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THE NEURAL UNDERPINNINGS OF VICARIOUS EXPERIENCE

Topic Editors
Bernadette M. Fitzgibbon, Jamie Ward
and Peter G. Enticott

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THE NEURAL UNDERPINNINGS OF VICARIOUS EXPERIENCE

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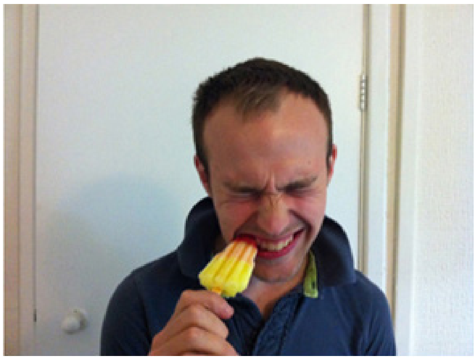

Image taken from: Derbyshire SWG, Osborn J and Brown S (2013) Feeling the pain of others is associated with self-other confusion and prior pain experience. Front. Hum. Neurosci. 7:470. doi: 10.3389/fnhum.2013.00470

Everyday we vicariously experience a range of states that we observe in other people: we may "feel" embarrassed when witnessing another making a social faux pas, or we may feel sadness when we see a loved one upset. In some cases this process appears to be implicit. For instance, observing pain in others may activate pain-related neural processes but without generating an overt feeling of pain. In other cases, people report a more literal, conscious sharing of affective or somatic states and this has sometimes been described as representing an extreme form of empathy.

By contrast, there appear to be some people who are limited in their ability to vicariously experience the states of others. This may be the case in several psychiatric, neurodevelopmental, and personality disorders where deficits in interpersonal understanding are observed, such as schizophrenia, autism, and psychopathy.

In recent decades, neuroscientists have paid significant attention to the understanding of the "social brain," and the way in which neural processes govern our understanding of other people. In this Research Topic, we wish to contribute towards this understanding and ask for the submission of manuscripts focusing broadly on the neural underpinnings of vicarious experience. This may include theoretical discussion, case studies, and empirical investigation using behavioural techniques, electrophysiology, brain stimulation, and neuroimaging in both healthy and clinical populations. Of specific interest will be the neural correlates of individual differences in traits such as empathy, how we distinguish between ourselves and other people, and the sensorimotor resonant mechanisms that may allow us to put ourselves in another's shoes.

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The neural underpinnings of vicarious experience

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In recent decades there has been an explosion of empirical research into the social cognitive processes that underlie our social interactions. Coinciding with, or perhaps driving, the interest within this area is the development of modern neuroscientific techniques bringing real world experiences into the laboratory to produce biological models of how we experience and interact with other people.

In this research topic, we present a range of expert manuscripts that focus on one primary aspect of social cognition: the ability to recognize, understand and, in some cases, "feel" the experience of another person. To date, neuroscience research in this area has identified shared neural networks whereby we process another's action, emotion or sensation through overlapping brain regions as if we were carrying out that same action or experiencing that same emotion or sensation. Intriguingly, this research has shown that such vicarious activation of brain networks can span from an automatic and unconscious process through to an overt experience of the emotion or sensation of that observed in another person.

By investigating vicarious processes as well as exploring the influence of interpersonal characteristics such as empathy, we are taking a step toward better understanding the relationship between the social brain and social behavior. This includes the decision to make a pro-social response vs. fleeing potentially dangerous, or even socially awkward situations, such as witnessing another person embarrass themselves. Moreover, this research area has substantial implications for understanding disease and improving treatment options for people who experience psychiatric or neurological illness including autism spectrum disorder, where impairment in aspects of social functioning is a key feature. However, even beyond disorders where social function may be diagnostic, social impairments and difficulties in social relationships can have substantial functional consequences, as is often reported in illnesses such as depression and schizophrenia. Ultimately, understanding the neurobiology of social processes will provide the platform for targeted and appropriate treatment interventions.

In the work that follows, this research topic brings together a number of opinions, perspectives, hypotheses and theories, general commentaries, reviews and original research articles. Several key themes can be identified ranging from:

(1) Definitional considerations including the distinction between vicarious and empathic experiences (Paulus et al., 2013), and why overt vicarious experiences may not represent a new form of synaesthesia, where sensory input in one domain results in a sensory experience in another (Rothen and Meier, 2013);
(2) Exploration of vicarious shared neural experiences in the general population from physical touch and injury (Bufalari and Ionta, 2013) through to ostracism (Wesselmann et al., 2013) and how vicarious experience may differ between people according to attention (Morelli and Lieberman, 2013), interpersonal and personality differences (Schaefer et al., 2013; Vandenbroucke et al., 2013) such as empathy, and the influence of psychopathic (Marcoux et al., 2013) or autistic (Cooper et al., 2013) traits. Additional modulating factors of vicarious experience are also considered including expertise seen in physicians (Newton, 2013), the influence of the mother-child bond (Manini et al., 2013), the experimental administration of oxytocin and the effect of visual orientation (i.e., self vs. other) (Burgess et al., 2013).
(3) The investigation of atypical vicarious experiences in the general population such as shared touch (Banissy and Ward, 2013) and pain and how feeling the pain of others may be linked with self-other confusion and prior pain experience (Derbyshire et al., 2013). Through to a physiological study exploring the experience of misophonia, describing a sensitivity to sound that can substantially limit ones ability to interact with others (Edelstein et al., 2013), and a commentary of why vicarious perception may drive contagious scratching (Ward et al., 2013);
(4) The discussion of vicarious experiences in atypical populations including evidence against an impairment in shared neural networks in ASD (Enticott et al., 2013) and an argument for how models of vicarious pain experience may help us understand the relationship between core ASD symptoms better (Fitzgibbon et al., 2013);
(5) Finally, the role of vicarious experience including vicarious motor system activation in understanding the behaviors of others (Avenanti et al., 2013) and how group membership may influence such processing and influence how we interact with others (Eres and Molenberghs, 2013).

Taken together, this research topic presents cutting edge research in a growing field which, while by no means definitive, represents exciting developments in the neurobiology underlying sharing experiences with others.

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On the distinction of empathic and vicarious emotions

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In the introduction to the special issue "The Neural Underpinnings of Vicarious Experience" the editors state that one "may feel embarrassed when witnessing another making a social faux pas". In our commentary we address this statement and ask whether this example introduces a *vicarious* or an *empathic* form of embarrassment. We elaborate commonalities and differences between these two forms of emotional experiences and discuss their underlying mechanisms. We suggest that both, vicarious and empathic emotions, originate from the simulation processes mirroring and mentalizing that depend on anchoring and adjustment. We claim the term "empathic emotion" to be reserved exclusively for incidents where perceivers and social targets have shared affective experience, whereas "vicarious emotion" offers a wider scope and also includes non-shared affective experiences. Both are supposed to be highly functional in social interactions.

Keywords: vicarious emotion, empathic emotion, anchoring, adjustment, vicarious embarrassment, mentalizing, mirroring, empathy

INTRODUCTION

The human ability to infer others' emotions, thoughts or intentions is a central mechanism in creating meaningful social interactions. Accordingly, the question of how we develop a representation of our interaction partners' minds and emotions has been the focus of various disciplines such as social psychology, philosophy, anthropology, and biology. In the last decade the social neurosciences, specifically, have put tremendous efforts into disentangling the neural networks involved in this ability. Most of this research has concentrated on the phenomenon of "empathy." Empathy has been defined as the state where people (i.e., *perceivers*[1]) represent the same emotion they are observing or imagining in another person (i.e., *social targets*) with full awareness that the source of their own experience is the other's emotion (De Vignemont and Singer, 2006). However, empathy only refers to a small amount of vicarious emotions people may experience while interacting with their social environment in everyday life (Singer and Lamm, 2009). With this commentary, we aim to broaden this perspective by proposing a clear-cut distinction between vicarious and empathic emotions, with the latter being a specific case of the first and both being mediated by two streams of simulation processes.

TWO PROCESSES OF UNDERSTANDING OTHERS' EMOTIONS: MIRRORING AND MENTALIZING

Mainly, two interacting processes have been proposed that allow perceivers to empathize (Keysers and Gazzola, 2007; Waytz and Mitchell, 2011). First, *mirroring* processes have been described as a direct mapping of another's observed actions and bodily states in one's own (i.e., the perceiver's) neural system that allow sharing the target's feelings in an embodied manner. Second, *mentalizing* processes which have been proposed to lead to comparable internal representations in perceivers, however, via a projection of oneself into the target's position (Keysers and Gazzola, 2007; Hein and Singer, 2008). Mentalizing thus involves imagining oneself in the same situation as the social target and helps to "intuitively" (Keysers and Gazzola, 2007) grasp the target's emotions as if they were one's own bodily states. These processes, mirroring and mentalizing, can be understood as forms of internal simulation that allow perceivers to experience another person's state on one's own body (see Waytz and Mitchell, 2011).

In order to shed light onto the neural mechanisms of these two processes to simulate the target's emotional state, the fundamental idea of these approaches is to compare neuronal networks involved in first-hand experiences of emotions or sensations (e.g., provoking pain or disgust through administration of electroshocks or unpleasant odors, respectively) with the neuronal networks engaged while observing emotions or sensations in interaction partners (Wicker et al., 2003; Singer et al., 2004; Jabbi et al., 2007). Overlap in cortical activation between these experimental conditions is then interpreted as evidence for shared, "isomorphic"[2] affective states between interaction partners and

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[1] Zaki and Ochsner (2011) described individuals focusing on someone else as "perceivers" and individuals being in the focus of the perceivers' attention as 'social targets'. For the present article we take on this labeling and will refer to perceiver and social target in the following.

[2] In the neurosciences the term isomorphism might be understood with at least two different meanings: on the one hand, "isomorphic" patterns of information refer to the similar firing of mirror neurons during self-initiated actions and the observation of corresponding actions of others thus allowing computational predictions. On the other hand, in the context of empathy research the term "isomorphism" has been used to describe similar affective states between targets and perceivers (De Vignemont and Singer, 2006). Whereas the earlier usage refers to the micro-level of information processing in the brain, the latter describes the subjective level of affective experiences.

thus as a neuronal manifestation of empathy (Wicker et al., 2003; Gallese et al., 2004; Singer et al., 2004; Jackson et al., 2006). Irrespective of the underlying processes, neuroscience research has shown that the anterior insula and the anterior cingulate cortex are most robustly involved in common mapping of one's own and another's affective states during empathic experiences (Craig, 2009; Lamm and Singer, 2010).

Depending on the available input, perceivers rely on sensory [i.e., mirroring of gestures, mimics, bodily postures, sounds etc. in a near-simultaneous isomorphic fashion (Waytz and Mitchell, 2011)] and/or contextual information (i.e., mentalizing using semantic information, prior knowledge, past experiences in similar situations etc.) in order to represent another person's state (Waytz and Mitchell, 2011; Zaki and Ochsner, 2011). Among others, the premotor cortex and primary as well as higher order somatosensory cortices are thought to mediate the mirroring process (Avenanti et al., 2005). Mentalizing is typically associated with medial prefrontal cortex (mPFC), temporal pole, and superior temporal sulcus activation (Hein and Singer, 2008). Within the mentalizing network, the mPFC has been specifically linked to reflective processes about oneself and another (Mitchell et al., 2005) or imagining oneself in past and future events (Buckner and Carroll, 2007; Schacter et al., 2007). This supports the conceptualization of mentalizing as a process where perceivers project themselves into to the position of the social target.

