is most likely to offer a sweet or tell someone off	x		x				

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Miyahara et al. (2007)	ASD; TD	20;20	CA; NVA	Identify expressions in static and dynamic real and cartoon faces (subtle group differences apparent when individual differences are explored)	x					x	
Wright et al. (2008)	ASD; TD	35; 35	CA; VA; NVA; FSA	Identify emotional expression in static faces or in richly contextual scenes (subtle group differences in relation to anger and happiness)	x		x	x	x	x	
Homer and Rutherford (2008)	ASD; TD	8; 12	CA; VA; NVA; FSA	Identify static facial expressions varying in intensity to determine category boundaries and match static expressions with one another after a delay	x	x	x	x	x	x	
Hubert et al. (2009)	ASD; TD	16; 16	CA	Identify dynamic facial expressions vs. identify the age (old/young) of the same stimuli (ASD group exhibited lower GSR responses)	x		x				
Krysko and Rutherford (2009)	ASD; TD	19; 19	CA; VA; NVA; FSA	Visual search for static facial expressions (subtle differences in terms of the effect of distracter numbers)	x		x				
Baker et al. (2010)	ASD; TD	19;19	CA	Identify emotions from prosodic vocalizations presented dichotically (one vocalization to each ear)	x	x	x				
Grossman et al. (2010)	ASD; TD	16;15	CA; VA; NVA	Identify emotions from prosodic vocalizations	x	x					
Williams and Happé (2010)	ASD; TD	21; 21	CA; VA; NVA	Define and describe experiences of target emotions and identify facial expressions of the same emotions in dynamic video-clips	x	x		x	x	x	x
Schwenck et al. (2011)	ASD; conduct disorder; TD	55; 70; 67	CA; FSA	Identify emotional expression as they emerge in dynamic face videos (subtle group differences in relation to sadness)	x	x	x	x		x	
Rosset et al. (2011)	ASD; TD	30; 30	CA	Visual search for static schematic facial expressions	x		x				
Chevallier et al. (2011)	ASD; TD	16–20; 16–20 across three Exp.	CA; VA	Identify (from two alternatives) the emotion or internal state expressed in vocalizations; ASD group performed quantitatively similar to TD but were slower to respond in Exp. 3 under high cognitive load	x	x	x	x	x	x	

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	**Sad**	**Anger**	**Fear**	**Surprise**	**Disgust**	**Other**
Jones et al. (2011)	ASD; DD; TD	99; 26; 31	CA; VA; NVA; FSA	Identify static facial expressions and expressions from prosodic verbal and non-verbal vocal stimuli (subtle group differences in relation to surprise)	x	x	x	x	x	x	
Brennand et al. (2011)	ASD; TD	15; 15	CA; ≠VA	Identify expression from prosodic vocalizations (group effect marginally significant; $p = 0.083$)	x	x	x	x			
Tracy et al. (2011)	ASD; TD	29; 31	CA; VA; NVA; FSA	Determine whether briefly presented static faces express a target emotion	x	x	x	x	x	x	x
STUDIES DEMONSTRATING EMOTION PERCEPTION DIFFICULTIES IN ASD											
Hobson (1986a)	ASD; TD; DD	23; 38; 11	CA; VA; NVA	Match static schematic facial expressions with gestures, vocalizations, and situational contexts	x	x	x	x			
Hobson (1986b)	ASD; DD	13; 13	CA; NVA	Match schematic drawings of gestures with videos of vocalizations and static facial expressions	x	x	x	x			
Weeks and Hobson (1987)	ASD; DD	15; 15	CA; VA	Sort static face photographs varying on emotional and non-emotional dimensions according to preference	x	x					
Hobson et al. (1988a)	ASD; DD	21; 21	CA; VA	Match vocal expressions with static facial expressions	x	x	x	x	x	x	
Hobson et al. (1988b)	ASD; DD	17; 17	CA; VA	Sort whole or partial static face photographs according to expression and sort upright and inverted faces according to expression or identity	x	x	x	x			
Braverman et al. (1989)	ASD; TD	15; 15	NVA	Identify and match static facial expressions with one another (no difference when matching on VA)	x	x	x	x			
Macdonald et al. (1989)	ASD; TD	10; 10	CA; NVA	Identify emotion from situational contexts and vocal recordings	x	x	x	x			
Tantam et al. (1989)	ASD; DD	10; 10	CA; NVA	Identify upright and inverted static facial expressions (no differences on identifying mismatching facial expressions)	x	x	x	x	x	x	
Ozonoff et al. (1990, Exp. 2)	ASD; TD	14; 14	NVA	Match static facial expressions with one another, with vocalizations, and with situational contexts (no difference when matching on VA)	x	x	x				

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Smalley and Asarnow (1990)	ASD; TD	9; 9	CA; NVA	Identify and match static facial expressions with one another	Not specified						
Ozonoff et al. (1991a)	ASD; DD	20; 20	CA; FSA; VA; NVA	Match static facial expressions with one another	x	x	x	x	x	x	x
Ozonoff et al. (1991b)	ASD; DD	23; 20	CA; FSA; VA; NVA	Match static facial expressions with one another	x	x	x	x	x	x	x
Capps et al. (1992)	ASD; TD	18; 14	CA; FSA; VA; NVA	Describe personal experiences of certain emotions (ASD group experienced difficulties describing pride and embarrassment)	x	x					x
Fein et al. (1992)	ASD; TD	15; 30	VA; NVA	Match static facial expressions with situational contexts	x	x	x	x			
Yirmiya et al. (1992)	ASD; TD	18; 14	CA; FSA; VA; NVA	Identify emotion experienced by protagonists in video segments and report own emotional reaction to it	x	x	x	x			x
Baron-Cohen et al. (1993)	ASD; TD; DD	15; 15; 12	CA; VA	Match schematic and photographed static facial expressions with one another	x	x			x		
Davis et al. (1994, Exp. 1)	ASD; TD; DD	20; 10; 10	CA; VA; NVA	Match static face photographs varying on emotional and non-emotional dimensions according to a sample		x	x		x		
Davis et al. (1994, Exp. 2)	ASD; TD; DD	19; 11; 20	CA; VA; NVA	Match static facial expressions with one another	x	x	x		x		
Bormann-Kischkel et al. (1995)	ASD; TD; DD	41; 41	CA; NVA	Identify static facial expressions	x	x	x	x	x	x	x
Loveland et al. (1995)	ASD; DD	28; 28	CA; ≠VA; NVA; FSA; gender	Match dynamic facial expressions with appropriate vocalizations that are either synchronous or not	x	x	x		x		
Buitelaar and van der Wees (1997)	ASD; DD/TD	40; 40	CA; VA; NVA; FSA; (TD ≠ CA and gender)	Match static facial expressions with one another and select static facial expressions to match with contextual scenes	x	x	x	x	x	x	x
Baron-Cohen et al. (1997, Exp. 3)	ASD; TD	16; 16	CA; FSA	Identify static facial expression from whole faces or only the eye-region (ASD group particularly worse on "complex" mental states)	x	x	x	x	x	x	x

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Moore et al. (1997)	ASD; TD; DD	13; 13	CA; VA	Describe point-light displays of people enacting emotional and non-emotional behaviors	x	x	x	x	x		
Celani et al. (1999)	ASD; DD; TD	10; 10; 10	CA; VA	Match static facial expressions with one another and select preferred expression	x	x					
Dennis et al. (2000)	ASD; TD	8; 8	CA; VA	Identify the emotional expression of a story character's actual feeling and the emotion that would be expressed for the purpose of deception	x	x					
Boucher et al. (2000)	ASD; DD; TD	19; 19; 19	CA; VA; NVA (TD ≠ CA)	Identify vocal expressions of emotions and match static facial expressions with vocalizations (ASD worse than TD but not worse than DD)	x	x	x	x	x	x	
Grossman et al. (2000)	ASD; TD	13; 13	CA; FSA; VA	Identify static facial expressions accompanied by no, congruent, or incongruent verbal labels	x	x	x	x	x		
Howard et al. (2000)	ASD; TD	9; 10	CA; VA;	Identify expressions from static faces	x	x	x	x	x	x	
Teunisse and de Gelder (2001)	ASD; TD	17; 48	Not specified	Identify and match static facial expressions with one another	x	x	x	x			
Pelphrey et al. (2002)	ASD; TD	5; 5	CA	Identify static facial expressions	x	x	x	x	x	x	
Bölte and Poustka (2003)	ASD; TD; schizophrenia	35; 22; 21	NVA	Identify static facial expressions	x	x	x	x	x	x	
Losh and Capps (2003)	ASD; TD	28; 22	CA; VA	Identify emotion experienced by protagonists in video segments and define emotions through verbal descriptions	x	x	x	x	x	x	x
Heerey et al. (2003)	ASD; TD	25; 21	CA; VA; FSA	Indentify static facial expressions	x	x	x	x	x	x	x
Gross (2004, Exp. 1)	ASD;DD	27; 81	CA; FSA	Identify static facial expressions of humans, orang-utans, and canines	x	x	x		x		
Gross (2004, Exp. 2)	ASD;DD	18; 30	CA; FSA	Identify static facial expressions from whole, top-half or bottom half of human, orang-utan, or canine faces	x	x	x		x		

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Gross (2005)	ASD; DD	24; 59	CA; FSA	Match static facial expressions of humans or canines with one another	x	x	x				
Ashwin et al. (2006b)	ASD; TD	26; 26	CA; FSA; VA	Identify static facial expressions	x	x	x	x	x	x	
Begeer et al. (2006, Test 1)	ASD; TD	28; 31	CA	Match static face photographs varying on emotional and non-emotional dimensions according to preference	x		x				
Golan et al. (2006)	ASD; TD	21; 17	CA; FSA; VA; NVA	Label static facial expressions and vocalizations	x	x	x	x	x	x	x
Kamio et al. (2006)	ASD; TD	18; 18	CA; FSA	Rate likeability of Japanese ideographs preceded by subliminal or supraliminal static facial expressions	x			x			
Lindner and Rosén (2006)	ASD; TD	14; 16	CA; VA	Match static facial expressions with static or dynamic facial expressions and with vocalizations	x	x	x				
Dyck et al. (2006)	ASD; DD; TD	30; 24; 449	≠CA; VA; NVA	Ability to identify emotions from static faces and prosodic vocalizations correlates atypically highly with VA in ASD	x	x	x	x	x	x	
Peppé et al. (2007)	ASD; TD	31; 72	VA; ≠CA	Prosodic assessment battery including test of ability to discern "liking" and "disliking" from prosody							x
McCann et al. (2007)	ASD; TD	31; 72	VA; ≠CA	Prosodic assessment battery including test of ability to discern "liking" and "disliking" from prosody							x
Rutherford and McIntosh (2007)	ASD; TD	10; 10	CA; VA; NVA; FSA	Decide which of two schematic facial expression drawings varying in emotional intensity looks more like the expressions seen in real life	x	x	x	x	x	x	
Ashwin et al. (2007); task outside scanner	ASD; TD	13; 13	CA; FSA	Identify static facial expressions		x	x	x	x	x	
Hubert et al. (2007)	ASD; TD	19; 19	CA	Describe point-light displays of people enacting emotional and non-emotional behaviors	x	x	x	x	x		

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Mazefsky and Oswald (2007)	AS; HFA compared to normative data	15; 14	CA; ≠VA; NVA; FSA	Identify static facial expressions and emotions from prosodic vocalizations. (HFA but not AS group compromised in comparison to normative data)	x	x	x	x			
Humphreys et al. (2007)	ASD; TD	20; 18	CA; VA; NVA; FSA	Identify static facial expressions that are blended in various proportions with one another (e.g., 20% fear – 80% surprise). (No differences when discriminating between blended emotions)	x	x	x	x	x	x	
Boraston et al. (2007)	ASD; TD	11; 11	CA; VA; NVA	Identify emotions in anthropomorphically animated shapes and in static facial expressions	x	x	x	x			
O'Connor (2007)	ASD; TD	18; 18	CA	Identify static facial expressions when presented alongside congruent or incongruent vocalizations (no differences on isolated modalities)	x	x	x				
Tardif et al. (2007)	ASD; TD	12; 24	≠CA; VA; NVA	Identify facial expressions in static images or dynamic videos varying in speed and that are or are not accompanied by concordant vocalizations	x	x			x	x	
Shamay-Tsoory (2008)	ASD; TD	18; 21	CA; years in education	Point out the target (out of four) of a character's (represented by a schematic face) envy and gloating by using emotional expressions as cues							x
Dziobek et al. (2008)	ASD; TD	17; 18	CA; FSA	Identify emotion experienced by protagonist in photographic scene and report own emotional reaction to it	Not specified						
Rosset et al. (2008)	ASD; TD	20; 40	CA; FSA	Categorize emotional expressions of upright and inverted static cartoon and human faces	x	x	x				
Santos et al. (2008)	ASD; TD	21; 21	CA	Identify static expressions from hybrid superimposed high-pass and low-pass face images	x	x					
Wallace et al. (2008, Exp. 1)	ASD; TD	28; 26	CA; VA; NVA	Identify static facial expressions	x	x	x	x	x	x	

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
Wallace et al. (2008, Exp. 2)	ASD; TD	15; 15	CA; VA; NVA; FSA	Identify expressions in static face parts (eyes only, mouth only, eyes + nose, mouth + nose, whole face)			x	x	x	x	
Corden et al. (2008a)	ASD; TD	21; 21	CA; VA; NVA; FSA	Identify static facial expressions	x	x	x	x	x	x	
Clark et al. (2008)	ASD; DD; TD	15; 10; 11	≠CA; VA	Identify emotion in briefly presented static faces	x		x				
Kätsyri et al. (2008)	ASD; TD	20; 20	CA; NVA; FSA; ≠VA	Identify expressions from static and dynamic face images that vary in the amount of low spatial frequency information	x		x	x		x	
Grossman and Tager-Flusberg (2008)	ASD; TD	25; 25	CA; VA; NVA	Order static whole face or eye-region images taken from dynamic expression videos in the correct order	x	x	x	x		x	
Da Fonseca et al. (2009)	ASD; TD	19; 19	CA	Identify emotions from situational contexts	x	x	x	x			
Kuusikko et al. (2009)	ASD; TD	57; 33	≠CA; gender	Identify expressions from the eye-region of static faces	x	x	x	x	x	x	
Akechi et al. (2009)	ASD; TD	14; 14	CA; VA; NVA; FSA	Discriminate between angry and fearful static whole face or eyes only expressions when gaze is direct vs. averted			x	x			
Rump et al. (2009, Exp. 1)	ASD; TD	19; 18	CA; VA	Identify facial expressions of varying intensities portrayed in dynamic video-clips	x	x	x	x			
Rump et al. (2009, Exp. 2)	ASD;TD	71; 72	CA; VA; NVA; FSA	Identify facial expressions of varying intensities portrayed in dynamic video-clips (particularly older adults with ASD were compromised)	x	x	x	x			
Atkinson (2009)	ASD; TD	13; 18	CA; VA; NVA; FSA	Identify emotions and instrumental action from whole body dynamic dot-light or fully illuminated bodies	x	x	x	x		x	
Bal et al. (2010)	ASD; TD	17; 38	CA; VA; NVA; FSA	Identify dynamic facial expressions as quickly as possible	x	x	x	x	x	x	
Law Smith et al. (2010)	ASD; TD	21; 16	CA; VA; FSA	Identify dynamic facial expressions varying in intensity	x	x	x	x	x	x	

(Continued)

Table 1 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied						
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other
García-Villamisar et al. (2010)	ASD; DD	19; 28	CA; ≠FSA	Identify and match static facial expressions	x	x					
Philip et al. (2010)	ASD; TD	23; 23	CA (subgroups also on FSA)	Identify emotions from face, gesture, and prosodic vocal stimuli	x	x	x	x	x	x	
Evers et al. (2011, three experiments	ASD; TD	17–23; 17–23 accross Exp.	CA; FSA	Match static facial expressions with one another or with dynamic expressions across varying task demands (ASD worse than TD as demands increase)	x		x		x	x	
Krebs et al. (2011)	ASD; TD	24; 24	CA; FSA	Classify static faces either according to emotional expression or identity. (ASD group slower in a manner that indicates qualitative differences)	x	x					
Farran et al. (2011)	ASD; TD	20; 40	subgroups on either CA or VA and NVA	Visual search for static facial expressions	x	x	x	x	x	x	
Mathewson et al. (2011)	ASD; TD	15; 16	CA; FSA	Emotional Stroop (name color of static face stimuli) and identify emotional expression of static faces	x			x			
Rutherford et al. (2012)	ASD; TD	19; 10	CA; FSA	Examination of expression adaptation effects (the phenomenon whereby prolonged exposure to a particular emotion biases one to perceive an opposing emotion on a subsequent neutral face)	x	x	x	x	x	x	
Heaton et al. (2012)	ASD; TD	20; 20	CA; VA; NVA; FSA	Identify emotions in prosodic vocalizations	x	x	x	x	x	x	
Wong et al. (2012)	ASD; social phobia; TD	19; 17; 21	≠CA; gender	Identify static facial expressions of varying intensities	x	x	x	x		x	

ASD, autism spectrum disorder; HFA, high functioning autism; TD, typically developing; DD, developmental delay; CA, chronological age; VA, verbal ability; NVA, non-verbal ability; FSA, full-scale ability; ≠, groups are not matched on this variable.

Table 2 | Studies examining the brain correlates of emotion perception in ASD.

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied							Principal brain related findings
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other	
Critchley et al. (2000)	ASD; TD	9; 9	CA; FSA	Identify expression vs. identify gender of briefly presented expressive faces	x		x					↓lSTG, lLG, ↓rFG, ↓lAmyg (only in implicit gender disk)
Hall et al. (2003)	ASD; TD	8; 8	CA; NVA	Match facial expression with emotional prosody	x	x	x		x			↓lIFG, ↓lLG, ↑rTP, ↑lACC, ↓rFG
Hubl et al. (2003)	ASD; TD	7; 7	CA; NVA	Detect happy faces vs. detect female faces vs. scrambled face baseline vs. geometric shape visual perception task	x	x	x					↓FG and subtle ↓INS
Oagi et al. (2003)	ASD; TD	5; 5	CA; VA; NVA; FSA	Concentrate on identifying static facial expressions (actual performance tested after scanning)	x			x		x		↓lINS, ↓lIFG, ↓lMFG, ↓lputamen
Piggot et al. (2004)	ASD; TD	14; 10	CA; FSA; VA; NVA	Match static facial expressions with one another vs. identify static facial expressions vs. match geometric shapes with one another			x	x	x			↓FG during matching
Wang et al. (2004)	ASD; TD	12; 12	CA; VA	Match static facial expressions with one another vs. identify static facial expressions vs. match geometric shapes with one another			x	x				↓FG, ↓task modulation of rAmyg; marginal ↑precuneus
Dawson et al. (2004)	ASD; TD	29; 22	CA; subgroup also on FSA	Passive viewing of static facial expressions				x				↓Emotion modulation of N300 and NSW (≈800–1200 ms)
Dalton et al. (2005, Exp1.)	ASD; TD	11; 12	CA	Identify whether or not an emotion is expressed in faces with direct or averted gaze	x		x	x				↓FG, ↑lAmyg, ↓rMFG, ↑lOFC
Kujala et al. (2005)	ASD; TD	8; 8	CA	Determine when the prosody of a spoken word ("Saara") deviated from neutral (on 21% of trials)		x	x				x	↓N300 to anger, topographical differences over frontal electrodes
O'Connor et al. (2005)	ASD; TD	30; 30	CA	Identify static facial expressions	x	x	x	x				Delayed P1, ↓N170; diff. more marked in adults than children
Dapretto et al. (2006)	ASD; TD	10; 10	CA; FSA	Imitate vs. observe static facial expressions vs. null events baseline	x	x	x	x				↓rIFG, ↓rINS, ↓rAmyg, ↑visual processing areas

(Continued)

Table 2 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied							Principal brain related findings
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other	
Ashwin et al. (2007)	ASD; TD	13; 13	CA; FSA	Respond as quickly as possible when a face is shown; faces expressing no fear, mild fear, or extreme fear presented randomly among scrambled faces				x				↓lOFC, ↓lAmyg, ↑rACC, ↑rSTS, ↑STG; ↓signal mod. by fear intensity
Deeley et al. (2007)	ASD; TD	18; 9	CA; FSA; VA; ≠NVA	Identify the gender of static faces expressing various intensities of emotions	x		x		x			↓FG, ↓LG, ↓mOG, ↓IOG; ↓signal mod. by intensity
Pelphrey et al. (2007)	ASD; TD	8; 8	CA; VA; NVA; FSA	Respond when a face appears on the screen; static expressive and neutral faces and dynamic emotion and identity morphs were presented			x	x				↓lFG, ↓lMFG, ↓rAmyg, ↓rSFG, ↓MTG, ↓rSTS; ↓mod. by static vs. dynamic emotions
Korpilahti et al. (2007)	ASD; TD	14; 13	CA	Passive listening (while watching a silent cartoon) of two one-word prosodic utterances			x					Ealiere and ↓N1, ↑eMMN (at around 200 ms)
Wicker et al. (2008)	ASD; TD	12; 14	CA	Identify emotion vs. identify age (young/old) of face stimuli where gaze direction changes dynamically from averted to averted or averted to direct	x		x					↓rTPJ, ↓rIFG, ↓SFG; ↓Amyg – frontal and frontal – STS connectivity
Wong et al. (2008)	ASD; TD	10; 12	CA; NVA	Identify gender of or discriminate emotion (against neutral) of static face stimuli	x	x	x	x				No group diff. for P1 and N170; ↑P2 mod. by expression; dipole source diff. in FG, MFG, left cuneus, and precuneus
Corbett et al. (2009)	ASD; TD	12; 15	CA; ≠FSA	Determine whether two static face images are of the same emotion or person vs. whether two static abstract shapes are the same	x	x	x	x				↓rFG, ↓lAmyg, ↑lSPL, ↑lMFG/IFG
Hadjikhani et al. (2009)	ASD; TD	12; 7	CA	Match static body postures of different individuals with one another		x	x	x				↓Amyg, ↓FG. ↓INS, ↓IFG, ↓putamen, ↓premotor, ↓pulvinar, ↓colliculus, ↓accumbens

(Continued)

Table 2 | Continued

Reference	Participant groups	*N*	Matching	Paradigm	Emotional expressions studied							Principal brain related findings
					Happy	Sad	Anger	Fear	Surprise	Disgust	Other	
Grézes et al. (2009)	ASD; TD	12; 12	CA; FSA	Oddball paradigm in which participants needed to detect 10 upside-down stimuli amongst static and dynamic body postures/movements				x				↓rAmyg, ↓lFG. ↓rPrecentral gyrus, ↓rITG (in fear vs. neutral contrast)
Greimel et al. (2010)	ASD; TD	15; 15	CA; VA; FSA; ≠NVA	Identify static facial expressions varying in intensity vs. report own emotional response to the same facial expressions	x	x						↓lIFG, ↓rFG (in self-report condition)
Kleinhans et al. (2010)	ASD; TD	29; 25	CA; VA; NVA; FSA	Match static facial expressions with one another vs. match shapes with one another			x	x				↓lIFG, ↑occipital lobe; rFG, ITP, and rAmyg activity to emotional faces correlated with anxiety
Monk et al. (2010)	ASD; TD	12; 12	CA; VA; NVA	Indicate the left/right position of an asterisk that is shown after static face pairs that include an emotional and neutral expression (or two neutral)	x	x	x					↑rAmyg; ↑rAmyg – ACC, ↓rAmyg – IMTG, and ↓rAmyg – IFG connectivity
Schulte-Rüther et al. (2011)	ASD; TD	18; 18	CA; VA; NVA (marginal); FSA	Identify static emotional expressions vs. report own emotions in response to these expressions								↑rdMPFC, ↓vMPFC, ↓precuneus/PCC in "other" task; ↑rdMPFC, ↑rMFG, ↑rIFC, ↑STS in "self" task
Bastiaansen et al. (2011)	ASD; TD	21; 21	CA; FSA	Observe dynamic facial expressions vs. express emotion vs. experience emotion	x					x		IFG activity correlated with CA only in ASD group
Davis et al. (2011)	ASD; TD	16; 16	CA; VA; NVA; FSA	Passive viewing of static facial expression with averted or direct gaze	x		x	x				↓vlPFC
Weng et al. (2011)	ASD; TD	22; 22	CA; VA; ≠NVA	Identify the gender of static faces expressing emotions; outside scanner identify the emotional expressions	x	x		x				↑Amyg, ↑striatum, ↑lFG; negative Amyg – CA correlation in ASD only

ASD, autism spectrum disorder; TD, typically developing; CA, chronological age; VA, verbal ability; NVA, non-verbal ability; FSA, full-scale ability; ≠, groups are not matched on this variable. l, left hemisphere; r, right hemisphere; ↑, increased signal contrast in ASD vs. comparison group; ↓, decreased signal contrast in ASD vs. comparison group. ACC, anteriro cingulate cortex; Amyg, amygdala; FG, fusiform gyrus; IFG, inferior frontal gyrus; INS, insula; LG, lingual gyrus; MFG, middle frontal gyrus; dMPFC, dorsomedial prefrongal cortex; vMPFC, ventromedial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; SPL, superior parietal lobe; TP, temporal pole; TPJ, temporal-parietal junction.

functional brain based studies for the same period[2]. In line with Harms et al. (2010), the available evidence reveals inconsistencies in behavioral findings with approximately one in every four studies failing to demonstrate atypical emotion perception in ASD. These inconsistencies do not appear to be systematically related to a single methodological factor such as the nature of the experimental paradigm used, the type or number of emotions studied, or sample characteristics (e.g., age, ability level) including the procedures used to match ASD and comparison groups (e.g., VA vs. NVA). In combination these factors do account for some of the inconsistencies and certain co-morbidities also appear to play a role (e.g., Cook et al., in press). Importantly, however, brain based studies reveal atypical neural correlates of emotion perception relatively consistently in ASD, suggesting that not all behavioral paradigms are sensitive to qualitative differences in *how* autistic individuals extract emotional information from the face. Overall therefore, the conclusions by Harms et al. (2010) in relation to facial emotion recognition hold for emotion perception on the whole, and to the best of my knowledge, no authors have ever claimed that autistic individuals identify and understand the emotional expressions of others in an entirely typical fashion.

Although studies of emotion perception are by far the most numerous, there is also a considerable literature on other facets of emotion related interpersonal behaviors in ASD (see Begeer et al., 2008 for a recent review). For instance, it is fairly consistently reported that autistic individuals are less likely than non-autistic individuals to direct emotional expressions at others during naturalistic interactions (Snow et al., 1987; Macdonald et al., 1989; Mundy and Sigman, 1989; Yirmiya et al., 1989; Dawson et al., 1990; Kasari et al., 1990, 1993; Sigman et al., 1992; Dissanayake et al., 1996; Charman et al., 1997; Joseph and Tager-Flusberg, 1997; Bieberich and Morgan, 1998; Zwaigenbaum et al., 2005; Hobson et al., 2009; Hudenko et al., 2009). Autistic individuals also tend to mimic the facial expressions of others less frequently and consistently than non-autistic individuals (McIntosh et al., 2006; Beall et al., 2008; Stel et al., 2008; Oberman et al., 2009; but, see Magnée et al., 2007; see also Sims et al., 2012) and they share the emotional experiences of others in a qualitatively different manner than comparison groups (Yirmiya et al., 1992; Baron-Cohen and Wheelwright, 2004; Lombardo et al., 2007; Rogers et al., 2007; Dziobek et al., 2008; Hobson et al., 2009; Hurdy and Slaughter, 2009; Minio-Paluello et al., 2009a; Bird et al., 2010; Greimel et al., 2010; Schulte-Rüther et al., 2011; Schwenck et al., 2011; see also the discussion between Minio-Paluello et al., 2009b; Smith, 2009). Although findings in this context are not always consistent (see Begeer et al., 2008), the weight of the evidence overall leaves little doubt that ASD is characterized by anomalies in multiple facets of interpersonal affective behaviors, and the real life consequences of these have been documented in a series of elegant naturalistic observations by Sigman and Kasari and their colleagues (Sigman et al., 1992; Dissanayake et al., 1996; Corona et al., 1998; see also Loveland and Tunali, 1991; Bacon et al., 1998; see also Hobson et al., 2009). In these studies, children with and without a diagnosis of ASD were videoed as they interacted with an experimenter or parent who suddenly expressed distress, fear, or discomfort. Not surprisingly, children with learning difficulties and typically developing children responded to the adult's expressions by interrupting their play behavior and orienting to the adult, often with marked concern. Autistic children, on the other hand, were more inclined to keep playing with their toys even when physiological arousal responses indicated that they had registered the event at some level (Bacon et al., 1998; Corona et al., 1998). An important consequence of this was that autistic children did not acquire avoidance behaviors toward the stimuli that had elicited the negative emotions in the adult. In other words, they were not only less attentive to the emotional displays of others but also missed opportunities to learn about the hedonic significance of objects in their environment as a result.

The evidence set out thus far suggests that autistic individuals are limited in multiple aspects of emotionally patterned communication. Laboratory experiments and naturalistic observations converge in showing that emotional expressions are not particularly salient to autistic individuals and although they identify emotional expressions during some circumstances, they appear not to engage the same processes in order to do so. They also make fewer attempts to initiate emotional exchanges and together these differences afford autistic individuals fewer opportunities to share their emotional experiences with others and to learn about the hedonic significance of environmental stimuli through them (see also Hobson, 1993, 2002). That these disturbances exist and that they have consequences for the developmental trajectory of the disorder is no longer disputed. What continues to divide opinion is what causes this facet of ASD in the first place.

THE THEORIES

Many theoretical frameworks are relevant to the social-emotional characteristics of ASD, including those that identify anomalies in domain-general processes such as perception, attention, learning, and executive function as critically important in mapping the developmental trajectory of the disorder. The focus of this review, however, lies with a group of theories that consider social-emotional difficulties in ASD to be the result of atypicalities in relatively domain specific processes that operate primarily (or even exclusively) in the context social interactions[3]. These theories include the idea that atypicalities in the development of a neural network mediating social-motivation are responsible (e.g., Dawson and Lewy, 1989; Schultz et al., 2003; Dawson et al., 2005; Schultz, 2005; Chevallier et al., 2012), the suggestion that differences in the self regulation of behavior play a critical role (e.g., Loveland, 2005; Bachevalier and Loveland, 2006), the view that a deficient mechanism for the understanding of mental states is to blame (e.g., Leslie and Frith, 1990; Baron-Cohen, 1995;

[2]Relevant studies were identified through cited reference searches and through a combination of search terms ("ASD" or "Autism," "Emotion Perception," "Emotion Recognition") in the Web of Knowledge. Studies are only included in the tables if (a) they included a comparison group, (b) the minimum sample size was at least five ASD and five comparison participants, and (c) at least one of six basic emotions (happy, sad, angry, fear, surprise, and disgust) was studied. The last criterion was loosened somewhat to allow for the inclusion of four studies that used other concretely defined emotions of interest (Hillier and Allison, 2002; Peppé et al., 2007; McCann et al., 2007; Shamay-Tsoory, 2008).

[3]Readers interested in the broader theoretical literature relating to ASD should consult the exhaustive overview by Bowler (2007).

Baron-Cohen et al., 2000; Frith, 2003) and the notion that a disruption in an infant's readiness to *relate to* and *identify with* the psychological orientations of others lies at the root of the problem (e.g., Hobson, 1993; Hobson, 2002; see also Loveland, 2005).

Social-motivational accounts

Social-motivational theories originate in observations of atypical face processing in ASD (see Weigelt et al., 2012 for a critical review). As noted above, one of the early studies by Hobson et al. (1988b) suggested that autistic children engage unusual perceptual processes to extract emotional expressions from faces, which several subsequent studies have confirmed (e.g., Tantam et al., 1989; Davis et al., 1994; Teunisse and de Gelder, 2001; Gross, 2005; Deruelle et al., 2008b). It has also become apparent, however, that atypical face processing interferes not only with the perception of emotional expressions but also with the perception of non-emotional information such as an individual's identity (e.g., Boucher and Lewis, 1992; Davis et al., 1994; Boucher et al., 1998; Joseph and Tanaka, 2003; Deruelle et al., 2008b; Wallace et al., 2008), age (Hobson, 1983; Gross, 2002, 2005), or gender (Deruelle et al., 2004). Moreover, eye-tracking studies suggest that autistic individuals fixate less on faces than non-autistic individuals when viewing complex social scenes and even when they do, they look less at the eye-region and more at the mouth or non-feature regions of the face (Klin et al., 2002; Pelphrey et al., 2002; Dalton et al., 2005; Speer et al., 2007; Spezio et al., 2007; Corden et al., 2008b; Bird et al., 2011; see Senju and Johnson, 2009 for further discussion). Broader than emotion related atypicalities in social perception are also evident in relation to biological motion (e.g., Moore et al., 1997; Blake et al., 2003; Cook et al., 2009; Koldewyn et al., 2011; Annaz et al., 2012) and vocalizations (McCann et al., 2007; Peppé et al., 2007). Thus, difficulties in the processing of emotional expressions can be seen to constitute only part of a broader anomaly in the perception and understanding of the social environment (i.e., other people).

To explain widespread social-perceptual difficulties, several authors have contributed to a social-motivational theory, which argues that a lack of motivation to attend to and interact with others early in life leads to the divergent development of a social brain network that is critical for the perception and understanding of the social environment (Grelotti et al., 2002; Schultz et al., 2003; Dawson et al., 2005; Schultz, 2005; Chevallier et al., 2012). The basic tenets of this account are the following. First, that human interaction is inherently rewarding. Second, that ASD is the result of a dysfunctional neural network comprising the amygdala, striatum, and orbital-frontal cortex that mediates both the experience and seeking of such reward. Third, that the consequence of this dysfunction is that autistic infants orient less to the social environment, thus compromising the maturation of a broader social brain network that encompasses areas critical for face processing (e.g., Fusiform Gyrus; see Kanwisher, 2000), mental state understanding (Superior Temporal Sulci, Medial Prefrontal Cortex, Temporal Poles, see Gallagher and Frith, 2003), and empathy/interpersonal affective behaviors (Anterior Cingulate Cortex, Anterior Insula, Amygdala, Striatum; see Baron-Cohen, 2005; Singer, 2006; Singer and Lamm, 2009). And finally, social-motivational accounts argue that it is the dysfunction of this broader social brain network that ultimately yields the clinically defining reciprocal social impairments of ASD, including the difficulties we, see in social-emotional behaviors. This account is consistent with a large body of evidence (Schultz, 2005; see Dawson et al., 2005; Grossmann and Johnson, 2007; Chevallier et al., 2011 for relevant reviews) that I will return to in more detail shortly when considering the concept of a "social brain" more closely.

The behavioral self regulation account

The view put forward by Loveland and colleagues (Loveland, 2001, 2005; Bachevalier and Loveland, 2006) in many ways complements the social-motivational view. Loveland points out that ASD is characterized by difficulties not only with respect to the perception of social-emotional signals but also with regards to the regulation of behavior in response to these signals. At first, this may seem a trivial point since it should come as no surprise that an individual who experiences difficulties in perceiving certain properties of the world should also respond to these properties differently. Loveland's arguments, however, are far from trivial, because they stress that perception and action are intimately linked (see Merleau-Ponty, 1964; Fogel, 1993 for additional discussion). Perceiving the emotional significance of someone else's facial and postural expressions is of little use if one does not know how to respond appropriately, and not understanding the behavioral affordances of emotional signals may be reason enough not to attend to them in the first place. Thus social-emotional difficulties in ASD may not arise because of a lack of motivation *per se* but because of a lack of understanding what emotional signals afford. Support for this argument stems from the studies by Sigman and Kasari and colleagues outlined earlier in which autistic children were consistently less responsive to the emotional displays of others (Loveland and Tunali, 1991; Sigman et al., 1992; Yirmiya et al., 1992) despite demonstrating an awareness of the emotional displays in question (Bacon et al., 1998; Corona et al., 1998). The behavioral self regulation view is also in line with studies that demonstrate typical physiological but atypical behavioral separation anxiety in autistic children (Willemsen-Swinkels et al., 2000; Sigman et al., 2003) and more generally it helps to explain why studies of emotion perception tend to yield less consistent behavioral differences between ASD and non-ASD groups than studies examining the ability to use such expressions to regulate interpersonal exchanges. At the neural level, Bachevalier and Loveland (2006) largely agree with the idea that abnormalities in a social brain network are likely to lie at the root of the developmental trajectory of ASD. They particularly emphasize interactions between the orbital-frontal cortex and amygdala as key to understanding the disorder, citing abundant evidence to support the idea that these areas play a critical role in the self regulation of behavior during social-emotional exchanges.

The interpersonal relatedness account

A view closely related to the behavioral self regulation account is that developed by Hobson (1993, 2002, 2012) who, like Loveland (2005), emphasizes the need to consider the social-emotional characteristics of ASD within the context of *inter*personal processes that encompass perception as well as action. Hobson, however, goes one step further by arguing that people do not simply inter*act*,

they *identify with* and *share* the psychological orientations and attitudes (including emotional) of others. This concept of "*interpersonal engagement*" may seem difficult to operationalize at first, but observers can reliably determine whether or not two individuals are engaged or not (Hobson and Lee, 1998; García-Pérez et al., 2007). Moreover, very persuasive arguments have been made about the utility of this concept in understanding both typical and atypical forms of interpersonal behavior (Hobson, 1993, 2002, 2012; Hobson and Lee, 1999; Agnetta and Rochat, 2004; Hobson and Meyer, 2005; Meltzoff, 2007; Hobson et al., 2009).

In relation to the social-emotional characterization of ASD, two aspects of Hobson's theory are important to highlight. First, he stresses that the earliest interactions between an infant and her caretakers are emotionally very rich. Caretakers exaggerate their emotional expressiveness and infants react to these with emotional expressions of their own (see Nadel and Muir, 2005 for a collection of reviews). Second, and similar to Loveland (2001, 2005), Hobson (2002) highlights the fact that perception and action are closely interlinked, which is evident soon after birth in the form of "entrainment" whereby infants synchronize their general motility levels with the patterning of adult speech (e.g., Condon, 1979; Kato et al., 1983). Whether innately specified or not, Hobson argues that the synchronized and emotionally patterned quality of early social exchanges forms an ideal and necessary basis for the development of interpersonal engagement (see also Trevarthen's concept of "primary intersubjectivity"; e.g., Trevarthen, 1979). It allows the infant first to discover a connection between her own behaviors and that of others, and through that a connection between behaviors and subjective experiences. In other words, the co-ordinated and affectively rich interactions with others early in life, lays the foundation for the infant to discover that other people are "like me." The argument in relation to ASD is that this capacity to *identify* with others never fully matures. Although Hobson does not emphasize the neural basis of interpersonal engagement and identification, his account is clearly in line with the notion of a social brain dysfunction and resonates with reports of atypical brain correlates of empathy in ASD (Greimel et al., 2010; Schulte-Rüther et al., 2011; but, see Bird et al., 2010)[4].

The mentalizing account

The final explanation to set out before drawing this section to a close is the idea that social-emotional difficulties in ASD are the result of a mentalizing impairment. Mentalizing[5] refers to the ability to understand, describe, and explain behavior in terms of mental phenomena (e.g., beliefs, desires, intentions, etc. . .) and it is well established that autistic individuals experience difficulties in this domain across a wide range of contexts (Frith, 2001, 2003; see Baron-Cohen, 2001; Boucher, 2012 for reviews). Given that emotions are, at least in part, mental phenomena, it is relatively straightforward to see how an impairment in mentalizing would have repercussions for emotion related social behaviors. Nevertheless, it is useful to consider one of the most detailed formulations of such an account more closely.

Baron-Cohen (1995, 2005) argues that the ability to mentalize reflects the operation of a Mindreading System that consists of six neuro-cognitive mechanisms – The Intentionality Detector (ID), Eye Direction Detector (EDD), Emotion Detector (TED), Shared Attention Mechanism (SAM), Theory of Mind Mechanism (ToMM), and The Empathizing System (TESS). In typical development, ID, EDD, and TED functionally mature first (between birth and 9 months of age) and endow infants with the ability to comprehend *Agent-Object* relations in terms of mental processes such as "wanting" something (ID), "seeing" something (EDD), or being "angry" about something (TED). In ASD, the functions of ID, EDD, and TED are thought to be qualitatively preserved although their development may be delayed. Next to mature in typical development (between 9 and 18 months) is SAM, which uses the dyadic representations from ID, EDD, and TED to compute more complex triadic representations of *Self-Agent-Object* relations. These representations allow infants to understand that the object of their own mental scrutiny may also be the object of another agent's mental scrutiny thus marking the beginnings of joint attention behaviors such as gaze monitoring, protodeclarative pointing, and social referencing. The relative absence of such behaviors is the first reliable clinical marker of ASD (Luyster et al., 2009; see Bruinsma et al., 2004 for a review). Since SAM integrates information from EDD and TED, a developmental failure of SAM should result in particular difficulties to extract mental states including emotions from the eye-region of the face. Both eye-tracking (e.g., Dalton et al., 2005) and behavioral evidence (Baron-Cohen et al., 1997, 2001) lend support to this notion. The final components of the Mindreading System to mature are ToMM (between 18 and 48 months) and TESS (around 14 months), which allow the developing child to understand that mental phenomena do not always represent the world as it truly is (ToMM) and to respond to a subset of mental phenomena – emotions – with appropriate empathy (TESS). Both of these competences are compromised in ASD (see Frith, 2003; Minio-Paluello et al., 2009b; Smith, 2009) although arguments have been levied against this conclusion (e.g., Bowler et al., 2005; Bird et al., 2010).

Similar to the accounts set out earlier, the notion of mentalizing difficulties is fully compatible with the idea that ASD is the result of a social brain dysfunction. Superior temporal and medial prefrontal regions involved in mentalizing constitute a core component of the social brain and Baron-Cohen (1995, 2005) highlights the amygdala as particularly important because of its known sensitivity to social-emotional information (Baron-Cohen et al., 2000; Buchanan et al., 2009). At the cognitive-developmental level, the mentalizing account diverges somewhat from the other three theories set out above, which consider the developmental trajectory of ASD to begin at birth, or soon thereafter. The mentalizing framework, by contrast, considers the failure of SAM to develop at 9–18 months as the starting point of the disorder (see Boucher, 2012 for an excellent discussion of the developmental plausibility of mentalizing accounts).

[4]This study showed that atypical empathic brain responses in ASD can be accounted for by co-morbid Alexithymia in this disorder, a point to which I will return in more detail in Section "Reconsidering the Role of Emotion Related Processes in the Development of Autism Spectrum Disorders."

[5]Although the term "Theory of Mind" is often employed to describe this ability, "mentalising" is preferred here to avoid the implication that mental states are understood through a process of theorising or inference – a view that is endorsed by some (e.g., Astington and Gopnik, 1991; Gopnik et al., 1999; Perner, 1991) but not all (e.g., Gordon, 1996; Hobson, 1991, 1993, 2002).

SUMMARY

I hope to have substantiated the three claims that I set out at the beginning of this section. First, that it is well established that autistic individuals experience difficulties in multiple aspects of interpersonal emotional behaviors and processes. Second, that a group of influential explanations of these limitations consider them as a facet or consequence of broader impairments in reciprocal social competences. And third, that it is widely believed that the neural basis of these impairments is a dysfunctional social brain network comprising regions of temporal and frontal cortex as well as sub-cortical limbic and striatal regions. In the next section I will consider the notion of a "social brain" more closely and suggest that its conceptualization in these terms – i.e., as a *social* brain – ignores many of the functions of its components that are critical for far more domain-general emotion related processes. More specifically, I am going to argue that it is premature to assume that only the "social" functions of the autistic brain are compromised.

THE SOCIAL BRAIN AND ITS DOMAIN-GENERAL RESPONSIBILITIES

Although the neuropathology of ASD is widespread and characterized by a complex developmental trajectory (Akshoomoff et al., 2002; Redcay and Courchesne, 2005; Courchesne et al., 2011), post-mortem, and structural imaging studies highlight the cerebellum, limbic regions (amygdala, hippocampus, insula, and cingulate cortex), temporal cortical areas (particularly the Fusiform Gyrus and Superior Temporal Sulcus), the dorsal striatum (Putamen and Caudate), and portions of the frontal lobes (Inferior, Medial, Middle, and Superior frontal gyri) as key regions of abnormality in the disorder (see Stanfield et al., 2008; Radua et al., 2010; Cauda et al., 2011; Duerden et al., 2012; Nickl-Jockschat et al., 2012 for reviews). At the functional level, the significance of cerebellar abnormalities is only just beginning to be understood (Strick et al., 2009; Schmahmann, 2010; Halloran et al., 2012) but it is consistently demonstrated that abnormalities in the striatum, limbic system (amygdala and cingulate cortex), temporal cortices (superior temporal sulcus and gyrus, fusiform gyrus, and temporal poles), and frontal cortical areas (medial prefrontal, orbitofrontal, and insular cortices) are linked to facets of the social-emotional impairments characterizing ASD (see Di Martino et al., 2009; Minshew and Keller, 2010; Sugranyes et al., 2011; Philip et al., 2010, 2012; Vissers et al., 2012 for reviews; see also **Table 2**). An abundance of evidence from neurotypical and other clinical populations furthermore supports a role of these same regions in social cognition and behavior (see Kanwisher, 2000; Gallagher and Frith, 2003; Singer, 2006; Adolphs, 2009; Singer and Lamm, 2009). In short, there is little doubt that "social functions" of the autistic brain operate differently.