DISSOCIATING VICARIOUS AND EMPATHIC EMOTIONS

The processes to infer the "physically invisible but psychologically real, internal state" (Zaki and Ochsner, 2011; p.159) can also result in "vicarious emotions" that are simulated in the absence of this specific emotional state in the social target. Although the terms "empathic emotions" (Batson, 1981; Lamm et al., 2007a; Hein and Singer, 2008; Pfeifer et al., 2008; Engen and Singer, 2012; Zaki and Ochsner, 2012) and "vicarious emotions" (Batson et al., 1987; Decety and Lamm, 2006; Keysers and Gazzola, 2009; Meyer et al., 2012; Niedenthal and Brauer, 2012) have been used with near identical meaning, we consider both concepts to have distinctive characteristics and consequences. This distinction is easily illustrated on the basis of vicarious embarrassment: in many social encounters perceivers feel vicariously embarrassed in the absence of embarrassment or any other emotion in the social target[3] (Hawk et al., 2011; Krach et al., 2011; Müller-Pinzler et al., 2012; Paulus et al., 2013). Thus, the social target is unaware about the ongoing threats to her social integrity in this situation (Krach et al., 2011). Consequently, in contrast to empathic manifestations, vicarious embarrassment reflects an emotional state in the perceiver that does not match the internal, psychologically real state of the social target. Nonetheless, recent studies provided first evidence that similar processes of mentalizing and mirroring contribute to the perceiver's vicarious embarrassment (Hawk et al., 2011; Krach et al., 2011).

We have previously discussed how mentalizing can result in vicarious emotions that do not match the emotional state of the social target (Krach et al., 2011). This has been explained through self-projections of perceivers who transpose themselves into the position of others thereby integrating their own perspective within the mental simulation (Hawk et al., 2011). However, for several reasons, the mapping of the social target's state in the perceiver's neural network through mirroring processes is also not independent of the perceiver's perspective. First, similar to the processing of sensory information of one's own body (Gazzola et al., 2012), mirroring the target's state in a near-simultaneous isomorphic fashion is modulated by other processes such as mentalizing. This is particularly important in social contexts that constrain the desirability of displayed emotions (e.g., at work). In these situations the enacted and thus mirrored expressions could deviate from the corresponding internal psychological state. Second, the mirror neuron functioning is deeply integrated in a neural network that is tailored and tuned to process information of the perceiver's body. In the most extreme example this is illustrated with mirror neuron activity in response to observing robotic arms grasping objects (Gazzola et al., 2007; Keysers et al., 2010). Those robots do not have any human sensations or form intentions about their actions, however, the perceiver's neural system mirrors the action as if it was human. Consequently, depending on the idiosyncratic learning experiences the mirrored representation should deviate across different perceivers even if the inputs entering the system were exactly similar. These arguments illustrate how mirroring is indeed anchored in the characteristics of the perceiver's neural system and might be modulated by additional information accessible exclusively from the observer's perspective. The resulting simulation of the social target's state through mirroring processes could represent a genuine vicarious emotion. Previous research has already demonstrated such automated vicarious responses while e.g., observing numbed limbs that undergo biopsy (Lamm et al., 2007b).

These thoughts raise the question of whether vicarious in comparison to empathic emotional experiences may serve a useful function in social interactions or have to be considered as the result of immature and maladapted processes to representing another person's internal psychological state. With the help of some examples we argue that these vicarious emotions may indeed provide useful information for perceivers, enable helping behavior, and foster social interactions. First, vicarious emotions contribute to the social regulation of the perceiver's behavior. For instance, many forms of psychological punishment are used as an "example" to induce avoidance of disobedience from norms, even if the social target does not respond to the situation. Perceivers will nonetheless do so and vicariously experience the suffering in that situation. Second, imagine observing the above described non-embarrassed presenter who is currently unaware of the ongoing threat to her social integrity. For perceivers, their vicarious emotional response provides insights about the severity of the threat to the image of the social target. This internal vicarious representation of the unfavorable condition may help to motivate interventions from the perceivers' side in order to re-establish the

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In the present manuscript we use the term "isomorphism" with the latter meaning.

[3] For example, vicarious embarrassment is experienced by attendees of a scientific conference when they observe the presenter of a talk returning from the rest room not realizing that toilet paper is sticking out of the back of her pants.

social integrity of the target. In contrast, perceivers who are tied to an empathically accurate response that matches the internal psychological state of the target may be less prone to develop such motivations. Similarly, with regards to observing physical injuries to another's body, vicarious pain experiences, even in the absence of a psychological state of pain in the target, might provide vital information for initiating costly helping behaviors (Hein et al., 2010).

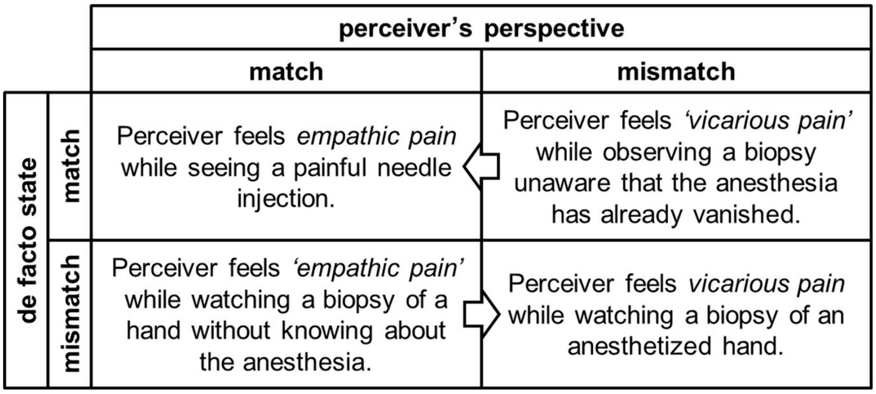
This line of argumentation supports the notion that human beings are not only passive perceivers in the context of social interactions but also active creators of shared emotional experiences. In a natural setting, they need to be aware of their own presence and the simulated vicarious emotions in response to another person's condition; is it in the presence or absence of an emotional state in the social target. The perceiver's construal of a social target's condition as the representation of an internal, "psychologically real" state might thus provide an unnecessarily narrow scope to examining vicarious emotions. Rather, vicarious emotions should be considered as the result of ongoing simulation processes that, depending on the social context as well as personal or task induced motivations are flexibly tuned to match another's internal psychological state.

The question remains if perceivers, even if they intend to, always have correct assumptions about the emotion of the social target. Accordingly, social neuroscience has to consider the match or mismatch of the emotional experiences between social targets and perceivers from *two* perspectives: first, the de facto match or mismatch of the emotions between the perceiver and the social target, and second, the subjective stance of the perceiver about the match or mismatch with the social target's emotions. In social interactions both perspectives may occur independently of each other, resulting in four different states (for examples see **Figure 1**). The neural responses should not differ between de facto and subjective empathic and vicarious emotions, respectively. The transition from one of the states to another might nonetheless offer great potential for unraveling yet neglected neural processes in social interactions. This is especially important considering upcoming second-person neuroscience paradigms that allow the investigation of true social interactions (Krach et al., in press; Schilbach et al., in press).

A PROCESS ORIENTED PERSPECTIVE ON VICARIOUS EMOTIONS

Ideas how to conceptually explain vicarious emotions can be derived from recent efforts in social psychology. Several behavioral studies have examined the process of understanding others' minds. Those studies indicate that people adopt others' perspectives by initially anchoring on their own perspective and then serially adjusting their internal representation to account for differences between themselves and others (Epley et al., 2004). This understanding has been mostly applied in context of cognitive inferences on another person's knowledge or attitudes but might be easily applicable for examining the neural underpinnings of vicarious emotions as well. In a shared social environment, perceivers have access to different inputs (i.e., internal and external, see **Figure 2**) allowing to simulate the social target's state. We have outlined above how both streams of simulation, mirroring and mentalizing, are anchored in the egocentric perspective of the perceiver. The social context then defines how the initial simulation needs to get adjusted in order to provide the foundation for successful social interactions. Depending on the appropriateness of the initial simulation (anchoring) the readjustment process might be more or less demanding and may finish after a "plausible" assessment is reached (Epley and Gilovich, 2001). Notably, the plausibility refers to both, vicarious and/or empathic emotional experiences (**Figure 2**).

So far, social neuroscience has predominantly investigated the two streams of simulation processes and their interactions (Zaki and Ochsner, 2012). We believe that focusing on the subprocesses of anchoring and adjusting in both streams of simulation has the potential to explain vicarious and empathic emotions in a parsimonious framework. A first fMRI study has indicated the potential for this approach in the social neurosciences (Tamir and Mitchell, 2010). While focusing on cognitive inferences, this



		perceiver's perspective	
		match	mismatch
de facto state	match	Perceiver feels *empathic pain* while seeing a painful needle injection.	Perceiver feels *'vicarious pain'* while observing a biopsy unaware that the anesthesia has already vanished.
	mismatch	Perceiver feels *'empathic pain'* while watching a biopsy of a hand without knowing about the anesthesia.	Perceiver feels *vicarious pain* while watching a biopsy of an anesthetized hand.

FIGURE 1 | Integrating the perceiver's perspective in vicarious and empathic emotions. The figure illustrates how the perceiver's assumption about the match of her emotions with the social target's emotion may dissociate from the de facto state. Notably, the neural response pattern within each state is determined by the subjective appraisals of perceivers. The arrows indicate the adjustment of a subjectively "incorrect" stance during the course of social interactions (e.g., feedback of the social target) in order to match the demands of the social context. These transitions might specifically help to dissociate neural processes that are involved in the adjustment and anchoring of one's own perspective.