A developmental perspective adds further weight to the above conclusion, particularly as formulated by social-motivational theories. The seminal work by Johnson and colleagues demonstrates that social brain functions are not entirely innately specified but rather subject to developmental maturation (see Karmiloff-Smith, 1998; Johnson, 2000, 2003, 2011; Johnson et al., 2009). What does seem to be innately specified is a drive to attend particularly to the social environment, or to stimulus patterns that bring about attention biases to the social world. Soon after birth, for instance, babies preferentially orient to stimulus configurations that contain more elements in the top than the bottom half, thus leading to a preference to attend to face stimuli over most non-face stimuli (Johnson et al., 1991; Valenza et al., 1996; Macchi Cassia et al., 2004). Similarly, they prefer to listen to speech sounds over non-speech sounds (Vouloumanos and Werker, 2004). These early attention biases provide the system with the necessary experience to drive the maturation of more and more specialized social-perceptual and social-cognitive functions. Recent studies suggest that 14 month old toddlers who go on to develop ASD demonstrate less of a preference to orient toward social over non-social stimuli (moving children vs. animated geometric patterns) than toddlers who do not develop the disorder (Pierce et al., 2011). Similarly, toddlers who go on to receive a diagnosis demonstrate atypical brain responses to speech stimuli over non-speech stimuli when they are asleep (Eyler et al., 2012). Thus, the existing evidence clearly supports the notion that the developmental trajectory of ASD is characterized by early emerging anomalies in social orienting and the processing of the social environment more generally. Does this mean that such anomalies are the *cause* of the developmental trajectory of the disorder? Not necessarily. To date, there is no convincing evidence to suggest that autistic infants process *specifically* "social" information differently. It is equally possible that ASD is characterized by more general atypicalities in orienting to and processing of biologically relevant stimuli of which other people are merely an example. A closer look at the concept of the "social brain" will show that this alternative is not farfetched.

History has taught us that describing a collection of neural structures under an umbrella that implies a domain specific function can introduce unwanted biases in our perceptions of what certain parts of the brain are important for. Thus when Papez (1937) first described the neuroanatomical basis of emotions and MacLean (1949) later introduced the concept of the "visceral brain," they inadvertently diverted attention from the critical role of the hippocampus in memory. In this vein, it is important not to lose sight of the fact that the areas purported to constitute the social brain are involved in a lot more than mediating social behaviors and cognitions (see Adolphs, 2003, 2009). The medial prefrontal cortex, for instance, is not only involved in mentalizing (Gallagher and Frith, 2003) but also more generally in the control of decision making and decision outcome monitoring (Ridderinkhof et al., 2004). The Fusiform Gyrus, though critical for face processing (see Kanwisher, 2000), is also involved in the processing of stimuli relevant to ones' area of expertise (Gauthier et al., 2000). Middle and superior temporal cortices play a role in language processing (Price, 2010) and social perception (Allison et al., 2000) but also in the general representation of abstract meaning (Binder and Desai, 2011). And of most interest in relation to the social-emotional characteristics of ASD, the striatal, and limbic areas of the social brain are critical for mediating the domain-general interactions between emotion and cognition that are of interest in the series of articles comprising this "Special Topic."

The amygdala is well known to be critical for alerting us to biologically relevant events in the environment and to prepare us for action by mobilizing physical as well as cognitive resources. Direct sub-cortical afferents from all sensory modalities allow for the "quick-and-dirty" detection of potentially significant stimuli in

the environment. Should a rapid response be required, direct efferent connections with hypothalamic and brain-stem nuclei activate arousal systems and "fight-or-flight" responses. A vast network of cortical inputs moderates this sub-cortical system and provides the means for a more controlled response to the environment and a multitude of reciprocal connections with cortical as well as sub-cortical regions allows the amygdala to moderate a wide range of cognitive processes, ranging from perception and attention, through memory and decision making to the most human of capacities – self aware thought (see LeDoux, 1995, 1996; Aggleton, 2000; Lane and Nadel, 2000; Davis and Whalen, 2001; Zald, 2003; Phelps, 2006; Whalen and Phelps, 2009; Dolcos et al., 2011; Ray and Zald, 2012 for a collection of relevant reviews). The dorsal striatum has equally widespread influences. In conjunction with frontal cortical regions and also the amygdala, it is involved in alerting us to reward contingencies in the environment and to facilitates decision making processes to optimize our chances of benefiting from them (e.g., Balleine et al., 2007; Delgado, 2007). There is no doubt that all of these processes are important for navigating the social world successfully – few processes are not! But before we conclude that *only* the processes relevant to dealing with the social environment are compromised in ASD we must examine these broader functions of the "social brain" carefully and consider how they might contribute to the developmental trajectory of the disorder. Closer scrutiny of the mechanisms that mediate the impact of emotion on cognition, in this context, seems particularly pertinent.

WHAT DO WE KNOW ABOUT THE IMPACT OF EMOTION ON COGNITION IN ASD?

AROUSAL RESPONSES IN ASD

Before we consider how the emotional salience of stimuli impacts on cognitive processes in ASD, it is important to establish to what extent environmental events elicit emotional experiences in this disorder in the first place. Stimulus elicited arousal responses such as changes in cardiac activity, galvanic skin responses (GSRs), or pupil dilation are of considerable interest in this context. **Table 3** summarizes studies that have examined such responses in ASD since 1980[6], grouped according to whether arousal was assessed in response to simple sensory stimuli, stimuli varying in emotional significance, stimuli varying on some social dimension (e.g., emotional expression, absence/presence of significant other, gaze direction, etc.), or stress induction procedures. The results are tabulated in terms of whether groups differed with respect to the overall magnitude of arousal responses (Mag.) and/or the extent to which arousal responses differentiated between stimulus categories and/or experimental conditions (Diff.).

Overall, the literature is clearly extremely varied. Importantly, however, there is little evidence to suggest that autistic individuals are either consistently hyper- or hypo-aroused by the social environment. Rogers and Ozonoff (2005) reached a similar conclusion in relation to simple sensory stimuli and it is curious that both the sensory and social environment should yield a mixed pattern of arousal responses in ASD. This varied pattern contrasts the observations of studies examining arousal responses to emotionally salient pictures, words, or narratives where responses to different stimulus categories are sometimes less differentiated but on the whole response magnitudes are relatively preserved. One could formalize this pattern by suggesting that autistic individuals only demonstrate typical arousal responses in relation to stimuli that are relatively unambiguous and invariable with respect to their emotional significance (e.g., spiders, startling noises, profanities, etc.). Responses to more ambiguous stimuli (e.g., arbitrary sensory stimuli or other people), on the other hand, are compromised in a manner that leads to very variable patterns of arousal across contexts. To illustrate, consider the contrast between the emotional significance of profanities and that of the ever-changing behaviors of other people. Profanities, no doubt, acquire their emotional significance within the context of social interactions. Early in development, they are typically encountered in highly emotive situations. A toddler might utter a profanity not knowing what it meant and be scolded, or he may witness a heated argument and be frightened by the aggression on display. Either way, encounters with profanities would fairly reliably be associated with the experience of fear. By contrast, encounters with other people are associated with a whole range of emotional experiences. One moment the adult smiles, the next he scolds and after that he may look puzzled, indifferent, or surprised. Probabilistically, therefore, profanities are associated much more reliably with a particular pattern of emotional experience than encounters with other people (or ambiguous sensory stimuli) and studies of associative learning suggest that this difference is critical in the context of ASD.

LEARNING ABOUT THE EMOTIONAL SIGNIFICANCE OF ENVIRONMENTAL EVENTS

One of the most important functions of the amygdala is to mediate the associative learning processes through which an organism is able to predict potential danger or reward. The nature of these processes has been studied most extensively through aversive and appetitive conditioning paradigms in which essentially neutral sensory stimuli come to elicit avoidance or approach behaviors because of their predictive validity over inherently harmful or pleasant events (for detailed reviews, see LeDoux, 1995, 1998, 2002; Murray et al., 2009; Öhman, 2009). Four studies have examined aversive conditioning in ASD to date.

Aversive conditioning

Bernier et al. (2005) examined fear conditioning through a fear potential startle paradigm in which participants were presented with consecutive trials comprising a red square (the Conditioned Stimulus, CS) that co-terminated with an overlapping 50 ms aversive air-puff to the throat (the unconditioned Stimulus; UCS). Following these acquisition trials, participants' eye-blink startle responses were examined to bursts of white noise that were either preceded by the red square ("threat trials") or not ("safe trials"). The results showed that both autistic and non-autistic individuals exhibited augmented eye-blink startle responses during the threat as compared to the safe trials, suggesting that the red square had

[6]Earlier studies are included in a review of the sensory processing literature by Rogers and Ozonoff (2005) but they are not included here because of the shift in the conceptualisation of ASD as marked by the publication of Wing and Gould (1979). Studies included in **Table 3** were identified primarily through cited reference searchers and a Web-of-Knowledge search using the terms arousal and autism.

Table 3 | Studies examining peripheral arousal responses in ASD.

Reference	Participant groups	*N*	Matching	Stimuli/paradigm	DVs	Results	
						mag.	diff.
STUDIES EXAMINING RESPONSES TO SIMPLE SENSORY STIMULI							
Stevens and Gruzelier (1984)	ASD; TD; DD	20; 20; 20	CA; NVA	Tones of different amplitude	GSR	=	↓
James and Barry (1984)	ASD; TD; DD	40; 40; 40	CA; FSA	Tone vs. white squares	CA; GSR; RP	↑	↓
van Engeland (1984)	ASD; TD; DD; psychiatric	35; 45; 20; 38	CA;	Tone	GSR	↑	=
Barry and James (1988)	ASD; TD; DD	32; 32; 32	CA; FSA	Tones of different amplitudes; white squares of different sizes	CA; GSR; RP	=/↑	↓
van Engeland et al. (1991)	ASD; TD; psychiatric	20; 20; 40	CA; NVA	Meaningless black-white patterns of different complexity; target detection paradigm	GSR	↓	=
Schoen et al. (2009)	ASD; SMD*; TD	38; 31; 33	Not specified	Tone, flash, siren, smell, touch, chair tip	GSR	↓Smell and touch	
Bernier et al. (2005)	ASD; TD	14; 14	CA; FSA; anxiety	Simple fear conditioning paradigm	EMG	=	
Gaigg and Bowler (2007)	ASD; TD	14; 14	CA; VA; NVA; FSA	Differential fear conditioning	GSR	↓	↓
South et al. (2011)	ASD; TD	36; 36	CA; VA; NVA; FSA	Simple fear conditioning paradigm	GSR	= Correlation: ↑fear acquisition/↓ADOS	=
STUDIES EXAMINING RESPONSES TO EMOTIONALLY SALIENT STIMULI/SITUATIONS							
Ben Shalom et al. (2003)	ASD; TD	10; 10	CA; ≠VA; NVA; FSA	Rate pleasant, unpleasant, and neutral photographs	GSR	=	=
Salmond et al. (2003)	ASD; TD	14; 18	CA	Startle response modulation by emotional photographs	EMG	=	=
Ben Shalom et al. (2006)	ASD; TD	10; 10	CA	Rate pleasant, unpleasant, and neutral photographs	GSR	=	=
Johnson et al. (2006)	ASD; TD	15; 14	CA; FSA, VA, NVA	Iowa Gambeling Task	GSR	↓	NA
De Martino et al. (2008)	ASD; TD	14; 15	CA; FSA, VA, NVA	Decide whether to choose a certain or uncertain monetary gain/loss	GSR	↑	↓
Bölte et al. (2008)	ASD; TD	10; 10	CA; NVA	Rate pleasant, unpleasant, and neutral photographs	CA; BP	=	↓
Gaigg and Bowler (2008)	ASD; TD	18; 18	CA; VA; NVA; FSA	Study neutral and emotionally salient words for memory test	GSR	=	=

(Continued)

Table 3 | Continued

Reference	Participant groups	*N*	Matching	Stimuli/paradigm	DVs	Results	
						mag.	diff.
Wilbarger et al. (2009)	ASD; TD	14; 14	CA; VA	Startle response modulation by emotional photographs	EMG	=	↓
Dichter et al. (2010)	ASD; TD	20; 37	≠CA	Startle response modulation by emotional photographs	EMG	=	↓
Maras et al. (2012)	ASD; TD	19/24; 19/24 in two Exp.	CA; VA; NVA; FSA	Memory test for narrated slide-show or video varying in emotional content	GSR; CA	=	=
STUDIES EXAMINING RESPONSES TO SOCIAL STIMULI							
Palkovitz and Wiesenfeld (1980)	ASD; TD	10; 10	CA	Tone vs. speech	CA; GSR	↑	=
Corona et al. (1998)	ASD; DD	22; 22	CA; FSA, VA	Simulated distress of adult	CA	↓	NA
Blair (1999)	ASD; TD; DD	20; 20; 20	CA; VA	Distress, threat, and neutral photographs	GSR	=	=/↓
Willemsen-Swinkels et al. (2000)	ASD; TD; DD	32; 19; 19	CA; FSA, VA, NVA	Separation vs. reunion with parent	CA	=	=/↑
Hirstein et al. (2001)	ASD; TD	37; 25	Not specified	Eye-contact with mother vs. papercup	GSR	↓	↓
Sigman et al. (2003)	ASD; DD	22; 22	CA; FSA, VA	Video of crying vs. playing infant; interaction with mother; separation vs. reunion with mother	CA	=	=/↓
Kylliäinen and Hietanen (2006)	ASD; TD	12; 12	CA; NVA	Detect direct vs. averted gaze	GSR	=	=/↑
Naber et al. (2007)	ASD; DD	11; 9	CA; FSA	Separation vs. reunion with parent	CA; cortisol	Number of autistic symptoms predicted lower cortisol response	
Hubert et al. (2009)	ASD; TD	16; 16	CA	Identify angry vs. happy faces	GSR	↓	↓
Bal et al. (2010)	ASD; TD	17; 38	CA; VA; NVA; FSA	Identify dynamic facial expressions as quickly as possible	CA	↑	NA
Riby et al. (2012)	ASD; WS; TD	12; 13; 25	CA	Watch live or videoed dynamic happy, sad, or neutral facial expressions	GSR	=	↓

(Continued)

Table 3 | Continued

Reference	Participant groups	*N*	Matching	Stimuli/paradigm	DVs	Results mag. diff.	
STUDIES EXAMINING RESPONSES TO STRESSORS							
Jansen et al. (2003)	ASD; DD; TD	10; 10; 12	CA; FSA	5 Min public speaking (social stress test)	CA; cortisol	↓CA	NA
Toichi and Kamio (2003)	ASD; TD	20;20	CA; VA; NVA	Rest vs. mental arithmetic	CA	=	=/↓
Corbett et al. (2006)	ASD; TD	12; 10	CA; ≠FSA	20 Min mock MRI scan	Cortisol	↑	NA
Corbett et al. (2008)	ASD; TD	22; 22	CA; ≠FSA	20 Min mock MRI scan followed by real scan for subgroup	Cortisol	= Higher variability in ASD group	=
Corbett et al. (2009)	ASD; TD	22; 22	Not specified but statistically controlled	20 Min mock MRI scan	Cortisol	= Higher variability in ASD group	=
Jansen et al. (2006)	ASD; TD	10; 14	CA; VA; NVA; FSA	10 Min public speaking (social stress test)	CA; cortisol; adrenalin	↓CA	NA
Levine et al. (2012)	ASD; TD	19; 11	CA; FSA	10 Min public speaking and other exercises (trier social stress test)	CA; cortisol	↓Cortisol	=

ASD, autism spectrum disorder; HFA, high functioning autism; TD, typically developing; DD, developmental delay; CA, chronological age; VA, verbal ability; NVA, non-verbal ability; FSA, full; CA as a dependent variable, cardiac activity; GSR, galvanic skin responses; EMG, elecromyogramm; BP, blood pressure; RP, respiratory pause.

↓, Decreased response magnitude or differentiation in ASD; ↑, increased response magnitude or differentiation in ASD; =/↑ and =/↓, indicate that responses were atypical in relation to only a subset of stimuli and/or in only a subgroup of participants. NA, not applicable.

acquired aversive properties for both groups. Gaigg and Bowler (2007) examined fear conditioning in a somewhat more complicated paradigm in which participants saw a random sequence of four colors, of which one (CS+) was paired with a startling foghorn sound (UCS) on a random 6 of its 12 presentations. The remaining colors (CS−) were never paired with the UCS and thus served as "safe" trials. Examination of GSR showed that fear acquisition to the CS+ color was significantly attenuated in autistic as compared to non-autistic individuals.

South et al. (2011) have recently employed a paradigm that sits somewhere in between those of Bernier et al. (2005) and Gaigg and Bowler (2007) in terms of the stimulus contingencies. Similar to Gaigg and Bowler (2007) these authors employed a differential conditioning paradigm involving a CS+ color that was paired with a startling noise UCS during acquisition and a CS− color that was never paired with the UCS. Similar to Bernier et al. (2005), however, South and colleagues always paired the CS+ color with the UCS during the acquisition trials whereas in Gaigg and Bowler (2008) the UCS followed the CS+ on only 50% of trials. Across three experiments that employed tones, colors, or angry face photographs as conditioned stimuli, South et al. (2011) observed no decrements in fear acquisition in ASD (GSR served as the dependent measure). Importantly, however, the authors did find that the amplitude of acquired fear responses was associated with autism symptom severity such that greater conditioned responses were associated with lower scores on the ADOS Reciprocal Social Interaction scores (i.e., fewer/less severe difficulties in this domain).

In the most recent fear conditioning report in ASD to date, South et al. (in press) employed a reversal paradigm modeled on Schiller et al. (2008). Here participants were presented with a random sequence of two colors of which one (CS+) co-terminated with an aversive puff of air to the throat (UCS) on 33% of trials. Unannounced, the contingency between color and air-puff reversed such that the previously unpaired CS− color now co-terminated with the UCS whilst the original CS+ color no longer did. The results showed that whilst fear acquisition in the first phase was preserved in ASD, reversal learning was significantly compromised such that autistic individuals were significantly slower to adapt to the new stimulus contingencies.

Importantly, in all four aversive conditioning studies to date, ASD and non-ASD individuals did not differ with respect to their physiological responses to the UCS, which suggests that the emotional salience of these aversive stimuli was similar for both groups. Although further studies are clearly needed to clarify what factors are critical for determining whether or not fear acquisition is preserved in ASD (number of competing stimuli, probability of reinforcement, timing of events, etc.), it seems clear already, that autistic individuals have difficulties adapting to ambiguous stimulus contingencies that would normally allow one to predict the occurrence of biologically relevant events on a probabilistic basis. In other words, ASD seems to be characterized by anomalies in the mechanisms by which emotional salience facilitates associative learning under conditions of uncertainty. Studies of reward contingency learning lend further support to this conclusion.

Reward contingency learning

Learning to predict when and where to expect rewards is mediated by a complex neural network involving interactions between many parts of the "social brain" including the amygdala and orbitalfrontal cortex (Holland and Gallagher, 2004) and the striatal reward system (Delgado, 2007). Johnson et al. (2006) were the first to examine reward contingency learning in ASD by drawing on a well established decision making paradigm known as the Iowa Gambling Task (IGT; Bechara et al., 1997, 2005). Participants in this task are told to try to make as much money as possible by choosing cards from one of four decks, with each choice yielding a certain monetary gain and loss (e.g., you win $0.50 but also lose $0.75). Two decks yield on average more gains than losses but the distribution of rewards across trials is extremely unpredictable. Johnson et al. (2006) found that autistic individuals were significantly slower to develop choice preferences for the advantageous decks than comparison individuals in this task. Solomon et al. (2011) recently observed similar group differences in a probabilistic learning task in which participants needed to discover which of a pair of symbols had the highest chance of being "correct." For different pairs of symbols, accurate feedback was given on only 80, 70, or 60% of trials and the learning profiles of ASD participants showed that they were less affected by these varying contingencies than comparison individuals (autistic individuals were less likely to demonstrate a "win-stay" pattern of decisions). Finally, Scott-Van Zeeland et al. (2010) examined reward contingency learning in ASD in the context of a categorization task that required participants to classify abstract fractal-like images as belonging to either one of two categories. Correct classifications were rewarded either with a certain amount of money or with a smiling female face whilst incorrect classifications yielded either no reward or a sad female face. Similar to Johnson et al. (2006) and Solomon et al. (2011), the reward contingencies were not entirely reliable such that on some blocks of trials inaccurate feedback was given. Again, autistic individuals were significantly worse at the categorization task – so much so that, in both the face and monetary reward conditions, their performance remained at chance whilst that of the comparison group reached over 80%.

Several studies, including that by Scott-Van Zeeland et al. (2010), have examined the neural correlates of reward processing in ASD and the overall consensus in this context is that striatal as well as frontal areas involved in predicting and acting upon rewards in the environment are functionally compromised in this disorder. Importantly, neural abnormalities are evident irrespective of whether the reward comes in the form of a social smile, money, or simple praise (Schmitz et al., 2008; Kohls et al., 2011; Dichter et al., 2012a,b)[7]. Together with the studies of fear conditioning, this evidence strongly suggests that it is not only the "social functions" of the "social brain" that are compromised in ASD. Instead, autistic individuals have difficulties adapting to stimuli that predict biologically relevant events only imperfectly, irrespective of whether these stimuli are other people or not. At the neural level this suggests anomalies in how basic associative learning processes mediated by sub-cortical amygdala systems are modulated by "higher-level" perceptual and conceptual processes that are critical for resolving ambiguities in the environment. Evidence

[7] Scott-Van Zeeland et al. (2010) argue that their data supports the idea that particularly "social" rewards are processed atypically in ASD but they do not provide the relevant Reward Condition × Group analyses, nor do their within condition analyses provide convincing evidence for this conclusion.

from other domains suggests that this may be part of a broader disruption of the interplay between basic emotional response systems (i.e., sub-cortical amygdala circuitry) and cognition.

THE EMOTIONAL MODULATION OF ATTENTION IN ASD

Besides eliciting arousal responses and facilitating associative learning, the amygdala also plays a critical role in orienting attention toward emotionally significant stimuli (see Vuilleumier, 2005, 2009). To date, only three studies have examined the emotional modulation of attention in ASD in relation to stimuli other than emotionally expressive others. South et al. (2008) employed a visual search task in which participants were asked to determine whether all images in a 3 × 3 display were of the same category or not. The arrays either comprised images of spiders, snakes, flowers or mushrooms, or one of these (the "odd-one-out") amongst eight of the others. Both autistic and non-autistic participants demonstrated a well established "threat advantage" effect, whereby the detection of threatening (snakes, spiders) stimuli amongst neutral ones (mushrooms, flowers) was faster than the detection of neutral stimuli amongst threatening ones. Interestingly, autistic individuals have also been shown to demonstrate a typical anger superiority effect in visual search tasks employing face stimuli (Ashwin et al., 2006a; Krysko and Rutherford, 2009; Rosset et al., 2011; but, see Farran et al., 2011)[8], suggesting that basic threat detection mechanisms may be functionally preserved irrespective of whether the danger comes from the social environment or not. Contrasting these observations from visual search paradigms, Corden et al. (2008b) and Gaigg and Bowler (2009a) observed atypical emotional modulation of the Attentional Blink (AB) phenomenon in ASD. In their studies, participants were presented with rapid sequences of words comprising several distracter items and two target words (T1 and T2) that participants were asked to identify. T1 was always neutral whereas T2 was either neutral or emotionally charged and across trials these two target items were separated by varying temporal delays. Typically, the detection of T2s is significantly attenuated in a period of approximately 100–500 ms following T1 but this "AB" is partially overcome when T2 is emotionally charged (e.g., Keil and Ihssen, 2004). Both Corden et al. (2008b) and Gaigg and Bowler (2009a) found that this emotional modulation of the AB was diminished in ASD.

Further studies are clearly needed to clarify to what extent emotionally salient events capture attention in ASD. In particular it will be important to resolve an apparent paradox between the studies outlined here and the evidence concerning emotional arousal responses in ASD outlined earlier. As noted earlier, arousal responses to stimuli such as emotionally significant pictures or words appear to be relatively preserved in ASD (Ben Shalom et al., 2006; Gaigg and Bowler, 2008) whereas responses to the social environment including the emotional expressions of others are much more varied (e.g., Hubert et al., 2009 vs. Bal et al., 2010). This appears at odds with the studies outlined in this section, which show that facial expressions of certain emotions and images displaying threats capture attention relatively typically in ASD whereas emotionally charged words do not. Importantly, the mechanisms that regulate peripheral arousal responses operate in parallel to those that regulate attention. The former are mediated primarily by sub-cortical connections between the amygdala's central nucleus and various brain-stem nuclei (e.g., LeDoux, 2002) whereas the latter involve reciprocal connections between the basal/lateral nuclei and sensory processing cortices, and between accessory basal nuclei and the orbital-frontal cortex (see Vuilleumier, 2005, 2009). It is possible, therefore, that sub-cortical amygdala pathways that mediate the expression of physiological arousal responses are relatively preserved in ASD, whilst those that moderate attention through reciprocal connections with cortical areas are compromised. Preserved attention modulation by inherent threat signals such as angry expressions and the sight of a spider could be accommodated within such a view because such stimuli are thought to capture attention by activating relatively simple sub-cortical response systems. The facilitation of attention in response to emotional words, by contrast, is likely to involve more extensive cortico-amygdala networks that include language processing areas.

Memory for emotionally salient events in ASD

Another important function of the amygdala is to facilitate declarative memory for emotionally significant events through connections with the hippocampus (see Phelps, 2004; Reisberg and Hertel, 2004; Uttl et al., 2006 for reviews). Six studies have explored this issue in ASD to date. The first was a study by Beversdorf et al. (1998) who presented participants with audio recordings of 10 emotional (e.g., "Carl shot his gun at someone") or 10 neutral (e.g., "Mike is talking on the phone") statements. Following each set participants were allowed unlimited time to write down as many statements as possible and results showed that only non-ASD participants recalled the emotional statements better than the neutral ones. Deruelle et al. (2008a) extended these observations to pictorial stimuli using a speeded recognition task. Here participants were asked to study sets of images including six neutral, six positive, and six negative items that were presented for only 150 ms each. Following every set participants were required to discriminate images they had seen from new ones within 1.5 s and in line with Beversdorf et al. (1998) only non-ASD participants demonstrated a memory advantage for emotional over neutral images.

South et al. (2008) and Maras et al. (2012) recently failed to demonstrate quantitative anomalies in memory for emotional over neutral material in ASD. In the two experiments by Maras et al. (2012), participants were presented with a neutral or emotionally charged audio-narrated slide-show (Exp. 1) or video clip (Exp. 2) for which memory was subsequently assessed through free recall and forced choice recognition procedures. In both experiments participants who viewed the emotional versions of the

[8]Ashwin et al. (2006a), Rosset et al. (2011), and Krysko and Rutherford (2009) all observed relatively typical anger superiority effects but subtle differences between groups in how the number of distracters affected performance. Ashwin et al. (2006a) suggests that these subtler differences are a reflection of more general face processing difficulties and it is worth noting that atypical effects of distracter numbers have also been noted in attention tasks employing letters as stimuli (Remington et al., 2009). Farran et al. (2011) failed to demonstrate an anger superiority effect, observing an advantage for happy expressions instead – this happy advantage was preserved in ASD. Although the ASD group was somewhat slower than TDs to respond to angry, sad and fearful faces this speed decrement was not significant when comparing autistic individuals to verbal ability matched comparison participants.

narratives demonstrated superior memory to those who viewed the neutral narratives and this emotional modulation of memory was similar for ASD and non-ASD participants. In the study by South et al. (2008) participants were asked to study a mixed list of negative (high and low arousal), positive (high and low arousal), and neutral words for a subsequent recognition test and here too autistic individuals demonstrated a preserved memory advantage for emotional words. Importantly, however, ASD participants in this study took significantly longer to respond during the test phase, which, in light of the observations of the speeded recognition test by Deruelle et al. (2008a) outlined above, may indicate that qualitative differences in *how* emotion modulates memory in ASD may go undetected by some experimental paradigms – reminiscent of studies of facial emotion recognition in this disorder (see The Evidence).

Two studies by Gaigg and Bowler (2008, 2009b) lend some support to the above conclusion. Gaigg and Bowler (2008) also failed to note group differences in memory for emotional over non-emotional words when comparing the free recall of autistic and non-autistic participants on an immediate test of memory. Importantly, however, the authors included categorically related neutral words (items of fruit) in their study and examined forgetting rates over time by testing free recall again after 1 and 24 h delays. Critically, these features of the experiment revealed that the memory advantage for emotional over non-emotional items on the immediate recall test was commensurate with the advantage for items of fruit over unrelated neutral words, both for ASD and non-ASD participant groups. Over time, however, comparison participants began to demonstrate a specific memory advantage for emotional over non-emotional items whereas autistic individuals did not. In other words, the memory advantage for emotional items observed by South et al. (2008) may simply be a reflection of the effects of semantic factors on memory rather than emotional factors and the narrative structure of the materials used by Maras et al. (2012) may play a similar role. The second study by Gaigg and Bowler (2009b) took a somewhat different approach by focusing on false rather than veridical memory. Participants here were asked to study lists of words comprising orthographic neighbors of critical non-presented items that were either emotionally charged (e.g., tell, fell, sell,. . . for *hell*) or neutral (e.g., look, took, book,. . . for *hook*). On a subsequent recognition test non-autistic participants were very unlikely to falsely endorse emotional items as having been studied but ASD participants made such intrusion errors as often for emotional as non-emotional words.

As is the case for studies of attention, further evidence is needed in order to clarify under what circumstances emotion facilitates memory in ASD typically and under what circumstances memory for emotional material may be hindered. Critical, in this context, is to bear in mind that ASD is generally characterized by a particular pattern of memory strengths and weaknesses (see Boucher and Bowler, 2008; Boucher et al., 2012) that may well contribute to inconsistent observations. On balance, however, it does not appear to be the case that emotional factors exert entirely typical effects on long-term declarative memory in ASD.

THE SUBJECTIVE EXPERIENCES OF FEELINGS IN ASD

The final issue to consider before drawing this section to a close concerns one of the most elusive questions – how do autistic individuals subjectively experience emotional stimuli? As noted in the preliminary comments, I use the term "feeling" in this review to describe the subjective experiences that arise when the perception of a stimulus or event triggers changes in arousal that, in turn, alter self-conscious thought. Although notions of consciousness and self-awareness continue to be the source of considerable debate, immense progress has been made over the past few years in tracing the neurobiological and psychological origins of subjective experiences. The emerging consensus in this context is that subjective experiences such as feelings critically depend on the convergence of representations of internal body states with representations of the sensory environment in medial frontal cortices and in particular the insula cortex, both of which are under the influence of the amygdala (Damasio, 1994, 1999, 2003; LeDoux, 2002; Critchley et al., 2004; Wiens, 2005; Craig, 2009; Critchley and Nagai, 2012; Seth et al., 2012).

Feelings have recently attracted a lot of attention in ASD because a series of studies have shown that a condition known as Alexithymia is commonly associated with the disorder (Hill et al., 2004; Tani et al., 2004; Berthoz and Hill, 2005; see also Fitzgerald and Bellgrove, 2006; Hill and Berthoz, 2006). Alexithymia is characterized by difficulties in identifying and communicating ones' own emotions and whilst it affects only approximately 10% of the general population (Mattila et al., 2006), the prevalence in ASD is estimated to be somewhere between 40 and 50% (Hill et al., 2004; Tani et al., 2004). An appealing explanation for this high co-morbidity is that it is a reflection of mentalizing difficulties. In non-autistic individuals, high levels of Alexithymia are associated with poor mentalizing (e.g., Moriguchi et al., 2006) and since autistic individuals are thought to experience difficulties not only with the understanding of other peoples' minds but also their own minds (see Williams, 2010 for an excellent discussion), high levels of Alexithymia are to be expected. Alternatively, however, high levels of Alexithymia in ASD may be regarded as the result of a disruption in the interplay between emotional arousal and subjective experience. In other words, rather than having difficulties in accessing or reflecting on their feelings, autistic individuals may experience feelings differently because the processes that give rise to them are disrupted. Ben Shalom (2000) was the first to raise this possibility and several studies lend support by showing that physiological arousal responses and subjective ratings of hedonic value in ASD do not co-vary typically (Ben Shalom et al., 2003, 2006; Bölte et al., 2008; Gaigg and Bowler, 2008; Dichter et al., 2010; see also Allen and Heaton, 2010). Moreover, a recent fMRI study has shown that the degree of anterior insula activity during emotional introspection in autistic and non-autistic individuals was moderated by scores on standardized Alexithymia questionnaires whereas activity in the mentalizing system was not (Silani et al., 2008; see also Ebish et al., 2011).

Interestingly, Bird et al. (2010, 2011) have recently shown that self-reported levels of Alexithymia account for abnormalities in empathic brain responses, atypical gaze fixations on the eye-region of faces, and poorer facial emotion recognition in ASD (Cook et al.,

in press), which suggests that difficulties in introspecting on own emotions and aspects of the reciprocal social impairments in ASD share a common neuro-cognitive basis. The nature and developmental origin of this common denominator remains unclear. One possibility is that ASD *per se* is not at all associated with emotion related anomalies but that the difficulties in this domain are fully explained by the high incidence of Alexithymia. Such a view, however, would leave unexplained why Alexithymia should co-occur with ASD far more often than would be expected by chance. A more appealing account, sees Alexithymia in ASD as a reflection of the same aberrant developmental process that also gives rise to varying social and emotion related difficulties. On this view, one might expect the nature of Alexithymia in ASD to differ qualitatively from that observed in non-autistic individuals and future studies are urgently needed to address this issue. In particular, it will be important to seek objective measures of Alexithymia that go beyond the self-report questionnaires currently available and it will be critical to clarify the developmental trajectory of Alexithymia in autistic as well as non-autistic individuals.

RECONSIDERING THE ROLE OF EMOTION RELATED PROCESSES IN THE DEVELOPMENT OF AUTISM SPECTRUM DISORDERS

I have reviewed evidence demonstrating that ASD is characterized by widespread and pervasive difficulties in social-emotional competences. Autistic individuals often struggle to identify the emotional expressions of others, they frequently do not reciprocate these expressions in a context appropriate manner and they often relate and react to the emotional experiences of others in atypical ways. A group of influential explanations of this facet of the autistic phenotype attribute it to broader abnormalities in social-cognitive processes that find their origin in an early emerging disruption in social-motivation and interpersonal engagement. Put simply the argument is that autistic infants are less motivated (or otherwise hindered) to engage and interact with others, which affords them fewer opportunities to learn from interpersonal experiences and ultimately leads to the clinically defining reciprocal social impairments of the disorder, including anomalies in emotion related interpersonal behaviors. At the neural level, this developmental cascade is thought to reflect abnormalities in the maturation of the "social brain," which comprises frontal and temporal cortical regions as well as parts of the striatum and limbic system (in particular the amygdala).

In the two sections that followed, I raised concerns about the view that emotion related processing anomalies in ASD need to be understood with reference to broader "social" impairments. I pointed out that many components of the "social brain" are critically involved in far more than the mediation of reciprocal social competences. In particular, the limbic and striatal regions encompassed by the social brain are well known to play a critical role in the domain-general emotion related processes that serve to alert an organism to biologically relevant events in the environment so that it may respond to them effectively and learn about contingencies that are likely to predict similar events in the future. In the light of these domain-general functions, greater empirical effort needs to be directed at establishing whether or not the emotion-related difficulties in ASD are merely a facet of social impairments.

In section three, I summarized the available evidence that speaks to this issue to date. I first considered evidence concerning peripheral arousal responses in ASD, which are widely agreed to constitute an important facet of emotional responses to the environment. Although the evidence in this context is very mixed, I noted that there is little support for the notion that autistic individuals respond specifically to their social environment with atypical patterns of arousal. Instead they appear more generally to react differently to objects and events that are either ambiguous (e.g., arbitrary sensory stimuli) or variable (e.g., other people) with respect to their emotional significance, which contrasts their relatively typical responses to clearly defined and invariable emotional signals (e.g., emotionally significant words, pictures, narratives, etc.). After hinting at the possibility that it is the ambiguous and unpredictable nature of certain events in the environment that poses difficulties for autistic individuals, I summarized evidence from aversive conditioning and reward contingency learning paradigms that is consistent with this suggestion. More specifically, I showed that autistic individuals experience difficulties learning about the (emotional) significance of stimuli that predict biologically relevant events or opportunities only imperfectly. They fail to anticipate danger under ambiguous circumstances and do not adopt efficient decision strategies to take advantage of uncertain reward opportunities. When the environment is regular and predictable, by contrast, they are indistinguishable from non-autistic individuals. Importantly, this pattern holds irrespective of whether or not social signals or arbitrary symbols serve as predictors of relevant events. At the neural level, this suggests that relatively basic amygdala functions that are mediated primarily by sub-cortical networks involving sensory efferents from the thalamus and afferents to brain-stem nuclei are preserved in ASD. Functions that rely on the modulation of this sub-cortical system by other cortical or sub-cortical areas, by contrast, appear to be compromised. I concluded section three with an overview of evidence from studies of attention, memory, and the subjective experience of "feelings" that are all consistent with the notion that interactions between "basic" amygdala networks and the rest of the brain may be compromised in ASD, which, incidentally, is also consistent with evidence of widespread abnormalities in interregional connectivity in the autistic brain (Cheng et al., 2010; Schipul et al., 2011; Shukla et al., 2011; Duerden et al., 2012; Vissers et al., 2012). In short, I outlined evidence that is beginning to lead us to question the notion that anomalies in interpersonal emotional behaviors in ASD are best understood with reference to "social" impairments.

IMPLICATIONS FOR DEVELOPMENTAL ACCOUNTS OF ASD

There is no question that social-motivational accounts of ASD provide an elegant explanation for the impairments in reciprocal social competences that clinically define the disorder. As appealing as such theories are, however, they seem insufficient as explanations for the broader emotion related anomalies I have set out in this review. This may seem relatively unproblematic at first. As Chevallier et al. (2012) point out, failing to explain all facets of the ASD phenotype is "*. . .only problematic if one considers that there ought to be a single explanation behind all the symptoms of ASD. . . if one agrees that ASD should be studied from a multiple-deficit perspective,. . . it is important to compare the explanatory power of*

social-motivation vs. social cognition in accounting for social deficits" (p. 236). This argument would be perfectly acceptable, were it not for the evidence set out in this review, which links the social and broader emotion related atypicalities at the neural level. Parsimony, therefore, dictates that we seek a developmental explanation that unifies at least the social and wider emotion related characteristics of ASD and one of the most pressing questions in this context is how best to conceptualize the causal relation between the social-emotional and broader emotion related anomalies set out in this review.

One possibility is that "social" explanations are correct after all and that the broader emotion related impairments reviewed in this paper are a direct consequence of abnormalities in the development of reciprocal social competences. Many of the findings set out in section three are amenable to such a view because it is undoubtedly true that we come to appreciate the emotional significance of objects and events in our environment in the context of rich social interactions (e.g., Bacon et al., 1998; Corona et al., 1998). One may counter this argument by pointing out that it is highly unlikely that atypicalities in the domains of fear conditioning and reward contingency learning would result from abnormalities in reciprocal social development. Cortical areas thought to constitute a critical component of the "social brain" – in particular frontal areas – mature much later in life than the amygdala (e.g., Happaney et al., 2004; Bachevalier and Loveland, 2006), rendering it improbable that the abnormalities that underlie atypical fear conditioning result from atypicalities in the maturation of the "social brain." Even this argument, however, is far from decisive because the highly complex nature of social interactions may well provide the kind of experience that drives not only the specialization of "social" functions of the brain (e.g., Johnson, 2000, 2003, 2011), but also the maturation of inherently non-social functions such as those involved in certain conditioning paradigms. On this account social interactions could be seen to lead to the development of neural circuitry that is intricately tuned to dealing with rapidly changing, ambiguous, and often unpredictable environments. Perturbations in this process as a result of impoverished experiences with the social environment could thus lead to more widespread abnormalities in how an individual adapts to ambiguous and unpredictable situations.

It is clear from the above discussion, that it would be premature to abandon "social" explanations of ASD altogether. It is equally clear, however, that we should no longer simply accept the assumptions on which such explanations are based. We need to begin to take an alternative seriously, one in which impairments in reciprocal social competences are the result of abnormalities in the domain-general processes that typically allow an infant to rapidly learn about the emotional significance of objects and events in its environment. As I have suggested in section three, the associative processes that mediate such learning may be compromised in ASD such that autistic individuals find it difficult to adapt to the (emotional) significance of particularly those stimuli that predict biologically relevant events only imperfectly. Other people happen to be the most ambiguous and unpredictable "stimulus" of all in this respect as they are not only biologically relevant in their own right but they also signal a whole range of biologically relevant events. One moment a smile indicates the imminent arrival of food, the next the playful withdrawal of a preferred toy and the next it is a simple sign of affection that relates to nothing in the external environment at all. And if this were not complex enough, the same face that produces smiles in a dozen different contexts is also the source of a multitude of other, mutually incompatible emotional signals that occasionally occur in the same context as the smile (e.g., a playful frown whilst withdrawing the preferred toy). Making sense of this organized chaos is a computational nightmare that the typically developing brain appears to master in a matter of months. For autistic individuals, however, the unpredictable nature of the social environment appears to remain to a large extent impenetrable.

CONCLUSION AND FUTURE DIRECTIONS

I have attempted to provide a complete overview of what we currently know about emotion related processes in ASD. On balance, the literature suggests that we may need to reconsider one of the core assumptions that underlies most dominant theories concerning the social-emotional difficulties characterizing the disorder, namely that these difficulties are simply a facet of broader social-motivational or social-cognitive impairments. Should the assumption not withstand empirical scrutiny, we face the difficult task of acknowledging that our conceptualization of the developmental trajectory of ASD as originating in impairments in "social" processes may in fact be false. Fortunately, this prospect is not as daunting as it seems, as there are appealing alternatives on the horizon. In particular, Pellicano and Burr (in press), in a very different context, have recently argued that autistic perception is relatively unbiased by prior experience. More specifically, they argue that whereas typical individuals anticipate, rather than experience the world, autistic individuals perceive the world as it actually is. At a neural level, this phenomenological description of the subjective experiences of autistic individuals is anchored in faulty computational mechanisms that iteratively formulate expectations of what might occur next on the basis of experience. These mechanisms are critical for our survival because they allow us to anticipate biologically relevant events, and in the context of our social environment, they allow us to predict the unpredictable. Pellicano and Burr (in press) suggest that ASD is the result of abnormalities in how current experience updates predictions for the future and this seems a promising idea to pursue in relation to the emotion related experiences of autistic individuals.

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Preserved and impaired emotional memory in Alzheimer's disease

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Patients with early atrophy of both limbic structures involved in memory and emotion processing in Alzheimer's disease (AD) provide a unique clinical population for investigating how emotion is able to modulate retention processes. This review focuses on the emotional enhancement effect (EEE), defined as the improvement of memory for emotional events compared with neutral ones. The assessment of the EEE for different memory systems in AD suggests that the EEE could be preserved under specific retrieval instructions. The first part of this review examines these data in light of compelling evidence that the amygdala can modulate processes of hippocampus-dependent memory. We argue that the EEE could be a useful paradigm to reduce impairment in episodic memory tasks. In the second part, we discuss theoretical consequences of the findings in favor of an EEE, according to which a compensatory mechanism in patients with AD solicits greater amygdala functioning or additional networks, even when amygdala atrophy is present. These considerations emphasize the relevance of investigating patients with AD to understand the relationship between emotion and memory processes.

Keywords: emotion, memory, Alzheimer's disease, amygdala

EMOTIONAL EFFECTS ON PRESERVED AND IMPAIRED MEMORIES IN ALZHEIMER'S DISEASE

Memory impairments are the core of cognitive dysfunctions reported in Alzheimer's disease (AD; Mori et al., 1997; Petersen et al., 2000). They are sustained by lesions of the medial temporal lobe (MTL), particularly of the hippocampus (Jack et al., 1997; Mori et al., 1997; Simic et al., 1997; Mizuno et al., 2000). Neuroimaging evidence suggests that, in parallel with the development of lesions in the hippocampus, the amygdala undergoes early atrophy in AD (Basso et al., 2006; Horinek et al., 2007; Poulin et al., 2011). The amygdala is strongly implicated in the context of emotional processing (Phelps and LeDoux, 2005) and memory (Cahill et al., 1995, 1996), raising numerous questions about possible impaired mechanisms in AD. While AD studies on emotional processing have sometimes revealed spared emotional abilities (Klein-Koerkamp et al., 2012) and preserved physiological responsiveness to emotion (Smith, 1995; Hamann et al., 2000), an important issue to evaluate could be how emotions modulate memory performance. In the context of normal aging, several studies have reported that emotional content might improve memory performance compared with non-emotional content (emotional enhancement effect: EEE; see; Broster et al., 2012). In this review, we investigate how the EEE on memory performance evolves in healthy older adults (HOA) compared with AD patients.