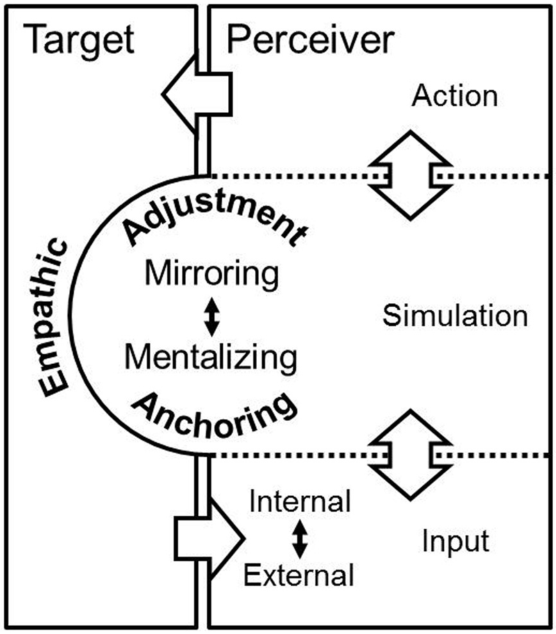


FIGURE 2 | Conceptualization of vicarious and empathic emotions in a unified framework. The figure illustrates how perceiver and social target may interact in a shared social environment and how the perceiver represents vicarious and empathic emotions based on simulation processes. On the most abstract level, the input for the simulation stems from external (e.g., gesture, mimic, prosody) or internal sources (e.g., prior knowledge, past experiences with the interaction partner). Simulation of internal states is realized through two different streams, mirroring and mentalizing, which depend on the available input. Both streams of simulation are anchored in the perceiver's perspective and get adjusted to obtain the adequate outcome in the shared social environment. This can be rather empathic and/or vicarious emotional experience.

study showed the mPFC to be specifically involved in the readjustment process during mentalizing. We would predict similar mPFC functioning in case of readjustment of vicarious emotions, both during mirroring or mentalizing processes. Extending on these findings, one can formulate more refined hypotheses on the involvement of neural networks in simulation processes and the specific functions of subunits within the system. These may allow differentiating vicarious and empathic emotions on the neural systems level and processes involved in the transitions from subjective to de facto vicarious or empathic states (see **Figure 1**). Here, we would predict the mPFC to play a pivotal role for remodeling the "incorrect" subjective state. Future studies on vicarious or empathic emotions, however, need to address the complexity of social situations and manipulate it to the extremes in order to elucidate the specific neural processes involved in the different stances.

Further, the modulatory role of contextual demands on brain and behavior can be tested. Among others, one could model the effects of time constraints or increased cognitive load on the perceiver side, or alter the perceiver's simulation by task induced manipulations. This understanding of simulation processes also is of clinical relevance. Instead of characterizing the impairments in both streams of simulation, research has to consider causes of clinical phenotypes on the level of anchoring and adjustment. The source of e.g., autistic symptomatology might rather originate from disturbed anchoring and adjustment and the inflexibility to modulate the simulation process according to social contextual demands (Paulus et al., 2013). Although, there is evidence for both simulation processes to be affected in individuals with autism (see Zaki and Ochsner, 2012) a theoretical work on autism-spectrum disorders also suggested that affected individuals have strong egocentrically anchoring that cannot be readjusted to the social target's perspective (De Vignemont and Frith, 2007) which might contribute to observed alterations in simulation processes.

In conclusion, we provide an argument for how to distinguish the terms "vicarious emotions" and "empathic emotions." Both originate from the simulation processes mirroring and mentalizing, however, the term "empathic emotions" should be reserved only for incidents where perceivers and social targets have shared, "isomorphic" affective experience (Engen and Singer, 2012). Vicarious emotions offer a wider scope and also include non-shared affective experiences which are nonetheless highly functional in social interactions. With several examples we have briefly illustrated how the two streams of simulation, mirroring and mentalizing, are imbued by the perceiver's perspective which might result in both vicarious and/or empathic emotions. In order to explain these emotional experiences in a parsimonious framework, we think that anchoring and adjustment are the yet neglected concepts that need to get integrated into the research on the neural underpinnings of vicarious experience.

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Why vicarious experience is not an instance of synesthesia

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A vicarious experience is an empathetic state in response to the observation of others' sensations, emotions, and actions (Keysers and Gazzola, 2009). Vicarious experiences in response to social stimuli are quite common in the general healthy population and they may even constitute an important basis for social behavior. Interestingly, vicarious experiences recruit similar neural processes as the primary experience of a certain sensation, emotion, or action, and it is assumed that the mirror neuron system is involved in these vicarious neural processes (e.g., Morrison et al., 2004; Singer et al., 2004; Jackson et al., 2005).

Synesthesia denotes a condition that leads to specific experiences in response to normal sensory input that is not experienced by non-synesthetes. Synesthetic experiences are characterized as idiosyncratic, involuntarily elicited, and consistent over time (Grossenbacher and Lovelace, 2001; Ward, 2013; but see, Simner, 2011). Synesthesia tends to run in families suggesting a genetic component and has a neural basis (Asher et al., 2006, 2009; Barnett et al., 2008). The best studied and most accepted form of synesthesia is grapheme-color synesthesia. People affected by this type of synesthesia experience colors for numbers and letters printed in black on a white background (e.g., Rothen et al., 2012). On a neural basis, it has been suggested that brain regions concerned with binding processes, the modality of the inducing stimulus, and the modality of the respective sensory experience are involved (e.g., Hubbard et al., 2011; Rouw et al., 2011).

Recently, it has been suggested that also vicarious experiences represent an instance of synesthesia. In particular, the term mirror-sensory synesthesia has been introduced in the scientific literature to describe instances of overt phenomenological experiences reflecting the actual state of an observed sensation and/or emotion (i.e., a phenomenologically overt vicarious experience, Fitzgibbon et al., 2012b). It has been suggested that people who report to have explicit and consciously accessible experiences of touch and/or pain upon the observation of other people being touched or in pain may be called mirror-touch and mirror-pain synesthetes, respectively (Fitzgibbon et al., 2010, 2012b). However, other mirror-sensory forms, such as for example mirror-disgust experiences, seem possible.

Here, we argue that the label synesthesia should be reserved for canonical cases of synesthesia (such as grapheme-color or lexical-gustatory) and we outline similarities and differences between synesthesia and vicarious experiences (**Table 1**) (for the use of the term synesthesia see also, Deroy and Spence, 2013). By using the term mirrored sensory experiences, we focus on phenomenologically open instances of vicarious experiences because as by the definition of "mirror-sensory synesthesia" phenomenologically less overt forms are not to be regarded as instances of synesthesia.

At a first glance, mirrored sensory experiences and synesthesia seem to share many features, but there are also marked differences as already mentioned by Fitzgibbon et al. (2012b). Thus, it is open to debate whether mirrored sensory experiences should be regarded as a form of synesthetic experiences. In order to keep the following critical comparison of the two conditions straightforward, we focus on grapheme-color synesthesia as a well-established form of synesthesia.

For both conditions, the mirrored sensor experience and synesthesia, there is a clear relationship between an inducing stimulus (i.e., inducer in the synesthesia literature) and a resulting concurrent experience (i.e., concurrent in the synesthesia literature). Specifically, this may be the observation of touch for mirrored touch experiences and a letter or number in grapheme-color synesthesia. In both cases the concurrent experiences are triggered automatically and involuntarily. Empirical evidence can be found with variants of the Stroop task (Stroop, 1935), where people experiencing mirrored touch show slower reaction times and more errors in reporting perceived touch for incongruent instances of perceived and observed touch in comparison

Table 1 | Commonalities and differences between synesthesia and mirrored sensory experiences.

Criterion	Synesthesia	Mirrored sensory experiences
Prevalence	Rare	Rare to frequent
Developmental trajectory	Early, stable	Late, variable
Neural basis	Specific	General
Bandwith	Typically moderate	Minimal
Consistency	High	Difficult to assess
Idiosyncrasy	High	Minimal
Genetic disposition	Likely and special	Likely but not special
Experience	Conscious	Often conscious

to congruent instances of perceived and observed touch (Banissy and Ward, 2007). Similarly, grapheme-color synesthetes show slower reaction times in real and synesthetic color naming when presented with graphemes incongruently colored to their experiences in comparison to graphemes congruently colored with their experiences (e.g., Dixon et al., 2004; Ward et al., 2007). However, these kind of Stroop effects do not proof the genuine nature of synesthetic experiences and can be found in non-synesthete controls trained on grapheme-color associations (e.g., Meier and Rothen, 2009; Rothen et al., 2011; Colizoli et al., 2012) or even swimming-style color associations (Rothen et al., 2013a).

Since synesthetic experiences are idiosyncratic and consistent over time, the gold-standard to establish synesthetic experiences is to assess the consistency of the inducer-concurrent relationship in a test-retest procedure. Due to their conscious *experiences*, synesthetes generally exhibit high test-retest consistency for individual inducer-concurrent pairings, but not so controls who have to rely solely on memory (e.g., Baron-Cohen et al., 1987; Eagleman et al., 2007). In contrast, it is not possible to use the test of consistency to mirrored sensory experiences because there is only a minimal bandwidth (i.e., one inducing stimulus such as observed touch or pain for individual forms of mirrored experiences only) and thus, there is no variability in the mirrored experience. Moreover and importantly, the vicarious experience is identical to the inducing stimulus (which is identical to the observed experience).

While the concept of bandwidth (Asher et al., 2006) did not receive much attention in the synesthesia literature, we are not aware of any form of synesthesia which bandwidth is theoretically limited to only one inducer. However, this seems to be the case for the different forms of mirrored sensory experiences (i.e., mirrored touch and mirrored pain). The fact that different levels of intensity of touch or pain, respectively, may or may not induce a mirrored experience has more to do with the associated characteristics of the specific stimulus than actually representing different stimuli (but see, Fitzgibbon et al., 2012b).

The lack of variability (and consequentially lack of categorical organization) in mirrored sensory experiences prevents individual forms of mirrored sensory experiences from sharing with established forms of synesthesia the core criterion of idiosyncratic inducer-concurrent pairings. That is, while A may elicit a red color experience for one grapheme-color synesthete, it may elicit a blue color experience for another grapheme-color synesthete (Grossenbacher and Lovelace, 2001). In contrast, mirrored sensory experiences seem rather systematic than idiosyncratic (for the use of "systematic" in relation to crossmodal correspondences or "weak synesthesia" see, Martino and Marks, 2001). That is, observed soft touch would result in perceived soft touch and observed strong touch would result in perceived strong touch.

The fact that the mirrored sensory experience is identical to the experience of the inducing stimulus constitutes a marked difference between mirrored sensory experiences and established forms of synesthesia, for which the inducer-concurrent relationship is typically somewhat arbitrary and idiosyncratic (but see, Rich et al., 2005; Simner et al., 2005). Due to this characteristic of mirrored sensory experiences, they may be more comparable to the hypothetical form of, for example, grapheme–grapheme synesthesia in which specific graphemes would elicit an experience of the very same grapheme in front of the mind's eye of the perceiver or projected in the space between the inducing grapheme and the eyes of the perceiver—two subtypes that exist in grapheme-color synesthesia described as associator and projector, respectively (Dixon et al., 2004; Ward et al., 2007).

As mentioned earlier, mirrored sensory experiences have a neural basis which is quite different from that of synesthesia. Mirrored experiences are thought to be associated with activity in mirror-neurons which respond not only to an action, sensation, or emotion but also to the observation of the same or a similar action, sensation, or emotion. Mirror-neurons can be found in various different regions of the brain (Keysers and Gazzola, 2009). Mirrored touch and pain experiences are supposed to be associated with activity of mirror-neurons in the somatosensory cortex and the insula (Blakemore et al., 2005; Osborn and Derbyshire, 2010). Hence, mirrored experiences seem to reflect intramodal activity. In contrast, synesthesia seems to reflect explicitly experienced crossmodal activity. That is, synesthesia is associated with brain activity not only related to the inducer but also to the respective specific concurrent (i.e., as if it were sensory in its nature). In grapheme-color synesthesia, these are a grapheme-sensitive region and human color area (hV4) both located in the region of the fusiform gyrus. Moreover, there seem parietal binding mechanisms involved which are thought to underlie the integration of the inducer and concurrent experience (e.g., Rothen et al., 2010; Rouw et al., 2011).

Hence, mirrored experiences seem to be lying on a continuum with vicarious experiences more generally. Indeed, vicarious experiences in the general population are found to activate similar brain areas as mirrored experiences and mirror experiences are found to activate similar brain regions as the respective perceived experience. Collectively, there is increasing evidence for vicarious, mirrored, and real experiences of pain and touch, respectively to have a common neural basis associated with insular, somatosensory, and cingulate cortex activation (e.g., Morrison et al., 2004; Singer et al., 2004; Blakemore et al., 2005; Jackson et al., 2005; Keysers and Gazzola, 2009; Osborn and Derbyshire, 2010). Interestingly, also in non-synesthetes interactions between systems for perceiving and observing touch can be found. That is, sub-threshold stimulation is more likely to be perceived by observing touch to own face than others faces or inanimate objects (Serino et al., 2008). In contrast, the presence/absence of synesthesia seems to reflect a bimodal distribution (Rothen et al., 2013b).

Accordingly, mirrored experiences have been interpreted as the result of an overactive mirror system (Blakemore et al., 2005; Fitzgibbon et al., 2012b). This would be in line with the notion that mirrored experiences are an extreme characteristic of an otherwise normal somatosensory experience on the same continuum (Fitzgibbon et al., 2012b). The relative high incidence (i.e., 30%) of mirrored pain within the general population (Osborn and Derbyshire, 2010) is also suggestive that mirrored experiences are rather normal. In contrast, mirrored touch experiences seem to be more special as the prevalence was estimated to be around 1.6% (Banissy et al., 2009). In addition, an association between enhanced self-rated empathy in people who experience mirrored pain (Osborn and Derbyshire, 2010) and mirrored touch (Banissy and Ward, 2007; but for mirrored pain and empathy in amputees see, Fitzgibbon et al., 2012a) further supports the notion of mirrored sensory experiences as being rather normal experiences on a somatosensory continuum that might be based on empathetic abilities.

Mirrored sensory experiences (i.e., mirrored touch and mirrored pain) seem to be very similar to socially contagious phenomena such as laughter (Provine, 1992), yawning (Provine, 1989; Platek et al., 2003), and itching (Holle et al., 2012). Watching someone laughing can induce a feeling of happiness and put a smile or laugh on the face of the perceiver, watching someone yawning can induce a yawning in the perceiver, and watching someone scratching himself can induce a feeling of itchiness and may lead to the perceiver scratching himself. That is, there is always an inducing stimulus and always a concurrent experience/action. The concurrent experience is elicited automatically, but there is no idiosyncrasy because the concurrent experience is not generally organized in categories. Furthermore, there is also a social component associated with the inducing stimulus (i.e., someone is being perceived doing something) which does not exist for classical forms of synesthesia, but for mirrored sensory experiences. Hence, mirrored sensory experiences may belong to the same category of experiences as socially contagious phenomena which in turn would follow the same continuum as mirrored experiences. Accordingly, it would be interesting to see whether people who are generally more prone to socially contagious phenomena also exhibit higher self-rated empathy (but see, Holle et al., 2012).

Evidence for the similarity between mirrored sensory experiences and socially contagious phenomena can be found on a neural basis. Exactly as mirrored sensory experiences are socially contagious phenomena based on mirror neuron activity and do in fact elicit similar brain activity in the perceiving person as well as the in the observing person (Holle et al., 2012). Accordingly, as used throughout the article, we suggest the terminology "mirrored sensory experience" as a subgroup of socially contagious vicarious phenomena instead of "mirror-sensory synesthesia" as a subgroup of synesthesia.

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The social and personality neuroscience of empathy for pain and touch

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First- and third-person experiences of bodily sensations, like pain and touch, recruit overlapping neural networks including sensorimotor, insular, and anterior cingulate cortices. Here we illustrate the peculiar role of these structures in coding the sensory and affective qualities of the observed bodily sensations. Subsequently we show that such neural activity is critically influenced by a range of social, emotional, cognitive factors, and importantly by inter-individual differences in the separate components of empathic traits. Finally we suggest some fundamental issues that social neuroscience has to address for providing a comprehensive knowledge of the behavioral, functional and anatomical brain correlates of empathy.

Keywords: empathy, personality, social cognition, somatosensory cortex, insula, ACC

INTRODUCTION

We refer to empathy as that fundamental process in human social interactions that allows the understanding of others people sensations and emotions by sharing their sensory and affective states. However, despite philosophers, developmental and social psychologists having long investigated empathy (Eisenberg et al., 1987; Batson, 1991; Eisenberg, 2000; Hoffman, 2000), there is still no universal agreement on its definition and on the different interrelated phenomena it subsumes (a review of this debate: Preston and de Waal, 2002; Blair, 2005a; de Vignemont and Singer, 2006; Batson, 2009). Numerous scholars suggested that empathy comprises several components and independent but interacting mechanisms (Davis, 1996; Eisenberg, 2000; Decety and Jackson, 2004), such as sensory-affective and emotional sharing (Preston and de Waal, 2002), cognitive perspective taking of others' states (Davis, 1996; Decety and Jackson, 2004), the ability to discern the other as the source of our own affective state (review in Singer and Lamm, 2009) and self-regulatory mechanisms that influence the extent of the empathic experience and the likelihood of prosocial behaviors (see Decety, 2011 for a critical discussion). Indeed, empathic reactions may stem from feelings of sorrow for others' pain (i.e., sympathy) to distress for an unpleasant scene (Batson, 1991; Davis, 1996).

Social neuroscience has only recently started to investigate the neural underpinnings of empathy being strongly influenced by the shared representation accounts which postulate that the human ability to understand others' motor, perceptual, and emotional states is sub-served by the activation of corresponding representations in the observer (Preston and de Waal, 2002; Gallese, 2003). At the neural level, such ability could rely on mirror-like mechanisms similar to the mirror neurons that (in primate brain) encode both executed and observed actions (di Pellegrino et al., 1992). Accordingly, since their discovery numerous studies in humans found shared neural representations between self and others in the domain of actions (Rizzolatti et al., 2001; Avenanti et al., 2013; Tidoni et al., 2013), emotions (Wicker et al., 2003; Bastiaansen et al., 2009; Borgomaneri et al., 2012) and sensations, like pain and touch (Keysers et al., 2010; Bernhardt and Singer, 2012).

Here we focus on the brain regions involved in first- and third-person experience of pain and touch, and illustrate their peculiar role in coding the sensory and affective qualities of these bodily sensations. Subsequently we show how—despite such vicarious activations seeming to occur automatically (i.e., without conscious and effortful processing)—they can be modulated by inter-individual differences in personality traits, dispositions, attitudes, and social and cognitive forms of interpersonal evaluation of the other. We conclude by suggesting that some fundamental issues have to be addressed by future research to improve knowledge on the complex relationship between behavioral and both functional and anatomical neural correlates of empathy.

VICARIOUS NEURAL ACTIVATIONS TO OTHERS' PAIN AND TOUCH

VICARIOUS PAIN

Experiencing pain involves two complementary but dissociable components (Craig, 2002) encoded in distinct nodes of the so-called "pain matrix" neural network (Melzack, 1999). The sensory discriminative component concerns the physical qualities of the stimulus (e.g., intensity) and is associated with activity in somatosensory and motor cortices. The affective-motivational component relates to the subjective aspects of pain perception (e.g., unpleasantness) and is encoded by the anterior insula (AI), which is known to be involved in representing and integrating internal and emotional feelings states (Craig, 2002) and by the anterior cingulate cortex (ACC) (Peyron et al., 2000), which is known to re-represent the emotional global states to control, select, and prepare appropriate responses (Medford and Critchley, 2010).

Yet, pain perception is not only a private state. Understanding others' pain is a fundamental ability in social interactions that is sub-served by the same neural structures as those involved in first-person experience of pain (Preston and de Waal, 2002; Gallese et al., 2004; Keysers and Gazzola, 2009; Decety, 2011). The sensory discriminative aspects of observed pain are associated with activity in primary (S1) and secondary (S2) somatosensory cortices (Bufalari et al., 2007; Saarela et al., 2007; Costantini et al., 2008; Valeriani et al., 2008; Akitsuki and Decety, 2009; Betti et al., 2009; Voisin et al., 2011; Aziz-Zadeh et al., 2012), as well as in primary motor cortex (M1) (Avenanti et al., 2005), while the affective-motivational qualities of observed pain are associated with activity in AI and ACC (Morrison et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2006; Saarela et al., 2007). Empathic responses in these regions could thus reflect a process that represents bodily and affective states in the self and in the others, with the final aim to guide homeostatic and behavioral responses (Singer and Lamm, 2009).

VICARIOUS TOUCH

Observing touch also elicits mirror-like responses. Increasing evidence points to the peculiar role of somatosensory cortices in processing sensory qualities of observed touch (Keysers et al., 2010; Morrison et al., 2011a). S2 is active both when being touched and observing someone else being touched (Keysers et al., 2004; Blakemore et al., 2005; Schaefer et al., 2006; Ebisch et al., 2008). Functional neuroimaging (Blakemore et al., 2005; Schaefer et al., 2009, 2012) and electroencephalography (Bufalari et al., 2007; Martinez-Jauand et al., 2012) studies showed that also S1 responds to observed touch, especially when the body is seen from a first-person perspective (Schaefer et al., 2009) and its activity (as indexed by early Somatosensory Evoked Potentials (SEPs)) correlates with intensity (but not with the unpleasantness) of the observed bodily sensations (Bufalari et al., 2007).

THE SOCIAL NEUROSCIENCE OF EMPATHY FOR PAIN AND TOUCH

SOCIAL PAIN

Fascinatingly, rather than being fixed, the empathic behavioral and neural responses can be reduced or increased by a broad range of cognitive (Lamm et al., 2007a), emotional, and social factors (de Vignemont and Singer, 2006), such as personal state and interpersonal relationship or appraisal of the other in pain.

For example, in acupuncturists—who must prevent distress to impair their ability to be of assistance—the ACC and AI neural responses to others' pain are significantly reduced (Cheng et al., 2007). Similarly, being in pain oneself while observing pain in others may reduce the vicarious activity of the somatic nodes of the pain matrix (Valeriani et al., 2008), suggesting that being in pain may bias the empathic relation with others towards self-centered empathic stances.