Findings on the effect of emotion on memory in AD have led to discrepant results, with some studies reporting an EEE or a beneficial effect of emotion on memory (i.e., the emotional material is more accurately recalled than neutral material), and others reporting no emotional advantage (i.e., emotional material is less recalled than neutral material, or equivalently recalled). Thus, in this report, we review these effects, along with factors that could modulate the EEE: the participant's characteristics and the emotional task design (i.e., emotions, stimuli, and procedure used). We further compare in detail these emotional effects in AD patients and HOA with respect to the differences in their overall memory performance. The literature that provides the basis for this review was obtained by searching PubMed, PsycARTICLES, PsychINFO, and Psychology and Behavioral Sciences Collection databases for English language articles containing the key terms "Emotion*" AND "Memory" AND "Alzheimer" in the title and/or the abstract and/or the keywords. No restrictions were placed on the year, with all articles up to May 2012 included. Relevant papers from the reference lists of identified papers were also reviewed. Given the focus on AD patients, only studies with samples of people with this dementia were included. In addition, only those studies were considered that included the diagnostic criteria used to identify AD patients [criteria recommended either by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS/ADRDA; McKhann et al., 1984)], or by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 1994). Two studies were excluded because the patient group did not differentiate between individuals with AD and those with mixed dementia (Blessing et al., 2006, 2010). Finally, the study had to include at least one explicit measure of the emotional effect on memory performance (i.e., a comparison of memory performance between an emotional and a neutral event). As a result of this last criterion,

the studies included in this review dealt mostly with declarative memory. Ultimately, 22 studies concerning the EEE on memory performance in AD were eligible for inclusion in the present review (**Table 1**).

The magnitude of the EEE on hippocampus-dependent memory (declarative memory) has been assessed in AD patients mostly by using recall and recognition tasks with intentional encoding. Additionally, various sets of emotional materials have been used: emotional short stories with illustrated pictures, visual scenes, video clips, word lists, and objects (**Table 1**). Although memory was typically found to be heavily impaired in patients with AD, the beneficial effect of emotions (EEE) was repeatedly demonstrated in patients by using various types of tasks and materials (Kazui et al., 2000, 2003; Boller et al., 2002; Fleming et al., 2003; Nieuwenhuis-Mark et al., 2009; Schultz et al., 2009; Borg et al., 2011; Nashiro and Mather, 2011; Werheid et al., 2011; Perrin et al., 2012). This EEE was sometimes retrieved for discrete emotional categories, such as only positive emotions (Hamann et al., 2000; Kalenzaga et al., 2012; Perrin et al., 2012), but also for both positive and negative emotions (Moayeri et al., 2000; Satler et al., 2007; Werheid et al., 2011). However, in contrast to these beneficial effects, a reduced EEE has also been reported, even when patients viewed the same emotional stimuli or performed very similar tasks to those used in studies reporting a preserved EEE (Hamann et al., 2000; Abrisqueta-Gomez et al., 2002; Kensinger et al., 2002, 2004; Budson et al., 2006; Brueckner and Moritz, 2009; Perrin et al., 2012). Some researchers (Kensinger et al., 2004; Budson et al., 2006; Kensinger, 2006) have suggested that the EEE on memory could be disrupted in AD. We argue that several factors could intervene in the presence or absence of EEE in AD. Intrinsic differences in memory functioning between controls and AD patients could lead to difficulties in raising an EEE. Researchers have also proposed that the retrieval instructions (e.g., recollection vs. recognition tasks; Kensinger et al., 2002, 2004; Sundstrom, 2011) or the type of emotional stimuli (Kensinger, 2006; Nashiro and Mather, 2011; Sundstrom, 2011) might modulate the magnitude of EEE in AD patients.

Several studies found that the EEE was present in AD patients despite it not being present in the control group (Moayeri et al., 2000; Boller et al., 2002; Fleming et al., 2003; Sundstrom, 2011; Kalenzaga et al., 2012), or, inversely, that it was present in HOA but not in the AD population (Boller et al., 2002; Kensinger, 2006). Some authors stressed that when the task to be performed is too easy for HOA, or too difficult for patients, the EEE is more likely to be obscured by a ceiling effect or a floor effect, respectively. These effects could result from overall between-group (AD vs. HOA) differences in memory functioning, which could overshadow the genuine emotional effect. For example, HOA have performed perfectly in recognition tasks (Moayeri et al., 2000; Sundstrom, 2011) or questionnaires (Boller et al., 2002), as these tasks are supposed to be easier for controls than patients. Similarly, previous studies have established that recognition memory was typically very high in HOA when they were tested immediately (Fleming et al., 2003) and that AD patients were particularly impaired in tasks involving a delay, leading to floor effects (Boller et al., 2002). Some studies offered modifications to address these ceiling and floor issues. For example, the study by Werheid et al. (2011) used a paradigm in which the presentation of the stimuli was repeated three times only in the AD group. This study showed that three repetitions permitted patients to benefit from emotional information to improve their memory performance. Further, Kalenzaga et al. (2012) offered a reduced time delay for AD patients compared with HOA. In addition, Hamann et al. (2000) and Kensinger et al. (2004) used two different control populations, one with the same memory task delay as for AD patients and the second with 2 weeks or 24 h of additional delay. The study in which the delay was 24 h longer did not allow equalization of overall memory performance and showed no EEE in the AD group (Kensinger et al., 2004), whereas the other study with 2 weeks of additional delay showed between-group memory performance and an EEE that was similar in HOA and AD patients for positive emotions (Hamann et al., 2000). The confusing pattern of EEE on declarative memories in AD could thus result from the complex interaction between changes in memory and emotion processes. The absence of an EEE in AD was thought by some to reflect the fact that emotion could not interfere with memory, since the disease severely impairs the memory system (Borg et al., 2011). This issue reflected the potential influence of confounding variables (Klein-Koerkamp et al., 2012). Rather than being a deficit in the impact of emotion on memory processing, however, the absence of an EEE could represent a deficit in overall cognitive performance (e.g., short-term memory, verbal abilities, semantic memory, executive functions, visuo-spatial abilities). Several authors argued that the presence of an EEE could result in access to cognitive abilities, such as executive functions (Borg et al., 2011; Broster et al., 2012). Knowing the influences of emotions on executive control (for review see Cohen and Henik, 2012, in this Research Topic), emotional memory enhancement would then be affected in individuals with impairments in executive functions. These considerations point out the need to consider cognitive deficits when exploring the EEE on memory in AD.

Further, we argue that distinguishing the differences in retrieval instructions (recollection versus recognition tasks) could be critical in explaining the EEE discrepancies in AD. Indeed, there is evidence that recollection tasks are more likely to induce an EEE in healthy aging (Ochsner, 2000; Talarico et al., 2004). Although recollection and recognition tasks both involve remembering specific details (e.g., contextual information) of an encoded episode, recollection tasks require a greater engagement of episodic memory (de Vanssay-Maigne et al., 2011). During recognition, processes of familiarity detection may compensate for episodic memory difficulties (Atkinson and Juola, 1974; Mandler, 1980). Familiarity refers to the ability to remember that an episode has been encountered previously when no other contextual information about it is available (Gardiner et al., 1998). In the context of emotional memory, the separation of studies by the function of their retrieval instructions suggests that the EEE remains preserved in patients with AD when recollection tasks are performed (Boller et al., 2002; Fleming et al., 2003; Nieuwenhuis-Mark et al., 2009; Nashiro and Mather, 2011; Perrin et al., 2012) rather than when recognition tasks are performed (Abrisqueta-Gomez et al., 2002; Kensinger et al., 2002, 2004; Budson et al., 2006;

Table 1 | Comparative review of studies investigating the EEE on memory.

Study	Participants	Emotions and Stimuli	Type of Encoding	Tasks	Emotional Assessment	Presence of EEE	Group Difference on Memory Performance
Abrisqueta-Gomez et al. (2002)	AD = 16; mean age = 70; m/f = 7/9; MMSE = 19,6; HOA = 19; mean age = 67; m/f = 7/12; MMSE = 28,9	Pleasant/unpleasant and neutral scenes	Intentional	Recognition (after 30 min)		Yes HOA (pleasant – unpleasant); no AD	AD < HOA
				Emotional categorization	AD = HOA		
Boller et al. (2002)	AD = 10; mean age = 75; m/f = 5/5; MMSE = 19,6; HOA = 12; mean age = 75; m/f = 8/4; MMSE = 28,8	Happy, sad, and neutral stories	Intentional	Immediate and delayed free recall (after 10 min)		Yes HOA (happy – immediate recall); Yes AD (happy and sad – immediate recall); No HOA (delayed recall); No AD (floor effects – delayed recall)	AD < HOA
				Questionnaire		No HOA (ceiling effects); yes AD (sad and happy)	AD < HOA
				Emotional categorization	AD < HOA		
Borg et al. (2011)	AD = 14; mean age = 80; m/f = 4/10; MMSE < 24; HOA = 14; mean age = 78; m/f = 5/9; MMSE > 27	Negative and neutral scenes (IAPS)	Intentional	Recognition (visual memory task)		Yes HOA; yes AD	AD = HOA
				Recognition (location task – memory binding)		No HOA; no AD	AD < HOA
Brueckner and Moritz (2009)	AD = 36; mean age = 72; m/f = 16/20; MMSE = 24; HOA = 20; mean age = 69; m/f = 8/12	Thematic word lists (depression; delusion; positive; neutral)	Intentional	Recognition		Yes HOA (true recognition); No AD (true recognition); Yes HOA (false recognition); Yes AD (false recognition)	AD < HOA (true recognition)
Budson et al. (2006)	AD = 19; mean age = 76; m/f = 9/10; MMSE = 23; HOA = 19; mean age = 73; m/f = 7/12; MMSE > 27	Thematic word lists (emotional and non-emotional)	Intentional	Recognition (after 5 min)		Yes HOA (true recognition); No AD (true recognition); No HOA (false recognition); No AD (false recognition)	AD = HOA (true recognition); AD > HOA (false recognition)
Fleming et al. (2003)	AD = 25; mean age = 75; MMSE = 21 HOA = 19; mean age = 70	Thematic word lists (negative, positive, neutral)	Intentional	Free recall		No HOA; yes AD (negative)	AD < HOA
Gallo et al. (2010)	AD = 18; mean age = 77; m/f = 7/11; MMSE = 23,9; HOA = 18; mean age = 72; m/f = 6/12; MMSE = 28,8 (HOA and AD results reported on the same experimental condition)	Negative, positive, neutral words and scenes (IAPS)	Intentional	Recognition		No HOA (true recognition); No AD (true recognition); Yes HOA (positive – false recognition); yes AD (positive – false recognition)	AD < HOA
				Arousal rating	AD = HOA (emotional > neutral)		

(Continued)

Table 1 | Continued

Study	Participants	Emotions and Stimuli	Type of Encoding	Tasks	Emotional Assessment	Presence of EEE	Group Difference on Memory Performance
Hamann et al. (2000)	AD = 12; mean age = 71; m/f = 5/7; MMSE = 21,5; HOA = 12; mean age = 70; m/f = 3/9; MMSE = 29,2	Negative, positive, neutral scenes (IAPS)	Incidental	Free recall (immediately or after 2 weeks for HOA; immediately after for AD)		Yes HOA (positive and negative); yes HOA (2 weeks' delay – positive + negative); yes AD (positive)	AD < HOA; AD = HOA (2 weeks' delay)
				Recognition		Yes HOA (negative); no AD	AD = HOA
				Arousal rating	AD = HOA (emotional > neutral)		
Kalenzaga et al. (2012)	AD = 22; mean age = 83; m/f = 2/20; MMSE = 18,1; HOA = 18; mean age = 85; m/f = 2/16; MMSE = 27,5	Negative, positive, neutral words	Intentional	Recognition (after 10 min for HOA; immediately after for AD)		No HOA; yes AD (positive)	AD < HOA
				Remember – know paradigm		Not determined (remember); no HOA; no AD (know responses)	AD < HOA
Kazui et al. (2000)	AD = 34; mean age = 71; m/f = 7/27; MMSE = 22,5; HOA = 10; mean age = 70; m/f = 3/7; MMSE = 28,6	Arousing (negative) and non-arousing stories with pictures	Intentional	Questionnaire (after 2 weeks)		Yes HOA; yes AD	AD < HOA
				Emotional rating	AD = HOA emotional > neutral		
Kazui et al. (2003)	AD = 56; mean age = 72; m/f = 14/42; MMSE = 23,3; no HOA	Arousing (negative) and non-arousing stories with pictures	Intentional	Questionnaire (after 2 weeks)		Yes AD	
Kensinger et al. (2004)	AD = 80; mean age = 71; m/f = 33/47; MMSE = 23,2; HOA (10 min delay) = 33; mean age = 71; m/f = 17/16; MMSE = 29,4; HOA (24 h delay) = 18; mean age = 68; m/f = 8/10; MMSE = 29,1	Negative and neutral stories	Intentional	Immediate and delayed free recall (after 10 min for AD and HOA [10 min delay] or 24 h for HOA [24 h delay])		Yes HOA (10 min delay – immediate and delayed recall); yes HOA (24 h delay – immediate and delayed recall); no AD (immediate and delayed recall)	AD < HOA (10 min delay – immediate and delayed recall); AD < HOA (24 h delay – immediate and delayed recall); AD = HOA (24 h delay – delayed recall)

(Continued)

Table 1 | Continued

Study	Participants	Emotions and Stimuli	Type of Encoding	Tasks	Emotional Assessment	Presence of EEE	Group Difference on Memory Performance
				Immediate and delayed recognition (after 10 min for AD and HOA [10 min delay] or 24 h for HOA [24h delay])		Yes HOA (10 min delay – delayed recall); no HOA (10 min delay – immediate recall); yes HOA (24 h delay – delayed recall); no HOA (24 h delay – immediate recall); no AD (immediate and delayed recall)	AD < HOA (10 min delay – immediate and delayed recall); AD < HOA (24 h delay – immediate and delayed recall); AD = HOA (24 h delay – delayed recall)
				Valence and arousal rating	AD = HOA (negative > neutral)		
Kensinger et al. (2002)	AD = 13; mean age = 75; HOA = 20; mean age = 73	Positive, negative, neutral pictures	Intentional	Recall		Yes HOA (positive and negative); no AD	AD < HOA
		Positive, negative, neutral words		Recall		Yes HOA (positive and negative); no AD	AD < HOA
		Neutral words in a positive, negative, or neutral context (sentence)		Recall		No HOA; no AD	AD < HOA
		Neutral or negative words		Recognition (after 5 min)		Yes HOA (negative); no AD	AD < HOA
		Neutral words in a negative or neutral context (sentence)		Recognition (after 5 min)		No HOA; no AD	AD < HOA
Moayeri et al. (2000)	AD = 28; mean age = 76; MMSE = 19,6; HOA = 16; mean age = 71; MMSE = 29	Arousing (negative) and non-arousing stories with pictures	Intentional	Recognition and questions (after 5 min)		No HOA (ceiling effect); yes AD (negative)	AD < HOA
Nashiro and Mather (2011)	AD = 18; mean age = 72; m/f = 11/7; HOA = 18; mean age = 72; m/f = 6/12	Arousing (positive and negative) and non-arousing scenes (IAPS)	Incidental	Free recall		Yes HOA (arousing – positive); yes AD (arousing – positive)	AD < HOA
				Recognition (location task – memory binding)		Yes HOA (arousing – positive and negative); yes AD (arousing – positive and negative)	AD < HOA
				Recognition		Yes HOA (arousing – positive and negative); yes AD (arousing – negative)	AD < HOA

(Continued)

Table 1 | Continued

Study	Participants	Emotions and Stimuli	Type of Encoding	Tasks	Emotional Assessment	Presence of EEE	Group Difference on Memory Performance
				Recognition (location task – memory binding)		Yes HOA (arousing – positive and negative); yes AD (arousing – positive and negative)	AD < HOA
Nieuwenhuis-Mark et al. (2009)	AD = 20; mean age = 83; m/f = 17/3; MMSE = 16,2; HOA = 38; mean age = 81; MMSE = 27,4	Positive, negative, neutral words	Intentional	Free recall		Yes HOA (positive and negative); yes AD (positive and negative)	AD < HOA
Perrin et al. (2012)	AD = 15; mean age = 80; m/f = 9/6; MMSE = 24,6; HOA = 15; mean age = 76; m/f = 7/8; MMSE = 28,1	Positive, negative, neutral pictures (with negative, positive, and neutral sound context: dialogs)	Intentional	Free recall (after 3 min)		Yes HOA (positive sound context); no AD (sound context); yes HOA (positive pictures); yes AD (positive pictures)	AD < HOA
				Questionnaire (gist and detail)		Yes HOA (positive and negative pictures for gist); yes AD (positive and negative pictures for gist); no HOA (sound context – for gist and detail); no AD (sound context – for gist and detail)	
				Emotional rating	AD = HOA (positive > neutral > negative)		
Satler et al. (2007)	AD = 10; m/f = 5/5; HOA = 10; m/f = 3/7	Arousal (negative) and neutral stories	Intentional	Questionnaire (after 2 weeks)		No HOA; yes AD (negative)	AD < HOA
				Emotional rating	AD ≠ HOA		
Satler et al. (2009)	AD = 14; mean age = 75; m/f = 6/8; HOA = 10; mean age = 70; m/f = 6/4	Arousal (negative) and neutral video clips	Intentional	Questionnaire (after 2 weeks)		No HOA (ceiling effect); no AD	AD < HOA
				Emotional rating	AD ≠ HOA		
Schultz et al. (2009)	AD = 20; mean age = 70; m/f = 10/10; MMSE > 20; HOA = 20; mean age = 66; m/f = 10/10 (results reporting on global HOA group – not on years of schooling subdivisions)	Negative, positive, neutral scenes (IAPS)	Incidental	Immediate and delayed free recall (after neuropsychological battery assessment)		Yes HOA (pleasant and unpleasant – immediate recall; delayed recall); yes AD (pleasant and unpleasant – immediate recall); yes AD (pleasant – delayed recall)	AD < HOA

(Continued)

Table 1 | Continued

Study	Participants	Emotions and Stimuli	Type of Encoding	Tasks	Emotional Assessment	Presence of EEE	Group Difference on Memory Performance
				Recognition Pleasantness and valence rating	AD ≠ HOA	Not determined	AD < HOA
Sundstrom (2011)	AD = 20; mean age = 73; m/f = 10/10; MMSE = 19,9; HOA = 20; mean age = 71; MMSE = 27,4	Emotional objects (gifts) and non-emotional objects (gifts)	Incidental	Free recall		No HOA; yes AD	AD < HOA (for both emotional and non-emotional)
				Recognition		No HOA (ceiling effect); no AD	AD < HOA (for both emotional and non-emotional)
Werheid et al. (2011)	AD = 18; mean age = 76; m/f = 5/13; MMSE = 24,6; HOA = 18; mean age = 75; m/f = 9/9; MMSE = 29,5	Happy, angry, neutral faces	Intentional	Recognition		Yes HOA (anger); yes AD (anger)	AD = HOA (accuracy)
				Emotional categorization	AD = HOA (anger > happy > neutral)		

If not indicated, recall and recognition were performed immediately. AD: Alzheimer's disease patients; HOA: healthy older adults; IAPS: International Affective Picture System (Lang et al., 1999); AD < HOA means that performances of AD patients were lower than those of HOA. AD = HOA means that performance was equivalent across groups.

Brueckner and Moritz, 2009; Gallo et al., 2010). This effect of recognition vs. recollection was also shown when AD patients could not create an elaborate conscious encoding strategy during incidental encoding (Hamann et al., 2000; Schultz et al., 2009; Sundstrom, 2011). Studies have consistently shown that, whereas recollection is sustained by the hippocampus area, recognition is associated with activities in the perirhinal cortex (for reviews, see Brown and Aggleton, 2001; Diana et al., 2007; Eichenbaum et al., 2007; Skinner and Fernandes, 2007). This distinction is crucial because current theoretical models of the EEE have proposed that emotion influences on declarative memory are sustained by functional connections between the amygdala and hippocampus (Cahill et al., 1995; McGaugh et al., 1996; Cahill and McGaugh, 1998; McGaugh, 2004; Phelps, 2004; Labar and Cabeza, 2006). Dolcos and collaborators (2005) demonstrated in particular that participants elicited greater activity in the amygdala, hippocampus, and entorhinal cortex when they successfully retrieved emotional stimuli than when they retrieved neutral pictures. Most importantly, in the amygdala and hippocampus, the activity for emotional pictures was greater for recollection than for recognition (familiarity; Dolcos et al., 2005), suggesting that successful retrieval of emotional items was related to an amygdalo-hippocampal interaction for recollection tasks. Although influences of amygdale activity during the encoding of emotional faces have been demonstrated in other brain areas (Kilpatrick and Cahill, 2003; Sergerie et al., 2005), findings have mainly been obtained for hippocampus-dependent declarative memory. In patients with AD, the successful recollection of emotional cues supports the concept that the interaction within MTL structures is partly preserved, even when the hippocampus and amygdala volumes are partially reduced. Results from the study by Mori et al. (1999) confirmed a significant correlation between the amygdalar volume of patients with AD and their personal memory but not between amygdalar volume and their factual knowledge about the Kobe earthquake. This suggests that in impaired memory systems, emotional charge could allow individuals to reduce deficits specifically for strictly episodic memory.

Another point considered to be critical in the elicitation of an EEE in AD is the type of emotional stimuli. It has been proposed that differences in stimulus properties, such as exposure time, tactile richness, and self-reference (whether the stimuli relates to oneself or not), might be the reason for the contradictory results of the EEE in AD (Sundstrom, 2011; Kalenzaga et al., 2012). By using objects that were emotionally connoted as gifts, Sundstrom (2011) demonstrated that the emotional load was increased, leading to the generation of an EEE in AD patients. The author then showed, by using a tactile self-reference dimension (the participant received a gift), that the gifts were better recalled than the non-gifts. In addition, in a study by Kalenzaga et al. (2012), the subjects had to perform a recognition task of emotional vs. neutral adjective traits and then had to characterize during encoding the extent to which the adjective described themselves (self-reference encoding). Results showed that this stimuli encoding strategy led to an EEE, in particular for negative adjectives. Thus, it can be expected that AD patients' attention is attracted by the emotional valence of material that is potentially congruent or emotionally related to themselves (Kalenzaga et al., 2012). This consideration could be

applied in the context of flashbulb memories, which are characterized by an enhanced memory for highly emotionally charged situations that have been experienced (Ikeda et al., 1998; Budson et al., 2004). Japanese patients with AD were more likely to be able to recall their emotional experience during the Kobe earthquake than they were to recall the magnetic resonance imaging scan that they underwent at about the same time. Further, Budson et al. (2004) found that patients with AD retained more personal than factual information about their experience during the events of September 11, 2001. Taken as a whole, these findings suggest that the use of different emotional stimuli could lead to different emotional loads, which might potentially generate an EEE, provided that the intensity and the self-reference of the stimulus are high enough.

In sum, the presence or the absence of an emotional effect on declarative memory could depend on several factors: the presence of severe cognitive decline (e.g., memory), the retrieval instruction, and the emotional stimulus (e.g., emotional load, self-reference). A large number of studies have found an EEE on memory in AD even when cautiously controlling the between-group difference in memory performance (Hamann et al., 2000; Werheid et al., 2011; Kalenzaga et al., 2012), thus reinforcing the beneficial effect of emotion on an AD patient's memory losses. Emotions could convey a conceptual representation that seems to remain partly accessible in these patients. Factors related to the task could also be used to reinforce the emotional trace in memory. The elicitation of an enhancement effect on declarative memory, which declines dramatically in AD, raises the potential benefits of using emotional stimuli in rehabilitations programs. Emotional cues could be a promising way to elaborate therapeutic interventions.

Outside the considerations of EEE on declarative memory, emotional influences in AD could also increase in the context of non-declarative memory (i.e., implicit memory). These emotional influences have not, however, been associated with an EEE, as no strict assessment of memory performances has been done that compared an emotional with a neutral stimulus. Several AD studies have investigated memory implicitly in the context of affective learning (Blessing et al., 2006, 2010), emotional priming (Quoniam et al., 2003; Labar et al., 2005; Garcia-Rodriguez et al., 2009), and fear conditioning (Hamann et al., 2002; Hoefer et al., 2008). The study of Blessing and coworkers (2006) showed that patients' affective ratings of neutral faces were systematically altered by the biographical information (pleasant or aversive stories) that was previously associated with the face. These authors suggested that implicit affective dispositions were relatively intact in dementia. Similarly, preservation of emotional priming in AD has been suggested, since emotional categorization was more accurate for previous emotional priming than for neutral priming (Labar et al., 2005; Garcia-Rodriguez et al., 2009). On the other hand, AD patients have presented deficits in the acquisition of fear conditioning responses, although normal reactivity to the aversive stimulus was found (Hamann et al., 2002; Hoefer et al., 2008).

Researchers have stressed that the pattern of spared and impaired types of non-declarative and declarative memory follows the pattern of brain regions affected by AD (Hamann et al., 2002; Blessing et al., 2006; Garcia-Rodriguez et al., 2009). Declarative memory is sustained by MTL structures, including the hippocampus and entorhinal cortex, which are first affected in AD. The amygdala was suggested to be a critical structure for the establishment of conditioned responses (Ledoux, 1992; Debiec et al., 2010) and emotional memory (Cahill et al., 1995). This brain structure undergoes pathological changes relatively early in AD (Poulin et al., 2011). In contrast, the visual and sensory cortical areas engaged by visual priming are usually spared in the early stage of the disease (Schacter and Badgaiyan, 2001; Blessing et al., 2006), suggesting that implicit emotional memory could be partly preserved in AD (Garcia-Rodriguez et al., 2009). These considerations point, however, to the notion that pathological lesions (e.g., in the amygdala) result in functional impairments, which is not always admitted by the scientific community (Dickerson et al., 2004; Wright et al., 2007). It is thus necessary to unravel how changes in limbic structures could modulate an emotional impact in AD.

AD NEUROPATHOLOGICAL CHANGES WITHIN THE AMYGDALA AND THEIR RELATION TO THE IMPACT OF EMOTIONS ON MEMORY

Alongside reports about the reduction in hippocampus volume, reports about the atrophy of other limbic areas have been published from the start of investigative work on the AD brain (Herzog and Kemper, 1980; Tsuchiya and Kosaka, 1990; Scott et al., 1991, 1992; Arriagada et al., 1992). In particular, several neuroimaging studies have focused on amygdala lesions (Cuenod et al., 1993; Lehericy et al., 1994; Mori et al., 1997, 1999; Krasuski et al., 1998; Basso et al., 2006; Horinek et al., 2007; Wright et al., 2007; Schultz et al., 2009; Cavedo et al., 2011; Poulin et al., 2011), suggesting that reduction in its volume could be similar to hippocampus atrophy (Killiany et al., 1993; Mizuno et al., 2000; Barnes et al., 2006; Schultz et al., 2009). A reduction in amygdala volume may have dramatic consequences for emotion processing in AD, since this structure is strongly involved in numerous emotional processes (Phelps and LeDoux, 2005; Phelps, 2006; Pessoa and Adolphs, 2010). In a recent meta-analysis of the AD population, we reported that the recognition of amygdala-dependent emotions is consistently impaired across studies (Klein-Koerkamp et al., 2012). In relation to memory, considerable supporting evidence in animal (Maren, 2001) and human studies (Hamann, 2001; McGaugh, 2004; Phelps and LeDoux, 2005; Phelps, 2006) suggests that the amygdala is able to modulate encoding, consolidation, and retrieval of emotional materials by increasing hippocampus activity. Insights from another model indicate that the amygdala could be a specific structure for emotional memorization (Ledoux, 2000). Consequences of specific amygdalar atrophy have been assessed in several neuropsychology studies of patients with bilateral and symmetrical calcification of the amygdalar complex [Urbach-Wiethe (UW) disease]. These works have confirmed that emotional memory disruption could result from amygdalar damage because patients with UW had a reduced EEE (Adolphs et al., 1997), whereas patients with amnesia whose amygdala was spared (but who had damage to other MTL regions) had intact emotional memory (Hamann et al., 1997). It has since been proposed that lesions in the amygdala observed in the early phase of AD could be sufficient to disturb this emotional process (Kensinger, 2006).

The assessment of the EEE on declarative memory in patients with AD and UW, offering a model of amygdala neuropathological

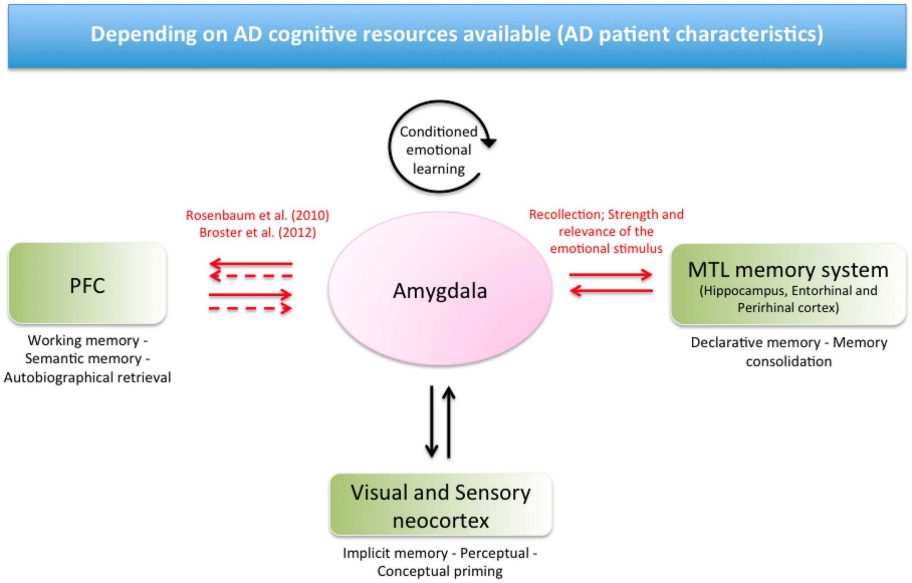

FIGURE 1 | The model based on potential mechanisms by which the amygdala mediates the influence of emotional effect on memory in AD, inspired by Labar and Cabeza (2006). The amygdala presents neural projections to several brain areas. In the context of AD, we propose a pattern of preserved or reinforced interactions between the amygdala and MTL structures in the context of successful emotional retrieval in declarative memory (potentially depending on the task and the emotional stimulus). A pattern of preserved or reinforced interactions between the amygdala and prefrontal cortex could act in the context of flashbulb memory, one form of autobiographical memory. Compensatory mechanisms have also been proposed in the context of working memory (Rosenbaum et al., 2010; Broster et al., 2012). On the other hand, non-declarative memory could be impaired in the context of fear conditioning, as this system takes place intrinsically in the amygdala. Emotional priming could be preserved, as visual and sensory cortices remain relatively preserved in AD, leading to potentially intact neural projections to the amygdala. The EEE requires that cognitive resources are available to help performance for a given task and for a given participant. Red arrows indicate a pattern of reinforced neural projections. Solid arrows indicate direct connections; dashed arrows indicate indirect connections. PFC, Prefrontal cortex; MTL, Medial temporal lobe; AD, Alzheimer's disease.

lesions, has, however, provided divergent findings. Whereas a deficit in EEE acquisition is observed in UW patients (Adolphs et al., 1997), it is not systematically the case in AD patients. Related to the amygdala, the major difference between these two populations is that patients with UW have complete calcification of both amygdales (for a detailed neuroanatomy description; Tranel and Hyman, 1990), whereas the level of amygdala atrophy in AD varies from 14 to 60% (Scott et al., 1991; Cuenod et al., 1993; Jack, 1997; Cavedo et al., 2011). In addition, a recent study suggests that, rather than affecting the whole structure, amygdalar atrophy in patients with AD affects mainly the lateral and basolateral ventromedial regions (Cavedo et al., 2011). Thus, according to the notion that pathological lesions result in functional impairments, these considerations emphasize that emotional memory deficits will be moderate in AD. Nevertheless, the hypothesis that localized amygdala lesions in AD are responsible for changes in EEE acquisition remains an open question, as (1) the functional role of the amygdala subregions in emotional memory is largely unknown, and (2) both preservation and disruption effects are reported in AD studies. This is inconsistent with the notion that proportional effects exist between pathological lesions and the functionality of the amygdala, which raises critical issues related to amygdala functioning in AD.

To date, very few works have brought new information to light regarding these issues, with most imaging studies investigating memory effect without emotionally arousing information (Grady et al., 2001; Rosenbaum et al., 2010). In these studies, functional connectivity data were obtained in patients with AD engaged in a delayed match-to-sample face recognition task (working memory task) of familiar and unfamiliar items. Results showed increased connectivity between the left amygdala and the neighboring and inferior prefrontal regions in AD compared with that in HOA (Grady et al., 2001; Rosenbaum et al., 2010). This pattern of altered connectivity was not clearly determined. As amygdala activation has consistently been reported during affective tasks, the authors suggested that the emotional content of the faces was incidentally processed to a greater degree by the patients than by the controls (Grady et al., 2001). Some authors have also proposed that the pattern of prefrontal involvement in AD represents an inhibitory system that suppresses emotional responses elicited by the faces, which is irrelevant to the task (Rosenbaum et al., 2010). This pattern of enhanced prefrontal activity (in particular the dorsomedial part of the prefrontal cortex) involved in regulatory mechanisms has been also reported in the context of healthy aging. It was suggested that older adults showed a greater prefrontal activity compared to young adults due to additional cognitive control involved in decoding and/or regulating negative emotions (Ebner et al., 2012). In the context of AD, researchers suggested, nevertheless, that this prefrontal activity reflected a compensatory mechanism, involving the amygdala and prefrontal networks to a greater extent than it does in HOA. In a similar task, a compensation system that included the amygdala was retrieved, as

shown when greater amygdala activation was reported in patients with mild cognitive impairments compared with HOA (pilot study reported in: Broster et al., 2012). This result corroborates findings of Wright et al. (2007), in which amygdala activity was shown to be significantly greater in AD patients for both neutral and emotional faces compared with HOA. The hypothesis that the preservation of emotional impact might be explained by a compensatory mechanism requiring greater recruitment of the amygdala and/or solicitation of an additional anatomical network thus seems valuable (Grady et al., 2001; Wright et al., 2007; Rosenbaum et al., 2010; Broster et al., 2012). Further studies investigating the functional interactions between prefrontal and amygdala areas in the context of emotional memory in AD are needed before conclusions may be drawn.

In another model, Labar and Cabeza (2006) emphasized the role of the amygdala and its interaction with other brain areas, including MTL structures and the prefrontal cortex, in the context of declarative and non-declarative memory. In this theoretical framework, the amygdala mediates the influence of emotional arousal on declarative memory via direct connections with the MTL structures by favoring memory consolidation. Indirect and direct connections between the prefrontal cortex and the amygdala mediate other forms of declarative memory, including semantic, autobiographical, and working memory. In addition to the conditioned emotional learning that takes place intrinsically in the amygdala, direct neural projections with sensory cortices target other non-declarative forms of memory, including perceptual and conceptual priming [see **Figure 1**, inspired by Labar and Cabeza (2006)].

As stated above in the context of AD and on the basis of this model, we hypothesize that a patient's successful recollection of emotional cues (vs. non-emotional cues) could relate to preserved or reinforced functional interactions between the amygdala and MTL structures in the context of declarative memory. These amygdala and MTL interactions for EEE elicitation could also depend on the arousal strength and relevance of the emotional stimulus (Ikeda et al., 1998; Satler et al., 2007; Sundstrom, 2011; Kalenzaga et al., 2012). In the case of enhanced flashbulb memory, one form of autobiographical memory, additional reinforced projections between the amygdala and prefrontal cortex could be recruited to enhance memory, providing that the emotional stimulus is strong enough (Mori et al., 1997; Ikeda et al., 1998; Budson et al., 2004). The model of Labar and Cabeza (2006) also fits with suggestions of Broster et al. (2012) and Rosenbaum et al. (2010) on the potential compensatory mechanism involving the prefrontal cortex and the amygdala in the context of working memory (studies involving match-to-sample tasks). Considering non-declarative memory, we hypothesize that the later impairments of sensory cortices could result in potentially intact projections between the amygdala and this area to maintain an emotional influence on priming scores. On the other hand, additional brain networks cannot compensate for fear learning impairments in AD, which mainly involve the amygdala.

Neuroimaging of emotional memory enhancement in aging and AD populations remains in its infancy (Broster et al., 2012). The model that we propose in the context of AD is based on current knowledge of brain networks that sustain emotional memory processes in healthy subjects (Labar and Cabeza, 2006). The AD population highly differs from normal subjects in the sense that patients have severe cognitive declines. Thus, our assumptions of reinforced neural projections between brain areas in the elicitation of emotional enhancement have to be considered in the context of cognitive resources that are available in the AD population (Borg et al., 2011; Broster et al., 2012). In this way, severe deficits in the overall memory system or executive functions could compromise an emotional effect on memory for a given task.

This AD model of neuropathological changes provides new input into the current staging of knowledge concerning emotional memory processes in humans. There may not be a linear explanation for the relation between amygdala volumes, its functional activity, and emotional memory disturbances. Further neuroimaging findings would be very helpful in describing the anatomical and functional signatures of emotional memory processes and how altered brain systems may compensate for emotional memory impairments in the context of AD.

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The detrimental effects of emotional process dysregulation on decision-making in substance dependence

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Substance dependence is complex and multifactorial, with many distinct pathways involved in both the development and subsequent maintenance of addictive behaviors. Various cognitive mechanisms have been implicated, including impulsivity, compulsivity, and impaired decision-making. These mechanisms are modulated by emotional processes, resulting in increased likelihood of initial drug use, sustained substance dependence, and increased relapse during periods of abstinence. Emotional traits, such as sensation-seeking, are risk factors for substance use, and chronic drug use can result in further emotional dysregulation via effects on reward, motivation, and stress systems. We will explore theories of hyper and hypo sensitivity of the brain reward systems that may underpin motivational abnormalities and anhedonia. Disturbances in these systems contribute to the biasing of emotional processing toward cues related to drug use at the expense of natural rewards, which serves to maintain addictive behavior, via enhanced drug craving. We will additionally focus on the sensitization of the brain stress systems that result in negative affect states that continue into protracted abstinence that is may lead to compulsive drug-taking. We will explore how these emotional dysregulations impact upon decision-making controlled by goal-directed and habitual action selections systems, and, in combination with a failure of prefrontal inhibitory control, mediate maladaptive decision-making observed in substance dependent individuals such that they continue drug use in spite of negative consequences. An understanding of the emotional impacts on cognition in substance dependent individuals may guide the development of more effective therapeutic interventions.

Keywords: addiction, emotion, cognition, reward, stress, decision-making

INTRODUCTION

Drug addiction is a persistent disorder characterized by compulsive-seeking and taking of drugs, loss of control over intake, and negative emotional states in withdrawal, such as dysphoria, anxiety, and irritability (Koob and Le Moal, 2008b). Many people try drugs; an estimated 36% of people aged between 16 and 59 have engaged in illicit drug use, the highest incidence of use being reported in young adults aged under 25 (Department of Health, 2011). For the majority, drug use is controlled, limited to a short period of time and does not result in problems. However, a small proportion develop substance dependence which is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) as excessive drug use that may result in tolerance and withdrawal symptoms, an inability to cut down on drug use, and continued drug use in spite of knowledge of negative consequences. The term "addiction" is used by the National Institute of Drug Abuse (NIDA) to describe a chronic, relapsing disorder characterized by compulsive drug use in spite of harmful consequences, and roughly corresponds to the DSM definition of dependence. Substance abuse is defined in DSM as recurrent use of a substance resulting in occupational, legal, social, and interpersonal problems.

Dependence is a major medical, social, and economic problem for many countries worldwide. For example, tobacco contributes to 8.8% of deaths worldwide, alcohol to 3.2%, and illicit drugs to 0.4% (WHO, 2008). In England alone, around 24% of adult men and 13% of adult women consume hazardous amounts of alcohol, costing the economy approximately £20 billion (NHS, 2009). In 2003/2004 class A drug use cost the UK roughly £15.4 billion (Singleton et al., 2006), 90% of this cost due to drug-related crime, with the health care costs amounting to approximately £1.4 billion per year (Lingford-Hughes et al., 2010). While an extensive range of drugs are abused, opiates, cocaine, and alcohol have been identified as the three drugs most dangerous to both the individual and society (Nutt et al., 2010) and they will be the focus of this review.

Drug dependence is associated with changes to brain structural, neuropsychological, and emotion systems (Asensio et al., 2010). These changes have the potential to influence vulnerability for substance dependence, contribute to the maintenance of problem drug use once it has started, as well as affecting the likelihood of relapse following detoxification. Clinically and therapeutically it is important to understand the mechanisms of each of these three stages of addiction. Identification of vulnerability markers

for problem drug use would allow the possibility of early intervention, or even preventative therapies in high-risk individuals. Understanding the mechanisms of maintenance of drug-taking behavior is important for preventing initial drug use from developing into dependence. Perhaps the most difficult problem facing the treatment of addiction is the very high rate of relapse following initially successful treatment (Sinha, 2011), and it is therefore crucial to understand the factors involved, in order to break the cycle of repeated detoxification and relapse.

It is clear that substance dependence is a multi-factorial problem, with a range of social, environmental, cognitive, and neurobiological factors contributing to vulnerability, maintenance, and relapse. The focus of this special issue is the interaction between cognition and emotion, and we therefore focus on this aspect of addiction research.

We will argue that substance dependence is a disorder characterized by dysregulation of emotional processes with a particular focus on reward circuitry, involved in motivation and reinforcement, and stress circuitry involved in defense. Reward and stress processing includes the modulation of cognitive performance by the presence (or absence) of motivationally salient outcomes, while stress responsivity additionally incorporates a component of achieving, or maintaining, successful cognitive performance under conditions of emotional stress and anxiety. Both these aspects of cognitive-emotional interaction are dysfunctional in individuals dependent on drugs, and we will describe how these dysfunctions may result in maladaptive behaviors that both initiate and maintain dependence and increase the risk of relapse during a period of abstinence. Specifically, we will consider how emotional dysregulation may contribute to cognitive impairments in the domains of impulsivity and decision-making, aspects of processing which may contribute to the development and maintenance of drug misuse.

WHAT ARE EMOTIONS?

The term emotion has been applied to a diverse array of perceptions, behaviors, and psychological states (Cardinal et al., 2002). We adopt the definition of emotion recently put forward by LeDoux—that emotions are phenomena that reflect functions of circuits allowing an organism to survive and thrive by detecting and responding to salient challenges and opportunities within the environment. That is, emotions are brain "responses that occur when in danger, or when in the presence of a potential mate, or in the presence of food when hungry or drink when thirsty ….." (LeDoux, 2012). By "emotional processing" we refer to the processing of information within these circuits. This operationalized definition removes the focus away from emotions reflecting subjective feeling states (which present problems when assessing emotions in animals) toward emotions reflecting processes that are experimentally tractable (LeDoux, 2000).

Emotional circuits detect key trigger stimuli (or unconditioned stimuli) on the basis of innate, hard-wired programming that has evolved through natural selection (LeDoux, 2012). These unconditioned stimuli can be potential sources of immediate pleasure, threat, or satisfaction of homeostatic need, such as immediate stress or withdrawal relief (Verdejo-Garcia and Bechara, 2009). Activation of emotional circuitry has a number of consequences within the brain and body. Changes include increased release of neurotransmitters such as dopamine, noradrenaline, and serotonin within the brain, and changes within the internal milieu and viscera of the body such as release of hormones and increased heart rate (Bechara and Damasio, 2005). In addition, emotional circuit activation can result in the conscious feeling states that are commonly associated with the word "emotion." Emotion circuit activation also results in hard-wired, innate behavioral responses such as approach, freezing, and fleeing (van der Meer et al., 2012).

PAVLOVIAN CONDITIONING

When emotional circuits are activated, learning occurs, with the establishment of an association between innate triggers or biologically significant events (referred to as unconditioned stimuli, UCS) and previously neutral stimuli that occurred in close association with them (Rescorla, 1988). The previously neutral stimuli acquires motivational value, reflecting the utility or value of the UCS (Seymour and Dolan, 2008), and acquires the ability to activate emotional circuitry themselves, thereby becoming conditioned stimuli (CS) (LeDoux, 2012). This emotional learning process is referred to as Pavlovian conditioning, after Ivan Pavlov, the discoverer of this phenomenon (Cardinal et al., 2002). This ability of the CS to predict the value or utility of the UCS results in an *expectancy* of the UCS upon presentation of the CS (Seymour and Dolan, 2008), which enables appropriate responses to be evoked by the CS in anticipation of the UCS. The amygdala is the brain structure that is considered to have a central role in Pavlovian conditioning, as well as a crucial role in emotional circuitry involved in processing reward and threat (Cardinal et al., 2002; LeDoux, 2007).

PATHWAYS INTO SUBSTANCE DEPENDENCE

EMOTIONAL PERSONALITY TRAITS AND THE RISK FOR SUBSTANCE USE AND DEPENDENCE

Motivation to engage in substance use, in addition to numerous psychosocial factors, has been related to the ability of a substance to produce positive emotional states (Volkow et al., 2011). This is also referred to as positive reinforcement. A desire for substance induced pleasure appears to be associated with certain personality traits. The trait of sensation-seeking is defined by the need for novel, varied, and intense experiences (Zuckerman, 1994) and, as will be reviewed later, is associated with functioning within the reward circuitry. Higher levels of sensation-seeking are found in alcohol-dependent individuals (Noel et al., 2011) and in young adults with alcohol use disorders (Shin et al., 2012). Higher levels of sensation-seeking have also been reported in cocaine-dependent individuals (Patkar et al., 2004; Ersche et al., 2010b) and shown to be negatively associated with treatment outcomes (Patkar et al., 2004). Mixed results have been found in opiate-dependent individuals, with higher levels of sensation-seeking found in some studies (Le Bon et al., 2004; Lemenager et al., 2011) but not others (Nielsen et al., 2012). The trait has also been shown to be associated with early alcohol use in adolescents (Martin et al., 2002; Gillespie et al., 2012; Nees et al., 2012) and is predictive of the later development of alcohol abuse (Cloninger et al.,

1988) and the frequency and quantity of alcohol and polysubstance use in young adults (Chakroun et al., 2004; Woicik et al., 2009).