On the other hand, adopting the perspective of a beloved person in pain increases activity in ACC and AI (Cheng et al., 2010). Conversely, affective sharing of pain of an unfair other is associated with reduced fronto-insular and ACC activity and increased activation of reward-related areas (Singer et al., 2006). Social in/out group membership can also modulate the brain activity related to agonistic or antagonistic motivation to empathize and to pro/antisocial behavior. Indeed, other-oriented feelings of sympathy and AI activity predicted the tendency to engage in costly behavior to reduce an affiliated soccer fan's pain, while subjective negative evaluations of the opponent fan and nucleus accumbens activations predicted the tendency to not make a sacrifice for this individual (Hein et al., 2010). Similarly, observing members of different ethnicity being in pain reduces the sensorimotor empathic response (Avenanti et al., 2010), while observing pain experienced by own- versus other-race individuals increases autonomic reactivity, ACC and AI activity (Xu et al., 2009; Azevedo et al., 2012) as a function of the observers' implicit racial biases (Avenanti et al., 2010; Azevedo et al., 2012; Sessa et al., 2013). The behavioral and neural empathic resonance can also be modulated by a priori attitudes toward the target group. Indeed, empathy ratings, AI and midcingulate activity are stronger for the observation of pain in HIV/AIDS transfusion targets, but weaker for HIV/AIDS drug targets (Decety et al., 2010).

Thus, empathic resonant activity in empathy-related neural networks may interact with (and be modulated by) the activity of other neural networks relevant for social cognition such as those involved in mentalizing, in coding reward, or in cognitive control and emotion regulation.

SOCIAL TOUCH

The affective and social meaning of touch can modulate behavioral and neural responses to observed human tactile interactions. Indeed skin-to-skin contact is crucial for social interactions sub-serving nonverbal communication of intentions and emotions. Observing a face being touched by fingers enhanced the detection of around-threshold tactile stimuli on the observer's face (Cardini et al., 2011), more strongly if the observers and the observed faces belong to the same (versus different) social group (Serino et al., 2009).

Also, the affective meaning conveyed by a hand stroking a body increases S1, S2, and insular activity (Morrison et al., 2011a). Particularly, S1 activity is stronger when observing human-based intentional touch (Ebisch et al., 2008) and is causal to understanding the affective consequences (Bolognini et al., 2013) of tactile interactions between people (Rossetti et al., 2012). Even when touch is physically experienced, S1, S2, and insular activity are stronger when participants receive a gentle stroking performed by a hand (with respect to a stick; Kress et al., 2011). Interestingly, S1 activity is further modulated by the believed (opposite) gender of the caresser, despite the sensory stimulation properties being the same across genders (Gazzola et al., 2012). These results highlight the twofold function of S1 in social interactions: it encodes the sensory qualities of first- and third-person experience of bodily sensations, and is further modulated by the attributed affective components of human tactile interactions. Modulation of S1 activity related to somatic and affective qualities of observed sensations is probably due to feedback projections from multimodal fronto-parietal (Macaluso and Driver, 2005) and insula areas. Indeed, processing gentle touch and its associated pleasant sensation is conveyed by the so-called tactile C (CT) fibers (Olausson et al., 2002), which project to the insular cortex (Bjornsdotter et al., 2010) that in turn is functionally connected to the sensorimotor cortices (Deen et al., 2011). Pathologically reduced CT-fiber density is associated with a less pleasant evaluation of observed interpersonal touch, and with absent modulation of insular activity (Morrison et al., 2011b). Conversely, in healthy participants the observation of somebody else's arms being stroked elicits a similar response in the posterior insula as when one is directly feeling touch (Morrison et al., 2011a). These results suggest that the representations of our feeling states in insula form the basis for understanding the feelings of others. Ebisch et al. (2011) found opposite activation patterns in posterior insula for first- and third-person experience of affective human touch and suggested this region can differentiate the stimulation source (self versus other), which is consistent with its role in mediating the sense of body ownership (Heydrich and Blanke, 2013).

THE PERSONALITY NEUROSCIENCE OF EMPATHY FOR PAIN AND TOUCH

EMPATHIC TRAITS

Empathic responses comprise cognitive, affective, and emotional components (Batson, 1991), and may reflect stable personality dispositions (trait empathy; Davis, 1996) or be linked to situational and contextual factors (state empathy; Batson et al., 1983). From a neuroscientific perspective this suggests that distinct neural mechanisms may underpin different types of empathy-related responses.

Indeed, empathy-related activity in the affective division of the pain matrix correlates with scores in trait empathy emotional scales (Singer et al., 2004; Lawrence et al., 2006; Lamm et al., 2007a; Saarela et al., 2007; Cheetham et al., 2009; Lang et al., 2011), such as the Balanced Emotional Empathy Scale (Mehrabian and Epstein, 1972), the Emotional Contagion Scale (ECS; Doherty, 1997), and both the Empathic Concern (EC) and Personal Distress (PD) subscales of the Interpersonal Reactivity Index (IRI; Davis, 1996). However, a recent meta-analysis suggested that empathic neural responses are better predicted by situational rather than by dispositional measures of emotional empathy (Lamm et al., 2011).

Also the empathy-related activity in the sensory division of the pain matrix shows a complex pattern of correlations with different empathic components. The empathic sensorimotor response is independently predicted not only by the sensory qualities of pain, but also: (i) positively by the participants' ability to imaginatively transpose into others' feelings and states (as indexed by IRI-PT subscale); and (ii) negatively by either the situational than the stable tendencies to experience personal distress as a result of others' pain (Avenanti et al., 2009). Interestingly, also vicarious pain-related activity in S1 is positively correlated with IRI-PT scores (Cheng et al., 2008; Martinez-Jauand et al., 2012). Additionally, functional and anatomical neuroimaging studies showed significant correlations between self-oriented emotional empathy (as indexed by IRI-PD) and (i) vicarious sensorimotor activations to others' pain (but only in females: Yang et al., 2009), and (ii) reduced gray matter volume in S1 (Banissy et al., 2012). These results thus suggest that both brain structure and vicarious activity in the sensory node of the pain matrix are independently influenced by distinct functional, not purely sensory, mechanisms.

Remarkably, the role exerted by inter-individual differences in cognitive empathy has been demonstrated also for touch-related vicarious activity in S1. PT scores are positively correlated with increased amplitude of early SEPs (Martinez-Jauand et al., 2012), S1 hemodynamic responses to observed touch (Schaefer et al., 2012), and impairments in encoding the affective valence of others' somatic feelings resulting from disruption of S1 activity (Bolognini et al., 2013). No associations, instead, have been reported between vicarious somatosensory activations to touch/pain and other trait cognitive (IRI-Fantasy Scale) or emotional empathy scales [IRI-PD, IRI-EC, Empathic Quotient (Baron-Cohen and Wheelwright, 2004) or ECS (Doherty, 1997)]. Interestingly, similarly to the domain of sensations PT—but not other IRI subscales—correlates also with S1 vicarious activity to heard human actions (Gazzola et al., 2006).

Thus, taking into account that different experimental designs and manipulations were used, it seems that a rather coherent picture emerges from the above-mentioned studies. Indeed, structures coding affective qualities of observed sensations are more closely related to emotional empathy traits, while vicarious activity in structures coding sensory qualities of observed sensations is differentially modulated by cognitive perspective taking abilities and self-oriented empathic responses.

THE INFLUENCE OF SOCIAL, AFFECTIVE, AND EMOTIONAL ABILITIES ON EMPATHY

The behavioral and neural empathic responses have been recently investigated in pathological conditions affecting the social and emotional sphere, as well as in participants with different affective styles.

Clinical studies indicate that psychopaths show cognitive empathy and mentalizing abilities in the normal range (if not higher) but they lack emotional reactivity and sympathy responses (Blair, 2005b). Autistics, instead, show reduced theory of mind and metalizing-related brain activity (Frith and Frith, 2006). Interestingly, the sensorimotor response to others' pain is greater in (healthy) subjects with high scores in a psychopathology scale (Fecteau et al., 2008) and absent in individuals with Asperger syndrome (Minio-Paluello et al., 2009).

Based on the assumption that awareness of one's own emotional states is a prerequisite for recognizing such states in others (Decety and Jackson, 2004), alexithymic patients—who have a deficit in identifying and expressing one's own emotional states—show reduced ACC activations to others' pain, and score low in empathy questionnaires (Moriguchi et al., 2007). Also, alexithymic scores of control participants are negatively correlated with left AI activity during imagination of a close other in pain (Bird et al., 2010). Interestingly, insular response to the observation of a beloved in pain is also associated with the tendency to regulate one's own emotional responses on the base of bodily-emotional states (Mazzola et al., 2010), i.e., with "inward" dispositional affective style (Arciero et al., 2004).

These results thus confirm that representations of our bodily and emotional feeling states in insula and ACC form the basis for understanding and reacting to the feelings of others.

FUTURE PERSPECTIVES

Recent theoretical and methodological advances in social and cognitive neuroscience critically improved the conceptualization of neurocognitive models of human empathy. Future studies might fruitfully address some fundamental issues on the relationship between behavioral, functional and anatomical brain correlates of empathy.

One important issue regards the causal nature of the relationship between empathy-related behavior and brain activity. Further studies are needed to show whether changes in empathy-related brain activity—as induced by brain stimulation techniques (such as TMS or transcranial Direct Current Stimulation)—can change empathic behavioral responses, as well as changes in empathic behavior—as induced by focused training or psychotherapy—can induce changes in empathy-related brain activity. Initial findings suggest a bidirectional influence by showing that (i) interfering/enhancing the activity of empathy-related brain structures produces impairments/enhancements in empathy tasks and traits (Balconi and Bortolotti, 2012; Rossetti et al., 2012; Bolognini et al., 2013), while (ii) focused training on empathic resonance increased vicarious activity in affective node of the pain matrix when witnessing people suffering (Klimecki et al., 2013).

An additional major issue is the association between anatomical and functional brain organization related to empathic personality features. Recent evidence shows that the same regions (in particular ACC and AI) were identified by both functional and structural neuroimaging as the neural substrate of specific empathic traits (Yang et al., 2009; Banissy et al., 2012). Despite the indication that structural and functional changes can be associated (Durston and Casey, 2006), the work on the relationship between anatomical and functional features of empathy is still very limited, and the conclusions have to be considered with caution.

A third main issue regards the relationship between personality dimensions, empathic traits, and vicarious brain activations to others' emotions and sensations. Despite it being known that different personality factors individuated by the Big Five theory of personality (McCrae and Costa, 1991) are related to distinct empathic components (EC is closely related to agreeableness, PD to neuroticism, while PT shows a complex interstitial relationships with the 5 factors; Mooradian et al., 2011), there are still limited data concerning this relationship (Marcoux et al., 2013; Schaefer et al., 2013). Gender also plays a role in this complex relationship. Indeed, women have higher empathic abilities, neuroticism, agreeableness, and extraversion scores (Goodwin and Gotlib, 2004), and seem to have also stronger vicarious-pain-related brain activations (Han et al., 2008; Yang et al., 2009). However, studies investigating the interplay between personality, gender, and empathy-related brain activity are still lacking and should involve highly representative samples, larger than those commonly used in neuroimaging experiments.

In summary the available data have enhanced the understanding of vicarious experience at both neural and psychological levels. However, in order to fulfill the needs of a comprehensive and predictive model of human empathy, further work will have to integrate converging evidence from the molecular, cellular, and systemic levels both in healthy and neurological conditions.

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Vicarious ostracism

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Ostracism—being ignored and excluded—causes distress and threatens psychological needs (i.e., belonging, self-esteem, control, and meaningful existence; Williams, 2009). Even subtle behaviors, such as withholding eye contact or staring through someone as if they did not exist, can induce feelings of ostracism (Wirth et al., 2010; Wesselmann et al., 2012). Most individuals experience ostracism at least once in their lives and some experience it daily (Williams, 2009; Nezlek et al., 2012).

Empathy research suggests that individuals vicariously experience others' pain. Most of this research has focused on vicarious physical pain, but might observers also experience vicarious *social* pain (i.e., ostracism)? We will review the emerging research on vicarious ostracism, highlighting the neural correlates of this phenomenon. Finally, we posit future research questions to strengthen the theoretical understanding of vicarious ostracism from social cognitive and evolutionary psychological perspectives.

STUDYING VICARIOUS OSTRACISM

We are aware of nine experimental studies demonstrating vicarious ostracism. These studies find that observers recognize an ostracized individual's distress and also feel ostracized themselves (Over and Carpenter, 2009; Wesselmann et al., 2009; Masten et al., 2010, 2011a, 2013a,b; Beeney et al., 2011; Meyer et al., 2012; Will et al., 2013). Vicarious ostracism has been demonstrated in both child/adolescent (Over and Carpenter, 2009; Masten et al., 2010, 2013a,b; Will et al., 2013) and adult samples (Wesselmann et al., 2009; Beeney et al., 2011; Masten et al., 2011a; Meyer et al., 2012; Will et al., 2013). Vicarious ostracism is enhanced when individuals actively perspective-take (Wesselmann et al., 2009), are higher in trait empathy (Masten et al., 2010, 2011a,b, 2013a), or are closely related to the target (Beeney et al., 2011; Meyer et al., 2012).

These studies used two different paradigms. The primary paradigm is Cyberball—a computer-based ball-tossing game in which participants interact with two computer-controlled confederates (Williams, 2009). These confederate players are programmed to either *include* all players equally or to *ostracize* the participant by giving them only two ball tosses at the beginning of the game. Seven studies (Wesselmann et al., 2009; Masten et al., 2010, 2011a,b, 2013a; Beeney et al., 2011; Meyer et al., 2012; Will et al., 2013) adapted this paradigm by programming all of the players' tossing behavior and telling participants they are *observing* a game already in progress. Over and Carpenter (2009) animated two shapes playing ball together. Eventually, another shape approaches the game—this new shape is either similar to the others (ostracism condition) or dissimilar (i.e., a butterfly; control condition). Regardless of condition, the ball-tossing shapes do not toss to the new shape and ultimately avoid the shape.

These studies have impressive diversity in outcome measures. Wesselmann et al. (2009) measured self-reported psychological need threat. Six studies (Masten et al., 2010, 2011a,b, 2013a,b; Beeney et al., 2011; Meyer et al., 2012) used fMRI measures of brain activity in regions associated with experiencing ostracism oneself (Eisenberger and Lieberman, 2004). Four studies using measures of prosocial/affilitative behavior (Over and Carpenter, 2009; Masten et al., 2010, 2011a,b; Will et al., 2013) found that vicarious ostracism increases prosocial/affiliative behavior much like directly experiencing ostracism does (Williams, 2009).

THE NEURAL STRUCTURE OF VICARIOUS OSTRACISM

Observing ostracism increased activity in the dorsal anterior cingulate cortex (dACC) and anterior insula (AI), two brain regions activated by directly experiencing ostracism (Eisenberger and Lieberman, 2004). Observing ostracism also activated the dorsomedial (DMPFC) and medial prefrontal cortexes (MPFC) and precuneus—brain regions associated with *mentalizing* (i.e., thinking about another's mental state; Masten et al., 2011a,b, 2013b). Individual differences in empathy predicted brain activation in both the mentalizing regions (i.e., bilateral DMPFC, MPFC, and temporal parietal junction) and social pain-related regions (i.e., AI and dACC) during vicarious ostracism (Masten et al., 2011a, 2013a). Vicarious ostracism involves different brain regions depending upon the ostracized target; observing a friend's ostracism activated regions associated with direct ostracism experience (i.e., dACC and insula), whereas a stranger's ostracism involved mentalizing-relevant regions (i.e., DMPFC, precuneus, and temporal pole; Meyer et al., 2012). Finally, brain activation in the AI and MPFC—regions associated with trait empathy—correlated with pro-social responses toward the ostracized target (Masten et al., 2010, 2011a).

FUTURE RESEARCH QUESTIONS

ADAPTATION?

Researchers have speculated that empathy is an adaptation (Decety and Jackson, 2004). Nairne (2010) argues that an adaptation argument must present evidence that the phenomenon helps organisms survive and reproduce; otherwise the phenomenon could be a byproduct of other psychological adaptations. A compelling case has been made for the survival-relevance of *directly* experiencing social pain (MacDonald and Jensen-Campbell, 2011), but future research should directly test whether vicarious ostracism facilitates differential survival and/or reproduction using evolutionary psychology methods. Otherwise, it is difficult to rule out the possibility that vicarious ostracism only occurs because the neural structures for experiencing both physical and social pain are yoked together (Eisenberger and Lieberman, 2004)?

SCHADENFREUDE?

In light of the research on vicarious ostracism a paradox emerges: why are rejection/ostracism-based reality television programs (e.g., *Survivor*) popular? When participants are eliminated, they are openly rejected (told they are not wanted; Williams, 2007), and ostracized from the show. Initial rejection undoubtedly hurts, but so does subsequent ostracism; they are no longer on the show, no longer included in activities, no longer talked with or about. These two types of social pain have similar psychological outcomes (c.f., Bernstein and Claypool, 2012). To our knowledge there have been no vicarious *rejection* studies, but based on the extant data on vicarious ostracism and other social pain (e.g., vicarious embarrassment; Krach et al., 2011), it is likely that observing rejection would have similar vicarious effects.

Williams (2009) argues attributions influence interpretations of and reactions to ostracism. Recent neural evidence suggests external attributions for being ostracized (i.e., racism) can help reduce the initial negative effects (Masten et al., 2011b). By extension, an observer's attributions about an ostracized individual may influence vicarious ostracism. Weiner (2006) argues individuals feel satisfaction in others' suffering if perceived as deserved (*Schadenfreude*). Schadenfreude research has found feelings of dislike, anger, or resentment can lead to perceived deservingness and pleasure at another's misfortune, both in self-reports and neurological measures (Weiner, 2006; Feather, 2008; Takahashi et al., 2009). If ostracized/rejected individuals are viewed as deserving their treatment, observers should feel less sympathy for them. Future research should explore if these attributions moderate empathic reactions to ostracism/rejection. Perhaps viewers of rejection-based reality shows lament for individuals unjustly rejected but rejoice when others get what they deserve for behaving anti-socially.

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The role of automaticity and attention in neural processes underlying empathy for happiness, sadness, and anxiety

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Although many studies have examined the neural basis of empathy, relatively little is known about how empathic processes are affected by different attentional conditions. Thus, we examined whether instructions to empathize might amplify responses in empathy-related regions and whether cognitive load would diminish the involvement of these regions. Thirty-two participants completed a functional magnetic resonance imaging session assessing empathic responses to individuals experiencing happy, sad, and anxious events. Stimuli were presented under three conditions: watching naturally, actively empathizing, and under cognitive load. Across analyses, we found evidence for a core set of neural regions that support empathic processes (dorsomedial prefrontal cortex, DMPFC; medial prefrontal cortex, MPFC; temporoparietal junction, TPJ; amygdala; ventral anterior insula, AI; and septal area, SA). Two key regions—the ventral AI and SA—were consistently active across all attentional conditions, suggesting that they are automatically engaged during empathy. In addition, watching vs. empathizing with targets was not markedly different and instead led to similar subjective and neural responses to others' emotional experiences. In contrast, cognitive load reduced the subjective experience of empathy and diminished neural responses in several regions related to empathy and social cognition (DMPFC, MPFC, TPJ, and amygdala). The results reveal how attention impacts empathic processes and provides insight into how empathy may unfold in everyday interactions.

Keywords: empathy, attention, automaticity, cognitive load, fMRI, happiness, sadness, anxiety

INTRODUCTION

Empathy allows us to understand and share others' emotions, creating a bridge between the self and the innermost experiences of another person. As we interact with others in our everyday lives, we may respond empathically to one person, but fail to connect with how another person is feeling. While previous research has suggested that certain factors—such as similarity to the target and familiarity with an experience—can trigger empathy (Preston and De Waal, 2002; Mitchell et al., 2006; Xu et al., 2009), very little research has examined how attention impacts our ability to empathize. Past research suggests that empathy may occur instantaneously and automatically when we recognize another's emotional state (Preston and De Waal, 2002), even if we are cognitively busy. However, other research suggests that empathy is disrupted when we are distracted and cognitively occupied (Gu and Han, 2007). Because attentional resources are often depleted during everyday interactions, it is important to know if empathy is automatically engaged or requires controlled and effortful processing. Thus, the current study examines the role of automaticity and attention in neural processes underlying empathy.

CORE NEURAL REGIONS FOR EMPATHY

A key reason to look at empathy for multiple emotions under a variety of attentional conditions is that it allows for an analysis of core neural regions for empathy. Previous research has identified neural regions that are consistently activated during empathy for physical pain (i.e., dorsal anterior cingulate cortex, dACC; and anterior insula, AI) (Morrison et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005; Zaki et al., 2007; Xu et al., 2009; Lamm et al., 2011). These reliable activations in the dACC and AI have led some researchers to conclude that these regions are part of a core network in empathy (Fan et al., 2011). However, it is unknown whether the dACC and AI are essential to empathic processes more generally (i.e., not just empathy for pain) and whether these regions are activated during empathy for both positive and negative emotions.

Recent neuroimaging research suggests that other neural regions—such as the medial prefrontal cortex (MPFC; BA 10), dorsomedial prefrontal cortex (DMPFC; BA 9), and ventromedial prefrontal cortex (VMPFC; BA 11)—may be involved in empathic processes. For example, accurate empathic judgments are associated with increased MPFC activity (Zaki et al., 2009). MPFC is also consistently activated in mentalizing or theory of mind tasks in which participants infer the mental states of others (Frith and Frith, 2006). In addition, empathy for social and emotional pain activates both MPFC and DMPFC (Masten et al., 2011; Bruneau et al., 2012; Meyer et al., 2012). For patients with neurodegenerative disease, atrophy in MPFC and DMPFC is associated with empathic deficits (Rankin et al., 2003, 2006). In addition, lesion patients with profound empathy deficits have damage in VMPFC (Shamay-Tsoory et al., 2003). Perspective-taking, a key component of empathy, also activates DMPFC (D'Argembeau et al., 2007) and VMPFC (Ames et al., 2008). Finally, judging the emotional states of others increases MPFC, DMPFC, and VMPFC activity (Farrow et al., 2001). Notably, many of these studies did not examine empathy for physical pain and instead focused on neural responses during empathy for other emotions (e.g., social pain). Thus, MPFC, DMPFC, and VMPFC may be involved in empathic processing more generally and may not have been implicated in previous research due to an exclusive focus on empathy for pain.