Motivations for drug and alcohol use in sensation seekers are associated with the enhancement of positive affect states (Comeau et al., 2001; Woicik et al., 2009). By contrast, another motive for engaging in substance use is to reduce negative affect states (Koob and Le Moal, 2008a), also referred to as negative reinforcement. Thus, a tendency to experience more negative states could increase the risk of developing substance dependence. In line with this hypothesis, high self-report measures of anxiety sensitivity are related to anxiolytic and opiate drug use in young adults, problem drinking in adolescents (Woicik et al., 2009), and early alcohol initiation in adolescents (Kaplow et al., 2001). Furthermore, the characteristic of "hopelessness," which closely relates to depressive personality traits, is associated with a higher degree of sedative drug use in young adults as well as quantity and frequency of alcohol use in adolescents (Woicik et al., 2009). Motivation for substance use in those with anxiety sensitive and depressive traits is associated with relieving these negative affect states (Comeau et al., 2001; Woicik et al., 2009). It is important to note that other studies in young adults have failed to find an association between increased negative affect states and drug and alcohol use (Chakroun et al., 2004; Gillespie et al., 2012). These discrepancies suggest that there is considerable variability, consistent with the hypothesis of multiple routes into drug and alcohol dependence. It is likely that different personality traits will confer vulnerability via interactions with different environmental triggers, and therefore studies in different populations may show discrepant results.

Another important issue is whether emotional personality traits confer differential risk for specific substance dependences, and there is some evidence suggesting this to be the case. Studies suggest that traits of anxiety sensitivity and hopelessness are more related to anxiolytic and opiate dependence respectively, while sensation-seeking and impulsivity confer a greater risk of alcohol and cocaine dependence respectively (Conrod et al., 2000). High scores on anxiety sensitivity are more associated with primary use of heroin compared to cocaine, or the use of both heroin and cocaine (Lejuez et al., 2006) and high scorers on anxiety sensitivity are less likely to identify cocaine as their drug of choice compared to those with moderate anxiety sensitivity (Norton et al., 1997). These preferences may reflect the anxiolytic and the anxiogenic effects of opiates (Lejuez et al., 2006; Colasanti et al., 2011) and cocaine (Yang et al., 1992) respectively.

However, once again the evidence is far from conclusive. While Conrod et al. (2000) observed no association between negative affect personality traits and alcohol dependence, Norton et al. demonstrated that high scorers on traits of anxiety sensitivity indicated alcohol to be their drug of choice (Norton et al., 1997). Carpenter and Hasin demonstrated that in a sample of heavy drinkers the tendency to drink in an attempt to cope with negative affect was a risk factor for the subsequent development of alcohol dependence (Carpenter and Hasin, 1998). Furthermore, longitudinal studies have shown that adolescents with symptoms of depression and anxiety were at a greater risk of developing alcohol dependence (Mackie et al., 2011; McKenzie et al., 2011). Such findings may reflect the ability of alcohol to reduce negative affect (Gilman et al., 2008). Negative affect has also been associated with cocaine use, with higher levels of associated with cocaine use in a community-based sample of young adults (Kilbey et al., 1992) and depression in adolescents predicted higher cocaine use the following year (Newcomb and Bentler, 1986). These findings are contrary to the hypothesis that negative affect traits selectively confer enhanced risk of opiate and anxiolytic abuse. Studies have shown that major depressive disorder is prevalent in cocaine-dependents and the presence of depression may impact upon the severity of addiction (Rounsaville, 2004), further supporting an association between negative affect traits and cocaine dependence. However, longitudinal studies assessing the relationship between these traits and the subsequent development of cocaine dependence are required to determine the degree to which negative affect can be considered a cause, and/or a consequence of cocaine dependence.

While questions remain about the relationship between traits and specific addictions, it is clear that in general, affective personality traits can modulate drug use, resulting in early, and more frequent substance use and substance dependence. Sensation-seeking appears to be related to enhancing positive affect states and may be associated with earlier, heavier, and more frequent substance use in young adults, and particularly with alcohol and cocaine dependence. By contrast, it appears that personality traits associated with negative affect are more likely to be associated with use of sedatives and opiates. However, this is by no means a complete dissociation. Some studies have indicated that sensation-seeking may be elevated in heroin users. Similarly, negative affect may play a role in cocaine and alcohol dependence, particularly the transition from heavy use to dependence.

NEUROBIOLOGY UNDERLYING PERSONALITY RISK FACTORS FOR SUBSTANCE DEPENDENCE

These personality risk factors for substance dependence are assumed to exert their influence via altered functioning of brain motivational systems, leading to differential susceptibility to seek out specific drug-reinforcement effects (Conrod et al., 2000). In this section of the review, we will outline the underlying neurobiology of traits of sensation-seeking, hopelessness, and anxiety/stress sensitivity and how these neurobiological markers may lead to the development and maintenance of substance dependence.

Sensation-seeking and reward neurobiology

Rewards have been defined as hedonic incentives that cause neural representations that elicit motivation and goal pursuit, and as stimuli that positively reinforce behavioral acts (Kelley and Berridge, 2002; Schultz, 2006), thus the term "reinforcer" is often used interchangeably with "reward." The processing of rewards is complex, involving different psychological components including "liking" or hedonic impact of rewards, "wanting" or motivation for rewards, and learning, the formation of associations through experience that allow for predictions of future rewards (Berridge and Kringelbach, 2008). Stimuli associated with a reward acquire the ability to elicit innate emotional responses that are normally associated with the reward itself, via Pavlovian conditioning.

Sensation-seeking is thought to reflect the function of an underlying motivational system or behavioral approach system (Gray, 1990) that is activated by reward signals, and represents a heightened sensitivity to these signals (Depue and Collins, 1999). Specifically, reward signals can elicit a motivational state referred to as "positive incentive motivation" which serves to guide approach behavior toward a goal. Positive incentive motivation is associated with strong positive affect such as desire, excitement, enthusiasm, energy, or self-confidence (Depue and Collins, 1999). Key brain areas involved with the processing of rewards include ventral striatum, orbitofrontal cortex (OFC), ventral pallidum, anterior cingulate cortex, and midbrain dopamine neurons (Haber and Knutson, 2010). Functional magnetic resonance imaging (fMRI) studies have demonstrated a positive correlation between blood oxygen level dependent (BOLD) response in these key reward processing areas and measures of reward sensitivity (Beaver et al., 2006; Hahn et al., 2009) and self-reports of excitement in response to reward cues (Bjork et al., 2004b, 2008c). A positive correlation has been reported between ventral striatal activation and trait measures of sensation-seeking (Bjork et al., 2008a), supporting the theory that sensation-seeking reflects enhanced reward sensitivity.

Dopamine and reward sensitivity. Seminal theories posit that ventral tegmental dopamine release into the ventral striatum mediates reward sensitivity by encoding the intensity or "salience" of reward related stimuli (Robinson and Berridge, 1993), or the predictive value of conditioned reward stimuli and the error in the prediction of unconditioned stimuli whenever they are surprising (Schultz, 1998). Therefore, dopamine may influence the motivational value of stimuli and their impact on emotional and behavioral responses (Depue and Collins, 1999).

In support of this theory, ventral striatal response to reward cues, measured by fMRI, has been shown to correlate with ventral striatal dopamine release, measured by positron emission tomography (PET) (Schott et al., 2008). Dopamine-enhanced incentive salience of stimuli has been suggested to increase incentive motivational states and make stimuli, or their associated reward, more attractive or "wanted." Dopamine-mediated enhancement of "wanting" has been suggested to underlie the craving that is often experienced by drug users after exposure to drug related stimuli (Robinson and Berridge, 1993).

Dopamine and sensation-seeking. Sensation-seeking is assumed to reflect heightened reward sensitivity, which is hypothesized to be modulated by dopamine. This may suggest that sensation-seeking could also be influenced by dopamine. Genetic linkage studies demonstrate associations between sensation-seeking and polymorphisms of dopamine-related genes (Zuckerman, 2005; Golimbet et al., 2007; Munafo et al., 2008) and a recent PET study reported an inverted "U" shaped relationship between striatal dopamine D2/D3 receptor availability and scores of sensation-seeking (Gjedde et al., 2010). Such a relationship indicates that dopamine receptor availability rises with sensation-seeking at lower scores, but falls in opposition to sensation-seeking scores at the higher end. The authors propose that high levels of sensation-seeking reflects a hyperdopaminergic state, that results in reduced D2/D3 availability for the competing PET radioligand, as opposed to a reduced D2/D3 receptor density in these individuals (Gjedde et al., 2010). This is supported by studies indicating higher sensation-seeking to be associated with reduced activity of monoamine oxidase, resulting in higher brain dopamine concentrations (Zuckerman, 1985; Golimbet et al., 2007). Furthermore the closely related trait of novelty-seeking is found to be inversely correlated with midbrain D2/D3 autoreceptor availability, with higher novelty-seeking related to lower autoreceptor availability (Zald et al., 2008). In contrast, to postsynaptic dopamine receptors, midbrain dopamine receptor availability remains relatively constant after pharmacological manipulations that alter dopamine levels. Therefore, receptor availabilities of midbrain autoreceptors found in this study are assumed to reflect receptor densities, rather than levels of competing endogenous dopamine (Zald et al., 2008). The DA autoreceptor exerts a powerful inhibitory effect on dopamine neuron firing (Aghajanian and Bunney, 1977), thus lower autoreceptor densities found in high novelty seekers might be expected to result in higher levels of dopamine release. This hypothesis is supported by studies demonstrating that novelty-seeking positively correlates with drug-induced dopamine release (Leyton et al., 2002; Boileau et al., 2006). In addition to the role of dopamine in sensation/novelty-seeking, other neurotransmitter systems may also be involved as interactive effects between dopamine- and serotonin-related genes and novelty-seeking have been reported (Zuckerman, 2005).

Negative affect traits and reward neurobiology

Depressive personality traits. Two core features of depression are a markedly reduced interest or pleasure in activities and low mood (feelings of sadness), thus depressive personality traits are also linked to dysfunction of brain reward and motivational systems, and may specifically relate to hypofunctioning of the mesolimbic dopaminergic system (Pizzagalli et al., 2009). Most neurobiological theories of depression focus on the serotonergic and noradrenergic systems, since all effective anti-depressant medications converge upon these systems. However, preclinical evidence suggests some of the therapeutic effects of antidepressants may be partly due to increased striatal dopamine transmission and enhanced sensitivity within the mesolimbic dopamine system (Markou et al., 1998). Furthermore, recent studies demonstrate that manipulations of proteins regulating ventral tegmental dopamine produce behavioral phenotypes relevant to depression (Nestler and Carlezon, 2006).

Anxiety sensitive personality traits. Anxiety sensitivity is thought to reflect functions of a defence system that is activated by aversive, novel, and innate fear stimuli (Barros-Loscertales et al., 2006). Anxiety is a motivational state that promotes adaptive behaviors; it is, however, distressing for the organism and impairs performance when excessive (Colasanti et al., 2011). The anxiety/stress system is modulated by numerous neurotransmitters including corticotrophin releasing factor, neuropeptide Y, substance P, noradrenaline, serotonin, dopamine, glutamate, and GABA—see Charney and Drevets (2002) for

detailed review. In contrast to sensation-seeking and depressive personality traits, anxiety sensitivity may not directly reflect abnormalities within the brain's reward system but instead may reflect indirect effects. For example, it has been suggested that concomitant inputs from key anxiety structures affect the way neural signals are "gated" within the nucleus accumbens such that they not rewarding but instead serve to increase motivation to deal with the threat at hand (Nestler and Carlezon, 2006).

REWARD SENSITIVITY THEORIES OF SUBSTANCE DEPENDENCE

These findings raise the crucial question of how sensation-seeking, depressive, and anxiety sensitive personality traits confer increased risk of developing addiction. There is evidence that sensation-seeking and depressive traits reflect dopaminergic disturbances which influence response to reward and control of incentive motivation. We have presented evidence that these pre-morbid traits result in early, more frequent use of substances. In the following sections we will also present evidence of additional drug-induced adaptations within the reward circuitry that are proposed to enhance the desire to engage in substance use, contributing to the subsequent development of substance dependence.

Dysfunction within brain reward systems, where dopamine signaling has important functions, has been widely studied in addiction. Alterations in reward responsiveness and incentive motivation represent an important way in which emotional processing can impact cognitive function, resulting in poorly controlled, and maladaptive behavior. In this section, we will briefly outline two major theories of impaired reward sensitivity in addiction.

INCENTIVE SENSITIZATION IN SUBSTANCE DEPENDENCE

Sensation-seeking is assumed to reflect heightened reward sensitivity and heightened positive incentive motivation. Sensation seekers may have enhanced motivation to engage in initial substance to further increase positive affect states. The transition from controlled recreational drug use to compulsive use is hypothesized to be the result of drug-induced sensitization of mesocorticolimbic brain systems that attribute incentive salience to reward-associated cues. The main points of this theory are that previously neutral stimuli acquire incentive motivational properties through association with drug rewards via Pavlovian conditioning mechanisms. Therefore, exposure to conditioned drug cues can produce dopamine release from mesolimbic dopamine neurons that causes drug wanting. Repeated exposure to addictive substances may result in neuroadaptation in mesolimbic dopamine neurons that sensitize these neurons (Robinson and Berridge, 1993). This effect has been demonstrated in animal models as an enhanced expression of psychomotor activating effects of all drugs of abuse, which is thought to be dependent upon the mesolimbic dopaminergic system (Robinson and Berridge, 2001). In humans, enhanced release of dopamine after a repeated dose of amphetamine has been observed (Boileau et al., 2006) and enhanced presynaptic dopamine function has recently been reported in ex-recreational users of psychostimulant drugs, although it is unknown whether this reflects a pre-existing hyperactivity or a drug induced effect (Tai et al., 2011). This sensitization of mesolimbic neurons is suggested to result in pathological levels of incentive salience being attributed to drugs and drug cues, thus creating a pathological incentive motivation for drugs which can persist for years (Robinson and Berridge, 2008).

REWARD DEFICIENCY SYNDROME

Dopamine is related to incentive motivational aspects of rewards which are in turn associated with strong positive affect such as excitement, enthusiasm, and self-confidence (Depue and Collins, 1999). Many drugs of abuse, either directly or indirectly, induce acute release of dopamine from mesolimbic dopamine neurons into the nucleus accumbens in rodents (Di Chiara et al., 2004), while stimulants but not heroin, have been demonstrated to increase dopamine release into the ventral striatum in humans (Lingford-Hughes et al., 2010) with mixed findings with respect to alcohol and dopamine release in humans (Boileau et al., 2003; Yoder et al., 2009). Pleasurable feelings of intoxication correlate with ventral striatal dopamine release for stimulants (Volkow et al., 1999) and alcohol (Boileau et al., 2003) and thus dopamine may be important for the rewarding effects of drugs of abuse (Volkow et al., 2011). However, the idea that drug-induced dopamine release mediates the hedonic impact of drugs of abuse is controversial (Wachtel et al., 2002; Berridge, 2007). Instead these rewarding effects may occur via the enhancement of the perceptual impact or incentive salience of environmental stimuli (Everitt and Robbins, 2005).

The opioid system is related to consummatory aspects of reward such as satiation, sedation, and "bliss" (Comings and Blum, 2000). Generally speaking the pleasurable feelings associated with opiate drugs are due to mu and delta opioid receptor agonism (Le Merrer et al., 2009). Heroin exerts its euphoric effects through mu opioid receptor agonism, as blockade of these receptors has been demonstrated to reduce opiate self-administration (De Vries and Shippenberg, 2002). However, emerging evidence suggests the opioid system is not only involved in the reinforcing effects of heroin, but also those of alcohol (Mitchell et al., 2012) and amphetamine (Jayaram-Lindstrom et al., 2008; Colasanti et al., 2012) via the release of endogenous opioids. Furthermore, increased mu opioid receptor binding has been found in cocaine users, suggesting an important role of the endogenous opioid system in cocaine dependence (Ghitza et al., 2010).

Comings and Blum put forward the "Reward Deficiency Hypothesis" (RDS) as one possible vulnerability for the development of substance dependence. This theory highlights the role of pre-morbid trait vulnerabilities in the subsequent development of substance dependence. According to this hypothesis, individuals with deficient reward-signaling systems may be at greater risk of developing substance dependence. In such individuals, natural rewards do not adequately stimulate the reward system, which may contribute to depressive traits associated with substance use. Therefore, it is proposed that such individuals use substances in order to enhance stimulation in deficient reward pathways.

After the development of substance dependence, the influence of negative affect becomes more apparent, suggesting that

chronic drug use may lead to changes to the brain's reward system. Therefore, in addition to trait vulnerabilities in the reward system, drug-induced neurobiological changes may result in additional deficiencies in reward sensitivity. Koob and colleagues have argued that these homeostatic or "opponent" processes occur to reduce the rewarding effects of drugs of abuse (Koob and Le Moal, 2005). In support of this theory, increased tolerance to the rewarding effects of cocaine (Kenny et al., 2003), opiates (Liu and Schulteis, 2004), and alcohol (Schulteis and Liu, 2006) occurs in rodents as demonstrated in intracranial self-stimulation experiments. Acute withdrawal is associated with reduced mesolimbic dopamine release (Koob and Le Moal, 2005). Therefore, these changes are likely to underlie anhedonia and amotivation associated with withdrawal from drugs of abuse.

HUMAN STUDIES ASSESSING REWARD FUNCTIONING IN ADDICTION

There are thus two distinct theories about how reward sensitivity may be abnormal in addiction. One theory is that substance dependence is characterized by ***enhanced*** sensitivity to reward and therefore enhanced incentive motivation toward drug and even non-drug cues (Hommer et al., 2011). However, drug use is also associated with negative affect states and the reward deficiency syndrome posits that ***reduced*** functioning of the brain's reward system underlies the motivation to engage in substance use in order to normalize these deficiencies. These theories make different predictions about how the brain reward systems will respond to a range of reward cues. Functional imaging techniques provide a means to investigate these predictions in human subjects.

Brain response to monetary cues

Studies have examined brain response to monetary reward using the monetary incentive delay task (Knutson et al., 2001). In alcohol-dependent individuals, there have been mixed findings. Two studies have found ventral striatal activation to be decreased in dependent individuals to controls, and negatively correlated with craving levels (Wrase et al., 2007; Beck et al., 2009). These findings therefore support the reward deficiency theory of addiction. However, another study found no difference between controls and alcohol-dependent individuals in response to monetary cues (Bjork et al., 2008c), but enhanced ventral striatal activation in response to reward outcome, a finding more consistent with the hypersensitivity hypothesis of addiction. The authors suggested that decreased ventral striatal activations for monetary cues found by Beck et al. and Wrase et al. may have been due to faster trial presentation putting too high a demand on attentional processing, rather than reduced reward sensitivity. However, a later study by the same group failed to replicate the finding of enhanced ventral striatal activation to reward outcome (Bjork et al., 2011). One possible source of the discrepant findings may be that the studies of Bjork and colleagues, in contrast to the studies of Beck et al. and Wrase et al., included alcohol-dependent participants reporting current or past substance dependence, most significantly, cocaine. Therefore, the evidence suggests that dependence upon alcohol only is associated with a reward system insensitivity. However, it is also important to note that studies in individuals already dependent on alcohol do not provide clear evidence for how that dependence developed initially. The lack of conclusive findings may reflect heterogeneity within the alcohol-dependent groups, consistent with the results of personality studies reviewed earlier. Both sensation-seeking (Conrod et al., 2000) and negative affect (Carpenter and Hasin, 1998) traits have been found to be associated with alcohol dependence. It is possible the discrepant reward sensitivity theories illustrate distinct routes into alcohol dependence for individuals with different personality traits.

Only one study to date has carried out the monetary incentive delay task in cocaine-dependent individuals, reporting no differences in ventral striatal responses between controls and cocaine-dependent individuals during reward anticipation, but enhanced ventral striatal response in cocaine-dependents for reward outcomes (Jia et al., 2011). BOLD responses during reward anticipation and outcome were found to be negatively correlated with abstinence measures and treatment retention. This finding, in addition to the enhanced vs. response in alcohol-dependent participants reporting significant cocaine dependence, suggests an enhanced reward sensitivity occurs in cocaine addiction.

Two other studies investigated brain response to monetary rewards in cocaine users with a related task, reporting no differences in ventral striatal BOLD response but disturbed OFC responsivity to different monetary value conditions within cocaine-dependent individuals (Goldstein et al., 2007a,b). Whilst OFC metabolism has been shown to depend on striatal dopamine receptor density (Volkow et al., 1993), it is difficult to draw conclusions regarding the direction of the sensitivity of mesocorticolimbic system based on these findings.

At the time of writing, we are not aware of any published brain imaging studies investigating response to monetary reward in opiate addiction. However, given that opiate addiction appears to be more related to depressive personality traits that are characterized by anhedonia and reduced motivation, that are considered to be related to deficient reward system functioning, it could be predicted that a reduced ventral striatal activation would be found to monetary cues and reward outcome in opiate addiction.

Brain response to drug cues

Assessing the brain response to conditioned drug-related stimuli or drug "cues" has been central to addiction research. Neural and psychological responses to drug cues are considered to be important in the maintenance of addiction and have been implicated in triggering relapse to drug use during periods of abstinence (Everitt et al., 2001).

Due to the huge number of studies assessing the brain response to drug stimuli, a comprehensive review of cue induced craving studies is beyond the scope of the current review. However, two recent activation likelihood estimation (ALE) meta-analyses of these studies have been conducted (Chase et al., 2011; Kuhn and Gallinat, 2011). Kuhn and Gallinat reported that enhanced brain response to drug cues compared to non-drug cues in alcohol and cocaine addiction converge upon the ventral striatum. Additionally, Chase et al. found areas of convergence in the ventral striatum, OFC, and amygdala in response to alcohol, heroin, and cocaine cues compared to control cues. Furthermore, ALE meta-analyses were carried out on all of the studies reporting correlations between brain response and self-reported craving.

Kuhn and Gallinat found that activity within anterior cingulate cortex, ventral striatum, and pallidum correlated with craving in alcohol studies, whereas the study of Chase et al. which included a wider range of studies, found amygdala correlations.

In summary, these results suggest that drug cues, compared to non-drug cues, result in increased brain activation in key reward processing areas, and greater activation in these regions is associated with subjective craving. Reward system activation to drug cues that results in increased drug wanting supports the incentive sensitization view of addiction. However, such findings seemingly contradict reports of reduced reward system activation to monetary cues in alcohol-dependent individuals, a finding more in keeping with the reward deficiency theory. It is possible that the reward system may be overactive specifically in response to drug cues, but not other reward cues (where it may be underactive), in line with theories suggesting a biasing of reward systems toward drug-related stimuli. To explore this idea further, we will review studies of responses to natural reward cues in drug dependence.

Drug cues vs. natural rewards

An alternative method of probing reward functioning is to examine brain response to natural reward stimuli, that is cues that have survival significance, such as cues for food, water, and sex. Garavan et al. compared the brain response to drug films and erotic films in cocaine users and healthy volunteers. Both films activated a similar network including medial and dorsal prefrontal, parietal, cingulate and insular cortices, and subcortical regions including caudate and thalamus in drug users. Between group comparisons revealed enhanced responses in anterior cingulate, inferior parietal lobe, and caudate in drug users compared with healthy controls for the drug video, but reduced responses to the erotic video (Garavan et al., 2000). Another study investigating responses to erotic images found that cocaine users had reduced ventral and dorsal striatal and medial prefrontal responses compared to healthy controls (Asensio et al., 2010). The authors suggest this hypoactivation indicates deficient reward evaluation, motivational, and saliency attribution for natural reward stimuli.

In contrast to these studies, where natural reward stimuli and drug stimuli activated a similar network of brain regions, a study examining responses to heroin and water cues in thirsty heroin users found differential activation for different cues (Xiao et al., 2006). Water cues activated anterior cingulate cortex, whereas heroin cues activated bilateral inferior frontal cortex, cerebellum, and visual processing areas. Whilst the authors suggest that heroin and natural rewards activate different reward-related brain areas, this is not supported by earlier studies reporting anterior cingulate activation to heroin cues (Daglish et al., 2001).

Brain responses to cues for drugs and natural rewards have been measured using electroencephalography (EEG). The P300 waveform is of particular interest for the processing of stimuli, appearing 300 ms after presentation. Stimuli classified as salient attract greater attentional processing and produce larger P300s (Lubman et al., 2007).

A recent study compared subjective and electrophysiological response to images of natural reward (food, erotic) and heroin stimuli in healthy controls and heroin users. Heroin users rated natural reward stimuli as less arousing than healthy controls, and less arousing than drug stimuli. A direct comparison between P300 amplitudes for drug and natural reward stimuli indicated that amplitudes were increased for drug stimuli and reduced for natural reward stimuli in drug users (with the opposite found in controls), indicating drug cues attracted more attentional processing. Furthermore, heroin users displayed less startle-elicited P300 attenuation whilst viewing images of natural rewards relative to neutral images, compared to controls, suggesting they did not attend strongly to images of natural reward. Subjective ratings of pleasantness for the natural rewards robustly predicted later heroin use with lower pleasantness ratings associated with greater heroin use (Lubman et al., 2009). These findings of enhanced responses to drugs cues but reduced responses to natural rewards provide support for both the incentive sensitization theory of addiction and the reward deficiency hypothesis respectively, compatible with a biasing of reward systems toward drug cues and away from non-drug cues.

Positron emission tomography studies indexing reward sensitivity

PET has also been used to index reward sensitivity of drug users, enabling quantification of brain DA receptors by measuring radioligand binding, and indirect measures of DA neurotransmission from changes in radioligand binding. Studies examining endogenous dopamine release in response to pharmacological challenge have found that striatal dopamine release is significantly blunted in cocaine- (Volkow et al., 1997; Martinez et al., 2007), alcohol- (Martinez et al., 2005), and heroin (Martinez et al., 2012) -dependent subjects. Furthermore, the greater the reduction in dopamine release in cocaine-dependent subjects, the more cocaine was used in the treatment setting (Martinez et al., 2007), although this relationship was not found in heroin users. Radioligand D2/D3 receptor levels have consistently been found to be reduced in the striatum of cocaine- (Volkow et al., 1993; Martinez et al., 2004), alcohol- (Volkow et al., 1996; Heinz et al., 2004), and heroin (Zijlstra et al., 2008; Martinez et al., 2012)-dependent individuals, leading to the conclusion that chronic drug use is associated with reduced concentration of D2 receptors. Moreover, the reduced ventral striatal D2/D3 binding in alcohol-dependent subjects was associated with enhanced alcohol craving and enhanced prefrontal brain activation to alcohol cues, as measured with fMRI (Heinz et al., 2004).

A potential confound of these studies may be that, due to the sensitization of dopamine neurons, dopamine levels were higher at baseline in the dependent groups, resulting in reduced availability of unbound D2/D3 receptor for the competing radioligand to bind to, rather than D2/D3 density being low *per se*. However, a PET study determining baseline dopamine levels in cocaine dependence demonstrated lower levels in cocaine-dependents, indicating dopaminergic neurotransmission and D2/D3 receptors are indeed reduced in these individuals (Martinez et al., 2009).

A blunted dopamine system supports the reward deficiency hypothesis of drug dependence. However, in line with the incentive sensitization view of addiction, studies have demonstrated enhanced striatal dopamine release in response to drug cues in cocaine (Volkow et al., 2006; Wong et al., 2006) and heroin (Zijlstra et al., 2008) dependence. This dopamine release to

conditioned drug cues was located to the dorsal, but not the ventral, striatum that has been implicated in habitual, stimulus-response type action selection (Everitt and Robbins, 2005; Redish et al., 2008). Cue-induced dorsal striatum dopamine release was positively correlated with acute craving levels and addiction severity in the cocaine studies and chronic craving level in the heroin study. Thus, it appears that baseline levels are low, however, in the presence of drug cues, high levels of dopamine are released that result in drug craving. This is consistent with the idea that there is an overall reward deficiency, but brain reward systems are biased to be sensitized specifically to drug cues.

Summary of reward system changes—the emergence of attentional bias for drug stimuli

From this brief review, it is clear that there is evidence for both the incentive sensitization and reward deficiency theories of addiction (see **Figure 1**). The incentive sensitization theory posits that stimuli associated with drugs obtain incentive motivational properties via Pavlovian conditioning mechanisms. Repeated exposure to addictive substances results in the sensitization of mesolimbic brain circuitry that results in excessive dopamine release in response to drug cues. This is proposed to produce a heightened incentive motivation to take drugs that underlies compulsive drug-seeking in addiction (Robinson and Berridge, 1993). This theory is supported by enhanced striatal and prefrontal BOLD response to drug cues across all dependencies, and enhanced cue-induced striatal dopamine release in cocaine and heroin dependence, that was associated with drug craving, and greater attentional processing of drug cues in opiate dependence. Furthermore, enhanced brain activation to monetary reward has been found in cocaine-dependents and comorbid alcohol- and cocaine-dependent individuals (Bjork et al., 2008c; Jia et al., 2011).

The reward deficiency hypothesis argues that reduced functioning of brain reward systems underlies addiction, such that individuals seek pharmacological enhancement of their deficient reward systems because natural rewards do not adequately stimulate them. Evidence comes in the form of decreased brain response for natural reward stimuli in fMRI studies in cocaine-dependent individuals (Garavan et al., 2000; Asensio et al., 2010), decreased BOLD response to monetary reward in alcohol dependence, decreased attentional processing of naturally rewarding stimuli in opiate users as demonstrated in EEG studies (Lubman et al., 2009), and increased reward thresholds across all dependencies as demonstrated in animal studies (Koob, 2009). PET studies have also demonstrated reduced striatal D2/D3 receptor density in alcohol-dependent subjects that is associated with enhanced craving (Heinz et al., 2004), and reduced endogenous dopamine release in cocaine users that was associated with greater cocaine use (Martinez et al., 2007).

There are numerous possible explanations for the reported findings. Different findings in response to monetary cues in alcohol and cocaine dependence suggest that different substances of abuse are associated with different reward system abnormalities. Such differences may reflect differences in pre-existing trait vulnerabilities for substance dependence that are hypothesized to reflect hyper and hypo activity of reward systems such as sensation-seeking and negative affect traits respectively (that result in different motives for the engagement of substance use), or distinct pharmacological effects of the different drugs themselves on brain reward systems. However, although behavioral sensitization is most commonly demonstrated with psychostimulant drugs, it has also been demonstrated with most drugs of abuse in animals (Narendran and Martinez, 2008). Furthermore, reward sensitivity may change over the course of one's drug using career, initially reflecting pre-existing traits that predispose individuals to engage in substance use, but then being modulated by sensitization of dopamine neurons after drug use that increases the motivational salience of drug rewards. Continual drug exposure may however, result in the dominance of opponent processes that counteract sensitization and the chronic presence of drugs of abuse. This may ultimately result in an allostatic shift to deficient reward functioning, producing a dependence upon substances of abuse in order to restore reward deficits. This is suggested

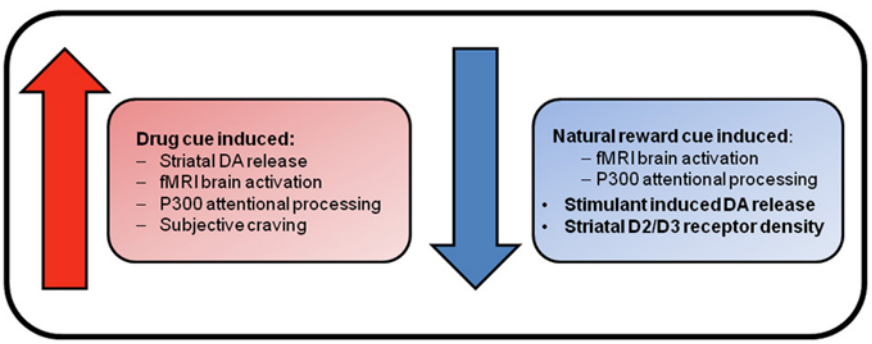

FIGURE 1 | Reward system changes associated with substance dependence. Enhanced brain response and craving elicited by drug cues supports the incentive sensitization view of addiction. This theory suggests that repeated exposure to drugs of abuse causes neuroadaptations within mesolimbic dopamine neurons that results in pathological levels of incentive salience being attributed to drugs and their associated stimuli. In contrast, reduced brain responses for natural rewards, and blunted dopaminergic functioning in the absence of drug cues, are suggestive of deficient reward functioning. This deficient reward signaling is hypothesized to result in the seeking of drug rewards as natural rewards do not adequately stimulate the deficient reward system.

by the finding that recreational psychostimulant use is associated with hyperactive dopaminergic activity (Tai et al., 2011), perhaps reflecting sensation-seeking traits and/or drug induced sensitization but chronic psychostimulant use is associated with blunted dopaminergic activity, the severity of which is associated with greater drug use (Martinez et al., 2009). Although enhanced brain and attentional responses to drug cues are detected in chronic drug users, the reward deficiency hypothesis posits that drug related cues are "framed" as especially salient in comparison to non-drug rewards, due to their greater ability stimulate deficient reward systems, resulting in bias toward drug-related stimuli (Hommer et al., 2011). Therefore, perhaps it is the *contrast* between dopaminergic response to drug cues compared to natural rewards and deficient baseline activity, that is the important factor in driving drug-seeking in chronic drug users, rather than overall higher activity levels of dopamine neurons (neuroimaging studies do not measure absolute levels of dopamine release or brain activity in response to drug cues, but instead use indirect measures that involve comparisons with an unknown baseline). The ability of drugs of abuse to potently activate brain reward systems is one reason why drugs of abuse are overvalued within the brain (Redish et al., 2008). In contrast, the relative impotence of natural rewards in activating deficit reward systems may result in natural rewards being undervalued in the brain of a chronic drug user. The amygdala is crucial for emotional associative learning and generating responses to CS, specifically allowing a conditioned stimulus to access the value of the reward that it predicts. This information can be used to modulate motivation via inputs to midbrain dopamine neurons, and instrumental actions via projections to ventral striatum and prefrontal cortex (Cardinal et al., 2002). Therefore, the amygdala may be an important neural structure involved in the "framing" of salience of drug cues over natural rewards by translating differences in stored value representations between drugs and natural rewards into differential activity of brain motivational systems.

An alternative explanation for the findings that support both the incentive sensitization and the reward deficiency hypothesis may be that both hyperfunctioning and hypofunctioning brain reward systems occur simultaneously in addiction depending upon the presence or absence of conditioned cues or contexts. Neural sensitization of dopamine neurons may be influenced by associative learning mechanisms such that enhanced neural sensitization occurs for drug cues and contexts but not for non-drug contexts (Leyton, 2007; Robinson and Berridge, 2008). In animals, sensitized increases in dopamine release to cocaine occurred only when animals were tested in an environment where they had previously experienced drug, and not in an unfamiliar environment (Duvauchelle et al., 2000). This may explain why increases in dopamine were detected in dependent subjects in response to drug cues, but not in response to pharmacological challenge in a novel environment in the absence of cues. Homeostatic "opponent" processes (Koob and Le Moal, 2005) may be initiated simultaneously in response to chronic elevations in dopamine and opioid levels, such that in the absence of drug cues, the reward system is hypoactive. Given the important role of the amygdala in associative learning and the generation of responses to CS, it is likely to be key structure involved in modulating the expression of incentive sensitization by allowing the high values of drugs of abuse to influence mesolimic dopamine systems after exposure to drug cues and contexts (Volkow et al., 2010).

Although the relationship between reward sensitivity and addiction is complex, it is clear that reward sensitivity is compromised, with a clear bias toward drug rewards once addiction is established. Enhanced motivational salience of drugs and related cues in addicted individuals leads to a biasing of attentional and cognitive processing toward drug-related cues (Goldstein and Volkow, 2002). This attentional bias, the automatic selective attentional response to emotionally salient stimuli, has been demonstrated in drug word Stroop (**Figure 2**) and dot probe detection tasks across heroin (Franken et al., 2000; Lubman et al., 2000; Marissen et al., 2006), alcohol and cocaine (Lusher et al., 2004; Hester et al., 2006; Ersche et al., 2010a) dependencies. Enhanced motivational salience of reward cues is attributed to increased dopamine release in the ventral striatum (Berridge, 2007) and enhanced attentional processing of drug cues may be mediated by this dopaminergic activity (Franken, 2003). In addition to this specific action, "general arousal" effects produced by emotional circuit activation may contribute to the biasing of attention toward emotional stimuli (LeDoux, 2012). Generally increased arousal, produced by the release of noradrenaline,

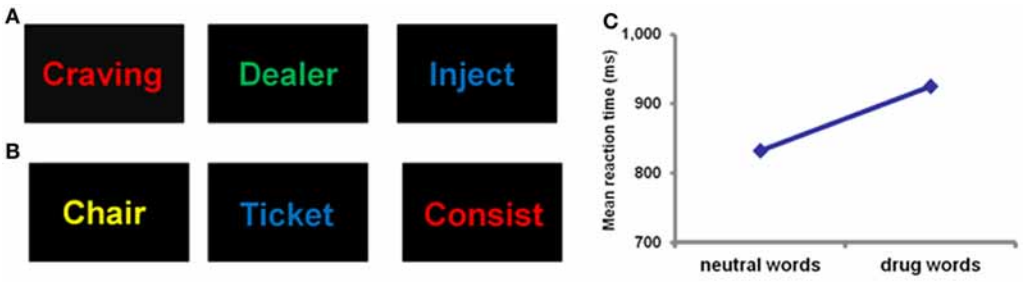

FIGURE 2 | Example of a drug word emotional Stroop task showing drug words (A) and neutral words (B). Participants are required to identify the color of the text as quickly as possible. Successful performance of this task requires the suppression of emotional responses to word meaning, and a direction of attention toward non-emotional content (word color). Slower reaction times are assumed to indicate a greater degree of emotional interference on cognitive processing. Panel **(C)** demonstrates that heroin dependent individuals have significantly slower reaction times for drug words compared to neutral words (Murphy et al., 2011), reflecting the emotional significance of the drug words compared to neutral words.

serotonin, and acetylcholine as well as dopamine, facilitates processing in the emotion circuit that triggered the arousal response initially, and in sensory, cognitive, and memory systems. The overall effect is that brain systems are coordinated and monopolized for the purpose of enhancing the ability of an organism to benefit from an opportunity or cope with a challenge (LeDoux, 2012). Whilst this action of emotional circuit activation normally serves to benefit an organism, this emotional influence over cognitive systems in substance dependence leads to maladaptive behavior. Unlike natural rewards such as food and sex, drugs of abuse do not have survival significance, but instead they simulate the action of natural rewards on the brain (Kelley and Berridge, 2002; Redish et al., 2008). Biasing attention toward stimuli of substances that are not beneficial for survival (and which actually may be detrimental) often at the expense of natural reward stimuli, is a clear example of the negative impact of emotional influence over cognitive systems. The degree of drug attentional bias has been shown to be related to craving levels (Franken et al., 2000; Field et al., 2009), such that greater bias is associated with enhanced drug craving. Furthermore, enhanced attentional bias after drug treatment predicts relapse to drug use in heroin (Marissen et al., 2006) and alcohol-dependent individuals (Garland et al., 2012). Thus, emotional biasing of cognitive processing appears to have a profound negative effect on clinical outcome.

ANXIETY AND STRESS SENSITIVITY IN SUBSTANCE DEPENDENCE

Whilst reward sensitivity is a long-established focus of substance dependence research, the contribution of changes within the brain's stress system is more recently being recognized as an important mechanism for the maintenance of addiction and also relapse to drug use during abstinence (Zhang et al., 2011).

Anxiety has been associated with substance use as a form of self-medication (Woicik et al., 2009) as alcohol and opiates have anxiolytic properties (Lejuez et al., 2006; Gilman et al., 2008; Colasanti et al., 2011). Anxiety is thought to reflect functions of a defence system that is activated by aversive, novel, and innate fear stimuli (Barros-Loscertales et al., 2006). In addition to threat stimuli, anxiety may also be produced by cognitive processes involved in the anticipation, interpretation, or recollection of perceived stressors or threats (Charney and Drevets, 2002).

The amygdala is critical in generating a response to such threat stimuli (LeDoux, 2007). Structures involved in anxiety that work in concert with the amygdala include other medial temporal structures, sensory cortices and thalamus, insula, hypothalamus, brain stem, and medial prefrontal cortex. The bed nucleus of the stria terminalis (BNST) mediates anxiety during exposure to less well-defined threatening environments or contexts that occur over several minutes (Charney and Drevets, 2002).

THE "ANTI-REWARD" SYSTEM AND SUBSTANCE DEPENDENCE

As reviewed above, chronic drug use results in changes in reward systems leading to anhedonic states in some substance dependent individuals. Koob and colleagues additionally propose changes in "arousal-stress" systems during chronic drug administration, which are recruited in an attempt to overcome the presence of the drug and restore normal functioning (Koob, 2009). These systems include the hypothalamic pituitary axis (HPA) and extended amygdala (comprising the central nucleus, BNST, and a sub region of the nucleus accumbens). The extended amygdala receives afferent inputs from the basolateral amygdala and hippocampus and sends efferents to ventral pallidum and hypothalamus. Thus, it is ideally placed for its hypothesized role in opposing the rewarding effects of drugs of abuse, and has been referred to as the "anti-reward" system. Chronic drug administration involves the dysregulation of stress/anti-reward systems and neurochemical changes in the extended amygdala associated with arousal/stress modulation (**Figure 3**) that are associated with the emergence of negative emotional states such as anxiety and mood disturbances. Preclinical studies have demonstrated that chronic administration of all major drugs of abuse is associated with a release of corticotropic releasing factor (CRF) within the extended amygdala upon withdrawal and after stress induction with a footshock, that produces anxiety-like effects and drug-seeking that are reversed by CRF antagonists (Koob, 2008). These changes persist into protracted abstinence and are thought to contribute to relapse to drug-seeking in order to reduce negative emotional states (Kreek and Koob, 1998). Noradrenergic transmission within the extended amygdala has been associated enhanced anxiety and increased drug-seeking and relapse during abstinence in alcohol, cocaine, and opiate dependence (Koob, 2008; Smith and Aston-Jones, 2008). Furthermore, administration of lofexidine, a drug that reduces noradrenaline release, reduces stress and craving and improves abstinence in opiate users (Sinha et al., 2007). Seemingly contradictory to theories of heightened stress sensitivity in substance dependence, studies have demonstrated an apparent *insensitivity* to aversive stimuli in rats after extended cocaine self-administration (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In these studies, the presentation of a CS that predicted an aversive event did not prevent responding for cocaine. However, the inability of the aversive CS to modulate

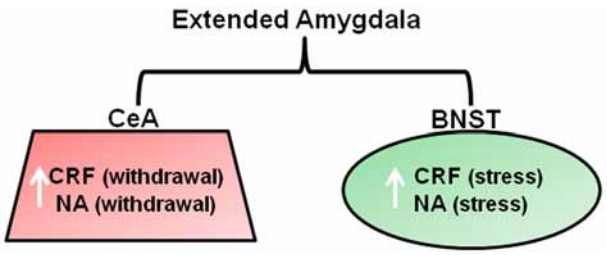

FIGURE 3 | Neurotransmitter changes within the brain stress system that are associated with withdrawal and stress-induced reinstatement of drug-seeking. Neurochemical changes are proposed to occur within the extended amygdala in order to overcome the chronic presence of drugs of abuse. Withdrawal from all major drugs of abuse is associated with CRF and NA release within the CeA that produces anxiety like responses that are thought to drive drug seeking via negative reinforcement mechanisms. CRF and noradrenaline release within the BNST is considered to be important for mediating drug seeking in response to a stressor, such as a footshock (Koob, 2008). Abbreviations: CRF, Corticotrophic releasing factor; NA, Noradrenaline; CeA, central nucleus of the amygdala; BNST, bed nucleus of the stria terminalis.

behavior was attributed to the behavior in question being controlled by habit action selection systems (see later section entitled "Systems Involved in Action Selection") that by their very nature, are immune to immediate changes to action outcomes.

HUMAN STUDIES OF ANXIETY IN DRUG DEPENDENCE

This hypersensitivity of the brain's anxiety/stress system is evident in clinical populations as opiate-dependents find unpleasant stimuli more arousing that controls (Aguilar de Arcos et al., 2005, 2008). Enhanced stress reactivity is also apparent in physiological measures of stress, such as systolic blood pressure (Sinha et al., 2008), cortisol response (Fatseas et al., 2011), and HPA response (Fox et al., 2005). For example, alcohol-dependent participants showed increased heart rate and cortisol levels compared to social drinking controls in response to stressful and alcohol-related images (Sinha et al., 2008).