Additionally, we posit that empathy may increase prosocial motivation and neural activity in SA. In fact, numerous animal studies have demonstrated that the septal area is critical for maternal caregiving (Stack et al., 2002; Gammie, 2005). Recent analyses on a subset of this data also provide tentative evidence that SA activation during empathy predicts daily prosocial behavior in humans (Morelli et al., in press). In addition, past fMRI research has shown that SA activity is related to prosocial behavior, such as charitable donations and providing support to others (Krueger et al., 2007; Inagaki and Eisenberger, 2012; Moll et al., 2011; Eisenberger and Cole, 2012). Thus, we speculate that the septal area, along with DMPFC, MPFC, and VMPFC, may be a core neural region for empathy. The current study examined these and other regions during empathy for three emotions (happiness, sadness, and anxiety), in order to identify regions commonly active during empathy.

EMPATHY UNDER DIFFERENT ATTENTIONAL CONDITIONS

Relatively little is known about the operational characteristics of empathy and how empathic processes are affected by different attentional conditions. Does being under cognitive load alter the degree of empathy a person feels? The influential Perception-Action Model of empathy suggests that empathy should not be affected by cognitive load (Preston and De Waal, 2002). Preston and De Waal (2002) wrote "attended perception of the object's state automatically activates the subject's representations of the state, situation, and object, and that activation of these representations automatically primes or generates the associated autonomic and somatic responses, unless inhibited" (p. 4). By this account, seeing someone else in an emotional state *automatically* generates emotion in the perceiver, regardless of cognitive load. Perhaps influenced by this statement, very few fMRI studies of empathy have asked participants to do anything besides passively watch empathically-relevant video or images.

Three studies have looked at cognitive load effects, all showing reduced neural responses in empathy-related regions (i.e., dACC, AI, MPFC) (Gu and Han, 2007; Fan and Han, 2008; Rameson et al., 2012). However, Rameson et al. (2012) also observed that those individuals highest in trait empathy showed no reductions, neurally or experientially, under load. In addition, Fan and Han (2008) demonstrated that an early component of empathic neural responses is unaffected by cognitive load, whereas a later component of empathic neural responses is dampened by cognitive load. Thus, the present study aims to more thoroughly explore this question and to examine how cognitive load impacts empathy for a variety of emotional experiences (i.e., happiness, sadness, and anxiety). Based on past research, we hypothesized that regions related to controlled processes, such as mentalizing (e.g., MPFC), would be reduced under cognitive load (Rameson et al., 2012). In addition, we posited that cognitive load would dampen affective responses to the targets, reducing activity in regions associated with positive affect during empathy for happiness (e.g., VMPFC) and regions associated with negative affect during empathy for sadness and anxiety (e.g., dACC and AI) (Morelli et al., in press).

While cognitive load instructions might diminish empathy-related processes that are not fully automatic, other instructions might amplify responses in those same regions. Although some studies have explicitly focused participants' attention on the experience of a target individual or the similarity between the observer and target (Lamm et al., 2007; Sheng and Han, 2012), studies have not typically compared neural responses during directed empathy instructions relative to passive watching instructions. Such a comparison is important not only because it can highlight the attentional malleability of empathic processes, but also because it can help characterize what participants are actually doing when unconstrained during passive watching. We previously reported on this comparison in the context of empathy for sadness and found no differences in dACC and insula, but found significantly greater MPFC activity during instructed empathizing compared to passive watching (Rameson et al., 2012). In the current study, we expand on this analysis to include a comparison of passive watching and instructed empathizing with three emotions (happiness, sadness, and anxiety). Based on past research, we predicted that instructions to empathize would amplify neural responses in regions related to mentalizing (e.g., MPFC), as well as affect-related regions (e.g., dACC, AI, and VMPFC).

OVERVIEW

In our past work, parts of the present dataset have been analyzed, and the results have begun to address some of these outstanding questions. For example, we have previously examined how cognitive load affects neural and behavioral responses during empathy for sadness (Rameson et al., 2012). In addition, we compared neural responses when participants were instructed to empathize versus passively observe others' sadness (Rameson et al., 2012). More recently, we also examined neural similarities and differences when participants actively empathized with positive emotions (i.e., happiness) and negative emotions (i.e., pain and anxiety) (Morelli et al., in press). However, we have not comprehensively assessed how different attentional conditions may impact neural and behavioral responses during empathy for happiness, sadness, and anxiety. Further, none of the current analyses have been previously published and represent a novel and systematic approach to addressing our key questions.

More specifically, the main goal of the current study was to explore how neural activity during empathy is affected by different attentional conditions (i.e., watching, empathizing, and under cognitive load). By measuring neural activity during empathy for various emotions, we first aimed to pinpoint core neural regions that are activated whenever one might be experiencing empathy.

We then examined whether observing others' emotional experiences (i.e., watch instructions) engaged similar or different neural regions than actively empathizing with others' emotional experiences (i.e., empathize instructions). We also tested if cognitive load would diminish the involvement of core neural regions for empathy. Lastly, we examined what neural regions were automatically engaged during empathy and active across all attentional conditions.

METHODS

PARTICIPANTS

Informed consent was obtained from 32 healthy, right-handed undergraduates (16 male; mean age = 19.9, *SD* = 1.4) who were told the purpose of the study was to learn how emotion is processed in the brain. A subset of the data from these same participants has been previously reported (Morelli et al., in press; Rameson et al., 2012).

PROCEDURE

Participants completed a functional magnetic resonance imaging (fMRI) empathy task using naturalistic stimuli, specifically photos of individuals in happy, sad, anxious, and neutral situations. Stimuli were presented under three conditions: watching naturally (*watch*), actively empathizing (*empathize*), and under cognitive load (*memorize*; memorizing an 8-digit number). After exiting the MRI scanner, participants rated their empathic concern for targets in the empathy task.

EMPATHY TASK IN MRI SCANNER

Conditions

In the neutral condition, participants viewed blocks of photos with people performing everyday non-emotional actions (e.g., ironing, cutting vegetables). For all other conditions, participants completed an empathy task involving three emotions—happiness, sadness, and anxiety—and three types of instructions—watch, empathize, and memorize. Each block consisted of a contextual sentence describing a situation followed by six photos depicting different individuals in that situation (**Figure 1**). Happy situations included events like being hired for one's dream job or being the first person in the family to graduate from college. Examples of sad situations were attending a loved one's funeral or being fired from a job. Anxiety situations described events such as potentially not graduating due to a bad grade or being medically examined for a serious illness.

Photo stimuli

For the neutral condition, the photo stimuli were adapted from Jackson et al. (2005). For all other conditions, the photo sets were developed by the authors. Within each block, half of the targets were male and half female. An arrow indicated the target individual if a photo depicted several people. Images were equated across conditions on arousal, valence, luminance, and complexity, and sentences were equated on length. Images were selected from a larger pool in order to equate them on a number of features.

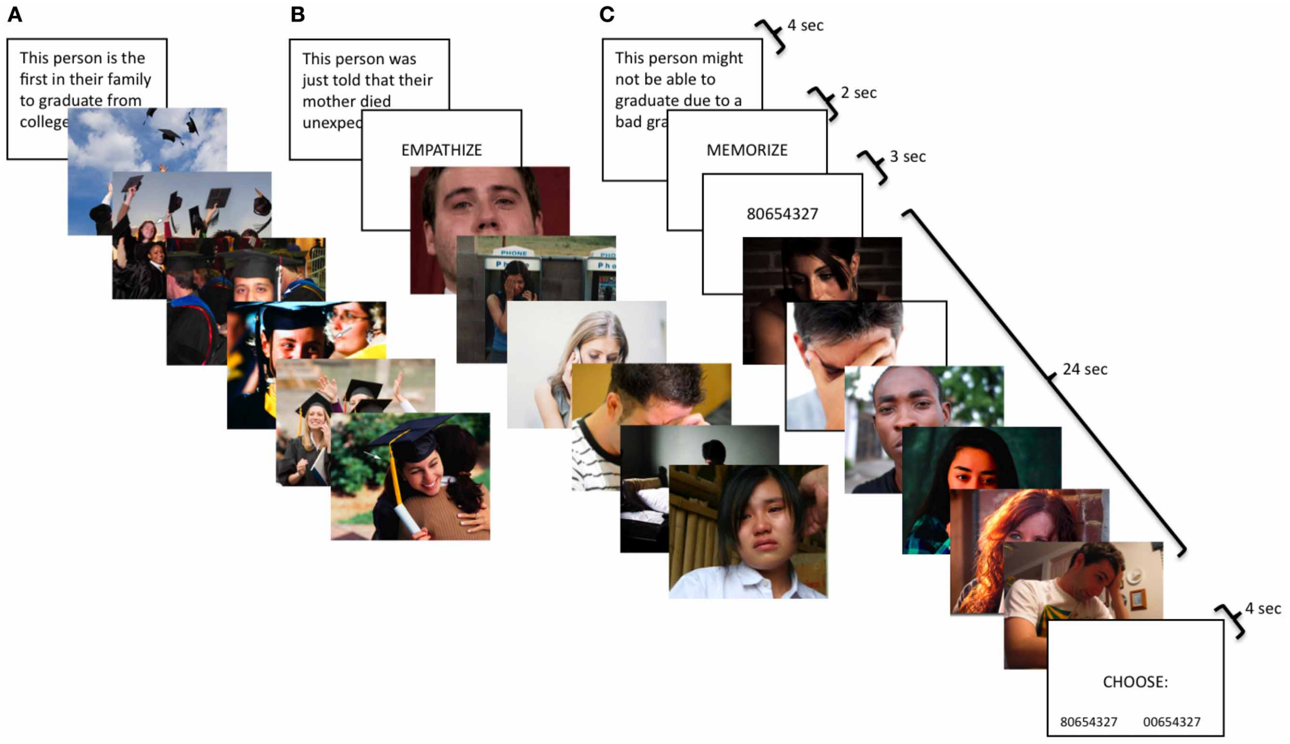

FIGURE 1 | Participants viewed naturalistic stimuli with three types of instructions: (A) watch, (B) empathize, and (C) memorize combined with three different emotions: (1) happiness, (2) sadness, and (3) anxiety. Therefore, participants saw nine different block types: happy watch, sad watch, anxiety watch, happy empathize, sad empathize, anxiety empathize, happy memorize, sad memorize, and anxiety memorize.

Blocks were equated across instruction type on arousal, luminance, complexity, and the number of letters in each contextual sentence preceding that block. Subjective ratings of valence and arousal were made by 16 (8 male) undergraduate pilot judges. Raters judged the valence of each photo on a scale from 1 (*very negative*) to 7 (*very positive*), and arousal on a scale from 1 (*very weak*) to 7 (*very strong*). Luminance was measured using Adobe Photoshop CS. Complexity was determined using the size of each image in jpeg (compressed) format (Calvo and Lang, 2004). In previous research, compressed image file sizes have been shown to be highly correlated with both subjective measures of complexity (Donderi, 2006; Tuch et al., 2009) and objective visual search performance (Donderi and McFadden, 2005).