Sensitized responses to stress are apparent in brain imaging studies. The extended amygdala and corticostriatal circuitry is involved in both reward and affective processing. Medial prefrontal cortex, anterior and posterior cingulate, striatum, and insula are associated with stress- and drug-cue-induced craving, which in turn are associated with increased susceptibility to relapse (Sinha and Li, 2007). Stress induction, using guided imagery of personal stressful and neutral situations in cocaine-dependent individuals and controls, resulted in increased response within the dorsal striatum that correlated with increased craving. Patients additionally demonstrated reduced activation in anterior cingulate and prefrontal regions compared with controls (Sinha et al., 2005). Using the same stress induction method, and drug cue exposure, a later study demonstrated that guanfacine, a α2 adrenoceptor agonist, increased prefrontal activity in response to induced stress and drug cue exposure, and reduced craving (Fox et al., 2012). A study in recently detoxified alcoholic-dependent individuals demonstrated that an NK-1 receptor antagonist reduced brain response to negative images in the inferior temporal gyrus, insula, and middle temporal gyrus and reduced serum cortisol levels and alcohol cue-induced cravings (George et al., 2008).

Anxiety/stress sensitivity is considered to maintain addiction (Heilig and Koob, 2007), and increase susceptibility to relapse during abstinence (Sinha, 2001; Duncan et al., 2007) in heroin (Fatseas et al., 2011), alcohol (Sinha et al., 2008), and cocaine-dependents (Karlsgodt et al., 2003).

IMPACT OF EMOTIONAL PROCESSES ON COGNITION IN ADDICTION

These dysfunctions influence the behavior of addicted individuals, tending to increase, and maintain drug-taking. In particular, emotional dysregulation and altered reward sensitivity may underpin impulsive behavior and poor decision-making. Both of these tendencies can be seen in the "real-world" behavior of addicted individuals, but can also be studied using laboratory-based paradigms.

AFFECTIVE IMPULSIVITY AND SUBSTANCE MISUSE

As has been outlined, drug dependence is associated with a relative enhancement of processing of drug-related stimuli at the expense of natural rewards. This attentional bias is associated with the emotional state of craving and impacts upon relapse vulnerability. Furthermore, changes occur in "anti-reward" systems that result in negative emotional states maintain addiction via negative reinforcement mechanisms. However, addiction is associated with a loss of control over drug use which continues in spite of individuals' awareness of serious negative consequences. Increased reward and anxiety sensitivity alone do not seem a sufficient explanation for this persistent maladaptive behavior. Instead there must be additional deficits in decision-making and/or inhibiting maladaptive behaviors. These deficits may be mediated by reward and anxiety sensitivity, but critically involve these emotional factors exerting a detrimental effect on cognitive function. The term "impulsivity" is often used to describe behavior characterized by excessive approach with an additional failure of effective inhibition (Hommer et al., 2011) and has consistently been found to be associated with substance dependence (de Wit, 2009; Dalley et al., 2011). Impulsivity is a complex multifaceted construct which has resulted in numerous additional definitions such as, "the tendency to react rapidly or in unplanned ways to internal or external stimuli without proper regard for negative consequences or inherent risks" (Shin et al., 2012), or "the tendency to engage in inappropriate or maladaptive behaviors" (de Wit, 2009).

These definitions reflect different types of impulsivity. Examples include reflection impulsivity (action without adequate evaluation of the situation), impulsive action (inadequate motor inhibition), risky decision-making (impulsive choices of immediate rewards over larger delayed ones) (Dalley et al., 2011), and attentional impulsivity, or lack of perseverance (inability to focus on a task or goal) (Cyders and Smith, 2008). In addition, the recently defined constructs of positive and negative urgency reflect the tendency to act rashly in response to extreme negative or positive affect (Cyders and Smith, 2008). Whilst these varieties of impulsivity involve different psychological processes, it is likely that they interact to modulate behavior (Evenden, 1999).

Questionnaire measures of emotional impulsivity

Self-report questionnaires are frequently used to assess impulsivity. Distinctions have been made between measures of cognitive impulsivity (reflection impulsivity, attentional impulsivity) and emotional impulsivity (positive and negative urgency) (Fernandez-Serrano et al., 2012).

Deficits in cognitive impulsivity have been identified across alcohol (Evren et al., 2012), heroin (Nielsen et al., 2012), and cocaine addiction (Ersche et al., 2010b) using measures such as the Barratt Impulsivity Scale (BIS-11) with higher scores predicting greater drug use (Ersche et al., 2010b) and relapse (Evren et al., 2012). Longitudinal studies have demonstrated that impairments in emotional and behavioral regulation confer a risk for the later development of substance abuse. The trait of behavioral disinhibition in young adults, which reflects impulsive novelty-seeking, was found to predict substance abuse 6 years later (Sher et al., 2000). The construct of neurobehavioral disinhibition is indexed by self-report measures of emotional regulation, parent and teacher indicated measures of behavioral control, and performance on tests of executive functioning. Neurobehavioral

disinhibition in 10–12 years old has been shown to be consistent in predicting later development of substance abuse in young adulthood (Tarter et al., 2003; Kirisci et al., 2007).

Thus, cognitive impulsivity appears to be associated with addiction, and may play a role in the development of substance misuse. However, in this review, we will focus on emotional impulsivity, which more closely reflects the interaction between emotional and cognitive processes. Impulsivity defined as "the inability to control behavior in the face of reward and/or punishment" is associated with increased substance use in young adults. Both positive and negative reinforcement motives are associated with this impulsivity trait (Woicik et al., 2009), suggesting that increased substance use may be related to an inability to control behavior when experiencing either positive or negative emotion. Both negative and positive urgency were found to be higher in polysubstance users. Positive urgency scores correlated with amount of cocaine use and binge drinking, whilst scores on measures of reflection impulsivity did not differ from controls (Verdejo-Garcia et al., 2010). In addition, both positive and negative urgency have been shown to be correlated with problem drinking in undergraduate students (Cyders et al., 2007), and to differentiate substance abusers from controls (Cyders et al., 2007). In a study investigating impulsivity dimensions, higher scores on measures of reflection impulsivity, attentional impulsivity, and negative urgency all differentiated substance dependents from controls, although negative urgency was found to be the best predictor of alcohol, drug, social, legal, medical, and employment problems (Verdejo-Garcia et al., 2007a).

Although impulsivity is a multifaceted construct, comprising different psychological processes, failings across all dimensions of impulse control occur in substance dependence. However, findings above highlight a specific role for emotion, both positive and negative, in producing impulsive behaviors. Emotional impulsivity traits appear distinct from other impulsivity traits and particularly pertinent for dependence, reliably differentiating substance users from controls, and also predicting poorer outcomes in dependent individuals.

Behavioral measures of affective impulsivity

Self-report measures rely upon the accuracy of the individual's introspection. Behavioral measures offer an index of impulsivity that is free of subject bias. There are two broad categories of behavioral impulsivity measures. One is characterized by deficits in the ability to inhibit a motor response, referred to as behavioral inhibition. The other is associated with a deficit in inhibition that is motivationally driven and is associated with reward processing (Castellanos-Ryan et al., 2011). Deficits in behavioral inhibition have been found in substance dependence (Forman et al., 2004; Hester and Garavan, 2004; Noel et al., 2007; Fu et al., 2008), consistent with the role of cognitive impulsivity in addiction. However, here we will focus on reward-based impulsivity, reflecting the impact of emotional processing on cognitive performance.

A common behavioral measure of impulsivity is the delay discounting task which measures the degree of temporal discounting. Temporal discounting describes the process by which the subjective value of a reward decreases as a function of delay to that reward (Bickel et al., 2007). Participants are faced with the choice of a small immediate reward, or a larger delayed reward; choosing the smaller immediate reward indicates a higher degree of impulsivity. Increased discounting of larger delayed rewards has been found in heroin- (Madden et al., 1997; Kirby et al., 1999; Kirby and Petry, 2004), cocaine- (Coffey et al., 2003; Kirby and Petry, 2004), and alcohol (Petry, 2001; Bjork et al., 2004a; Mitchell et al., 2007) -dependent individuals. Drug rewards are discounted at an even higher rate than monetary rewards (Madden et al., 1997, 1999; Kirby et al., 1999). Enhanced discounting is also seen during mild opiate withdrawal, possibly reflecting the emergence of negative affect states during withdrawal (Koob and Le Moal, 2005). There is evidence that delayed discounting is influenced by emotional state in healthy controls, with positive mood induction increasing discounting of larger delayed rewards in extraverted individuals (Hirsh et al., 2010). This effect, reflecting a complex interaction between reward sensitivity, emotional state, and cognition, does not appear to have been tested in drug users, although it is an obvious area for study, given that all three intersecting factors are abnormal in addiction.

Emotional influences on decision-making can be measured empirically, using tasks where higher level cognitive processing is regulated by emotion and feeling (Bechara, 2005). The Iowa Gambling Task was developed to test "emotional" decision-making in a laboratory setting for patients with ventromedial prefrontal cortex damage (Bechara et al., 1994). This task presents choices between large monetary gains (but with associated even larger losses, such that the overall long-term outcome is loss) and small monetary gains (but with associated smaller losses, such that the overall long term outcome is gain) (Bechara et al., 1994). Impairments in this task, in the form of disadvantageous choices despite rising losses, have been found in cocaine (Stout et al., 2004; Verdejo-Garcia et al., 2007b; Cunha et al., 2011), heroin (Petry et al., 1998; Verdejo-Garcia et al., 2007b), and alcohol addiction (Bechara et al., 2001; Noel et al., 2007). In the Iowa Gambling Task, reward outcome probabilities are unknown, therefore participants have to learn reward contingencies. This places high demands on "cold" executive processing as well as "hot" emotional processing that may bias decision-making toward high rewards in spite of the negative consequences. The task thus provides an ideal test of how emotional processing impacts upon cold cognition, but does not dissociate the contribution of affective and cognitive processes to any deficits. The Cambridge Gamble (Rogers et al., 1999a) and the Cambridge Risk Task (Rogers et al., 1999b) require less learning and working memory processing, as outcome probabilities are presented explicitly. Studies with the Cambridge tasks also find deficits in opiate (Rogers et al., 1999a; Fishbein et al., 2007; Passetti et al., 2008), stimulant (Rogers et al., 1999a,b), and alcohol-dependent subjects (Bowden-Jones et al., 2005; Lawrence et al., 2009). Furthermore, poorer decision-making confers a greater risk of relapse in opiate- (Passetti et al., 2008) and alcohol (Bowden-Jones et al., 2005) -dependent individuals.

Bechara et al. demonstrated an enhanced affective response to anticipated and actual gains during the IGT in substance dependent individuals in the form of elevated skin conductance, and a reduced skin conductance response before making a risky

decision (Bechara et al., 2002; Bechara and Damasio, 2002). They concluded that hypersensitivity to reward and an impaired ability to use affective signals to guide behavior, underlie impaired decision-making in these individuals. In support of reward hypersensitivity underlying IGT deficits in substance abusers, measures of novelty-seeking have been found to predict poor IGT performance in alcohol-dependent subjects (Noel et al., 2011). Note that hypersensitivity to rewards in this context is somewhat at odds with the findings from the monetary incentive delay task reported earlier. Money can be considered to be a drug cue (Garavan et al., 2000), as it is necessary for obtaining drugs, however, only when presented in sufficient quantities. Gambling tasks typically involve presentations of much larger and more salient sums than the monetary incentive delay task.

Impaired decision-making in the face of motivationally salient outcomes is a core deficit in addiction, with individuals opting for immediate rewards, despite negative longer-term outcomes. Substance dependence involves the choice of immediate drug reward despite negative long term consequences (e.g., health, family, economic, and criminal problems) and these deficits thus provide an extremely plausible model of how motivational factors negatively influence real world decision-making.

Studies demonstrate the impact of emotional state on decision-making

Specifically assessing the influence of emotional processing on decision-making, studies in healthy volunteers have demonstrated that high levels of trait anxiety (Miu et al., 2008), negative affect (Suhr and Tsanadis, 2007), sensation-seeking (van Honk et al., 2002; Suhr and Tsanadis, 2007), and stress sensitivity (van den Bos et al., 2009) are predictive of poor decision-making on the IGT.

High levels of negative affect, anxiety/stress sensitivity and sensation-seeking in substance dependent individuals may therefore contribute to observed deficits on decision-making tasks. Reward and stress mechanisms are considered to be important mechanisms underlying relapse (Stewart, 2008), suggesting these emotional traits impair real life decision-making. Studies directly assessing the role of emotional states on decision-making in opiate addiction have shown that trait and state anxiety are negatively correlated with performance on the IGT (Lemenager et al., 2011). Furthermore, stress induction using the Trier Social Stress Test, was shown to produce a significant deterioration in IGT performance in long term abstinence and newly abstinent heroin users, but not in comparison subjects. Treatment with the B adrenocepter antagonist propranolol blocked the deleterious effect of stress on IGT performance, supporting the role of the noradrenergic system in the generation of negative emotional states in substance dependence (Zhang et al., 2011). A later study from the same group found that drug cue exposure increased craving and impaired performance of the IGT in long term and newly abstinent heroin users (Wang et al., 2012), indicating that conditioned emotional responses impair decision-making. Interestingly, in a group of heavy drinkers, the induction of anticipatory stress (by making participants believe they were required to carry out an embarrassing speech) before the IGT task *improved* performance of the IGT. This effect was attributed to a greater sensitivity to losses after stress induction (Gullo and Stieger, 2011). Similarly, the induction of negative affect via exposure to negative images from IAPS, improved performance on the IGT task in cocaine-dependent participants (Fernandez-Serrano et al., 2011). These latter studies suggest stress induction can have bivalent effects on decision-making.

The reviewed studies demonstrate that decision-making is influenced by both trait and state affective processes in addiction. A deleterious effect of both trait and state anxiety was found in opiate addiction, although the induction of negative affect states improved performance in heavy alcohol drinkers and cocaine-dependent subjects. The tendency of stress in opiate users to bias decision-making in the favor of immediate rewards at the expense of long term goals is consistent with the finding that enhanced stress reactivity increases relapse susceptibility (Karlsgodt et al., 2003; Sinha et al., 2008; Fatseas et al., 2011). By contrast, stress induced enhancement of decision-making in cocaine and alcohol-dependent individuals seems at odds with the predicted roles of stress in addiction (Koob, 2008), and warrants further study with tasks designed to probe specific sub-processes.

One explanation for these contradictory findings may be the notion that stress can have differential effects on decision-making depending upon the degree of stress experienced. The stress response is an adaptive response to enable organisms to adequately deal with threats within the environment, however, an excessive or unduly persistent stress response can be detrimental (McEwen, 2007). It has been suggested that a certain levels of stress can be optimum for decision-making—according to the somatic marker hypothesis (Damasio, 1994) (see section "Influence of Somatic Markers" for a detailed description of this hypothesis), emotions can facilitate decision-making by rapidly signaling the prospective consequences of an action and accordingly assists the selection of the most advantageous response (Bechara and Damasio, 2005). Anxiety is considered to increase arousal and sensitivity to stimuli signaling punishment (McNaughton and Corr, 2004). Gullo and Stieger (2011) demonstrated that stress induction increased attention toward losses in heavy drinkers. Induced moderate stress/negative affect may improve IGT performance by enhancing punishment sensitivity (Fernandez-Serrano et al., 2011). More intense emotion however, may have a deleterious effect on decision-making. It has been suggested that excessive stress, anxiety and worry require emotional regulation, which may tax cognitive resources (Tice et al., 2001) and therefore impair performance on decision-making tasks (Miu et al., 2008). High levels of stress may produce a high level of "background" emotion that "drowns out" affective signals during performance of decision-making tasks (Gullo and Stieger, 2011).

A related explanation for the different findings of the impact of stress on decision-making may be different methods used for stress induction resulting in different levels of stress in each study. Zhang et al. induced stress using the Trier Social Stress Test, where participants are asked to carry out a short presentation and then perform difficult mathematical subtractions, all whilst being filmed. Gullo and Stieger induced stress by *informing* participants they would have to carry out an embarrassing

presentation, although the participants did not actually do so. Fernandez-Serrano et al. induced negative affect by viewing negative and aversive pictures. It therefore could be argued that the levels of stress induced by the actual carrying out of the stressful procedures of the Trier Social Stress Test were greater than those induced by the anticipation of carrying out stressful procedures or by viewing negative pictures.

Another factor that may influence task performance may be due to differences in study populations. Lemenager and Zhang studied opiate-dependent individuals, whereas Gullo and Steiger and Fernandez-Serrano studied a group of heavy drinking undergraduate students (who were drinking harmful levels of alcohol) and cocaine-dependent subjects respectively. Anxiety sensitive traits have been shown to be more specifically associated with heroin dependence than cocaine use (Lejuez et al., 2006). Whilst anxiety sensitive traits have been associated with alcohol dependence (Norton et al., 1997), this trait was not found to be associated with heavy drinking in young adults, rather, heavy drinking was more associated with sensation-seeking in this sample (Woicik et al., 2009). It is therefore likely that baseline anxiety levels and susceptibility to stress were higher in the studies of Lemengaer and Zhang than those of Fernandez-Serrano et al., and Gullo and Stieger. Therefore, different procedures and different populations (**Figure 4**) may combine to account for discrepancies in this literature.

THE IMPACT OF EMOTION ON IMPULSIVE ACTION AND DECISION-MAKING

The preceding sections have reviewed evidence of emotional disturbances and impaired decision-making in substance dependence. Decision-making involves processes of deciding upon the most appropriate actions to take after consideration of the predicted value of an action (Redish et al., 2008), and the automatic selection of actions that an agent has learnt, through past experience, delivers high valued outcomes. The predicted value of an action can be defined in terms of the expected reward it is expected to elicit (after consideration of the probability of, and delay to, receiving the reward), minus any costs associated with the action (Daw et al., 2005). The following sections will review how decision-making can be modulated by emotional processes, and how dysregulation of these processes in substance dependence contributes to decision-making deficits.

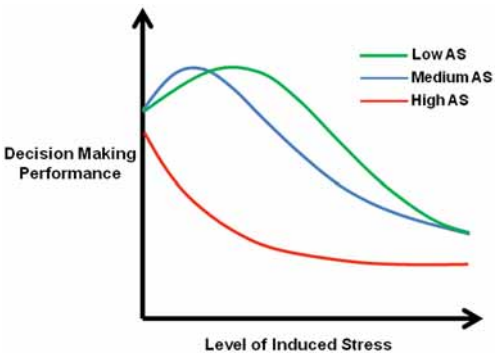

FIGURE 4 | Hypothetical relationship of the effect of stress on cognitive performance in substance dependence according to different trait levels of stress sensitivity. Mild stress improves performance in those of low and medium AS traits by enhancing arousal and sensitivity to punishment signals. Increasing stress results in an increasing need for affect regulation, thus resulting in reduced task-related cognitive resource allocation and impaired performance. High trait AS is associated with impaired decision-making performance before stress induction (Lemenager et al., 2011) and thus further increases in stress are likely to lead to further significant task impairments. Abbreviations: AS, Anxiety Sensitivity.

Systems involved in action selection

Primate and rodent studies suggest systems controlling behavior can be separated into planning and habit systems. Planning systems (also referred to as deliberative, cognitive, reflective or executive systems) are "goal-directed" systems that allow an agent to consider the possible consequences or outcomes of its actions to guide behavior. Habit systems mediate behaviors that are triggered in response to certain stimuli or situations but without consideration of the consequences. Given the differential consideration of action outcomes, behaviors controlled by the planning system are sensitive to outcome devaluation, whereas habitual behaviors are not (Niv et al., 2006; Redish et al., 2008). In addition, emotional circuit activation in response to a biologically significant event, or the cues that predict it, can elicit a series of evolutionary hard-wired Pavlovian actions such as approach, freezing and fleeing arising from an expectancy generated by the CS-UCS association. Brain areas underlying Pavlovian responses include the amygdala, which identifies the emotional significance or value of external stimuli, and the ventral striatum, which mediates motivational influences on instrumental responding (Cardinal et al., 2002), and their connections to motor circuits (van der Meer et al., 2012). Thus, it has been argued that emotions constitute a decision-making system in their own right, exerting a dominant effect on choice in situations of opportunity or threat (Seymour and Dolan, 2008; van der Meer et al., 2012).

There are computational differences in how the habitual and planning systems decide upon appropriate actions to take. The process of action selection in the planning system is complex. It involves searching through and predicting the possible consequences of actions. Consequences are evaluated online, taking current needs and motivational state, time, effort, and probability of receiving the desired outcome into consideration before a decision is made (Redish et al., 2008; van der Meer et al., 2012). Due to the numerous searches of different actions and their potential consequences, this process is slow, requiring extensive cognitive processing. Action selection processes are flexible, allowing an organism adapt behavior to changing environments and needs. The habit system chooses actions based upon stored associations of their values from past experience; through training, an organism learns the best action to take in a certain situation. Upon recognition of the situation again this "best action" will automatically be initiated, without consideration of consequences of such an action. This process is very fast but inflexible, unable to adapt quickly to changes in the value of outcomes (Daw et al., 2005; Redish et al., 2008). Under appropriate conditions, habitual actions may be overridden by planning systems (Redish et al., 2008).

The influence of emotional processes on action selection

Emotional processing involves detecting and responding to salient challenges and opportunities within the environment to enable an organism to thrive and survive. Key brain circuits involved in these processes are the reward and stress circuitry that are involved in reinforcement, motivation, and defence. In the following section we will argue that brain emotional systems have a key role in decision-making.

Influence of emotion in the planning system: neural substrates. As described, the planning system selects actions after consideration of potential outcomes, and is sensitive to changes in outcome value. Therefore, the planning system will be influenced by brain areas involved in evaluating and predicting outcome values (Redish et al., 2008; Balleine and O'Doherty, 2010). The OFC of the planning system has been demonstrated to be involved in the valuation of reward outcome (Elliott et al., 2003) and the predictive value of CS (Tremblay and Schultz, 1999), therefore emotional processing by the OFC is integral to the planning system. The OFC additionally works in concert with subcortical emotional systems in the valuation of outcomes; the amygdala is considered to be a key neural substrate for outcome valuation due to its sensory and hypothalamic afferents which allow for the integration of specific sensory features of outcomes with emotional feedback (Balleine and O'Doherty, 2010). The basolateral amygdala also mediates the influence of CS on goal directed behavior by allowing a CS to access the current value of the UCS that it predicts (Seymour and Dolan, 2008; Cardinal et al., 2002). Basolateral amygdala lesions rendered the instrumental performance of rats insensitive to outcome devaluation (Balleine et al., 2003) and blockade of opioid receptor signaling in the basolateral amygdala with naloxone prevented the effect of food deprivation to increase food-seeking (Wassum et al., 2009). Both of these results suggest that disrupting basolateral amygdala functions prevents the use of new outcome values to guide behavior within the planning system. Other neural structures assumed to be important in the valuation of outcomes include the ventral pallidum, encoding the hedonic impact of rewards (Tindell et al., 2004), and the ventral striatum that appears to have a role in encoding reward value (Schultz et al., 1997; McDannald et al., 2011).

Pavlovian CS can influence instrumental performance by a process known Pavlovian-instrumental-transfer (PIT). A reward associated CS can enhance instrumental responding specifically for the reward that it associated with (outcome specific PIT) or it may enhance responding generally by enhancing arousal (general PIT) (Corbit and Balleine, 2011). PIT is considered to reflect an effect of increased incentive motivation to increase response vigor (Everitt and Robbins, 2005). PIT depends upon the amygdala and nucleus accumbens, with the latter thought to have a role in translating motivation into action (Cardinal et al., 2002; Balleine and O'Doherty, 2010).

Influence of emotion within the habit system. Behaviors controlled by the habit system are carried out without consideration of outcome value, but instead reflect automatic responses to a stimulus or situation. As we have seen, emotional processing appears to have an important role in integrating homeostatic needs in the calculation of outcome values, creating incentive motivation toward highly values outcomes. It might therefore be expected that incentive motivation would not affect habitual behaviors that act independently of outcome value. However, this is not the case: shifts in primary motivation (e.g., from hunger to satiety) have been shown to affect the vigor of habitual actions. This is thought to be due to a "generalized drive" effect that is distinct from specific outcomes (Niv et al., 2006), suggesting there is a general activating effect of motivation state. Habitual actions are additionally influenced by Pavlovian predictors of rewards (Balleine and O'Doherty, 2010)—overtraining actions that increase insensitivity to outcome value (i.e., reflecting a transition from planning system to habit system control) render actions more sensitive to appetitive CS effects on response vigor (Belin et al., 2009). Furthermore, it has been demonstrated that a CS continues to influence instrumental actions that result in the outcome it predicts, even after the earlier devaluation of the outcome (Rescorla, 1994), suggesting both general PIT and outcome specific PIT effects influence habitual actions. Thus, whilst outcome values do not affect habitual actions, general shifts in motivation and Pavlovian cue values, encoded by the ventral striatum and OFC, do in a manner that is independent of representation of current outcome value (Balleine and O'Doherty, 2010).

Influence of somatic markers. An important component of the emotional response is changes within the internal milieu and viscera of the body such as a release of hormones and increase in heart rate (Bechara and Damasio, 2005). These physiological changes within the body are relayed back to the brain with areas such as the insula and the somatosensory cortices suggested to convert these physiological signals into subjective feeling states (Damasio, 1994). Damasio's Somatic Marker Hypothesis highlights the specific role of these physiological signals arising from the body in the guidance of behavior (Damasio, 1994). The term "somatic state" is used to describe the brain and body responses to UCS and CS (referred to as "primary inducers"). Once a somatic state has been triggered by a primary inducer and experienced at least once, a representation of this somatic state is formed. The theory proposes that somatic state can be "reactivated" by thoughts and memories of real or imagined emotional events (referred to as secondary inducers'). This reactivation of somatic states by secondary inducers is proposed to guide future decisions by signaling the prospective consequences of an action.

Brain areas important for generating somatic states from primary inducers include the amygdala and effector structures such as the hypothalamus, autonomic brain stem nuclei, the ventral striatum and periacqueductal grey (PAG). The medial orbitofrontal/ventromedial prefrontal cortex (defined as VMPFC) is responsible for triggering somatic states from secondary inducers. It is proposed the VMPFC couples recalled or imagined scenarios (supported by the hippocampus and DLPFC) with brain areas important for the representation of somatic states within the insula, somatosensory cortices, posterior cingulate/precuneus region. Somatic states may influence decision-making with or without conscious knowledge in the striatum and

in the prefrontal cortex respectively (Verdejo-Garcia and Bechara, 2009).

Distracting effect of emotions. Emotion can guide decision-making when it is integral to the task at hand, emotional responses that are unrelated, or excessive, can be detrimental (Bechara and Damasio, 2005). Dorsal prefrontal regions are involved in the regulation of affective states (Phillips et al., 2003a). Excessive emotion is likely to require regulation by these areas (Phillips et al., 2003b; Amat et al., 2005; Robbins, 2005). Dorsal prefrontal regions are additionally important in decision-making and inhibitory control, thus high levels of emotion that require regulation may limit resources available for these functions, which may contribute to deficits in decision-making.

The effects of emotional processing in substance dependence

Given the crucial role of emotions in the processes of decision-making as described above, along with evidence that both craving and stress are significant drivers of relapse (Weiss, 2005; Sinha, 2007), it follows that dysregulation of emotional processing may contribute to the observed decision-making deficits observed in substance dependent individuals.

Effects within the planning system. As reviewed, the brain's reward system has a heightened sensitivity to conditioned drug stimuli. Various mechanisms are proposed to underlie this effect including pre-morbid vulnerabilities in brain emotional systems and the action of drugs of abuse within brain emotional systems. One mechanism is drug-induced sensitization of dopamine neurons that may act to enhance the incentive salience of drug cues, increasing "wanting" of drug outcomes (Robinson and Berridge, 1993). Given that CSs reflect the value of the reward that they predict (Seymour and Dolan, 2008), an additional explanation of the heightened response to drug cues is due to overvaluing of drugs of abuse within the reward system (Redish et al., 2008). This overvaluing has been attributed to an increased hedonic impact of drugs of abuse, via enhanced opioid receptor signaling (Berridge and Kringelbach, 2008; Redish et al., 2008). Pharmacological actions of drugs of abuse to increase dopamine release in the nucleus accumbens have also been suggested to mediate their pleasurable effects (Volkow et al., 2011). Therefore, dopamine mediated increases in hedonic impact may also contribute to overvaluation. However, the role of dopamine in drug "liking" has been questioned (Berridge, 2007). Drug induced dopamine release may also influence decision-making via effects on Pavlovian learning. Learning of Pavlovian values is mediated by the difference between what is expected after presentation of a CS, and the outcome actually received, referred to as a prediction error. This prediction error can either be positive, indicating a better outcome than expected or negative, indicating a worse outcome than expected (Balleine and O'Doherty, 2010). Prediction errors result in modification of the predictive outcome value assigned to a CS. Dopamine neuron firing appears to encode prediction errors (Schultz, 1998), suggesting phasic dopamine signaling may be the teaching signal that enables the learning of Pavlovian associations. Therefore, increases in phasic dopamine release produced by drugs of abuse, may signal a positive "better than expected" prediction error, resulting in an increase in the predictive outcome value assigned to drug cues (Redish et al., 2008). However, the role of dopamine in learning is still under debate, as it is suggested that dopamine neuron firing is not the teaching signal that causes learning, but instead is a consequence of learning that occurs elsewhere (Berridge, 2007).

Homeostatic and allostatic changes associated with chronic drug use may result in withdrawal symptoms, excessive anxiety sensitivity, and depressive symptoms. This may result in an overvaluing of drugs of abuse that satisfy a homeostatic need, such as immediate withdrawal, anxiety and depressive symptom relief (Redish et al., 2008; Verdejo-Garcia and Bechara, 2009). Increased drug use to alleviate negative emotional states is suggested to underlie the compulsive nature of drug use in substance dependence. Compulsive disorders are associated with anxiety and stress before committing a compulsive act, and relief from that stress by carrying out the act (Koob and Volkow, 2010). In addition, allostatic changes within the reward system appear to have the effect of undervaluing natural rewards, thus further biasing decision-making in favor of drug rewards.

As reviewed, the planning system guides decisions after considering the outcome value of actions, in the context of current needs. Therefore enhanced outcome values of drug use may bias decision-making systems in favor of drug use. The amygdala, which plays a key role in detecting the emotional significance of a CS and generating appropriate responses, mediates the influence of overvalued drug outcomes on drug-seeking behavior after exposure to drug-related stimuli (Bechara, 2005). According to the somatic marker hypothesis, the VMPFC is involved in guiding behavior in line with long term goals (such as of abstinence) by evoking somatic states from thoughts or memories.

In addition to being important for the generation of somatic states, prefrontal regions are also crucial for cognitive and motor inhibitory control (Aron, 2007). A consistent finding of neuroimaging studies of decision-making in substance dependence is hypoactivation of the prefrontal cortex (Bolla et al., 2003; Tanabe et al., 2007; Bjork et al., 2008b), although hyperactivation in the lateral OFC has also been found in opiate and amphetamine-dependent individuals (Ersche et al., 2005). Chronic drug use is consistently associated with VPFC, DLPFC and ACC gray matter loss in cocaine and alcohol dependence (Fein et al., 2002a,b; Makris et al., 2008; Fein et al., 2010; Goldstein and Volkow, 2011; Ersche et al., 2011) and reduced prefrontal neuronal viability in opiate dependence (Haselhorst et al., 2002; Yucel et al., 2007). VPFC and DLPFC loss have been shown to predict both impaired performance on the IGT (Tanabe et al., 2009) and preference for immediate gratification in delay discounting tasks (Bjork et al., 2009) Such findings suggest that the prefrontal regions of the planning system is impaired in substance dependence, compromising both the ability to generate affective states relating to long term goals (Bechara and Damasio, 2005) and the ability to exert executive inhibitory control over drug-seeking thoughts and actions (Goldstein and Volkow, 2011).

Dorsal prefrontal regions are involved in the regulation of affective states (Phillips et al., 2003a). Therefore excessive anxiety or craving would require regulation by these areas. Studies

have shown dorsal prefrontal regions to be important in regulating craving and reducing amygdala activity in cue induced craving paradigms (Brody et al., 2007; Kober et al., 2010). Considering these prefrontal regions are important for decision-making, craving and anxiety regulation would limit the resources available for effective decision-making within the planning system.

Effects within the habit system. A transition from control over drug-seeking by planning systems to control by habit systems has been proposed to underlie compulsive drug use (Everitt and Robbins, 2005). As reviewed, Pavlovian cues have motivational impacts upon habitual actions in a manner that is independent of representation of current outcome values (Balleine and O'Doherty, 2010). Therefore, drug cues have the ability to increase drug-seeking actions controlled by habit systems. This transition to habitual control in substance dependence means drug-associated cues come to enhance drug-seeking, via PIT mechanisms, without consideration of the consequences of drug-seeking actions.

Preclinical studies have demonstrated that the transition from goal-directed to habitual behavior is associated with a change from dopamine release in the ventral striatum to the dorsal striatum in response to drug associated stimuli (Everitt et al., 2008). PET studies have demonstrated cue induced dopamine release to occur in the dorsal, but not ventral, striatum of cocaine (Volkow et al., 2006) and heroin-dependent individuals (Zijlstra et al., 2008), providing evidence that habitual system control may underlie compulsive drug-seeking in these dependent groups.

The mechanism of this transition to dorsal striatal control appears to be a dopamine-dependent mechanism, and thus drug-induced sensitization of dopamine neurons, and pharmacological action of drugs of abuse to increase striatal dopamine release, may accelerate this transition (Everitt et al., 2008). Prediction error dopamine neurons innervate the dorsal as well as the ventral striatum (Everitt and Robbins, 2005) and thus drug induced positive prediction errors may result in overvaluing of actions that lead to drug use, enhancing the consolidation of these stimulus-response relationships (Everitt et al., 2008; Redish et al., 2008). Furthermore, recent evidence suggests a role of stress in shifting goal-directed control to habitual control of behavior (Schwabe and Wolf, 2011). This effect appears to be mediated by the action of both cortisol and noradrenaline (Schwabe et al., 2010). Therefore sensitization of the brain's stress system occurring with chronic drug use is likely to contribute to the development of habitual drug-seeking.

A shift in the control of drug-seeking to habitual system control is disadvantageous, potentially reflecting a "loss of control" over drug-seeking that is insensitive to devaluation of drug rewards. This may explain the persistence of drug use despite explicit knowledge of negative consequences, which under goal-directed control, should reduce the propensity for drug-seeking. Whilst there is evidence that automatic, habitual actions may be overridden by controlled, planning-like systems (Redish et al., 2008), impaired function of prefrontal planning system regions observed in substance dependence suggest the ability to regain control of drug-seeking may be compromised in substance dependent individuals.

SUMMARY AND CONCLUSIONS

It is clear that substance dependence is associated with significant emotional dysregulation that influences cognition via numerous mechanisms. This dysregulation comes in the form of heightened reward sensitivity to drug-related stimuli, reduced sensitivity to natural reward stimuli, and heightened sensitivity of the brain's stress systems that respond to threats. Such disturbances have the effect of biasing attentional processing toward drugs with powerful rewarding and/or anxiolytic effects at the expense of natural rewards, resulting in profound negative effects on clinical outcome. Emotion dysregulation can also result in impulsive actions and influence decision-making, via a range of mechanisms. Overvaluing of drug rewards may enhance goal directed drug-seeking behaviors controlled by planning systems. Furthermore, learned Pavlovian values associated with drug stimuli motivate drug-seeking controlled by habit systems, resulting in automatic drug-seeking when exposed to drug cues and environments. Actions of drugs within brain reward and stress systems may additionally accelerate the transition from planning system to habit system control over drug-seeking. Such accelerations of this transition are extremely detrimental clinically, as drug-seeking behaviors under habit system control are impulsive, initiated without consideration of potential negative consequences of drug use. This has implications for treatment of substance dependence. Psychological therapies aimed at focusing upon the negative consequences of drug use or punitive measures aimed to reduce drug use, will be more effective when drug-seeking is under planning system control, but possibly ineffective for drug use that is under habitual control. Reducing exposure to drug associated cues and contexts is crucial in reducing habitual drug-seeking, although this may not be practical. An exciting area of research that may prove promising for the treatment of habitual drug-seeking is to effectively "wipe" drug memories via the combination of drug memory reconsolidation and extinction processes (Xue et al., 2012).

Impulsive drug-seeking and insensitivity to negative consequences are worsened by impairments of prefrontal systems that serve to generate "warning" somatic emotional signals when considering drug use. This result in the amygdala dominating somatic signaling, acting to incentivize drug-seeking by creating expectancies of large rewards after drug cue exposure. Extreme emotion requiring regulation from frontal brain regions, such as excessive anxiety associated with substance dependence, may further impair decision-making within the planning system by limiting available resources that can be allocated to assessing possible consequences of each action. There is likely to be significant variability in the extent to which these distinct, but inter-related mechanisms confer vulnerability to developing long-term addictions. This variability is influenced by differences in the pharmacological actions of the drugs abused, pre-morbid individual trait differences, and differences in the environments of drug users.

We have outlined evidence that emotional processing significantly impairs cognition in substance dependence. Emotionally influenced cognitive impairments have serious negative effects on clinical outcome, with both attentional bias and decision-making deficits being predictive of drug relapse. However, emotional processing has evolved to enable an organism to take advantage of

opportunities, and effectively cope with challenges within the environment. The influence of emotion is clearly detrimental in substance dependence, and many of the detrimental effects observed are due to the ability of drugs of abuse to mimic the effects of stimuli or events that have survival significance. Drugs of abuse effectively trick the brain's emotional systems into thinking that they have survival significance, resulting in their high valuation and overvaluing of actions that lead to drug use. The biasing of cognition in favor of the procurement of highly valued substances is an entirely adaptive process. Unfortunately, for substance dependent individuals, the most highly valued substances (drugs) are devoid of positive survival significance, instead having a significant negative impact upon survival.

FUTURE DIRECTIONS

Although the current review focuses on drug dependence, the study of non-substance addictions may help improve understanding of addiction. Investigation of these maladaptive behaviors allows us to explore fundamental mechanisms of addiction, without the confounding neurotoxic effects of substance use (Bechara, 2003; Verdejo-Garcia et al., 2008). Pathological gambling and other so-called "behavioral addictions," involving activities such as playing computer games, eating and shopping, appear to share some common mechanisms with substance dependence (Shaffer et al., 2004; Verdejo-Garcia et al., 2008). Behavioral addictions are associated with emotional and cognitive dysfunctions within the reward (Potenza, 2008; Balodis et al., 2012) and stress systems (Meyer et al., 2000; Moodie and Finnigan, 2005) as well as in impulsive and decision-making processes (Bechara, 2003) which negatively impact on outcome (Elman et al., 2010). Therefore further work on a generic "addiction endophenotype" is warranted.

It is also important to emphasize the need for future investigations into the differences between different substance dependences, particularly in relation to vulnerability to dependence. It is likely that drugs with different pharmacological properties have distinct actions on brain reward and stress systems. However, studies are typically confounded by polydrug use in the UK and other western countries. Studies of single drug addiction may be more feasible in countries where polydrug use is less prevalent.

Substance dependence research would also greatly benefit from longitudinal studies assessing factors conferring risk for initial substance use; how these factors relate to the subsequence development of dependence; how these factors change within the course of long term dependence; and how these factors impact upon outcome. It is likely that each "stage" of drug use is associated with specific cognitive mechanisms, but they are all likely to be characterized by dysregulated emotional processes influencing behavior and cognition. There is also a need for more sophisticated assessments of emotion processing and decision-making, particularly building on recent advances in understanding brain and behavioral mechanisms of socioeconomic decisions and social cognition.

Longitudinal studies will inform treatment development, particularly of therapies targeting prevention in individuals at high-risk. As we have emphasized in this review, once heavy drug use is initiated, changes within structures involved in reward, stress and executive functioning create a reinforcing cycle which is extremely difficult to break. However, treatment strategies based on emotion regulation and strengthening cognitive control processes in high-risk individuals could potentially prevent the cycle developing, and therefore holds enormous promise in preventing addiction and its many associated harms.

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Neural systems supporting cognitive-affective interactions in adolescence: the role of puberty and implications for affective disorders

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Evidence from longitudinal studies suggests that adolescence may represent a period of vulnerability that, in the context of adverse events, could contribute to developmental trajectories toward behavioral and emotional health problems, including affective disorders. Adolescence is also a sensitive period for the development of neural systems supporting cognitive-affective processes, which have been implicated in the pathophysiology of affective disorders such as anxiety and mood disorders. In particular, the onset of puberty brings about a cascade of physical, hormonal, psychological, and social changes that contribute in complex ways to the development of these systems. This article provides a brief overview of neuroimaging research pertaining to the development of cognitive-affective processes in adolescence. It also includes a brief review of evidence from animal and human neuroimaging studies suggesting that sex steroids influence the connectivity between prefrontal cortical and subcortical limbic regions in ways that contribute to increased reactivity to emotionally salient stimuli. We integrate these findings in the context of a developmental affective neuroscience framework suggesting that the impact of rising levels of sex steroids during puberty on fronto-limbic connectivity may be even greater in the context of protracted development of prefrontal cortical regions in adolescence. We conclude by discussing the implications of these findings for future research aimed at identifying neurodevelopmental markers of risk for future onset of affective disorders.

Keywords: emotion, cognition, cognitive control, development, adolescence, puberty, affective disorders

INTRODUCTION

A plethora of clinical and epidemiological studies examining developmental trajectories toward psychopathology have identified adolescence as a potential window of vulnerability (Costello et al., 1996, 2011; Pine et al., 1998; Merikangas et al., 2007). Early adolescence, with the onset of puberty, represents a particularly vulnerable developmental period for the onset of behavioral and emotional health problems. Indeed, although adolescence represents one of the healthiest periods of the life span with respect to physical health, paradoxically, there is mounting evidence suggesting that overall morbidity and mortality rates increase 200–300% (Ozer et al., 2002). For instance, in addition to the increase in the prevalence for mood disorders and substance use disorders, the rate of accidents, suicide, alcohol and substance use, eating disorders, HIV, unwanted pregnancies all increase drastically during this developmental period (Force, 1996; Ozer et al., 2002). The sources of this drastic increase in the rates of adolescent death and disability appear to be primarily related to problems with emotion regulation.

Research in the fields of developmental cognitive and affective neuroscience has blossomed over the past decade allowing researchers to generate neural models that could help elucidate some of the potential neurodevelopmental mechanisms underlying vulnerability for emotion dysregulation in adolescence and risk for psychopathology such as affective disorders and substance abuse disorders (Nelson et al., 2005; Ernst et al., 2006; Steinberg, 2007; Blakemore, 2008; Casey et al., 2010). Some of these models have emphasized adolescent social reorientation toward peers (e.g., Nelson et al., 2005), changes in social cognition (Blakemore, 2008), reward processing (Bjork et al., 2004), and the balance and/or integration of emotional reactivity (i.e., threat, reward) and cognitive control (Steinberg, 2005, 2007; Casey et al., 2010). Despite some points of divergence across these various models, there is agreement that the onset of puberty is associated with increased reactivity in subcortical regions to emotionally salient information (e.g., amygdala, ventral striatum) in ways that create new challenges for cognitive control processes supported by prefrontal systems that mature later in adolescence. Such a maturational gap is therefore thought to contribute to increased vulnerability for emotion dysregulation and possibly the onset of psychopathology such as affective disorders in at-risk youth. Indeed, there is mounting evidence demonstrating the influence of sex hormones on the regulation of emotional responses and affective states in adults (Van Wingen et al., 2010, 2011; Volman et al., 2011) along with recent findings suggesting that sex hormones impact adolescent brain

development (for a review, see Blakemore et al., 2010; Peper et al., 2011; Ladouceur et al., 2012). Furthermore, there is growing evidence that puberty is more associated to the onset of depression than age (Angold et al., 1999; Joinson et al., 2012). For instance, a recent population-based study investigating a wide range of influences on the health and development of children reported an association between depression symptoms and pubertal maturation in girls (i.e., breast development, which is linked with a rise in estrogen (Joinson et al., 2012). It is therefore reasonable to conceive that increased risk for affective disorders in adolescence may be mediated by altered puberty-specific changes in the functioning of fronto-limbic systems that support cognitive control-emotion interactions underlying emotion regulatory processes.

The current review will focus particularly on adolescent development of fronto-limbic systems that support processes at the interface of cognitive control and emotion as a way to elucidate potential neurodevelopmental mechanisms underlying vulnerability for emotion dysregulation and onset of affective disorders in at-risk youth. In particular, the focus will be on cognitive control-emotion interactions implicated in the modulation of cognitive resources in the context of emotionally salient information in view of generating an appropriate response as this would appear to be of particular relevance for emotion dysregulation and its consequences in adolescence. As such, the review will feature particular studies that document developmental changes in the influences of emotionally salient cues (e.g., threat-related or appetitive) on cognitive control processes such as attention, working memory, and response inhibition, given that dysfunction in these areas have been implicated in affective disorders (Phillips et al., 2003, 2008). The review will not include findings related to cognitive control processes having emotional stimuli as the object of cognition (e.g., maintaining emotional stimuli in working memory) or processes that involve emotional decision making (i.e., risk taking). Though these are important areas of study, particularly with regard to adolescent behavioral and emotional health, they involve various networks beyond those involved in the cognitive modulation of emotional distracters. Furthermore, it is important to note that there have been recent reviews on the neural substrates of cognition-emotion interactions in normative samples (Elliott et al., 2010; Dolcos et al., 2011), adult mood disorders (Elliott et al., 2010), and development (Mueller, 2011). Consequently, the current review will focus primarily on evidence from animal studies and human neuroimaging studies documenting puberty-specific influences on fronto-limbic systems and how such evidence may enhance our understanding of the development of cognitive-affective processes in adolescence. Finally, I will discuss these findings with regard to their implications for contributing to the vulnerability of emotion dysregulation and potentially the onset of affective disorders in at-risk youth.

STUDIES OF COGNITIVE-AFFECTIVE PROCESSES IN ADOLESCENCE

Using a paradigm that more or less constrains attention to the emotional features of facial expressions, Monk et al. (2003) reported that adolescents relative to adults showed greater activation in the anterior cingulate, bilateral orbitofrontal cortex, and right amygdala in response to the fearful relative to neutral faces (Monk et al., 2003). This was one of the first fMRI studies to examine selective attention to emotional and nonemotional features of stimuli in adolescence. These findings suggest that developmental changes in attentional capacities may play an important role in the modulation of attention to emotionally salient information. Using the same task in adolescents diagnosed with generalized anxiety disorder, Mcclure et al. (2007) reported that while attending to their own subjective fear, anxious youth, but not healthy controls, exhibited greater amygdala, ventral prefrontal cortex, and anterior cingulate cortex to fearful vs. happy faces (Mcclure et al., 2007). Such findings suggest that anxious adolescents may exhibit altered functioning of threat systems in the context of subjective fearful experiences.

In a developmental study, Tottenham et al. (2011) examined the performance of children (5–12 years old), adolescents (13–18 years old), and adults (19–28 years old) using a block design emotional go/no-go task. In this study, participants were instructed to press a button (go) to particular emotional faces and to not press the button (no-go) to other emotional faces (Tottenham et al., 2011). Findings indicated that performance on the task improved with age. Nevertheless, across the age groups, false alarms occurred more frequently to emotional face no-go stimuli relative to neutral face no-go stimuli, which were interpreted as indexing reduced inhibitory control in the context of emotionally salient emotional information. Using a similar version of the task in the fMRI scanner, Hare et al. (2008) documented elevated amygdala activation in adolescents relative to children and adults on this task (Hare et al., 2008). Furthermore, elevated amygdala and reduced ventral prefrontal cortical activation positively correlated with slower reaction times to the fearful (vs. happy) face target stimuli. Functional connectivity analyzes revealed that strength of VLPFC-amygdala coupling was correlated with greater habituation of amygdala activity to fearful face targets in adolescence (Hare et al., 2008).

Using a visual n-back working memory task with emotional face distracters (i.e., Emotional Face n-back (EFNBACK) task), we examined performance on trials with emotional (i.e., happy and fearful face) distracters and varying in working memory load (i.e., 2-back versus 0-back condition) in a normative sample of children (8–10 years old), young adolescents (mean age = 11–13 years), older adolescents (14–17 years), and adults (18–27 years). Results indicated that youth high in trait anxiety exhibited slower reaction times to fearful face distracters in the 2-back condition and that such an effect was greater in children than adolescents (Ladouceur et al., 2009). Such findings are consistent with previous behavioral data on a similar emotional working memory task in a clinical sample of children and adolescents diagnosed with anxiety, depression, and comorbid anxiety and depression (Ladouceur et al., 2005). In that study, we showed that relative to healthy controls, youth with depression and comorbid anxiety and depression had significantly slower reaction times on negative emotional backgrounds compared to neutral backgrounds. In contrast, youth in the healthy low-risk group showed slower reaction times to the positive emotional background, suggesting an attentional bias to

positively valenced stimuli; such an effect was not present in the groups with affective disorders (Ladouceur et al., 2005). Recent neuroimaging studies using cognitive-affective tasks with fMRI in youth with anxiety and mood disorders have reported alterations in the functioning of VLPFC and amygdala, suggesting that VLPFC modulation of amygdala may contribute to affective biases reported in these clinical populations (Monk et al., 2008; Pavuluri et al., 2008). Together, these findings suggest that using cognitive-affective tasks such as the emotional working memory paradigm enables researchers to investigate the development of attentional control processes (implicated in resisting interference from emotionally salient distracters) and examine to what extent the development of the neural systems that support these processes may be altered in youth at risk for or diagnosed with affective disorders.

Some researchers have also examined the influence of incentives on cognitive processes. For instance, using an emotional antisaccade task, Geier and colleagues reported differences in performance and associated neural activation in fronto-striatal regions in adolescents relative to adults (Geier et al., 2010). An antisaccade is an eye movement to the opposite direction of a suddenly appearing target. This movement requires inhibiting a prepotent response to the target, and the initiation of an alternate goal-relevant response in the opposite direction signaled by the sudden onset of the stimulus. Geier and colleagues examined the effects of reward on antisaccades, during the cue stage, saccade preparation stage, and saccade execution stage. In order to assess neural responses across these three stages, a time-course analysis over 18 s post-trial onset was employed. They reported greater ventral striatum activity to the saccade preparation in adolescents than adults but during the incentive cue, it was recruited more strongly in adults than adolescents; there were no group differences in the saccade execution stage. Neural regions commonly recruited during antisaccade were generally less activated in adolescents than adults in response to neutral trials and showed no age-group differences to reward trials. Interestingly, however, this study demonstrated that adolescents tended to exhibit greater recruitment of reward circuitry during saccade preparation to incentive trials. These findings are consistent with those of another recent study in which adolescents exhibited greater activation in reward circuitry and prefrontal regions than adults on a continuous performance task (CPT) (Smith et al., 2011). In this study, Smith and colleagues compared, in adolescents relative to adults, behavioral performance and neural activity on three types of trials (non-targets, rewarded targets, and on-rewarded targets) of CPT. Findings from behavioral data analyzes revealed that adolescents responded significantly faster to rewarded vs. non-rewarded targets whereas no such differences were observed in adults. These behavioral findings suggest that being rewarded had significant impact on sustained attention in adolescents than adults. Moreover, findings from fMRI analyses revealed a significant positive correlation between age and neural activity to rewarded (vs. non-rewarded) targets in neural regions implicated in sustained attention (e.g., dorsolateral prefrontal cortex, ventromedial orbital frontal cortex), suggesting that age modulated the effects of reward on activity in neural regions implicated in sustained attention.

In sum, these findings suggest that cognitive control may be more challenged in the face of emotionally salient or incentive-laden distracters in adolescents relative to adults. We acknowledge that our review of cognitive-affective findings in adolescence was not exhaustive. The purpose was not to provide an exhaustive literature review since this has been accomplished elsewhere (e.g., Mueller, 2011). Rather the aim was to provide some examples of research findings demonstrating that the influence of emotionally salient information on the functioning of neural systems supporting cognitive processes including cognitive control undergo important neuro-maturational changes in adolescence. In this review, I will demonstrate that the onset of puberty is associated with increased reactivity to emotionally salient information in ways that create challenges for cognitive control systems. Furthermore, these pubertal influences on fronto-limbic systems may be associated with reduced modulation of attention in the context of emotional distracters and increased vulnerability to emotion dysregulation. Such a framework complements existing neurobiological models of adolescent brain development (Casey et al., 2010; Ernst et al., 2011) but attempts to move beyond age-related effects to focus more specifically on neurodevelopmental changes occurring at puberty and how such changes may help explain increases in the escalating rates of adolescent death and disability related to problems of emotion regulation (e.g., mood disorders, suicide, accidents, etc.).

WHAT DEVELOPMENTAL FACTORS MIGHT INFLUENCE COGNITIVE-AFFECTIVE PROCESSES?

RISE IN SEX HORMONES DURING PUBERTY

Puberty refers to a specific set of processes implicating changes in physical and reproductive maturation. Although the majority of these changes occur early to mid-adolescence, as described below, some (e.g., adrenarche and luteinizing hormone secretion), however, can start in childhood. As such, puberty is often considered as the beginning of adolescence, a developmental period between childhood and adulthood that encompasses changes at multiple levels. This transitional developmental period not only implicates changes associated with pubertal maturation but also changes in physical growth, psychological functioning, and social experiences (Dahl and Spear, 2004; Dorn et al., 2006).

Puberty includes important changes in the functioning of the neuroendocrine system (for a review, see Dorn et al., 2006; Natsuaki et al., 2009; Blakemore et al., 2010). The earliest phase of puberty or "prepuberty," which begins between 6–9 years old in girls and about 1 year later in boys (Cutler et al., 1990; Parker, 1991), involves the rising of androgens that are secreted by the adrenal glands. These include dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and androstendione (Grumbach and Styne, 2003). The rising of these hormones refers to what is known as the beginning of *adrenarche*. The maturation of primary sexual characteristics (i.e., ovaries and testes) and the full development of secondary sexual characteristics (i.e., pubic hair, breast, and genital development) is associated with the activation of the hypo-thalamic-pituitary gonadal (HPG) axis (Demir et al., 1996; Delemarre-Van De Waal, 2002). The rising of these sexual hormones represents a second phase of puberty known as *gonadarche*, which begins at about 9–10 years old in girls and

approximately 1–2 years later in boys (Marshall and Tanner, 1969, 1970). This pubertal period includes the onset of menses, or *menarche*, in girls, and the onset of nocturnal emission, or *spermarche*, in boys. Menarche in girls tends to be an event that occurs rather late in the pubertal process. Spermarche in boys represents the transition from prepubertal to pubertal, and occurs on average at approximately 13–14 years old (Marshall and Tanner, 1969, 1970). The development of secondary sexual characteristics occurs gradually and as such, has been organized into stages (e.g., Tanner stages), which has allowed clinicians and researchers to assess variations in pubertal maturation.

Individual variations in pubertal maturation processes

Most adolescents will exhibit the above-described endocrinological changes associated with pubertal maturation but not in a uniform manner as there is considerable individual variation in both the "timing" and "tempo" of puberty (Styne and Grumbach, 2002; Dorn et al., 2006). Variation in the timing refers to the level of pubertal maturation relative to same-age peers and variation in the tempo refers to the adolescent's rate of intra-individual change in pubertal status (i.e., the amount of time brains are exposed to sex hormones). Because pubertal maturation is a dynamic biological process, variations in this process may be influenced by multiple developmental factors some of which can precede the onset of puberty *per se* (e.g., nutritional history, stressful life events, and family conflict). Discussion about research findings documenting how each of these factors contributes to variations in pubertal timing and tempo is beyond the scope of this review (for addition information, see Ellis, 2004; Ellis et al., 2011a,b). Nevertheless, there is a general trend toward younger age of puberty onset in the United States—particularly age of breast development and menarche among girls (Biro et al., 2012). Variations in both pubertal timing and pubertal tempo have been related to emotional functioning, particularly in girls (Ellis et al., 2011b). For instance, there is growing evidence that girls who mature earlier than their on-time or later-developing peers are at increased risk for psychopathology, including depression, early initiation of substance use, early sexual initiation and pregnancy and other emotional, and behavioral problems (Dick et al., 2000; Deardorff et al., 2005; Mendle et al., 2010; Joinson et al., 2012). In particular, Joinson et al. (2012) recently reported that more advanced breast development was associated with increased depressive symptoms in adolescence. This was a large multiwave longitudinal study, which included measures of the different hormonal axes of puberty (i.e., secondary sexual characteristics associated with adrenarche and gonarche) (Joinson et al., 2012). Because breast development is due to a rise in estrogen, these findings support previous data demonstrating that estradiol levels in girls is linked with increased depression in girls (Angold et al., 1999). Fewer studies have reported similar influences in boys. Some have reported, however, that the influence of pubertal timing and tempo on emotional functioning may be mediated by the quality of peer relationships (Mendle et al., 2012). In light of evidence from animal studies showing high densities of gonadal hormone receptors in medial temporal regions implicated in emotion processing (e.g., amygdala, striatum) (Simerly et al., 1990; Sarkey et al., 2008), it is thus reasonable to predict that adolescents who exhibit onset of puberty earlier than their on-time or later developing peers would also exhibit greater reactivity to emotionally salient information.

HEIGHTENED EMOTIONAL REACTIVITY IN THE CONTEXT OF PROTRACTED DEVELOPMENT OF REGULATORY CONTROL

Prominent models of adolescent brain development highlight a temporal "mismatch" in the development of neural systems supporting emotional reactivity and regulation (Steinberg, 2005; Ernst et al., 2006; Casey et al., 2011). These models propose that adolescence represents a period of increased emotional reactivity during early adolescence along with a more gradual and protracted development of regulatory control. Neural regions that subserve cognitive control functions show age-related functional changes that continue well into late adolescence and early adulthood (Lewis, 1997; Sowell et al., 2003; Luna et al., 2004) and are thought to mature irrespective of pubertal timing (Steinberg, 2005). With the onset of puberty occurring earlier over the past century (Worthman, 1999) and prefrontal systems supporting regulatory control not reaching full maturity until early adulthood, this creates a potential maturational gap creating a possible "imbalance" in fronto-limbic circuitry that may lead to dysregulated behavior and affect, particularly in vulnerable youth. This has led to a metaphor for the historical advancement of puberty as "starting the engines with an unskilled driver" (Dahl and Spear, 2004). This dilemma has been proposed to explain, in part, the fact that adolescents often make poor decisions that lead to negative consequences (e.g., accidents, drug use) despite cognitively understanding the risks involved (Cauffman and Steinberg, 1995; Reyna and Farley, 2006). Although such models could serve to help explain developmental effects observed in adolescence during the performance of cognitive-affective tasks, most of the research thus far has focused on age-related changes in the development of cognitive control processes and we know very little about the influence of pubertal maturation on the development of these systems—particularly as it relates to effects on neural activity in subcortical limbic regions and their modulation by prefrontal cortical circuitry.

SOCIAL REORIENTATION: CHANGES IN MOTIVATIONAL TENDENCIES

Early adolescence is also characterized by concurrent changes in motivational tendencies geared toward social peer interactions. As discussed in (Forbes and Dahl, 2010) the increase of sex hormones with the onset of puberty plays a crucial role on the re-orientation of social behavior in adolescence (Forbes and Dahl, 2010). Specifically, social affiliation with peers and romantic interests becomes increasingly important thereby eliciting strong emotional reactions (Larson and Asmussen, 1991). Testosterone, for instance, plays an important role in sensation-seeking (Martin et al., 2002), risk taking (Vermeersch et al., 2008), and social dominance (Eisenegger et al., 2011). Consequently, the saliency of social cues becomes reconfigured according to expectations of potential gain or loss in social status or affiliation. Some have argued that neural regions involved in processing motivationally relevant information undergo remodeling during adolescence (Spear, 2000). Such remodeling has been observed in non-human species and is believed to have adaptive value in

preparing the individual to survive away from parental caretakers by encouraging the adolescent to develop new bonds and explore novel areas (Spear, 2000). These changes in motivational tendencies would therefore promote a natural tendency to explore new things and take more risks—particularly when these have social salience (e.g., gain attention and/or admiration from peers). Such social reorientation in adolescence would therefore magnify the emotional saliency of social cues in ways that would impact the functioning of fronto-limbic circuitry that support cognitive-affective processes.

SEX STEROIDS MODULATE ACTIVITY IN AND CONNECTIVITY BETWEEN NEURAL REGIONS SUPPORTING COGNITIVE-AFFECTIVE PROCESSES

As discussed previously, puberty is associated with significant endocrinological changes, such as a vast increase in the sex steroids testosterone and estradiol released from the gonads. Findings from animal studies indicate that sex steroids such as testosterone, estradiol, and their antecedents (DHEA) impact the organization of neural circuits that support social, sexual and emotional behavior (Sisk and Zehr, 2005; Ahmed et al., 2008; Schulz et al., 2009). These effects may be mediated by the influence of sex hormones on fronto-striatal-limbic systems given the high densities of steroid hormone receptors in medial temporal regions (Simerly et al., 1990; Sarkey et al., 2008), such as striatum, amygdala, and hippocampus, as well as the prefrontal cortex (Pfaff and Keiner, 1973; Simerly et al., 1990). As reviewed in Eisenegger et al. (2011) and Bos et al. (2011), testosterone is produced in both boys and girls and is viewed as a "social hormone" because of its role in promoting the search for, and maintenance of, social status and alterations in the appraisal of threats and rewards—particularly when these are relevant to social status (Bos et al., 2011; Eisenegger et al., 2011). Estradiol, a metabolite of testosterone that is critical for female reproductive function, has been linked to emotional behavior (Walf and Frye, 2006) and to various cognitive functions (Berman et al., 1997; Jacobs and D'esposito, 2011).

Recent neuroimaging studies examining the influence of sex steroids on fronto-limbic systems in adults provide important clues about potential mechanisms regarding the influence of puberty-related neuroendocrine changes on fronto-limbic function. The majority of the studies have focused on individual differences in testosterone levels and few studies have examined the effects of estradiol (for a review see, Walf and Frye, 2006), with the exception of work in post-menopausal women (Naftolin and Malaspina, 2007). For instance, a number of studies have demonstrated that testosterone influences neural activity in amygdala and regions of the prefrontal cortex (Stanton et al., 2009; Manuck et al., 2010; Mehta and Beer, 2010; Van Wingen et al., 2010). Specifically, amygdala response to emotional faces (i.e., fearful/angry) was associated with higher levels of serum testosterone concentrations in young men (Derntl et al., 2009; Manuck et al., 2010) and women (Hermans et al., 2008; Derntl et al., 2009; Van Wingen et al., 2010). A potential mechanism underlying these changes in amygdala responses might be that testosterone influences fronto-limbic connectivity implicated in emotion regulation. Indeed, Van Wingen et al. (2010) demonstrated that testosterone induces a "functional decoupling" between amygdala and ventral prefrontal cortex (i.e., BA47) activity, which they interpreted in terms of reduced (automatic) regulatory influence of the prefrontal regions over the amygdala (Van Wingen et al., 2010). A more recent study employed a cognitive-affective task, the Approach-Avoid Task, which was designed to assess implicit approach-avoidance action tendencies by manipulating the congruency of the stimuli to which participants respond (Volman et al., 2011). In that study, young male participants were asked to use a joystick to respond to visually presented emotional facial expressions (happy, anger, neutral), which are known to produce automatic approach (happy) and avoidance (angry) tendencies. The neutral face served as the control condition. They were asked to either pull the joystick toward themselves (approach) or push it away from themselves (avoid) based on the valence of the emotional facial expressions. Volman et al. (2011) examined the influence of endogenous hormones on the functional connectivity between VLPFC and amygdala, based on evidence that such regions are implicated in the (voluntary) regulation of prepotent emotional action tendencies. As depicted in **Figure 1**, results demonstrated that endogenous testosterone modulated effective connectivity between VLPFC and frontal pole (FP) and the amygdala in the affect-incongruent condition reflecting regulation of emotional action tendencies (Volman et al., 2011). These findings suggest that high levels of endogenous testosterone in healthy males are associated with less recruitment of VLPFC/FP to modulate amygdala activity. Although these findings are intriguing, the specific neurochemical mechanism by which testosterone could influence fronto-limbic systems remains uncertain (e.g., perhaps mediated in part through its conversion to other streroids) (Bodo and Rissman, 2006). Nevertheless, these findings suggest that sex hormones (i.e., testosterone) appear to influence not only activity in but also connectivity between neural regions implicated in emotion regulation.

PUBERTY-RELATED CHANGES IN ADOLESCENT BRAIN DEVELOPMENT

The above findings provide compelling evidence for the direct influence of sex hormones on brain function. As such, given the increase of sex hormones that occurs with the onset of puberty (and during prepuberty), it is reasonable to expect that pubertal maturation may exert direct and indirect influences on neurodevelopment. We next briefly review recent findings that demonstrate how changes in pubertal maturation may influence changes in the functioning of neural systems implicated in emotion processing and regulation.

STRUCTURAL NEUROIMAGING STUDIES

A number of studies have demonstrated the influence of pubertal maturation on gray matter development (Giedd et al., 2006; Peper et al., 2009; Bramen et al., 2010, 2012) and more recently white matter development (Asato et al., 2010; Herting et al., 2011; Peper et al., 2011; Ladouceur et al., 2012). Gray matter is composed of cell bodies, dendrites, and nonmyelinated axons of neurons, including glial cells and capillaries. Cross-sectional and longitudinal studies have documented non-linear age-related changes in gray matter volume, density, and thickness (mostly cortical areas),

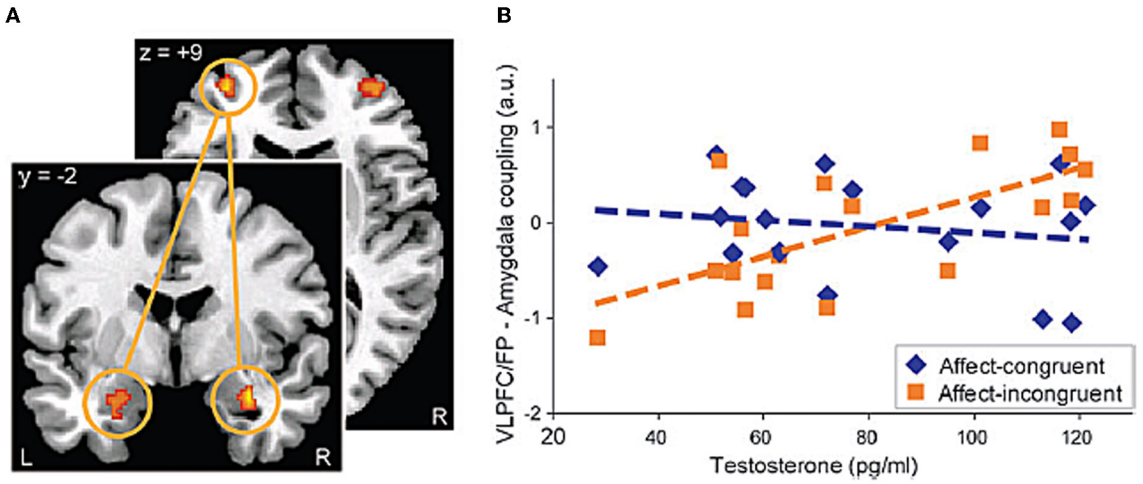

FIGURE 1 | Example of the effects of testosterone on the functional connectivity between prefrontal cortical regions (i.e., VLPFC/FP) and subcortical regions (i.e., amygdala) during a task that recruits cognitive-affective processes. (A) Coupling between left VLPFC/FP and right amygdala, which was significantly (FWE, $p < 0.05$) modulated by testosterone during the affect-incongruent compared to the affect congruent condition of the Approach-Avoid task. **(B)** Scatter plot visualizing the positive correlation between testosterone and the VLPFC/FP-amygdala connectivity for the affect-incongruent versus the affect congruent trials. (Reprinted with permission from Cerebral Cortex, Oxford Publishers).

which would appear to follow an inverted-U shape reaching a peak in adolescence (Giedd et al., 1999; Sowell et al., 2003). White matter provides the structural architectural organization of the brain. It is made up primarily of myelinated axons that serve to facilitate communication between neural regions creating neural networks, which subserve complex cognitive and affective functions (Paus, 2010). Several MRI studies have documented linear age-related increases in white matter volume between childhood and adolescence, reaching a plateau in adulthood (Giedd et al., 1999).

Numerous studies have reported sex differences in the development of gray and white matter during adolescence (for a review, see Lenroot and Giedd, 2010). Given that puberty typically onsets later in males than females, such findings provide some initial clues with regard to the potential influences of pubertal maturation on brain development (i.e., sexual dimorphism). That is, even though certain MRI studies do not include direct measures of pubertal maturation (e.g., hormone levels, self-report), findings indicating significant sex differences and sex by age interactions could be interpreted in terms of hormonal influences on gray and white matter development or onset of puberty. Although these findings are compelling, they are beyond the scope of the current review and have been described in previous reviews (e.g., Giedd et al., 2006; Lenroot et al., 2007; Lenroot and Giedd, 2010; Ladouceur et al., 2012). Indeed, a more direct approach is to include measures of pubertal maturation such as self-report, physical exams, or saliva or blood essays of reproductive hormones. Another important methodological consideration that few studies have incorporated is the recruitment of males and females according to the approximate age of puberty onset (i.e., gonarche), which is begins at about 9–10 years old in girls (Marshall and Tanner, 1969) and approximately 1 year later in boys (Marshall and Tanner, 1970).

Recent research studies have begun to document the role of pubertal maturation on the developing brain (Perrin et al., 2008; Blakemore et al., 2010; Bramen et al., 2010, 2012; Peper et al., 2011). Such studies reveal that sex hormones exert unique influences on gray matter volume (Neufang et al., 2009; Bramen et al., 2010), density (Peper et al., 2009), and thickness (Raznahan et al., 2010; Bramen et al., 2012). A few recent studies have reported associations between pubertal maturation, changes in sex hormones, and white matter development (Peper et al., 2011; Ladouceur et al., 2012). Such changes included, for instance, associations between testosterone levels in boys and increases in white matter volume (Perrin et al., 2008) and increased integrity of white matter tracts connecting frontal and temporal regions as well as frontal and subcortical regions with more advanced pubertal status (based on Tanner stage assessment) (Asato et al., 2010). Interestingly, there is also evidence for associations between increasing level of relationship between levels of luteinizing hormone (LH) in 9-year old twins, which is considered as one of the first endocrinological markers of puberty in both boys and girls, and larger white matter density (Peper et al., 2008). Furthermore, there is evidence that the androgen receptor gene, whose length modulates the action of the androgen receptor, would appear to play an important role in regulating gray matter (Raznahan et al., 2010) and white matter development (Perrin et al., 2008; Paus, 2010). Given the relatively small number of studies that have examined specifically associations between pubertal maturation and brain structure development, findings thus far indicate a significant contribution of puberty, in particular testosterone in boys and its precursor LH (in both sexes), on the development of frontal and temporal regions (and their structural connections), which may have implications for the development of cognitive-affective processes supporting emotion processing and regulation in adolescence.

FUNCTIONAL NEUROIMAGING STUDIES

To date, only a handful of studies have investigated effects of puberty and sex hormones using functional neuroimaging. Before describing these findings, it is important to first note that the use of appropriate methodological designs is critical in order to examine specific pubertal influences on the functioning of fronto-limbic systems. To what extent are studies able to disentangle age effects from pubertal maturation is key to addressing puberty-specific developmental questions since age and puberty are closely correlated with each other (and chronological age is measured with a much greater precision than categories for pubertal stage) (Shirtcliff et al., 2009; Spear, 2010). Given that boys typically reach puberty later than girls, it is important, for instance, to recruit participants within a narrow age-range to account for potential age-related effects but also to take into account sex differences in pubertal maturation (Dorn et al., 2006; Shirtcliff et al., 2009). Such methodological designs have inherent constraints with regard to subject recruitment, which might explain the paucity of research in this area. Nevertheless, there is an emerging literature that demonstrates the feasibility of using such designs in order to address these important developmental questions. Many other factors are important to consider and these have been reviewed elsewhere (Dorn et al., 2006; Shirtcliff et al., 2009).

Using such methodological approaches our group and others have examined the influences of puberty on psychophysiological and neural indices of emotional reactivity during emotion processing and regulation tasks. For instance, Silk et al. (2009) examined associations between pubertal maturation and physiological and subjective reactivity to emotional words (Silk et al., 2009). In this study, pupil dilation was assessed among 32 pre-/early pubertal and 34 mid-/late pubertal typically developing children and adolescents while they an emotional word valence identification paradigm with positive, negative, and neutral words. Pupil dilation, which is a peripheral index of brain activation, is generally greater in response to stimuli that require greater cognitive load or that have greater emotional intensity (Siegle et al., 2004). Our findings showed that mid-/late pubertal youth had greater peak pupil dilation to affective words than pre-/early pubertal youth, even controling for participants' age. This peak pupil dilation was correlated with heightened memory for emotional but not neutral words on an unexpected free recall task, suggesting that such peak pupil dilation measure may be linked to emotionally-relevant processing. These findings are consistent recent associations between pubertal maturation and neural activity to emotional facial expressions (Moore et al., 2012). There is also evidence that adolescent-levels of testosterone correlates with maturational changes in neural systems supporting reward processing in adolescents (Forbes and Dahl, 2010; Op De Macks et al., 2011). Furthermore, threat-related reactivity to social cues has been associated with levels of depression symptoms in peri-pubertal adolescents (Forbes et al., 2011). Taken together, these findings of pubertal changes in the functioning of fronto-limbic circuitry implicated in emotion processing and regulation has tremendous implications for understanding potential developmental mechanisms implicated in risk for affective disorders in adolescence.

CONCLUSION AND FUTURE DIRECTIONS

The goal of this review was to briefly synthesize research findings demonstrating developmental changes in cognitive-affective processes and underlying fronto-limbic circuitry. The second and perhaps more important goal was to highlight evidence that speaks to the potential influence of puberty on the development of this circuitry in ways that could have implications for understanding risk for affective disorders. Notwithstanding the importance of age-related neuromaturational changes to the functioning of this circuitry (Mueller, 2011; Tottenham et al., 2011), very little attention has been dedicated to the potential impact of pubertal maturation on the reactivity of subcortical regions (e.g., amygdala, ventral striatum) and how such heightened emotional reactivity early in adolescence may create new challenges for later developing cognitive control and underlying neural systems. As illustrated in **Figure 2**, I propose that with the increase in sex hormones during puberty, adolescents may exhibit reduced modulation of attention to emotionally salient distracters because of the potential influence of sex hormones on the functional connectivity between prefrontal cortical regions implicated in the modulation of subcortical regions. The extent to which puberty-related changes in circulating levels of sex hormones impacts cognitive-affective interactions remains largely unexplored. To date, the emerging literature has focused on emotion information processing (e.g., Moore et al., 2012) or reward processing (e.g., Forbes et al., 2011) and few studies have used tasks

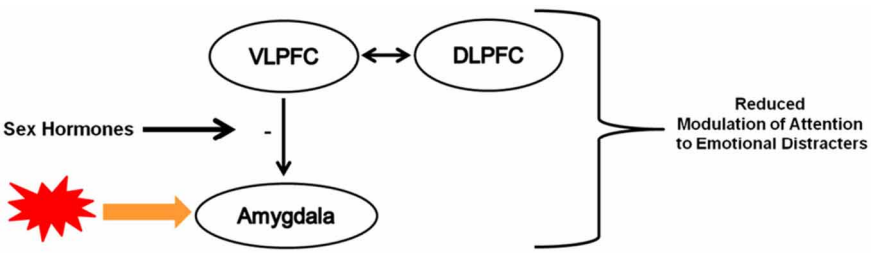

FIGURE 2 | Simplified illustration of heuristic model describing the potential influence of the increase in sex hormones during pubertal maturation on the functioning of fronto-limbic circuitry implicated in the modulation of attention to emotionally salient distracters. For simplicity, involvement of other neural regions and their interactions with these and other regions were omitted. (+): positive modulation, (−) negative modulation, thickness of arrows reflects relative weight of impact. VLPFC: ventrolateral prefrontal cortex; DLPFC: dorsolateral prefrontal cortex.

that recruit higher-order cognitive control processes. However, findings from Hare et al. (2008) showing that the strength of VLPFC-amygdala coupling was correlated with greater habituation of amygdala activity to fearful face targets in adolescence during an emotional go-nogo task provide some interesting clues about the potential effects of pubertal maturation on these systems (Hare et al., 2008). Future research employing appropriate methodological designs are needed to determine whether these findings are indeed age- versus puberty-related effects.

In addition to pubertal changes in the functioning of these fronto-limbic systems, there are also notable puberty-related changes in motivational tendencies that become increasingly oriented toward peer social contexts (Nelson et al., 2005). This new set of motivational tendencies brings about a reconfiguration in the saliency of emotional and social cues because of their prediction of potential changes in social status/evaluation (e.g., heightened reactivity of threat system to emotional facial expressions that could be linked to worries of being rejected by unfamiliar peers) (Forbes and Dahl, 2010; Silk et al., 2012a). Some have demonstrated that these social information processing systems become more sensitive or reactive during puberty, particularly to cues of social threat or reward (Dahl, 2001; Nelson et al., 2005; Steinberg, 2007; Spear, 2010). For example, Silk et al. (2012a,b) recently reported increased sensitivity to social evaluation across adolescence in a virtual peer interaction chatroom task. Specifically, pupillary reactivity to peer rejection and visual biases toward acceptance stimuli increased linearly with age among 9- to 17-year-olds (Silk et al., 2012b). Therefore, it is possible that the social nature of emotional distracters may require greater modulation of attention and recruitment of modulatory prefrontal cortical systems because of the heightened motivational saliency of such stimuli.

Another factor to consider is the individual variation in pubertal maturation processes and how these might contribute to increased vulnerability to emotion dysregulation and possibly the onset of psychopathology such as affective disorders in at-risk youth. The general trend toward earlier onset of puberty, particularly in girls, may be associated with greater reactivity in subcortical regions. Such reactivity may be enhanced in the context of threat to social status (i.e., being rejected by a peer), stressful life events, and in youth having a family history of affective disorders. Such heightened reactivity in young at-risk youth in the context of protracted development of prefrontal cortical systems supporting regulatory processes and potentially reduced fronto-limbic connectivity associated with changes in the level of hormones could contribute to developmental trajectories toward affective disorders. Of note, there is evidence showing that stressful family environment (i.e., family conflict) influences pubertal timing and tempo (Ellis, 2004) and that this effect might be greater in a subset of youth who are particularly biologically sensitive to social context (Ellis et al., 2011b). Future research is therefore needed to investigate the specific influence of pubertal maturation on fronto-limbic function supporting cognitive control-emotion interaction in normally developing adolescents and at-risk youth in order to test the above hypotheses and elucidate potential mechanisms for the increased risk of affective disorders in adolescence, particularly in girls.

In sum, there is an emerging literature suggesting that pubertal maturation may exert specific influences on adolescent brain development (e.g., Silk et al., 2009; Blakemore et al., 2010; Forbes et al., 2011; Op De Macks et al., 2011; Peper et al., 2011; Ladouceur et al., 2012; Moore et al., 2012). Such influences may have greatest impact on cognitive-affective processes and as such, potentially alterations in emotion regulation in vulnerable youth. Animal studies indicate that sex hormones impact dopamine function (e.g., Aubele and Kritzer, 2011). It is therefore possible that the impact of sex hormones on fronto-limbic function may be mediated by their impact on neurotransmitter systems such as dopamine—which undergoes important maturational changes in adolescence (Wahlstrom et al., 2010; Ernst et al., 2011). Given the role of dopamine in modulating cognitive control processes (Jacobs and D'esposito, 2011), one avenue of research might be to examine the role of dopamine and associations with functioning of neural systems supporting processes at the interface of cognition and emotion. Furthermore, evidence from structural as well as functional neuroimaging studies demonstrate that fronto-limbic systems are implicated in the pathogenesis of affective disorders, especially ventromedial-amygdala and frontal-thalamic-striatal systems (Mayberg, 2001; Phillips et al., 2008; Savitz and Drevets, 2009; Price and Drevets, 2010). Because rates of depression (Angold et al., 1998, 1999) are more strongly associated with puberty than age, it is possible that puberty-specific influences on the development of these neural systems may render particularly vulnerable youth (i.e., genetic predisposition, early-life stressors) at increased risk for affective disorders. Thus, future longitudinal research studies investigating the neuroendocrine, social, and age-related influences on the maturation of neural systems supporting cognitive-affective processes and associations with emotion regulation processes would contribute to advancing the field of developmental cognitive and affective neuroscience as well as our knowledge about potential neurodevelopmental markers of risk for affective disorders in adolescence.

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The trade-offs of emotional reactivity for youths' social information processing in the context of maternal depression

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Although research demonstrates that emotional experiences can influence cognitive processing, little is known about individual differences in this association, particularly in youth. The present study examined how the emotional backdrop of the caregiving environment, as reflected in exposure to maternal depression and anxiety, was linked to biases in youths' cognitive processing of mother-referent information. Further, we investigated whether this association differed according to variation in youths' emotional reactivity to stress. Youth (50 boys, 46 girls; *M* age = 12.36, SD = 1.05) completed a behavioral task assessing cognitive bias. Semi-structured interviews were administered to assess (a) youths' emotional reactivity to naturally occurring stressors, and (b) maternal depression and anxiety. Hierarchical multiple regression analyses revealed that emotional reactivity to interpersonal stressors moderated the linkage between maternal depression and cognitive bias such that maternal depression predicted a greater negative bias in youth exhibiting high and average, but not low, levels of emotional reactivity. At low levels of maternal depression, youth with heightened interpersonal emotional reactivity showed a greater positive cognitive bias. This pattern of effects was specific to interpersonal (but not non-interpersonal) emotional reactivity and to maternal depression (but not anxiety). These findings illuminate one personal characteristic of youth that moderates emotion-cognition linkages, and reveal that emotional reactivity both enhances and impairs youths' cognitive processing as a function of socialization context.

Keywords: differential susceptibility, emotional reactivity, maternal psychopathology, social information processing, cognitive bias

INTRODUCTION

Despite recognition of mutual and dynamic connections between emotion and cognition at both proximal and distal levels, developmental scientists traditionally have examined normative and atypical emotional and cognitive processes in isolation (Calkins and Bell, 2010). Contemporary experimental paradigms have helped address this gap by examining a variety of integrated emotion-cognition associations, as well as individual differences in these links (e.g., Henderson et al., 2012; for a review, see Dolcos et al., 2011). In particular, cognitive and affective neuroscience research highlights the interplay between characteristics of affect (e.g., emotion generation and regulation) and cognition (e.g., attention, memory). This research suggests that emotional systems can both enhance and impair cognitive functions (i.e., improving versus reducing accuracy and efficiency; for reviews, see De Raedt et al., 2010; Dolcos et al., 2011). Building on prior research and extending it to an interpersonal context, the primary goal of this study was to examine the association between emotional facets of caregiving and youths' cognitive processing, and to explore personal characteristics of youth that determine the strength of this link. In particular, we investigated (a) how the emotional backdrop of the caregiving environment, as reflected in exposure to maternal psychopathology, was linked to biases in youths' cognitive processing of mother-relevant information, and (b) whether the magnitude of this association differed according to variation in youths' emotional reactivity to stress.

PERSON X ENVIRONMENT MODELS OF DEVELOPMENT

Several theoretical models have been proposed to explain individual differences in sensitivity to environmental experiences. Traditional vulnerability or dual-risk models hold that adverse environmental experiences more strongly predict detrimental outcomes in individuals who carry personal vulnerabilities, or diatheses (Monroe and Simons, 1991; Heim and Nemeroff, 1999). A substantial body of research supports this type of model and, in particular, highlights interactions between personal characteristics and interpersonal stressors on maladaptation in at-risk youth and young adults (e.g., Hammen et al., 1995; Shahar et al., 2004; Flynn and Rudolph, 2007, 2010; Agoston and Rudolph, 2011).

A contemporary refinement of vulnerability models posits that individual variation in contextual sensitivity can take the form of plasticity, as reflected in reactivity to both disadvantageous

and beneficial contexts. Specifically, differential susceptibility theory (Belsky et al., 2007, 2009; Belsky and Pluess, 2009) proposes that personal and environmental characteristics interact to predict heightened risk in adverse milieus *and* enhanced adaptation in supportive settings (for a similar model of biological sensitivity to context, see Boyce and Ellis, 2005). For instance, children with a difficult temperament, or a propensity toward negative emotionality and reactivity, demonstrate more responsiveness to certain facets of caregiving, such as supportiveness (Stright et al., 2008), sensitivity (Bradley and Corwyn, 2008; Pluess and Belsky, 2010; Roisman et al., 2012), enriching engagement (Bradley and Corwyn, 2008), and characteristics of non-maternal child care (e.g., type, quantity; Pluess and Belsky, 2010). This research reveals that children with a difficult temperament experience more adverse developmental outcomes in the presence of low quality caregiving but more beneficial developmental outcomes in the presence of high quality caregiving (Bradley and Corwyn, 2008; Stright et al., 2008; Pluess and Belsky, 2010). Notably, support for this model thus far has been obtained during infancy and childhood. Accordingly, the first goal of this study was to examine differential susceptibility interactions between youths' emotional reactivity and attributes of the caregiving environment during early adolescence. Further, given the interpersonal context of caregiving, we investigated the specificity of moderation to youths' emotional reactivity to interpersonal versus non-interpersonal stress.

MATERNAL PSYCHOPATHOLOGY AND YOUTH COGNITIVE PROCESSING

Although a large body of research highlights the negative impact of maternal psychopathology, particularly depression, on the emotional backdrop of the caregiving environment, maternal psychopathology has yet to be examined within a differential susceptibility framework. Observational studies demonstrate that depressed mothers display more sadness, anger, and disengagement (Hops et al., 1987; Field et al., 1990; Pelaez et al., 2008; for a meta-analysis, see Lovejoy et al., 2000) and less positive affect (Field et al., 1990; Feng et al., 2007) during interactions with offspring. In addition, depressed mothers demonstrate more intrusive interaction styles with offspring (Field et al., 2006), express greater criticism about their children (Goodman et al., 1994; Frye and Garber, 2005), and evince less empathic understanding while observing children's challenging experiences (Coyne et al., 2007). Finally, mothers with a history of depression are more likely to react adversely (i.e., magnify, punish, neglect), and are less responsive and supportive, in response to children's expressions of negative emotions (Shaw et al., 2006; Silk et al., 2011).

Importantly, the negative emotional climate evoked by maternal depression is likely to influence youths' cognitive representations of mothers. Specifically, cognitive representations, or schemas, of caregiving relationships are believed to emerge from prior interactions and to reflect generalized knowledge and expectancies that guide information processing (Main et al., 1985; Crittenden, 1990). Whereas a history of interactions with depressed mothers is apt to produce schemas in which negative mother-relevant information is processed more efficiently, a history of interactions with emotionally sensitive and available (non-depressed) mothers is apt to produce schemas in which positive mother-relevant information is processed more efficiently. In support of this hypothesis, research reveals that never-disordered daughters of depressed mothers selectively attend to negative emotional information while never-disordered daughters of never-disordered mothers selectively attend to positive emotional information (Joormann et al., 2007). Further, consistent with a differential susceptibility model, we anticipated that this pattern of effects would be observed in youth with high, but not low, levels of emotional reactivity to stress.

Less research has investigated how maternal anxiety influences emotional facets of the caregiving environment. Preliminary observational findings reveal that anxious mothers display less positive affect and engagement, and more criticism and withdrawal, than non-anxious mothers in interactions with their children (Whaley et al., 1999; Woodruff-Borden et al., 2002). Such similar parenting difficulties observed across depressed and anxious caregivers guide the proposal that these impairments may reflect mothers' generalized negative affect, a trait that characterizes both depression and anxiety (Lovejoy et al., 2000). However, theory also suggests that parenting styles may differ across depressed and anxious mothers due to the presence of disorder-specific cognitive styles (i.e., attentional bias to sadness in depression and attentional bias to threat in anxiety; Williams et al., 1997; Clark et al., 1999). Accordingly, we investigated whether a history of interactions with anxious mothers would produce comparable schemas to those anticipated in offspring of depressed mothers (i.e., more efficient processing of negative mother-relevant information) whereas a history of interactions with non-anxious mothers would produce comparable schemas to those anticipated in offspring of non-depressed mothers (i.e., more efficient processing of positive mother-relevant information). Again, we tested whether this pattern of effects was evident in youth with high, but not low, levels of emotional reactivity to stress.

STUDY OVERVIEW

The overarching goal of this study was to examine whether youths' emotional reactivity to stress determined the strength of the association between maternal psychopathology and biases in youths' cognitive processing of mother-relevant information. Moreover, we investigated whether this interactive effect was specific to (a) exposure to maternal depression versus anxiety, and (b) youths' reactivity to interpersonal versus non-interpersonal stress. Biases in the cognitive processing of mother-relevant information were assessed using a levels-of-processing (LOP) task (Rudolph et al., 1995), a behavioral paradigm designed to assess youths' cognitive schemas. Specifically, youth were unexpectedly prompted to recall a list of previously presented adjectives self-rated as descriptive of their mothers; cognitive bias was quantified as the relative recall of negative versus positive information. Maternal depression and anxiety were conceptualized along a continuum from no symptoms to diagnostic-level disorder.

METHODS

PARTICIPANTS

Participants were a subset of a larger sample of 4th–8th graders and their primary female caregivers (87.5% biological mothers;

2.1% stepmothers; 2.1% adoptive mothers; 8.3% other) involved in a longitudinal study examining youth development during the transition to adolescence. Youth were included based on the availability of relevant data. Specifically, the LOP task was administered to 102 of 167 youth (administration of this task was discontinued part way through the study due to time limitations). Of the 102 youth, six did not have either interpersonal or non-interpersonal emotional reactivity ratings, thereby yielding the present sample of 96 youth. Youth who had relevant data did not differ significantly from those who did not in terms of sex, $\chi^2(1; N = 167) = 1.16$, *ns*, age, $t_{(165)} = 0.69$, *ns*, ethnicity [white vs. minority; $\chi^2(1; N = 167) = 0.43$, *ns*], or income $t_{(160)} = 0.72$, *ns*. Participants ranged in age from 9 to 14 years (50 boys, 46 girls; M age = 12.36, SD = 1.05) and were somewhat diverse in ethnicity (76.0% White, 13.5% African-American, 10.5% other). Families represented a range of socioeconomic backgrounds (total annual family income was below $30,000 for 13% of the sample and above $75,000 for 18% of the sample).

PROCEDURES

Youth and their primary female caregivers participated in a laboratory assessment. Written consent was provided by caregivers and written assent was provided by youth. Youth completed a behavioral task assessing cognitive processing of mother-referent information. Trained graduate students, advanced undergraduate students, and a post BA-level research assistant administered the Youth Life Stress Interview (Rudolph and Flynn, 2007) to youth and caregivers. A clinical psychology faculty member and post-doctoral student, several psychology graduate students, and a post BA-level research assistant completed a semi-structured diagnostic interview assessing maternal depression and anxiety during the previous year. Both the life stress and diagnostic interviews include a set of standardized probes; supplemental questions are flexibly generated based on previous responses from individual participants to elicit more detailed information necessary for coding. Importantly, this interview method allows for the disqualification of inaccurate endorsements (i.e., elimination of false positives) and the development of additional queries when inaccurate declines are suspected (i.e., protection against false negatives), and maximizes the amount of relevant information obtained about the nature and occurrence of stressors and symptoms. Different interviewers administered the life stress and diagnostic interviews to prevent biases and preserve the objectivity of assigned ratings (for instance, prior knowledge of life stress may influence interpretations of symptoms of psychopathology, or prior knowledge of symptoms may influence interpretations of life stress). Caregivers received a monetary compensation and youth were given a gift certificate for their participation.

MEASURES

Cognitive bias

Youth completed a LOP task (Rudolph et al., 1995) to assess cognitive processing of mother-referent information. This task activated schemas about the mother by presenting youth with a series of interpersonally descriptive adjectives, half of which were positive (e.g., loving, fun, kind) and half of which were negative (e.g., mean, strict, unfair). Following the oral and written presentation of each word, youth were asked one of two randomized questions: (1) Does this word describe your mother? (i.e., mother-referent); or (2) Is this word in capital letters? (i.e., structural). After all adjectives were administered, youth were unexpectedly prompted to recall as many words as possible. Cognitive bias is reflected in enhanced recall of positively versus negatively valenced information.

The word list included 44 adjectives that reflected four categories of 11 words each: positive mother-referent, negative mother-referent, positive structural, and negative structural. To prevent bias due to primacy and recency effects on memory, the two first and last words, each of which represented one of the four categories, were excluded from analyses. Because of our interest in cognitive processing of mother-referent information, the present analyses focused on words encoded under the mother-referent probe and rated "yes" by youth (i.e., mother-referent words). Two scores were calculated: proportion of positive mother-referent words recalled (i.e., the number of recalled yes-rated positive mother-referent words divided by the total number of yes-rated positive mother-referent words) and proportion of negative mother-referent words recalled (i.e., the number of recalled yes-rated negative mother-referent words divided by the total number of yes-rated negative mother-referent words). Consistent with previous research (Rudolph et al., 1995), relative recall of negative versus positive mother-referent words was computed. Specifically, the proportion of yes-rated negative mother-referent words recalled was subtracted from the proportion of yes-rated positive mother-referent words recalled. Thus, higher scores reflect a more positive cognitive bias toward mother-referent information and lower scores reflect a more negative cognitive bias toward mother-referent information.

Converging lines of evidence support the validity of the LOP task. Specifically, children demonstrate greater recall of self-referent than structural or semantic words (Hammen and Zupan, 1984) and the content of children's self-schemas correlates with relevant constructs such as depressive symptoms (Hammen and Zupan, 1984; Zupan et al., 1987) and low self-esteem (Hammen and Zupan, 1984). Moreover, mother-referent LOP scores are associated with other assessments of cognitive schemas of mothers (Rudolph et al., 1995).

Maternal psychopathology

Interviewers administered the nonpatient version of the Structured Clinical Interview for DSM (SCID IV-NP; First et al., 1996) to assess caregivers' symptoms of depression and anxiety during the previous year. In consultation with a clinical psychology faculty member or post-doctoral student, ratings were assigned according to DSM-IV-TR (American Psychiatric Association, 2000) criteria on a 5-point scale: 0 = No symptoms, 1 = Mild symptoms, 2 = Moderate symptoms, 3 = Diagnosis with mild to moderate impairment, and 4 = Diagnosis with severe impairment. Ratings were assigned based on the number, severity, frequency, duration, and resulting impairment associated with symptoms of each type of depressive disorder (i.e., major depression, dysthymia, bipolar disorder, and depressive disorder not otherwise specified) and anxiety

disorder (i.e., generalized anxiety disorder, panic disorder, agoraphobia, social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, specific phobias, anxiety disorder not otherwise specified). Consistent with prior research (Davila et al., 1995; Rudolph et al., 2000, 2009; Hammen et al., 2004; Flynn and Rudolph, 2011), these ratings reflect multiple indicators and include both diagnosable episodes and subthreshold symptoms of depression and anxiety. Ratings were summed across episodes and within major categories of psychopathology to create separate continuous symptom summary scores for depression and anxiety. Thus, higher scores indicate a greater number or severity of symptoms within a single diagnostic category and/or the presence of symptoms from multiple diagnostic categories. This continuous scoring system coheres with findings from taxometric studies demonstrating that depression (Haslam, 2003; Fergusson et al., 2005; Hankin et al., 2005) and anxiety (Ruscio et al., 2001; Haslam, 2003; Kollman et al., 2006) are dimensional, as opposed to categorical, disorders.

Validity of the depression summary scores was established through a significant correlation with the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ; Clark and Watson, 1991; $r = 0.31, p < 0.01$). Validity of the anxiety summary scores was established through a significant correlation with the general distress anxiety subscale of the MASQ ($r = 0.24, p < 0.05$). These correlations are likely moderate given that the MASQ scores reflected only recent symptoms whereas the SCID ratings reflected past-year symptoms. Based on independent coding of audiotapes of 42 interviews, strong inter-rater reliability (one-way random-effects intraclass correlation coefficient [ICC]) was found for the depression ratings (ICC = 0.98) and the anxiety ratings (ICC = 0.97). Of the 96 caregivers, 16% met diagnostic criteria for a depressive disorder (a rating of three or four for at least one episode) during the prior year; an additional 15% experienced subclinical depressive symptoms (i.e., a rating of one or two for at least one episode). Thirty-eight percent met diagnostic criteria for an anxiety disorder during the prior year; an additional 28% experienced subclinical anxiety symptoms.

Emotional reactivity

Interviewers administered the Youth Life Stress Interview (Rudolph and Flynn, 2007), an adaptation of the Child Episodic Life Stress Interview (Rudolph and Hammen, 1999; Rudolph et al., 2000) separately to youth and caregivers. This semi-structured interview assesses the incidence and intensity of episodic stressors experienced by youth during the prior year using the contextual threat method (Brown and Harris, 1978). Following a general query probing exposure to any type of stressful experiences, a sequence of standardized questions was asked to determine the occurrence of episodic stressors in a variety of life domains (e.g., family, peer, and romantic relationships; academics; health). Events were categorized by a team of coders as interpersonal (events that involved a significant interaction between the youth and another person or that directly affected the relationship between the youth and another person) or non-interpersonal (all other events) (Cohen's $k = 0.92$ for classification of event content). Immediately following youths' report of each event, they provided ratings on a 5-point scale (1 = *Not at All* to 5 = *Very Much*) of the extent to which they felt sad, scared/worried/nervous, angry/mad, and guilty following the event. Average emotional reactivity scores were calculated separately for interpersonal and non-interpersonal events by taking the mean of all four emotion ratings across the relevant events.

RESULTS

PRELIMINARY CORRELATIONAL ANALYSES

All analyses were conducted using SPSS Statistics Version 19 software. **Table 1** presents descriptive information and correlations among the variables. Significant positive correlations were found between interpersonal and non-interpersonal emotional reactivity, and between maternal depression and anxiety. A marginally significant positive association was found between maternal depression and a negative cognitive bias.

EXAMINATION OF MODERATION

Two hierarchical multiple regression analyses were conducted to examine whether emotional reactivity moderated the association between maternal psychopathology and cognitive bias in the processing of mother-referent information. In each analysis, the mean-centered main effects of maternal psychopathology and emotional reactivity were entered in the first step, and the Maternal Psychopathology × Emotional Reactivity interactions were entered in the second step. Separate regressions tested the specificity of the interactive effects to interpersonal versus non-interpersonal emotional reactivity. Significant interactions were interpreted by solving the unstandardized regression equations to predict cognitive bias from maternal psychopathology at high (one standard deviation above the mean), medium (mean), and low (one standard deviation below the mean) levels of emotional reactivity (Aiken and West, 1991).

Table 1 | Descriptive information and intercorrelations among the variables.

Measure	*M*	(SD)	1	2	3	4	5
Cognitive bias	0.07	(0.32)	–				
Interpersonal emotional reactivity	2.10	(0.73)	−0.03	–			
Non-interpersonal emotional reactivity	2.02	(0.72)	−0.02	0.48**	–		
Maternal depression	0.89	(1.54)	−0.18*	0.03	0.02	–	
Maternal anxiety	3.21	(3.49)	−0.05	0.07	0.10	0.30**	–

*$p < 0.10$; **$p < 0.01$.

Results from the first regression revealed a marginally significant negative main effect of maternal depression, and nonsignificant main effects of maternal anxiety and interpersonal emotional reactivity. Examination of the interaction terms revealed that interpersonal emotional reactivity moderated the effect of maternal depression, but not maternal anxiety, on cognitive bias (**Table 2**, Regression 1). Decomposition of this interaction revealed that maternal depression was significantly negatively associated with cognitive bias (higher scores reflect more positivity) in youth exhibiting high ($\beta = -0.52$, $t_{(82)} = -3.21$, $p < 0.01$) and average ($\beta = -0.23$, $t_{(82)} = -2.05$, $p < 0.05$), but not low ($\beta = 0.06$, $t_{(82)} = 0.39$, *ns*), levels of interpersonal emotional reactivity (**Figure 1**). At high levels of maternal depression, youth with high interpersonal emotional reactivity showed negative cognitive biases 0.65 SDs stronger than youth with low interpersonal emotional reactivity. At low levels of maternal depression, youth with high interpersonal emotional reactivity showed positive cognitive biases 0.48 SDs stronger than youth with low interpersonal emotional reactivity.

Results from the second regression revealed nonsignificant main effects of maternal depression, maternal anxiety, and non-interpersonal emotional reactivity on youths' cognitive bias. Further, non-interpersonal emotional reactivity did not moderate the effect of maternal depression or maternal anxiety on cognitive bias.

Table 2 | Predicting cognitive bias in processing of mother-relevant information.

	Predictors	*B*	*t*
REGRESSION 1			
Step 1	Maternal depression	−0.22	−1.91*
	Maternal anxiety	0.04	0.33
	Interpersonal emotional reactivity (ER)	−0.03	−0.24
Step 2	Maternal depression × Interpersonal ER	−0.26	−2.19**
	Maternal anxiety × Interpersonal ER	−0.02	−0.15
REGRESSION 2			
Step 1	Maternal depression	−0.16	−1.39
	Maternal anxiety	−0.01	−0.05
	Non-interpersonal emotional reactivity (ER)	−0.02	−0.17
Step 2	Maternal depression × Non-interpersonal ER	0.19	1.67
	Maternal anxiety × Non-interpersonal ER	−0.09	−0.79

*$p < 0.10$; **$p < 0.05$.

DISCUSSION

Findings from this research support a novel integrated emotion-cognition differential susceptibility model in which youths' sensitivity to context predicted a more adverse developmental outcome in the presence of a low quality caregiving environment but a more beneficial developmental outcome in the presence of a high quality caregiving environment during early adolescence. Specifically, whereas exposure to maternal depression predicted a stronger *negative* bias during cognitive processing of mother-relevant information in youth exhibiting high and average levels of interpersonal emotional reactivity, youth with heightened interpersonal emotional reactivity showed a stronger *positive* cognitive bias at low levels of maternal depression. In contrast, maternal depression did not predict cognitive bias in youth exhibiting low levels of interpersonal emotional reactivity. Notably, this interactive effect was specific to interpersonal (but not non-interpersonal) emotional reactivity and to maternal depression (but not anxiety).

Emotional reactivity as assessed in this research reflects youths' negative emotional reactions (i.e., sadness, anxiety, anger, guilt) to a comprehensive array of naturally occurring stressors experienced during the prior year. Importantly, youth who display more emotional reactivity in response to stress signal their distress to others. In the context of emotionally sensitive and available (non-depressed) mothers, the expression of

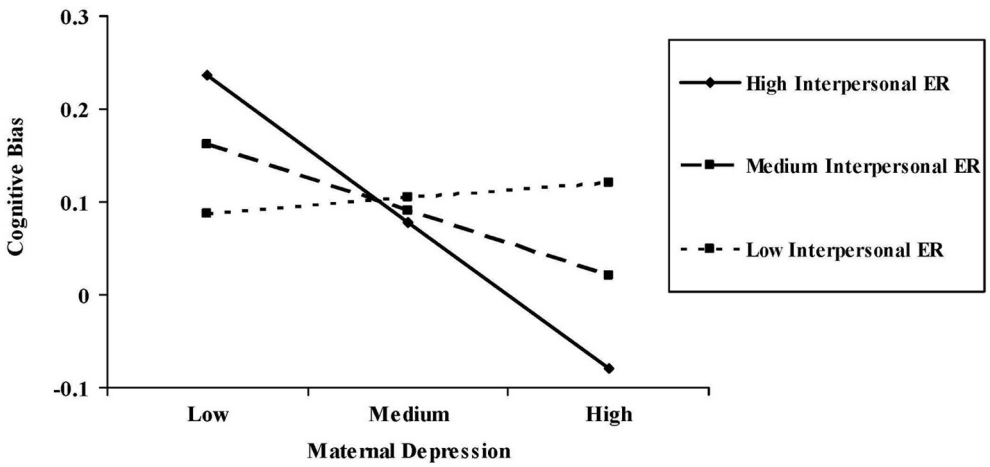

FIGURE 1 | Interaction between maternal depression and interpersonal emotional reactivity predicting youths' cognitive bias during the processing of mother-relevant information. Negative scores on the *y*-axis indicate greater negative cognitive bias; positive scores on the *y*-axis indicate greater positive cognitive bias.

heightened emotional distress likely prompts mothers to engage youth in adaptive emotion regulatory and coping processes. Consequently, offspring of mothers with low levels of depression might attend to, encode, or recall interactions with mothers in a more positive manner. Conversely, depressed mothers may experience difficulty identifying and implementing effective strategies to help highly emotionally reactive youth relieve distress. In turn, offspring of depressed mothers might attend to, encode, or recall interactions with mothers in a more negative manner.

The specificity of these results to maternal depression, but not anxiety, is consistent with intergenerational models of depression transmission. Specifically, beyond the direct expression of depressive symptoms, such as anhedonia, irritability, and fatigue, depression is uniquely accompanied by a cognitive style characterized by maladaptive self-perceptions and internal, stable, and global attributions about negative events (Beck, 1967; Abramson et al., 1989). Research suggests that depressed mothers transmit this excessive emotional and cognitive negativity to offspring through their parenting behaviors (for a review, see Goodman and Gotlib, 1999), thereby transferring markers of depression risk, including attentional biases toward negative emotional information (Joormann et al., 2007), to youth. In fact, whereas non-depressed youth show a positive cognitive bias when recalling mother-referent adjectives on the LOP, youth with elevated depressive symptoms do not (Rudolph et al., 1997). Moreover, when jointly examined, depression (but not anxiety) predicts greater relative negativity during children's cognitive processing of mother-relevant information (Rudolph et al., 1997). Together with the present results, these findings suggest that negatively biased information processing may reflect one mechanism contributing to the intergenerational transmission of depression.

Additionally, maternal depression interacted with youths' emotional reactivity to interpersonal, but not non-interpersonal, stress to predict biases in youths' cognitive processing. This finding coheres with theory (e.g., Coyne, 1976; Hammen, 1991) and research (e.g., Rudolph et al., 2009; Flynn and Rudolph, 2011) emphasizing the specific role of interpersonal stress in depression onset and continuity. Heightened emotional reactivity likely perpetuates dysregulated interpersonal stress responses and interferes with the formulation of adaptive coping, particularly when mothers are unable to redirect youth toward efficacious reactions. Difficulty resolving interpersonal stress may cause youth to negatively process information about relationships, perhaps intensifying interpersonal discord and generating risk for depression. In contrast, emotionally sensitive mothers may recognize youths' maladaptive reactivity to interpersonal stress and implement strategies to facilitate constructive coping responses. Accordingly, youth who successfully negotiate interpersonal disturbances may positively process information about relationships and experience protection against depression.

STRENGTHS, LIMITATIONS, AND CONCLUSIONS

Overall, this research represents a novel investigation of emotion-cognition linkages framed within a differential susceptibility model, and includes several methodological strengths. First, use of a behavioral paradigm to index cognitive processing eliminated distortion due to response biases such as social desirability, which may occur when informants select responses that will be viewed favorably by others (e.g., the endorsement of positive but not negative maternal attributes). Second, emotional reactivity was assessed in response to naturally occurring events, thereby minimizing confounds associated with estimating reactions to hypothetical stressors. Finally, the administration of semi-structured diagnostic interviews provided a comprehensive and refined assessment of maternal psychopathology.

In spite of these strengths, several limitations are worth noting. First, maternal psychopathology served as a proxy for the emotional quality of caregiving experiences; it would be helpful in future research to assess specific parenting behaviors during mother-child interactions (e.g., maternal sensitivity) that may shape youths' cognitive processing. Second, the study included a relatively small sample of youth, in which only a subset of caregivers experienced diagnoses or subclinical symptoms of psychopathology. Thus, future research will need to replicate these findings in a large, ethnically diverse sample of youth as well as in samples of caregivers with diagnostic levels of psychopathology. Third, our emotional reactivity index reflected the experience of negative emotionality in response to stress. Although this index is consistent with the construct of difficult temperament, which is the focus of theory and research on differential susceptibility, it is unclear whether the cognitive benefits accrued to youth with high emotional reactivity resulted from non-depressed mothers' ability to react in an emotionally supportive manner when youth are stressed or whether the same youth also displayed heightened positive emotionality in response to support, thereby resulting in positive cognitive biases. Finally, this study specifically examined cognitive biases during the processing of mother-referent information, and it remains to be determined whether results generalize to youths' cognitive processing of other relationships (e.g., peers, siblings) or non-interpersonal domains (e.g., academics, health).

In sum, these findings illuminate one personal characteristic of youth that shapes emotion-cognition linkages during early adolescence, and reveal trade-offs of emotional reactivity for cognitive processing such that both enhancing *and* impairing effects emerge as a function of socialization environment. That is, in the context of maternal depression, youths' heightened emotional arousal and distress may impair cognition by generating a perseverative focus on negative features of the environment, including information about emotionally insensitive or unavailable caregivers. In contrast, in parenting contexts characterized by low maternal depression (and, perhaps, accompanying warmth and sensitivity), youths' emotional reactivity may enhance cognition by allowing youth to interpret caregiving interactions in a positive light. Given that negative cognitive biases represent a risk factor for depression, these findings implicate youths' emotional reactivity and maternal depression as joint targets of intervention and prevention endeavors. Overall, this research emphasizes the importance of considering integrative, developmentally sensitive perspectives of the complex interplay between emotion and cognition, which may involve mutually enhancing or impairing

associations, particularly as emotion-cognition linkages pertain to the onset and maintenance of psychopathology across the lifespan.

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From emotions to consciousness – a neuro-phenomenal and neuro-relational approach

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The James–Lange theory considers emotional feelings as perceptions of physiological body changes. This approach has recently resurfaced and modified in both neuroscientific and philosophical concepts of embodiment of emotional feelings. In addition to the body, the role of the environment in emotional feeling needs to be considered. I here claim that the environment has not merely an indirect and instrumental, i.e., modulatory role on emotional feelings via the body and its sensorimotor and vegetative functions. Instead, the environment may have a direct and non-instrumental, i.e., constitutional role in emotional feelings. This implies that the environment itself is constitutive of emotional feeling rather than the bodily representation of the environment. I call this the relational concept of emotional feeling. The present paper discusses recent data from neuroimaging that investigate emotions in relation to interoceptive processing and the brain's intrinsic activity. These data show the intrinsic linkage of interoceptive stimulus processing to both exteroceptive stimuli and the brain's intrinsic activity. This is possible only if the differences between intrinsic activity and intero- and exteroceptive stimuli is encoded into neural activity. Such relational coding makes possible the assignment of subjective and affective features to the otherwise objective and non-affective stimulus. I therefore consider emotions to be intrinsically affective and subjective as it is manifest in emotional feelings. The relational approach thus goes together with what may be described as neuro-phenomenal approach. Such neuro-phenomenal approach does not only inform emotions and emotional feeling but is also highly relevant to better understand the neuronal mechanisms underlying consciousness in general.

Keywords: consciousness, emotion, emotional feeling, insula, James–Lange theory

INTRODUCTION

The well-known James–Lange theory determined feelings as perceptions of physiological body changes in the autonomic, hormonal, and motor systems. Once we become aware of physiological bodily changes induced by danger, we feel fear and subjectively experience emotional feelings. James (1884, p. 190) consequently considered bodily changes as central to emotional feelings; "we feel sorry because we cry, angry because we strike, afraid because we tremble, and not that we cry, strike, or tremble, because we are sorry, angry, or fearful, as the case may be." Modern empirical versions of this theory resurface in current neuroscientific models of emotion as, for instance, in Damasio and others (Damasio, 1999, 2010; Craig, 2003, 2004, 2005, 2009, 2011; Bechara, 2004; Niedenthal, 2007).

Conceptually, the embodied approach to emotion emphasizes the crucial role of the body in emotional feeling. If the body and its vegetative and sensorimotor function play a crucial role in constituting emotional feelings, the body can no longer be considered in a merely objective way but rather as subjective and experienced – the mere Koerper as objective body must be distinguished from the lived body as subjectively experienced body in emotional feeling (Colombetti and Thompson, 2005, 2007; Colombetti, 2008)[1].

The emphasis on the body raises the question for the role of the environment in constituting emotional feelings. The body stands in direct contact with the environment via its sensorimotor functions which are emphasized in recent body-based, e.g., embodied concepts of emotional feelings (see Niedenthal et al., 2005; Niedenthal, 2007). The body is supposed to represent the environment in sensorimotor terms and it is these bodily representations that are considered crucial in constituting emotional feelings. The environment may have then an indirect and modulatory role via the body in the constitution of the emotional feelings.

One could also imagine that the environment has a direct and constitutive role in emotional feeling; the environment may then

[1]It should also be pointed out that feelings cannot be considered to be conscious perceptions of the neural activity in those brain regions that induce emotion as for instance LeDoux assumes. We cannot become conscious of neural activity in the first-order emotion regions (see also Bennett and Hacker, 2003, 208) since we remain principally unable to perceive our brain's neural activity as such which I recently called "autoepistemic limitation" (Northoff, 2004; Northoff and Musholt, 2006, see chapter 1 and 2 in Northoff, 2011).

directly constitute emotional feeling independent of the body's sensorimotor (and vegetative) functions. In this case, emotional feelings should be constituted directly by the respective person's and its brain's relation to the social environment (see below for definition) rather than indirectly via bodily representations. Since the person-environment relation is crucial here, I call such approach the relational concept of emotional feeling (see Northoff, 2004 for a general outline of such relational approach and Ben-Ze'ev, 1993 for the characterization of perception as relational).

The general aim of the present paper is to review recent human imaging data on emotional feelings in relation to both interoceptive processing and the brain's intrinsic activity. This will be accompanied by discussing the empirical and conceptual implications of these data which I assume to favor a relational approach to emotions. Such relational concept characterizes emotions and emotional feeling to be intrinsically affective and subjective. Neuronally I assume this to be related to the interaction of the stimuli with the brain's intrinsic activity, i.e., rest-stimulus interaction (see below for definition). Finally, the empirical and conceptual implications of such relational approach to emotions for consciousness are pointed out.

EMPIRICAL DATA: INTEROCEPTION AND EMOTIONAL FEELING

BRAIN IMAGING OF INTEROCEPTIVE AWARENESS

Recent imaging studies using fMRI investigated neural activity during interoceptive stimulus processing like evocation of blood pressure changes during isometric and mental tasks, heart beat changes and perception, anticipatory skin conductance during gambling, and heart rate modulation during presentation of emotional faces (Critchley, 2005 for a review, Craig, 2002, 2003, 2004, 2009, 2011; Pollatos et al., 2007a,b). These studies observed neural activity changes in the right insula, the anterior cingulate cortex extending from supragenual to dorsal regions (SACC/DACC), and the amygdala. This led to the assumption that specifically the right insula and the SACC/DACC integrally represent autonomic and visceral responses that are transferred from the spinal cord through the midbrain, the hypothalamus, and the thalamocortical pathway to the right insular cortex (Craig, 2002, 2003, 2004, 2009; Critchley, 2005). Based on these results, these regions are assumed to be involved in re-presenting the autonomic and visceral state of the body and thus interoceptive processing. Craig (2002, 2003, 2004, 2009, 2010, 2011) assumes specifically the right insula to be crucially involved which receives autonomic and visceral afferences from lower centers (see above) and re-represents the interoceptive body state in an integrated way. This allows the insula to give rise of a "mental image of one's physical state" which, according to Craig, provides the basis for subjective awareness of emotional feeling and one's self as "material me."

See **Figure A1** in Appendix for the different regions, and Glossarium for the terms.

If these regions mediate interoceptive processing, the question for their role in the subjective experience of bodily and thus interoceptive changes as the basis for emotional feeling arises. Critchley et al. (2004) led subjects evaluate whether the own heart beat was synchronous or asynchronous with an auditory feedback note which allowed to compare interoceptive- and exteroceptive-directed attention. Interoceptive attention to the own heartbeat increased activity in the right insula (and the SACC/DACC and the somatomotor cortex) while exteroceptive attention to the tone suppressed activity in the very same region. Activity in the right insula also correlated with both the performance in the heartbeat detection task and subjective anxiety symptoms which also correlated with each other. These findings suggest close relationship between interoceptive awareness and emotional feeling.

Other studies demonstrated the modulation of these interoceptive stimulus changes by exteroceptive stimuli. Using fMRI, Critchley (2005), for instance, investigated regional neural activity changes during presentation of happy, sad, angry, and disgusted faces. They observed heart rate changes to be dependent upon the emotional category with sad and angry faces inducing the strongest heart rate changes. Emotional face-responsive regions like the right (and left) insula, the SACC/DACC, the midbrain/brain stem, and the right amygdala were also found to be correlating with the changes in heart rate magnitude. These results indicate that different emotions may be mediated by differential interoceptive response patterns which may be mediated by neural activity in the right insula, the SACC/DACC, the midbrain/brain stem, and the amygdala. According to the authors themselves, these results provide support for the hypothesis that interoceptive stimulus processing may be involved in differentiating between different types of emotional feelings.

The group around Pollatos conducted a series of studies on heartbeat perception and emotional feeling. Pollatos et al. (2007a) investigated attention toward heartbeats and cardiovascular arousal; regions implicated in both conditions included the right insula, the somatomotor cortex, the SACC/DACC, and the dorsomedial prefrontal cortex (DMPFC). They observed activity in the right insula and the DACC to be correlating with the degree of interoceptive awareness while negative feelings correlated with the BOLD response of the interoceptive awareness condition in the DACC and DMPFC. Using EEG, they distinguished between good and poor heartbeat perceivers. Good heartbeat perceivers (Pollatos et al., 2005, 2007a,b) showed higher arousal ratings as well as higher P300 amplitudes and slow-wave latency ranges than poor heartbeat perceivers during presentation of emotional pictures.

Taken together, these studies show behaviorally a close relationship between interoceptive awareness, arousal, and emotional feeling. While neuroanatomically, they confirm the involvement of the right insula, the SACC/DACC, and the DMPFC in mediating the relationship between interoceptive awareness and emotional feeling.

INTEROCEPTIVE AND EXTEROCEPTIVE AWARENESS

The question is whether the above described data support an embodied concept of emotional feeling with exteroceptive stimuli being merely modulatory and instrumental or epiphenomenal. Or whether the data might be interpreted rather in favor of a relational concept of feelings with interoceptive stimuli in relation to exteroceptive stimuli being constitutive and thus central. Presupposing the James–Lange theory, most of the above cited authors have interpreted their data in favor of the interoceptive-based concept. However, I will argue that there are strong arguments which make

the data rather compatible with what I call the intero-exteroceptive relational concept of emotional feeling. I argue that there seems to be a mismatch between empirical data and their interpretation in current imaging studies on emotional feelings and interoceptive processing which I want to support by making the three following points.

First, all paradigms employed did not investigate interoceptive stimuli in isolation from exteroceptive stimuli but rather in relation to them. Critchley et al. (2004), for instance, investigated heart beat perception in relation to auditory tones as exteroceptive stimuli while Pollatos et al. (2005, 2007a,b) directly compared both conditions with each other. Neural activity changes assumed to be specific for interoceptive awareness thus reflect a relation or dynamic balance between intero- and exteroceptive processing rather than mirroring isolated interoceptive stimulus processing remaining (more or less) independent of exteroceptive stimulus processing. Dynamic modulation of the right insula activity as observed by Critchley may thus reflect a dynamic balance between intero- and exteroceptive attention in the heartbeat-auditory tone detection task rather than pure interoceptive heartbeat stimulus processing. Such intero-exteroceptive relational concept would thus assume that the above mentioned regions like the right insula, the SACC/DACC, and the DMPFC are rather responsive to changes in intero-exteroceptive balance than to isolated interoceptive changes remaining independent of exteroceptive changes.

Second, neither of the above mentioned studies addressed the question of emotional valence that indicates whether a feeling is positive or negative (see also Colombetti, 2005 for a discussion of the concept of emotional valence). Pollatos et al. (2005, 2007b) did not observe any significant difference between good and poor heartbeat perceivers in terms of their emotional valence ratings while both groups did differ in emotional arousal. Interoceptive awareness may thus be linked to emotional arousal and subjective experience of emotional intensity while it apparently does not seem to determine the valence of the emotional feeling. Regions that have been associated with emotional valence, as distinguished from emotional arousal, include the medial orbitofrontal cortex (MOFC), the subgenual and pregenual anterior cingulate cortex (PACC), and the ventromedial prefrontal cortex (VMPFC; Craig, 2002, 2009; Phan et al., 2002; Critchley, 2005; Kringelbach, 2005; Grimm et al., 2006).

Interestingly, these regions are densely and reciprocally connected with the right insula, the SACC/DACC, and the DMPFC that are supposed to represent the body's interoceptive state (Ongur and Price, 2000). The connectivity pattern thus argues strongly in favor of the intero-exteroceptive relational concept of emotional feeling which seems to make isolated interoceptive processing and thus an interoceptive-based concept of emotional feeling rather unlikely. What however is needed to further support this point are investigations of both regional activity and connectivity patterns during intero- and exteroceptive stimulus processing (see Hurliman et al., 2005 for some first support).

Third, Pollatos et al. (2005, 2007b) investigated the temporal course with EEG during heartbeat perception task. They observed that good heartbeat perceivers showed higher heart-evoked potentials and stronger dipole strength in cortical sources that included the SACC/DACC, the right insula, the DMPFC, and the secondary somatosenory cortex when compared to poor heartbeat perceivers. Interestingly, they also observed the dipole sources in the SACC/DACC and DMPFC to occur earlier (around 280 ms) than the ones in the insula and the somatosensory cortex (around 370 ms). A similar temporal distribution is suggested by Tsuchiya and Adolphs (2007) who assume involvement of subcortical regions like brain stem nuclei and hypothalamus that mediate interoceptive stimuli to occur after and later than activation in higher regions like the DMPFC. If the interoceptive-based model were true, one would rather expect the opposite temporal pattern with early insula and somatosensory involvement and late SACC/DACC and DMPFC involvement.

Late SACC/DACC and DMPFC involvement may then reflect some abstract internal cognitive evaluation of interoceptive stimulus processing with consecutive top-down modulation of interoceptive brain regions as interpreted by advocates of the interoceptive-based concept (Craig, 2002, 2009; Tsuchiya and Adolphs, 2007). What is the role of the SACC/DACC and the DMPFC? These higher cortical regions have been associated with processing of higher-order exteroceptive stimuli particularly those that are highly self-related to the organism (Northoff and Bermpohl, 2004; Northoff et al., 2006).

The fact that these regions are apparently implicated from early on in interoceptive awareness gives some though indirect support to the assumption that exteroceptive stimuli are involved early in interoceptive processing. Such early involvement indicates that the role of exteroceptive stimulus processing goes beyond mere modulation of interoceptive processing which would be better compatible with late involvement. In other terms, early involvement of these regions may indicate that interoceptive stimulus processing is coded in relation to exteroceptive stimuli going beyond mere modulation of the former by the latter. The observed early spatio-temporal pattern may thus reflect neural coding of the relationship between intero- and exteroceptive stimulus processing, i.e., their actual balance. Otherwise there would be no need for regions predominantly associated with exteroceptive stimulus processing to be implicated so early. While it seems to be less compatible with the assumption of primarily independent interoceptive processing that becomes secondarily modulated by exteroceptive stimuli.

Finally, direct empirical support for intero-exteroceptive convergence comes from a recent study by Farb et al. (2012). He investigated interoceptive awareness (i.e., attention to breathing rate) and exteroceptive awareness (i.e., visual attention) in the same subjects. While both intero- and exteroceptive awareness yielded dissociable networks (i.e., visual cortex and posterior insula), they overlapped in especially the anterior insula. Unlike the posterior insula that responded strongly to interoceptive awareness, the anterior insula activity was as much predicted by exteroceptive awareness as interoceptive awareness. Hence, there seems to be intero-exteroceptive convergence in especially the anterior insula with both being integrated in the middle insula as bridge from posterior to anterior parts of the insula.

EMPIRICAL IMPLICATIONS: CONNECTIVITY AND CODING

ANATOMICAL CONNECTIVITY AND INTERO-EXTEROCEPTIVE CONVERGENCE

The MOFC and the VMPFC have been demonstrated to be implicated in interoceptive processing. Using biofeedback arousal and relaxation tasks in fMRI, Nagai et al. (2004) demonstrated that resting state activity in the VMPFC and MOFC co-varied with the basal level of sympathetic skin conductance. While regions like the SACC/DACC, the insula, and the hypothalamus were related to the rate of change in skin conductance. The level of neural activity in VMPFC and MOFC, which are part of the so-called anterior cortical midline structures (aCMS), may thus represent the basal sympathetic or autonomic tone independent of some actual stimuli. Since the aCMS have been shown to be modulated also by exteroceptive stimuli, neural activity within these regions may mirror a dynamic balance between attention to extero- and interoceptive stimuli (see also Nagai et al., 2004). This assumption is well compatible with the connectivity pattern of these regions.

The MOFC and VMPFC as the entrance door to the aCMS receive connections from all regions associated with primary and/or secondary exteroceptive sensory modalities (olfactory, gustatory, somatosensory, auditory, and visual; see Rolls et al., 1999; Barbas, 2000; Rolls, 2000; Damasio, 2003, 2010; Kringelbach and Rolls, 2004). The aCMS are also densely connected to regions (insula, hypothalamus, and nuclei in the brain stem as such PAG, colliculi, etc.) processing interoceptive sensory signals; these include the proprioceptive and vestibular senses, the visceral sense, and the sense of the interoceptive milieu which can be taken together with that of pain and temperature (Carmichael and Price, 1996; Price, 1999; Rolls et al., 1999; Rolls, 2000; Damasio, 2003, 2010; Barbas, 2004; Kringelbach and Rolls, 2004). The aCMS, especially the MOFC, VMPFC and SACC/DACC, are also connected to regions associated with distinct functional domains including motor (premotor and motor cortex, basal ganglia), cognitive (lateral prefrontal cortex), and emotional (amygdala, brain stem) domains (Carmichael and Price, 1996; Rolls et al., 1999; Barbas, 2000; Ongur and Price, 2000; Rolls, 2000; Kringelbach and Rolls, 2004). Due to such extensive intero- and exteroceptive connections, the MOFC and VMPFC (and, in conjunction with the amygdala) can be characterized as polymodal convergence zone (Rolls et al., 1999; Rolls, 2000; LeDoux, 2002; Schore, 2003).

This connectivity pattern predisposes the aCMS for neural processing irrespective of the sensory modality of the respective stimulus, i.e., supramodal processing. The assumption of supramodal processing in aCMS is supported by results from imaging studies. Emotions in either exteroceptive modality (visual, auditory, gustatory, olfactory) induce neural activity in various regions of the aCMS (see above as well as Phan et al., 2002; Northoff and Bermpohl, 2004). Moreover, processing of interoceptive stimuli induces also activation in aCMS regions like MOFC, VMPFC, and ACC (Craig, 2002, 2003, 2004, 2009; Wicker et al., 2003; Critchley et al., 2004; Nagai et al., 2004). Finally, stimuli from different origins, i.e., of different sensory modalities or of different functional domains (motor, emotional, cognitive, and sensory) induced analogous activation in aCMS (Northoff and Bermpohl, 2004; Northoff et al., 2006).

Taken together, both connectivity pattern and imaging data suggest that neural processing in aCMS is supramodal and domain-independent: what apparently matters for inducing neural activity in the aCMS is not so much the modality or domain, i.e., the origin of the stimulus, as either intero- or exteroceptive or cognitive, motor, sensory, or emotional. Instead it is important how the neural activity in the aCMS is related to the respective intero- or exteroceptive stimulus (see below for further discussion).

In addition to the aCMS, subcortical midline regions like the periaquaeductal gray (PAG), the colliculi, the dorsomedial thalamus, and the ventral striatum may also be considered in processing interoceptive stimuli in relation to exteroceptive ones. Panksepp (1998; and also Damasio, 1999, 2010), for instance, assumes that these regions are crucial in constituting emotional feelings. Since the very same regions are also characterized by strong motor connections both afferent and efferent, he and others like Ellis (2005; unlike Damasio who assumes a sensory-based view of feelings) assume emotional feeling to be motor-based. This is well compatible with Panksepp's characterization of emotional feeling as reaching-out to the environment thus reflecting what I called the relational concept of emotional feeling.

Unfortunately, subcortical regions have often been neglected in imaging studies of emotions which, at least in part, may be due to the fact that neural activity in these regions is rather difficult to reliably visualize in current imaging techniques like fMRI. However, animal experiments demonstrate the crucial role of these subcortical midline regions in constituting emotional feelings (Panksepp, 1998, 2005). Future studies in humans are thus needed to investigate subcortical neural activity during emotional feeling in order to bridge the current gap between animals and humans. Furthermore, the relationship between emotional feeling and motor function also needs to be investigated in detail by, for instance, investigating emotional feeling in dependence on variation of motor function and its neural underpinnings (and vice versa).

TRANSLATIONAL VERSUS RELATIONAL CODING

What is the implicit presupposition that drives most of the above cited authors to interpret their data in favor of the James–Lange theory? They seem to presuppose a clear-cut distinction between intero- and exteroceptive stimulus processing with both systems being separate, distinct, and only interacting at specific node points. According to such view, exteroceptive stimuli are translated into interoceptive stimulus processing whose perception, in turn, is supposed to induce feeling. Exteroceptive stimuli thus have at best an only indirect and mediated impact on emotional feeling in that they must first be translated into interoceptive stimulus processing before they can modulate feelings. I therefore call this model the interoceptive-based translational concept of feeling. Since exteroceptive stimuli have only an indirect and mediated, the interoceptive-based translational concept attributes no constitutive role of exteroceptive stimuli and the environment thus presupposing an "embodied" concept of emotional feeling.

However, anatomical connectivity suggests otherwise. Throughout the brain at all levels both subcortical and cortical and especially in the subcortical-cortical midline system there is

convergence between intero- and exteroceptive inputs. This is especially true for regions like the colliculi, the PAG, the tectum, and the aCMS where both intero- and exteroceptive afferences converge onto common neurons (see Panksepp, 1998, 2005; Rolls et al., 1999). This suggests that interoceptive stimuli are not only modulated by exteroceptive stimuli at specific node points but rather that the relation, e.g., the degree of convergence and divergence, between intero- and exteroceptive stimuli is coded in neural activity in the subcortical-cortical midline regions. Exteroceptive stimuli are not translated into interoceptive stimulus processing but rather directly and unmediated related to them and it is this relation that seems to be coded in neural activity. I therefore call this model the intero-exteroceptive-based relational concept of feelings (see also **Figure 1**).

Is there any empirical evidence in favor of the intero-exteroceptive relational model of neural coding? Critchley (2005, p. 162), one of the main investigators of interoceptive processing in imaging, states, that the "right insula maps bodily arousal states" and "it does so contextually" which therefore "represents an integration of external emotional information with peripheral states of arousal" (Critchley, 2005, p. 759). What seems to be coded in the brain is not so much the interoceptive stimulus itself but its relation to the respective exteroceptive stimulus. If neural activity codes the actual relationship and balance between intero- and exteroceptive stimuli, one would expect strong contextual dependence of emotional feelings.

The constitution of the emotional feeling, the type of feeling, should then depend on the respective emotional context which implies that different contexts may lead to different types of emotional feelings even in identical situations. In other terms, the environmental context does not only modulate emotional feelings but actively participates in constituting emotional feelings. This is well in accordance with the Schacter/Singer experiments where different contexts resulted in different types of emotional feelings. If the role of the context were merely modulatory, subjects would not have shown completely different and opposing emotional feelings in the two situations but rather variants of the same feeling. These experiments thus lend further support to the assumption of a constitutive role of the environmental context in emotional feelings (rather than remaining merely modulatory).

How are intero- and exteroceptive stimuli related and balanced with each other in relational coding? Rather than coding the intero- or exteroceptive stimulus itself, the degree of correspondence between intero- and exteroceptive stimuli is coded. If, for instance a lion approaches, the heart rate may increase, which may signal strong correspondence and convergence between intero- and exteroceptive stimuli. This consecutively leads to the constitution of a corresponding emotional feeling, the feeling of fright and anxiety. If, in contrast, the approach of the lion is not accompanied by heart rate increases, as for instance if one is not clear whether the lion is real or not, there may be a mismatch between intero- and exteroceptive stimuli. This may result in a different emotional feeling, the feeling of doubt and hesitation. The degree of convergence and divergence between intero- and exteroceptive stimuli may thus determine the kind of emotional feeling. That is well in accordance with the relational concept rather than with the translational one that claims for an interoceptive- and thus bodily based approach.

Taken together, I assume that our brain's design is such that there is no way for interoceptive stimuli other than to be processed in relation to exteroceptive stimuli and vice versa.

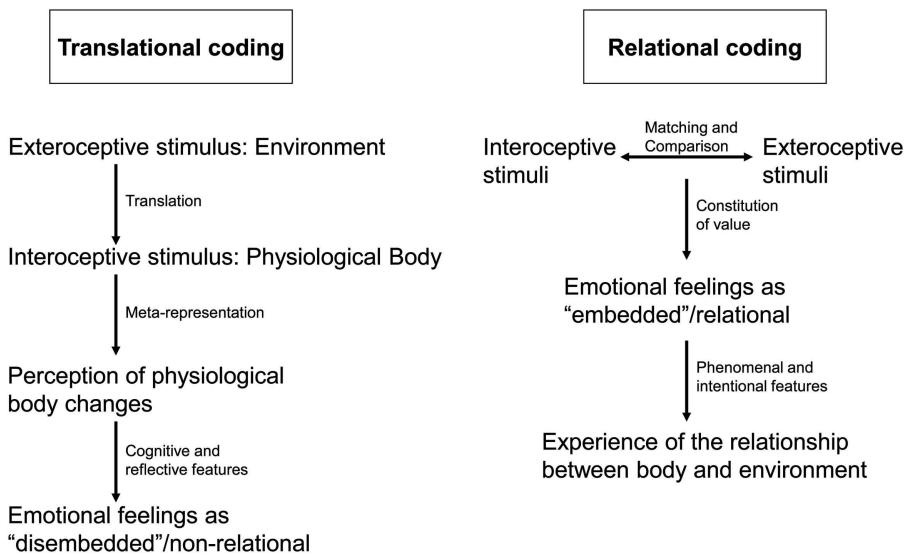

FIGURE 1 | The figure compares two different ways of neural coding in emotional feeling. On the left side translational coding describes how intero- and exteroceptive stimuli are separately represented and meta-represented in the neural activity of the brain. This meta-representation is then perceived which following Damasio and the James–Lange theory leads to emotional feelings. This is different in relational coding on the right side. Here intero- and exteroceptive stimuli are coded in relation to each other with this relation resulting in emotional feeling and subsequent experience of the relationship between body and environment.

Interoceptive stimulus processing remaining isolated, unrelated and independent from exteroceptive stimulus processing is consequently assumed to remain (principally) impossible. This implies what I call intero-exteroceptive relational coding while it excludes interoceptive-based translational coding. What does this imply in experimental regard? The experimental efforts to isolate interoceptive stimulus processing and to search for its specific neural correlates may be futile since exteroceptive stimulus processing may always already be implicated in interoceptive stimulus processing. One may better focus on experimentally investigating different intero-exteroceptive stimulus configurations and thus different constellations between body and environment as nicely demonstrated in the Schacter/Singer experiments (see Northoff, 2012a for more details on the question of neural coding).

CONCEPTUAL IMPLICATIONS: RELATIONAL APPROACH TO EMOTIONAL FEELING

RELATIONAL CONCEPT OF EMOTIONAL FEELING

The philosopher Hurley (1998, pp. 10, 341–342, 362–364) distinguishes between instrumental and non-instrumental dependence (see also Colombetti, 2008 who also applies this distinction) with regard to the relationship between input and output in perceptual content. If the relationship between input and output is indirect and thus merely instrumental, changes in perceptual content are dependent upon changes in the input. Every change in motor output has to modulate sensory input in order to have an impact on perceptual content implying that the output can not change independently of the input: "This kind of dependence of perceptual content on output is merely instrumental. It operates via changes in input; changes in output are a means to changes in input" (Hurley, 1998, p. 10).

What does this mean with regard to emotional feelings and their relation to the environment? Presupposing instrumental dependence, the environment can impact emotional feelings only indirectly via the body, i.e., by being represented either in the body's sensorimotor (and vegetative) functions or in those brain regions that register the body's sensorimotor (and vegetative) functions. The latter approach is, for instance, advocated by the proponents of Damasio's theory of emotional feeling where the relation between body and environment remains at best modulatory (and contributing but not as constitutive). This is nicely reflected in a quote from a recent paper about emotion and consciousness: "Here, we follow the common view that emotion and consciousness emerge as a result of neuronal activity in the brain, but some accounts view emotions or consciousness as relationships between an organism and its environment (here we acknowledge such relationships as contributing but not as constitutive)" (Tsuchiya and Adolphs, 2007, p. 159; see also Bechara and Naqvi, 2004).

Non-instrumental dependence, in contrast, is described by Hurley as direct dependence of perceptual content on motor output independent of sensory input; even if the sensory input remains the same and fixed, perceptual content can vary depending on motor output. This means that motor output has direct access to perceptual content independent of sensory input and therefore no longer operates indirectly via sensory input as in instrumental dependence; instead, perceptual content may vary in orientation on motor output independent of sensory input and thus directly.

What does such non-instrumental or constitutional, as I will call it in the following (see also Colombetti, 2008), dependence imply for the relationship between body and environment in emotional feeling? If the relationship between emotional feeling and environment is direct and therefore constitutional, i.e., non-instrumental, changes in the environment should be able to impact and constitute emotional feelings independently of the body's sensorimotor representation. The environment itself may then directly involved in constituting emotional feelings. Thereby, the concept of environment is meant here in a social sense, social environment, as distinguished from the merely physical world (or physical environment).

This has empirically been paradigmatically exemplified in a recent study on reward (Fliessbach et al., 2007). Two subjects a and b were simultaneously scanned while receiving rewards. While the reward for the subject a was fixed, the one for subject b was varied; this and the converse case, increasing rewards for subject a and fixed rewards for subject b, allowed to investigate its impact of the environment, i.e., subject b, on subject a. Interestingly, emotional feelings and neural activity in reward circuitry in subject a did not so much depend on the size of the reward it received but rather on the relation of or balance to its own reward when compared to the one received by subject b. If, for instance, subject a received 60$ and subject b only 30$, subject a showed happiness and increased reward circuitry activation. If, in contrast, subject b received 120$ with subject a still receiving 60$, subject a no longer showed happiness and increased neural activity in reward circuitry. Though sensorimotor input was exactly the same for subject a in both cases (only subject's b reward amount changed), playing the same game and receiving the same reward, emotional feelings, and neural activity in reward circuitry differed in dependence on the amount of reward subject b received when compared to the amount subject a received.

This means that, to put it into conceptual terms, emotional feelings and neural activity in subject a were not merely instrumentally dependent upon the social environment (since then changes in subject b could have impact subject a only if they had changed subject's a reward) but rather instrumentally or constitutionally. More specifically, it is the relationship between person and (social) environment, the actual difference or balance between subjects' a and b rewards, that seemed to determine emotional feelings and neural activity. It is such constitutional, i.e., non-instrumental, dependence of emotional feelings on the social environment and its relationship to the person that I will characterize as the relational concept of emotional feelings[2]. Such intrinsic linkage between emotional feelings and the social environment is empirically further supported by the observed overlap between emotion processing and social processing (like social intentions; see Ciaramidaro et al., 2007) in especially aCMS like the anterior cingulate

[2]The here advanced relational concept may be considered an extension of the embodied approach by Colombetti and Thompson, who also emphasize the situated, extended and thus embedded nature of emotional feeling. Since the main focus here is on the neurophilosophical aspect, I cannot go into the philosophical details about the relational approach (see below for the discussion of some philosophical implications and Northoff, 2004 for a general outline). See also Ben-Ze'ev (1993, 81–99) who advocates a relational approach to perception and, in some part, also to emotion (see Ben-Ze'ev, 2000)

cortex and the DMPFC (see Schilbach et al., 2012). These (and other) data end strong support to an intrinsically social and thus relational concept of emotional feeling.

EMBEDDED APPROACH TO EMOTIONAL FEELING

The relational approach shifts the focus of attention from the body, as in the embodied approach, to the role of the environment in emotional feelings. Rather than modulating emotional feelings indirectly via bodily representations, the environment is supposed to be involved directly in constituting emotional feelings. How does the person-environment relation account for the variety of different specific emotional feelings? The lack of specificity concerning distinct emotions has often been criticized in feeling theories like the James–Lange theory (see also Niedenthal et al., 2005). Autonomic bodily changes like arousal are rather unspecific reactions that do not allow to distinguish between distinct emotions. This criticism has been furnished by the Schachter and Singer (1962) experiments demonstrating that subjects with autonomous nervous system stimulation, as induced by epinephrine, experienced the resulting arousal as either anger or euphoria in dependence on the respective context (they were placed in a room with either an angry or happy actor).

The conclusion is often drawn that physiological bodily changes and arousal themselves remain unspecific and cannot contribute to determine specific emotions); determination and distinction of specific feelings can consequently not be based upon physiological bodily changes but must be found elsewhere. This argument of the lack of specificity of bodily representations has been countered in different ways by referring to motor, cognitive, or neural representation. Zajonc (1998, 2000), for instance, claims that the motor system allows for extremely subtle distinctions which means that even a number of limited bodily states can support a very large number of representational distinctions of distinct emotional feelings. Rather than referring to motor capacities, cognitive theories, e.g., appraisal theories (Solomon, 2004; and also Schachter and Singer, 1962) resort to cognitive representations and higher-order cortical brain functions which may allow for a much more fine-grained distinction between different emotional feelings.

Damasio (1999, 2003, 2010) suggested a middle way between motor and cognitive representation. He focuses on those subcortical brain regions that register physiological bodily states which may allow for a wider representational spectrum than the muscles and viscera themselves that are actually represented in the respective neural states. All these approaches have in common that they still presuppose representation of emotional feelings in motor, cognitive, or neural-subcortical functions.

The relational approach, in contrast, claims that the wide variety of different emotional feelings may ultimately be traced back to the relation between person and environment rather than to motor, cognitive, or neural-subcortical representation. Since an abundant variety of different person-environment relations are possible, different emotional feelings can be constituted. The question for the specificity of emotional feelings is thus traced back to the possible (and impossible) person-environment relations rather than to the representational capacities of specific functions, i.e., motor, cognitive, or physiological-registering.

If emotional feelings are intrinsically relational, i.e., depending upon the person-environment relation rather than some representational capacities in motor, cognitive, or neural-subcortical function, one would expect different feelings to reflect different kinds of person-environment relationships. Ratcliffe (2005, 2008) does indeed assume exactly this and assumes what, relying on Heidegger's phenomenology, he calls "existential feelings." "Existential feelings" include feelings of homeliness, belonging, separation, unfamiliarity, power, control, being part of something, being at one with nature, and "being there." These feelings have in common that they describe "ways of finding ourselves in the world" which metaphorically circumscribes what I called the person-environment relation. What Ratcliffe calls existential feeling presupposes what I here advance as relational concept of emotional feeling. How does the person and thus the subject come into play in emotional feelings? This will be the focus in the next sections.

EMPIRICAL DATA: INTRINSIC ACTIVITY AND EMOTIONAL FEELING

EMOTIONS AND RESTING STATE

I so far focused on the relationship between intero- and exteroceptive stimulus processing in emotional feeling. Neurobiologically this was supposed to be related to the anatomical convergence between the respective pathways and the kind of coding, i.e., relational coding rather than translational coding. While conceptually this implied a shift from the embodied concept of emotional feeling to a relational concept (or as the philosophers may want to say an extended concept). This pointed out the intrinsic relation to emotional feelings to the environment as bridge between body and environment.

What remains unclear though are two aspects: why are emotional feelings not objective but rather subjective as manifest in an emotional experience? And why are emotional feelings affective and thus emotional? Taking a purely logical stance one could well imagine mere feelings without any emotions. Both questions dent deeply in various domains of research including consciousness (see Northoff, 2012a,b) which though I will avoid here to keep matters simple. I will here focus only on some neurobiological mechanisms while leaving the philosophical implications open. In order to shed some light on these questions, I turn to recent results about the relation between resting state activity and emotions.

A recent study by Sreenivas et al. (2012) investigated different emotional faces (sad, happy, neutral) in fMRI and focused thereby predominantly on the midline regions of the default-mode network (DMN). They demonstrated that sad faces induced a higher degree of deactivation, i.e., negative signal changes in the VMPFC, the PCC, and the precuneus when compared to happy faces. In contrast, activation and thus positive emotional signal changes were observed in the lateral fronto-parietal regions (except in left middle frontal gyrus). Finally, functional connectivity pattern also differed between sad and happy emotions for the connections between the midline and the lateral regions with VMPFC, PCC, and precuneus being central nodes.

While this study demonstrates that emotions are associated with midline regions that show high resting state activity, it leaves open whether that is related to intero- or exteroceptive stimuli. This was tested for by a study by Wiebking et al. (2011) from our group. Subjects had to perform the above mentioned intero-exteroceptive awareness with long resting state intervals (8–13 s) in-between. These served to subtract both intero- and exteroceptive signal changes from the resting state which, as expected, yielded higher activity changes in the midline regions. We then determined the degree of deactivation during both intero- and exteroceptive awareness. That yielded stronger deactivation in exteroceptive awareness when compared to interoceptive awareness.

How is all that related to emotions? For that Wiebking et al. (2011) included psychological measures of emotions (i.e., the Florida Affect battery and the Beck Hopelessness scale) and correlated them with the signal changes in the midline regions during the different conditions. Interestingly, we did not observe any correlation of the emotion measures with the midline signal changes during interoceptive awareness alone. Instead, the emotion measures significantly correlated with especially signal changes in VMPFC, DMPFC, and PCC during rest and exteroceptive awareness: The stronger the emotion score, the smaller the degree of deactivation in the midline regions thus being closer to the resting state activity level. In contrast, no correlation was observed with signal changes during interoceptive awareness. Hence, these results underline the central importance of intrinsic and thus resting state activity for emotions.

MODULATION OF RESTING STATE BY EMOTIONS

These results show the strong association between resting state activity and emotions. They though leave open whether emotions can also modulate resting state activity or whether the latter predict the former. Several recent studies demonstrated the prediction of stimulus-induced activity by the preceding resting state activity implying rest-stimulus interaction (see Northoff et al., 2010 for a review). This was mainly shown in the in the sensory domain while, as to my knowledge, such studies are not yet available in the domain of emotions. There are though a couple of studies that show the reverse, modulation of resting state activity by preceding emotions.

Focusing on emotions, Eryilmaz et al. (2011) investigated the impact of fearful, joyful, and neutral movie clips (50 s presentation) on subsequent resting state activity (90 s eyes closed). They asked the participants after the resting state period about their thoughts. This revealed that the subjects' personal relevant issues in their thoughts were increased after neutral movies, less increased after joyful movies, and significantly decreased after fearful movies. These results show a clear behavioral or better psychological effect of emotions on the thought contents in subsequent resting state periods; fearful movies seem to leave apparently the strongest traces in the subsequent resting state's thought contents.

Neuronally, they showed that the resting state periods after fearful faces showed higher neuronal activity in subcortical regions (pallidum, anterior thalamus, hypothalamus) than the ones following neutral movies (rest after fearful larger than rest after neutral). Most interestingly, the reverse comparison (rest after neutral larger rest after fearful) revealed higher signal changes in various regions of the DMN (VMPFC, PACC, DMPFC, STG). This means that the inclusion of fearful emotions in the preceding movie had a clear effect on the level of subsequent resting state activity. The stronger resting state effects of the preceding emotional movies are further confirmed by the more delayed recovery of the signal changes during the resting state period (90 s) after emotional movies.

This study clearly demonstrates that emotions have an impact on the subsequent resting state thus implying what we coined as stimulus-rest interaction (see Northoff et al., 2010). This was also observed in another study. Veer et al. (2011) investigated a psychological stress task in healthy subjects and scanned them in their resting state one hour later in fMRI. This revealed increased functional connectivity from the amygdala to the cortical midline structures like the MPFC, the PCC, and the precuneus. This indicates that psychological stress implicating strong and negative emotions can affect the subsequent resting state activity thus implying stimulus-rest interaction.

Taken together, these studies demonstrate the close relationship between resting state activity and emotion-related activity. This seems to be especially apparent in the midline regions as core nucleus of the DMN. The high intrinsic activity in these regions seems to be closely related to emotion processing in though yet unclear ways. Different emotions seem to modulate the degree of stimulus-related deviation from the high resting state activity in different ways. The close relationship between emotions and resting state is further supported albeit indirectly by the observation of severe resting state alterations in major depressive disorder (see Alcaro et al., 2010; Northoff et al., 2011; for recent overviews).

EMPIRICAL IMPLICATIONS: INTRINSIC ACTIVITY AND THE SUBJECTIVE NATURE OF EMOTIONAL FEELING

In order to better understand the potential role of the brain's intrinsic activity in emotional feeling, we need to go back to the psychological level. For that I turn to two of the major proponents of emotional feeling, Jaak Panksepp and Jim Russell, and how they conceptualize especially the subjective-experiential component of emotional feeling. This will be then linked in subsequent sections to the above described findings of the close relationship between intrinsic activity and emotions.

PANKSEPP AND RUSSELL ON EMOTIONAL FEELING

Based on the centrality of affect and emotions, Panksepp (1998, 2010) developed a neuroscientifically based theory of primary process affects as raw emotional feelings which he associates with evolutionary ingrained subcortical circuits. Russell (2003) shifted from an earlier Psychological Construction Theory of emotions to the assumption of what he calls "Core Affect" as a basic and foundational unit (or building block) of any specific emotional feeling. While Panksepp's concept of "primary process affect" overlaps at least conceptually (and also to some degree empirically) with Russell's concept of Core Affect (see especially Russell's p. 6–7 commentary on Panksepp), they are not the same.

Panksepp distinguishes between three distinct kinds of primary process affects, homeostatic, sensory, and emotional. Homeostatic affect provides information about the body and thus interoceptive

stimuli, sensory affect is related to exteroceptive stimuli, and emotional affect is associated with the brain (or BrainMind as Panksepp says) and hence with what one may call "neural stimuli." These distinctions make it clear that primary process affect is linked with stimuli generally, and more specifically with stimuli of different origins, be they of bodily (i.e., interoceptive), environmental (i.e., exteroceptive), or neural origin. Hence, primary process affect must be somehow assigned to stimuli since otherwise Panksepp could not associate primary process affect with stimuli of such different origins. I call such association of stimuli with affect or primary process affect "affective assignment" meaning that a stimulus of whatever origin can be assigned affect.

Analogous to Panksepp, Russell must also presuppose affective assignment though in a slightly different way. He does not associate what he describes as Core Affect itself with a specific type of stimulus since unlike Panksepp he does not speak of sensory, homeostatic, or emotional Core Affect. Instead, Core Affect is continuously present independent of the presence or absence of particular stimuli. One though has to mention that Russell seems to refer here only to the absence of exteroceptive stimuli since he does not explicitly talk about interoceptive or even neural stimuli in this context. This means that it cannot be excluded that Core Affect may be related to the assignment of affect to either neural or interoceptive stimuli. Hence Russell's concept of Core Affect would then also presuppose what I call affective assignment.

Rather than to interoceptive stimuli, Russell explicitly refers to the assignment of affect to exteroceptive stimuli when he describes the transition from Core Affect to emotional episodes and emotional meta-experience. In the moment when the continuously present Core Affect is related to an episodically occurring exteroceptive stimulus, an emotional episode and meta-experience may occur. This however is possible only if the Core Affect is linked and thus assigned to the exteroceptive stimulus thus presupposing what I here call affective assignment.

While both Panksepp and Russell seem to presuppose the assignment of affect to stimuli, the exact functional mechanisms that enable and predispose such affective assignment remain unclear in their accounts. What functional mechanisms are necessary to enable and predispose the transformation of a non-affective stimulus into an affective one? I call this the "non-affective-affective transformation." The "non-affective-affective transformation" raises the question how it is possible that a stimulus is suddenly associated with either Core Affect or primary process affect. It is especially worthwhile to consider that the stimulus of interoceptive, exteroceptive, or neural origin must be non-affective. Hence "non-affective-affective transformation" raises the question: what kind of functional mechanisms and neural input the brain must provide in order to assign affect to the stimulus.

The question about the "non-affective-affective transformation" raises another issue. Both Panksepp and Russell consider affect to be essentially subjective rather than objective. Panksepp refers to primary process affect as subjective by describing it as an "internal experience" while Russell describes Core Affect as subjective in the sense of a private experience. Hence, Panksepp distinguishes internal from external and Russell private from public when they characterize Core Affect or primary process affect as subjective rather than objective. One should need to make a conceptual remark here. The meaning of the term subjective refers here only to the experience of affect, it does not say anything about the underlying neuronal mechanisms that may well be objective.

This raises the question how affective assignment makes it possible to transform the originally objective stimulus, interoceptive, exteroceptive, or neural, into a subjective one. Hence, "non-affective-affective transformation" is not limited to transforming a non-affective into an affective stimuli but with transforming the objective into a subjective stimulus. I therefore speak of "objective-subjective transformation." "Objective-subjective transformation" raises the following question: how do the neuronal mechanisms enable the transformation of an objective stimulus into a subjective one? Such that, in conjunction with "non-affective-affective transformation" the stimulus can be subjectively and thus internally and privately experienced.

"OBJECTIVE-SUBJECTIVE TRANSFORMATION"

Both Russell and Panksepp seem to presuppose some kind of intrinsic stimuli to be crucial in generating affect. Russell does so by explicitly distinguishing Core Affect from extrinsic stimuli and related emotional episodes, while Panksepp argues that neural activity in the subcortical circuits is not dependent upon extrinsic stimuli, i.e., exteroceptive stimuli. This means that both must presuppose some kind of intrinsic activity for the generation of affect (**Figure 2**).

What could such intrinsic activity be? One may assume it is that activity that can be observed in the absence of any extrinsic stimulation by either intero- or exteroceptive stimuli. Intrinsic means then that the origin of that activity must be traced back to the brain itself as distinguished from body and environment. One may refine such intrinsic activity as the brain's resting state activity, or that activity in the brain in the absence of any intero- and exteroceptive stimuli (see Northoff et al., 2010). And it is such resting state activity as intrinsic activity that can be observed in all brain regions cortical and subcortical (see Northoff et al., 2010).

The fact that resting state activity is present throughout the whole brain means that there may already be some neural interactions between the different brain regions within the resting state itself. For instance the resting state activity level in the sensory cortex may interact with the resting state activity level in the subcortical regions so that one may want to speak of rest–rest interaction. The above described results lend clear empirical support to the assumption that such resting state activity in especially the midline regions is central for emotions and most likely for emotional feelings.

And there is further interaction. As soon as an inter- or exteroceptive stimulus enters the brain it interacts with the brain's resting state activity level thus yielding what can be called rest-stimulus interaction (Northoff et al., 2010). Such rest-stimulus interaction may be specified according to the stimulus type either rest-interceptive stimulus interaction or rest-exteroceptive stimulus interaction (which in the following I will describe as rest-intero and rest-extero interaction).

How do the three types of interaction, rest–rest, rest-intero, and rest-extero relate to affective assignment and more specifically to the non-affective-affective transformation and the objective-subjective transformation? The resting state activity level

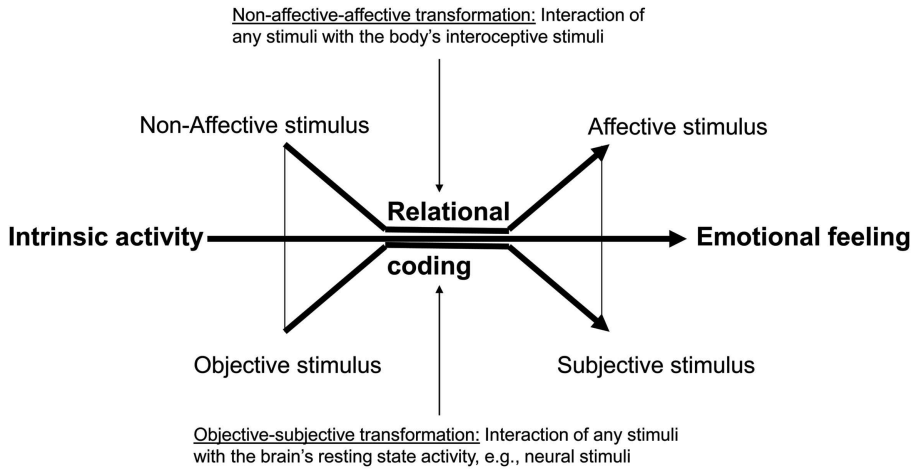

FIGURE 2 | The figure shows the relationship between intrinsic activity and stimuli (on the left) and emotional feeling (on the right). The intrinsic activity of the brain interacts with the stimuli that are by themselves non-affective and objective. That rest-stimulus interaction leads to the assignment of affect and subjectivity to the stimulus resulting in emotional feeling.

is different not only between different regions but even more importantly, different between different persons. This means that the same stimulus encounters a different brain in different persons meaning it must interaction with a different resting state activity level. Rest-stimulus interaction individualizes the stimulus and adapts its processing according to an individual brain's resting state activity level. Due to the individual resting state activity level and its impact on rest-stimulus interaction, the stimulus is processed in a very individual and ultimately private way.

By individualizing and privatizing the stimuli with respect to the brain's actual resting state activity level, the originally objective stimulus is transformed into a subjective one. Hence what I called above objective-subjective transformation may correspond on a functional level to rest-stimulus interaction. Any processing of the stimulus, interoceptive or exteroceptive, in relation to the brain's resting state activity level (and hence its neural stimuli) may privatize and individualize the stimuli, and thereby transform it from an objective to a subjective one.

Russell and Panksepp may now want to argue that this accounts only for half of the story. Panksepp may say that this leaves emotional affects as based on the stimuli from the BrainMind itself and hence its neural stimuli out; this may be so because rest-stimulus interaction concerns only the interaction with intero- and exteroceptive stimuli. Hence, my assumption of rest-stimulus interaction corresponding to objective-subjective transformation may well account for what Panksepp calls homeostatic affects and sensory affects, but not emotional affects.

Russell may want to make an even stronger point. My assumption of rest-stimulus interaction misses Core Affect altogether because Core Affect is neither related to interoceptive nor exteroceptive stimuli. Instead the core affect precedes both kind of stimuli that becoming relevant only in emotional episodes. Hence, my assumption that rest-stimulus interaction corresponds to objective-subjective transformation may hold for emotional episodes and emotional meta-experience but not for Core Affect itself.

This however is to neglect that the brain's resting state can interact with itself, as for instance the resting state activity level in the subcortical circuits interacting with cortical regions. There may thus be what could be called "rest–rest interaction" where the neural stimuli of one particular region's resting state may interact with those of another region. Recent imaging data show that such rest–rest interactions do indeed occur (see Northoff et al., 2010 for recent review). In the case of such rest–rest interaction, the resting state activity level of one network is set against that of another network.

SUBJECTIVE CHARACTER OF EMOTIONS

This has major implications for the conceptual characterization of emotions. Any stimulus, internal, external, or neural, cannot avoid but to interact with the brain's resting state activity. If that very same resting state activity individualizes and privatizes stimuli and their encoding into neural activity, any emotions must be individualized and privatized. That though means that any emotions must necessarily be subjective meaning that it cannot avoid objective-subjective transformation. There is consequently no emotion without emotional feeling with the latter being at the very core of the former. This nicely corresponds to what Russell describes as "Core affect" and Panksepp as "primary process affect" and, more generally as "BrainMind."

To empirically support this assumption, future studies are needed to test whether the preceding level of resting state activity predicts the degree of especially the subjective-experiential component of emotions, i.e., the emotional feeling. I would hypothesize that the preceding resting state activity predicts especially the subjective-experiential component of emotions. While other components like the vegetative and the cognitive aspects of emotions may rather be predicted by the degree of stimulus-induced activity itself.

One may finally raise the question how the here suggested role of the resting state in objective-subjective transformation stands to the above proposed relational coding. I would argue that both

are well compatible. While above I focused on the relation between intero- and exteroceptive stimuli, I now extend the focus to include the brain's intrinsic activity and thus its neural stimuli into the equation of relational coding.

Let me be more specific. The incoming stimulus must be coded in relation to the intrinsic activity level and thus relative to it. The resulting neural activity must then be considered the integral of their interaction, i.e., rest-stimulus interaction, rather than being related to the stimulus alone. That though is possible only if neural activity is coded in terms of a relation between stimulus and intrinsic activity as distinguished from neural coding of the stimulus by itself. I thus assume rest-stimulus and stimulus-rest interaction to presuppose relational coding in very much the same way as the relation between intero- and exteroceptive stimuli is encoded into neural activity (see Northoff, 2012a for more details on the question of neural coding).

"NON-AFFECTIVE-AFFECTIVE TRANSFORMATION"

How about the second feature of affective assignment, that non-affective-affective transformation? What functional mechanisms correspond to the transformation of a non-affective stimulus into an affective one? Panksepp (2010, p. 13) himself gives one hint in this direction. He considers primary process affect to be intrinsically valuative (in a wider sense as not being restricted to reward) in that it mirrors the value of environmental, bodily, and neural information for the organism. How can such value be generated, and what kind of functional mechanisms are necessary in order to value stimuli of different origin, exteroceptive, interoceptive, or neural?

In order for stimuli of various origins to be valued for the organism, they must be related to the organism itself, including its body and brain. More specifically, exteroceptive stimuli from the environment need to be related to the brain's neural stimuli leading to rest-extero interaction and the body's interoceptive stimuli leading to intero-extero interaction. The same holds for interoceptive stimuli which need to be related to the brain's neural stimuli thus requiring rest-intero interaction. Finally, as demonstrated above, the brain's resting state activity itself may be valued when rest–rest interaction occur.

How does affect enter these various interactions? Russell tells us that Core Affect is continuously present even in the absence of exteroceptive stimuli. Unlike exteroceptive stimuli which arise more episodically, there is continuous interoceptive input and thus continuous rest-intero interaction in the brain. Due to the continuous presence of the body, continuous interoceptive input and subsequent continuous rest-intero interaction cannot be avoided.

One may consequently consider rest-intero interaction as one possible candidate functional mechanism that may correspond to what Russell describes as Core Affect. It is by the continuous neural processing of the body's interoceptive stimuli against the brain's neural stimuli that affect may be generated. Hence, interaction of the interoceptive stimuli with the neural stimuli may transform the originally non-affective interoceptive stimulus into an affective one. The hypothesis is thus that rest-intero interaction may correspond on the functional level to the non-affective-affective transformation and thus to what Russell described as Core Affect.

However, there is not only Core Affect but also emotional episodes (Russell) or sensory affect (Panksepp) in relation to exteroceptive stimuli. How can exteroceptive stimuli be assigned affect and how can they undergo the non-affective-affective transformation? Very simple. They may be linked to interoceptive stimuli resulting in an intero-extero interaction. They would thereby be valued, which in turn would lead to a non-affective-affective transformation with the subsequent assignment of affect. Hence, one may consider the interaction of stimuli of various origins with specifically interoceptive stimuli from the body as a necessary condition for the non-affective-affective transformation. This may apply to the brain's neural stimuli with rest-intero interaction which then leads to what Russell described as Core Affect and Panksepp as homeostatic affect. It may also apply to exteroceptive stimuli with intero-extero interaction that may then result in what Russell characterized as emotional episodes and Panksepp as sensory affect.

DISSOCIATION BETWEEN SUBJECTIVITY AND AFFECTIVITY

One may now be puzzled. I characterized objective-subjective transformation by the interaction of any kind of stimulus with the brain's resting state activity, i.e., its neural stimuli, so that any kind of rest-stimulus interaction will do the job. And I considered the interaction of any stimulus with interoceptive stimuli from the body as being necessary for the non-affective-affective transformation. Hence, both transformations, objective-subjective and non-affective-affective are characterized by interactions with different stimuli, the brain's neural stimuli and the body's interoceptive stimuli.

As on a psychological level where affectivity and subjectivity co-occur, non-affective-affective, and objective-subjective transformations also co-occur in the "normal" case. There is interaction with the body's interoceptive stimuli (e.g., intero-extero interaction), and there is interaction with the brain's resting state and thus its neural stimuli (e.g., rest-intero and rest-extero interaction). This means that affectivity and subjectivity are co-constituted, which is reflected in both Panksepp and Russell definitions of affect by.

If one interaction takes over at the expense of the respective other, the co-constitution between affectivity and subjectivity may become dysbalanced. This is, for instance, the case in schizophrenia where rest-intero and rest-extero interactions may be reduced leading to an abnormal loss of subjectivity (Northoff and Qin, 2011). There is thus still non-affective-affective transformation while the objective-subjective transformation seems to fail: These patients thus still experience emotional feelings while their respective contents are no longer experienced as subjective but objective.

While the reverse seems to be the case in depression, where rest-intero interaction seems to predominate over intero-extero interaction (Alcaro et al., 2010; Northoff et al., 2011). In the most extreme case, depressed patients say that they no longer feel any emotion, the feeling of non-feeling. Hence, non-affective-affective transformation may be blocked while at the same time this state is experienced as highly subjective implying objective-subjective transformation. The cases of depression and schizophrenia thus indicate the possibility of dissociation between both forms of transformation.

Interoceptive processing and consecutively intero-extero interaction may also be altered or disrupted in alexithymia that

concerns the inability to identify and describe emotional feeling. The exteroceptive stimuli and their respective contents can then no longer be associated with emotional feelings: While the contents are experienced as subjective (due to functioning rest-intero and rest-extero interactions), they are not assigned emotional feeling (due to deficient intero-extero interaction). Empirically this is supported by a recent study that shows the degree of interoceptive awareness to predict the degree of alexithymia with high interoceptive awareness going along with a low degree of alexithymia (Herbert et al., 2011).

CONCEPTUAL IMPLICATIONS: EMOTIONAL FEELING AND CONSCIOUSNESS

RELATIONAL APPROACH TO EMOTIONAL FEELING

How should emotional feelings be conceptualized on the basis of the intero-exteroceptive relational model of neural coding? What we subjectively experience as emotional feeling is thus not so much mere perception of an interoceptive stimulus like the heartbeat perception but rather the relation between intero- and exteroceptive stimulus processing relative to our brain's intrinsic activity. Emotional feelings can no longer be determined in an interoceptive-based way as perceptions of physiological body changes. Instead, emotional feelings may better be described in an neural-intero-exteroceptive relational way thus focusing more on the relation between brain, body and environment than on either the body or the environment itself[3]. What is constitutive of emotional feelings is thus the relation between brain, body, and environment so that feelings reflect the respective person's relationship to the world.

This is paradigmatically reflected in what the philosopher Ratcliffe (2005, 2008) calls existential feelings. Based on Heidegger, he describes existential feelings as feelings that characterize our relation to the world, i.e., as ways of "finding ourselves in the world." This is also pointed out by Solomon (2004, pp. 77–78, 84) in a more recent writing when he claims for "an existential notion of emotions" which he considers to be "subjective engagements within the world[4]." For instance, different existential feelings characterize different relations to the world like feelings of homeliness, separation, belonging, power, control, etc. Most important, emotional feelings like anger, grief, etc. presuppose existential feelings so that both emotional and existential feelings can be characterized as relational. If so, the body itself may only be considered the medium through which feelings can be constituted. Feelings are the relation between person/body and environment rather than some perception of either bodily or environmental changes; in other terms, feelings are this relation implying that this relationship is felt.

Due to the very basic and foundational character of the brain-body-environment relation, the relational concept considers emotional (and existential) feelings basic and primary for emotions, i.e., feelings are then the "core nucleus" of emotions. This is very much in line with the neuroscientific approach by Panksepp (1998, 2005) who assumes what he calls "primary affective consciousness." He regards "primary affective consciousness" as basic and crucial for all forms of subjective experience and thus for consciousness in general. Analogously, the relational view considers our relation to the world primary, basic and crucial to our subjective experience or, as Ratcliffe would probably say, the relation is existential.

NEURO-PHENOMENAL APPROACH TO EMOTIONAL FEELING

Since the relational concept characterizes the brain-body-environment as basic, primary, and constitutive of feelings, the here advanced relational concept of emotional feelings seems to complement the empirical approach by Panksepp in conceptual regard. Feelings and thus affective consciousness can only be primary and basic, as Panksepp claims, because they are our relation to the world. Another complementary point is Panksepp's (and other authors like M. Sheets-Johnstone, N. Humphrey and R. Ellis) insistence on the close linkage between motor function and emotional feeling, i.e., the primary motor basis of affective consciousness.

In contrast to Damasio (2010), who opts for a rather sensory-based view of emotional feeling, Panksepp (and others like Ellis, 2005) argues for a primary "motor view" of affective consciousness and emotional feeling because all presumably involved subcortical regions like the PAG, the colliculi, etc. show strong connections to the motor system receiving motor afferences from and sending out motor efferences to other cortical and subcortical regions. Accordingly, Panksepp (and others like Ellis, 2005) claims that there is intrinsic linkage between motor action and emotional feeling resulting in what may be described as "I act, therefore I feel." The assumption of motor underpinnings as being crucial to emotional feeling is well compatible with the relational concept.

The here suggested relational approach also needs to be distinguished from cognitive approaches. Cognitive approaches focus on the awareness and thus reflection of emotional and cognitive contents thus presupposing access or reflective consciousness, the awareness of subjective experience. For that various cognitive functions are assumed to be necessary. This is different in the relational approach that focus on phenomenal consciousness and thus on subjective experience itself and how it is generated and transformed into a phenomenal state (see below) on the basis of the brain's neuronal states.

The relational approach can thus be characterized as "neuro-phenomenal approach" rather than "neuro-cognitive approach" (see Northoff, 2012b). Since the cognition, i.e., awareness and reflection, of subjective experience and its contents presupposes its generation, I assume the "neuro-phenomenal approach" to be more basic and prior to the neuro-cognitive approach. Future studies may therefore want to investigate how the here described neuronal processes of non-affective-affective and objective-subjective transformation impact cognitive functions and their respective neural substrates.

[3]This is well compatible with the relational approach to meaning and personal significance as suggested by Ben-Ze'ev (1993, 2000) that undercuts the traditional assumption that higher-order cognitive functions are necessary to give meaning and personal significance to otherwise meaningless and personally insignificant sense data.

[4]One may off course argue that we can have subjective experience without emotion in for instance so-called "cold" cognitions. "Cold" cognitions may however be considered just as an extreme case on a continuum in the relationship between emotion and cognition where feelings may still be involved in the background though being maximally suppressed.

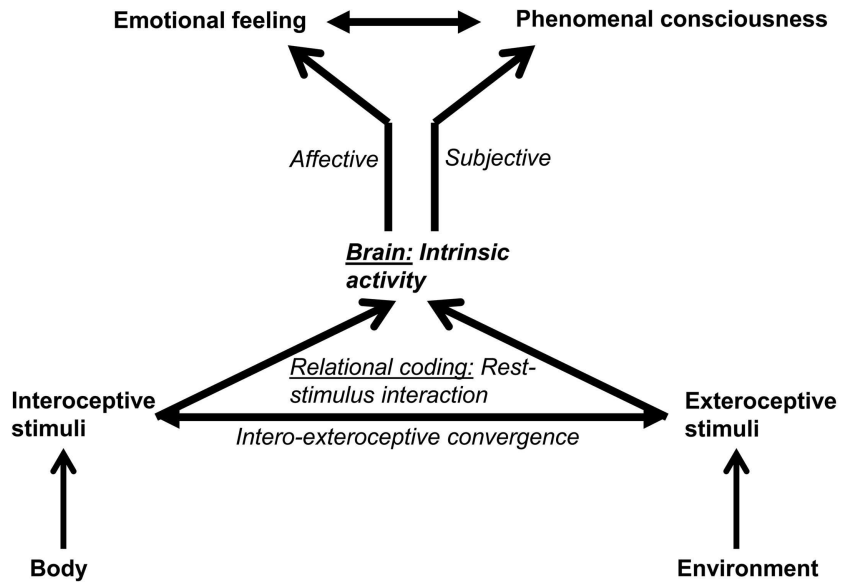

FIGURE 3 | The figure shows the relationship between emotional feeling and phenomenal consciousness. By interacting with the brain's intrinsic activity via relational coding affect and subjectivity is assigned to the intero- and exteroceptive stimuli. This in turn makes possible the generation of emotional feeling and phenomenal consciousness.

EMOTIONS AND CONSCIOUSNESS

How is the transformation of the brain's neuronal states into the phenomenal states of consciousness possible? The relational concept presupposes bilaterally dependent and constitutive linkage between brain, body, and environment. Mere linkage by sensory function would result in unilateral and rather instrumental linkage where the person/body cannot directly impact the environment. It is only by motor function that the person/body becomes intrinsically anchored in and non-instrumentally, i.e., constitutionally linked to the environment. In other terms, motor function must be considered the empirical means by means of which what I conceptually described as relational becomes possible. Panksepp's insistence on motor underpinnings of emotional feelings may thus be considered complementary to the here advanced relational concept of emotional feeling (**Figure 3**).

Once emotional feelings are considered to be the core nucleus of both emotions and consciousness, the often made distinction between "having an emotion" and "feeling an emotion" becomes no longer applicable. Following Bennett and Hacker (2003, pp. 210–214), there is no principal distinction between "having an emotion" and "feeling an emotion" since, as Kripke (1972) already pointed out, the having of pain is to be identified with the feeling of pain. Either we have pain and subjectively experience or feel pain or we do not feel any pain and then we have no pain. "Having an emotion" is consequently to be identified with "feeling an emotion" and their distinction remaining untenable and implausible.

According to Bennett and Hacker (2003, p. 214), the main difference should better be drawn between "feeling an emotion," as being identical with "having an emotion," and "realizing what emotion one feels." "Feeling an emotion" might then indicate subjective experience and thus what currently is called phenomenal consciousness (see below for further explication). In contrast, "realizing what emotion one feels" might be considered to implicate higher-order cognitive functions and thus be associated with what has been called reflective consciousness.

By considering feeling as constitutive of emotion and phenomenal consciousness, the relational concept of emotional feeling argues against the explanation of feelings in terms of higher-order cognitive and reflective functions mirroring what is called reflective consciousness. Roughly, reflective consciousness describes the person's awareness that it has subjective experience and thus phenomenal consciousness – reflective consciousness may thus focus on higher-order cognitive functions.

Phenomenal consciousness, in contrast, does not describe cognitive and behavioral aspects associated with subjective experience. Instead, it focuses on the subjective-experiential aspect itself that is described as the "phenomenal aspect" (Chalmers, 1995; Block, 1996). A number of alternative terms and phrases pick out approximately the same core property of phenomenal consciousness. These include "qualia," "phenomenology," "subjective experience," and "what it is like" which, despite subtle differences, we here consider to describe the same phenomenon for pragmatic purposes. I characterize emotional feeling by "qualia" and "what it is like" thus presupposing phenomenal consciousness.

The here proposed relational account is well in accordance with Peter Goldie's approach who emphasizes the phenomenal, e.g., unreflective, qualitative, and "what it is like" character of emotional feeling (Goldie, 2000, pp. 68–69). Goldie (2000, pp. 1–2, 41) argues that the phenomenal character of feelings is due to the involvement of a point of view, a perspective, by means of which they become "fundamentally personal." The relational concept claims that such personal point of view is established by constituting the relationship between brain, body, and environment and thus by

constituting feelings be they existential or emotional. How such personal point can be established by relating brain and body to the environment remains to be discussed in detail which however is beyond the scope of this paper (see Northoff, 2004, 2012b; Northoff and Bermpohl, 2004; Northoff et al., 2006).

Finally, the here proposed neuronal mechanisms underlying especially the subjective nature of emotions may be relevant for consciousness in general. The yet to be specified and defined neuronal mechanisms underlying rest-stimulus interaction are assumed to be central for the subjective component. If so they must be regarded necessary of consciousness in general that is essentially defined as subjective. Even if not sufficient by themselves as neural correlates of consciousness (NCC), specific yet unknown ways of rest-stimulus interaction must then be regarded a necessary or predisposing condition of consciousness. One may consequently want to speak of neural predispositions of consciousness (NPC) as distinguished from the NCC (see Northoff, 2012b).

CONCLUSION

The often favored James–Lange theory and many current neuroscientific approaches that consider feeling as mere perception of bodily changes and thus as "embodied" may be extended by considering the crucial role of the environment in directly constituting emotional feelings. I therefore suggested in this paper to complement the embodied concept of emotional feelings by a relational concept that assumes emotional feelings to be constituted by the brain-body-environment relationship. The relational concept assumes that the environment and the brain itself have not only instrumental and thus indirect impact on emotional feelings via the body but also a direct, e.g., non-instrumental and thus constitutional role in constituting emotional feelings.

The present paper focuses on whether such relational concept of emotional feelings is compatible with current empirical data on the neuroscience of emotion processing. If the relational concept of emotional feeling is empirically plausible, even interoceptive awareness should implicate brain regions that process exteroceptive stimuli. Both, e.g., intero- and exteroceptive brain regions, should then also be closely linked to each other in terms of anatomical, i.e., structural and functional connectivity.

Human brain imaging data show strong involvement of the VMPFC and other aCMS in emotional feelings. These regions can be characterized by strong convergence between intero- and exteroceptive inputs as well as of both with the brain's high intrinsic activity, its resting state activity. This presupposes what I describe as the neural-intero-exteroceptive relational mode of neural coding rather than interoceptive-based translational neural coding (see also Northoff, 2012a). In short I assume relational coding to be the predominant neural code that allows to link emotions to brain, body, and environment. Emotions and emotional feelings may then be considered, metaphorically speaking, the bridge or glue between brain, body, and environment.

The intrinsic linkage between brain, body, and environment accounts for the subjective and affective nature of emotional feelings. By being processed in the brain relative to its intrinsic activity (at least in the human brain as it is designed) emotions cannot avoid becoming subjective and affective. The subjective and affective components must therefore be regarded intrinsic to and thus defining features of emotions. As such emotions and emotional feeling may be considered paradigmatic cases of consciousness in general which in the current neuroscientific and philosophical debate is rather often neglected (see also Northoff, 2012b).

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APPENDIX

GLOSSARIUM

Coding: Formal measure according to which stimuli are encoded into neural activity.

Consciousness: Subjective experience characterized by "what it is like" and a point of view. Referring here mainly to phenomenal consciousness as distinguished from access or reflective consciousness.

Embeddedness: Constitutional (as distinguished from mere modulatory) dependence of consciousness and emotional feeling on the (social) environment.

Embodiment: Constitutional (as distinguished from mere modulatory) dependence of consciousness and emotional feeling on the body and its sensorimotor functions.

Exteroceptive stimuli: Input into the brain from the environment.

Interoceptive stimuli: Input into the brain from the own body.

Neural stimuli: Input into the brain from other regions and time points within the brain itself.

Non-affective-affective transformation: Processes that underlie the assignment of affect to a primarily non-affective stimulus that thereby becomes transformed into an affective stimulus.

Objective-subjective transformation: Processes that underlie the assignment of subjectivity to a primarily objective stimulus that thereby becomes transformed into a subjective stimulus.

Relational coding: Coding of different stimuli in relation to each other into neural activity in the brain.

Resting state: The state of the brain in the absence of any specific stimulus from outside the brain as from the body or the environment.

Rest–rest interaction: Changes in neural activity in the resting state. These changes may occur between different regions and/or across time as fluctuations in the spontaneous activity of the brain.

Rest-extero interaction: Interaction of the brain's resting state activity with exteroceptive stimuli from the environment.

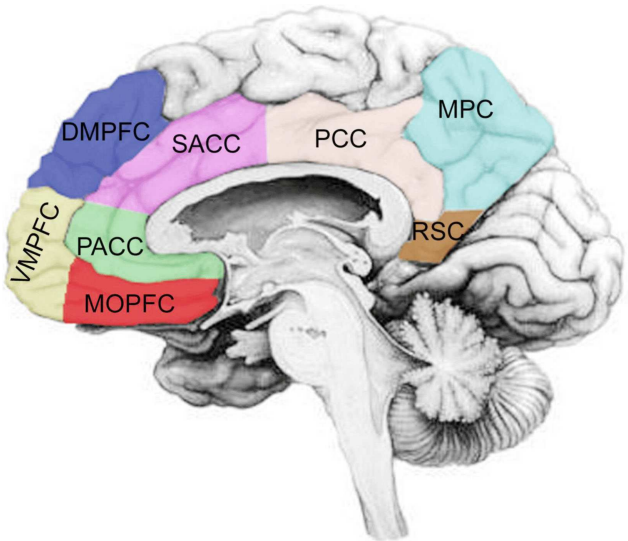

FIGURE A1 | The figure illustrates schematically the relevant midline regions in the cortex. The image is a sagittal slice of the brain take in its midline. MOPFC, medial orbitofrontal cortex; VMPFC, ventromedial prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; PACC, perigenual anterior cingulate cortex; SACC, supragenual anterior cingulate cortex; PCC, posterior cingulate cortex; RSC, retrosplenial cortex; MPC, medial parietal cortex.

Rest-intero interaction: Interaction of the brain's resting state activity with interoceptive stimuli from the own body.

Rest-stimulus interaction: Term for the interaction of interoceptive and/or exteroceptive stimuli with the brain's resting state activity.

Translational coding: Coding of each stimulus by itself into neural activity in the brain with subsequent translation of the different neural activities into each other.