Task instructions

For all conditions, participants were told photos depicted real events drawn from news stories, documentaries, and blogs. For the neutral condition, participants were simply asked to look at the photos for the whole time they were on the screen. For the watch condition, participants were instructed to respond to the photos naturally, as if they were at home and had come across the images in a magazine. For the empathize condition, participants were told to take each target's perspective and imagine how he/she felt about the situation and how it affected his/her life. These instructions have previously been shown to induce empathic concern (Toi and Batson, 1982). For the memorize condition, participants were told to keep an 8-digit number in memory while looking at the images.

Task timing and display order

The neutral condition consisted of four blocks; each block displayed 16 neutral photos for 2 s each. For the empathy task, each emotion had a total of nine blocks, divided into three instruction types: watch (3 blocks), empathize (3 blocks), and memorize (3 blocks). For the watch blocks, the contextual sentence was displayed for 4 s, followed by 6 photos presented for 4 s each. The empathize blocks displayed the contextual sentence for 4 s, followed by the instruction to "empathize" for 2 s, then ended with 6 photos for 4 s each. For memorize blocks, the contextual sentence was displayed for 4 s, followed by the cue to "memorize" for 2 s, then an 8-digit number for 3 s, then the block of 6 photos for 4 s each, and finally a memory test for the number for 4 s. Participants chose between the correct number and a number that was identical except for one digit. For all conditions, each block was separated by a 12-s rest period. The first run consisted exclusively of three watch blocks for each emotion, as this instruction type was meant to capture unprimed, spontaneous reactions. In the next two runs, participants were cued to trial type by the word "empathize" or "memorize," which appeared for 2 s after each sentence. Three empathize blocks and three memorize blocks were included for each emotion, intermixing empathize and memorize blocks across the two runs. Lastly, the third run included the four neutral blocks.

fMRI ACQUISITION AND DATA ANALYSIS

Scanning was performed on a Siemens Trio 3T. Functional images were acquired using an EPI gradient-echo sequence ($TR = 2000$ ms, $TE = 30$ ms, 4 mm slice thickness/no gap, $FOV = 19.2$ cm, matrix $= 64 \times 64$, flip angle $= 90°$). A T2-weighted structural image was acquired coplanar with the functional images ($TR = 5000$ ms, $TE = 34$ ms, 4 mm slice thickness/no gap, $FOV = 19.2$ cm, matrix $= 128 \times 128$, flip angle $= 90°$). All images were scalped using the Brain Extraction Tool of FSL (FMRIB Software Library; Oxford University, Oxford, UK) and realigned within runs using MCFLIRT. Images were then checked for residual motion and noise spikes using a custom automated diagnostic tool (thresholded at 2 mm motion or 2% global signal change from one image to the next). In SPM8 (Wellcome Department of Imaging Neuroscience, London), all functional and anatomical images were reoriented to set the origin to the anterior commissure and the horizontal (y) axis parallel to the AC-PC line. Also in SPM 8, functional images were realigned within and between runs to correct for residual head motion, and coregistered to the matched-bandwidth structural scan using a 6-parameter rigid body transformation. The coregistered structural scan was then normalized into Montreal Neurological Institute (MNI) standard stereotactic space using the scalped ICBM152 template and the resulting parameters were applied to all functional images. Finally, the normalized functional images were resliced into voxels of 3 mm^3 and smoothed using an 8 mm full width at half maximum Gaussian kernel.

All single subject and group analyses were performed in SPM8. First-level effects were estimated using the general linear model and employing a canonical hemodynamic response function convolved with the experimental design. Low-frequency noise was removed using a high-pass filter. Group analyses were conducted using random-effects models to enable population inferences (Nichols et al., 2005). To keep all instruction types as well-constrained and equivalent as possible, empathize, watch, and memorize trials were modeled using only the 24 s of image presentation that was invariant across instruction types. The remaining trial elements—the instruction prompts, contextual sentences, 8-digit number presentation and memory test (for memorize blocks)- were modeled separately and were not included in the baseline condition. In addition, the neutral condition was modeled using only the 32 s of image presentation for each neutral block.

Whole-brain group-level analyses

Whole-brain group-level analyses were performed using an uncorrected p-value of <0.005 with a cluster threshold of 43 based on a Monte Carlo simulation in AFNI's Alphasim effectively producing an FDR of $p = 0.05$ (Lieberman and Cunningham, 2009). For visualization of results, group contrasts were overlaid on a surface representation of the MNI canonical brain using the SPM surfrend toolbox and NeuroLens (http://spmsurfrend.sourceforge.net; http://www.neurolens.org/NeuroLens/Home.html).

Masked regions of interest analyses

Masked regions of interest (ROI) analyses were conducted using SPM8. Anatomical ROIs were created for regions commonly involved in empathy (dACC and AI), emotion (SA; amygdala; and rostral anterior cingulate cortex, rACC), and mentalizing (DMPFC, MPFC, and TPJ). Anatomical ROIs were constructed using the Wake Forest University Pickatlas Tool (Maldjian et al., 2003) with the Automated Anatomical Labeling Atlas (AAL; Tzourio-Mazoyer et al., 2002) or using Marsbar (http://marsbar.sourceforge.net).

A cingulate ROI that combined Brodmann Areas (BA) 24 and 32 (dilated to 2 mm) as well as the AAL anterior, middle, and posterior cingulate was divided into the dACC (bounded between $y = 33$ and $y = 0$) and the rACC (bounded between $y = 54$ and $y = 34$) (Bush et al., 2002; Vogt et al., 2003; Beckmann et al., 2009). AAL insula was bounded caudally at $y = 0$ to include only the anterior region and did not include pars opercularis, pars triangularis, or pars orbitalis. The SA ROI consisted of a box that extends from $x = -6$ to $x = 6$, $y = -2$ to $y = 0$, and $z = 0$ to $z = 10$, and is based on the Atlas of the Human Brain (Mai et al., 2004). The amygdala ROI was taken directly from AAL.

The MPFC and DMPFC ROIs were manually constructed in FSLview in a voxel-by-voxel fashion, informed by recent meta-analyses and reviews pertaining to MPFC function (both anterior rostral and dorsal aspects) and using the AAL labeling scheme as implemented in the WFU Pickatlas for comparison and reference (Steele and Lawrie, 2004; Amodio and Frith, 2006; Northoff et al., 2006). The DMPFC ROI was bounded ventrally at $z = 26$ to distinguish from MPFC, laterally at $x = \pm 20$ to include only the medial aspect, and caudally at $y = 44$ to exclude anterior cingulate. The MPFC ROI was bounded dorsally at $z = 24$ to distinguish from DMPFC, ventrally at $z = -10$ to distinguish from VMPFC, laterally at $x = \pm 20$ to include only the medial aspect, and caudally at $y = 46$ to exclude anterior cingulate. The TPJ ROI was created using the union of BA 22, 39, and 40, bounded between $x = \pm 38$, $y = -40$ and -68, and $z = 22$ and 38 (Decety and Lamm, 2007).

An overall mask for all cortical ROIs was submitted to Monte Carlo simulations, which determined that an uncorrected p-value of 0.005 with a cluster threshold of 28 voxels yielded a $p < 0.05$ FDR correction. Because subcortical regions tend to be substantially smaller, individual masks were created for SA and amygdala. Monte Carlo simulations indicated that for these smaller regions an uncorrected p-value of 0.005 with a cluster threshold of 3 voxels provided the same FDR correction.

POST-SCANNER EMPATHY RATINGS

Immediately post-scan, participants rated their empathic reaction to each block in the empathy task. Participants viewed the original task again, but with shorter presentation times (1 s per image) and without the neutral condition. Participants were told to remember how they felt when they first saw the images. For happy blocks, participants rated how happy they were for the targets on a scale from 1 (*not at all*) to 7 (*very much*). For sad and anxiety blocks, participants rated how concerned they felt for the targets on a scale from 1 (*not at all*) to 7 (*very much*). Participants were told "concerned" meant how compassionate, sympathetic, and moved they felt, as these adjectives have been used to assess empathy in previous research (Toi and Batson, 1982).

RESULTS

POST-SCANNER EMPATHY RATINGS

Due to technical difficulties, post-scan ratings for three participants were not collected. A three (happy, sad, anxiety) by three (watch, empathize, memorize) repeated-measures ANOVA revealed a main effect of instruction type on experienced empathy, $F_{(2,\ 56)} = 29.64$, $p < 0.001$, as well as a main effect of emotion type on experienced empathy, $F_{(2,\ 56)} = 7.25$, $p < 0.005$. However, the interaction between emotion type and instruction type was not significant. Follow-up paired samples t-tests showed that participants reported less empathy during memorize blocks ($M = 5.23$, $SD = 0.96$) than during the empathize blocks ($M = 5.55$, $SD = 0.76$), $t_{(28)} = -2.78$, $p < 0.05$, or during the watch blocks ($M = 5.57$, $SD = 0.84$), $t_{(28)} = -3.30$, $p < 0.005$ (**Figure 2**). Empathize and watch blocks did not differ significantly on reported empathy. Participants also reported experiencing reduced empathy for anxiety ($M = 4.97$, $SD = 0.90$) compared to happiness ($M = 5.67$, $SD = 0.84$), $t_{(28)} = -5.67$, $p < 0.001$, and to sadness ($M = 5.70$, $SD = 0.87$), $t_{(28)} = -9.00$, $p < 0.001$. Self-reported empathy did not differ significantly for happiness and sadness.

fMRI RESULTS

Behavioral performance during memorize blocks

Accuracy rate was 84% ($SD = 20\%$) for the memory test after each memorize block, indicating that participants were performing the memory task as intended.

Overview of effects

Given that our 3 × 3 experimental design yielded many potential comparisons, we wanted to provide an overview of the data and identify patterns across the nine cells of our design. Therefore, we looked for effects in the eight ROIs for each of the nine conditions compared to the neutral condition. We conducted masked ROI

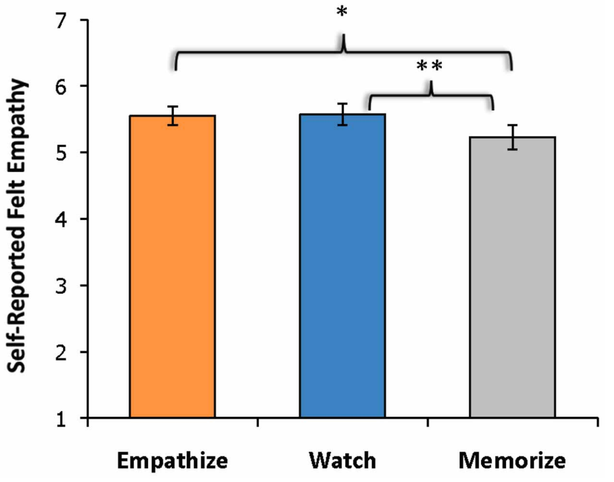

FIGURE 2 | Self-reported empathy showed a main effect of instruction type with participants reporting less empathy during memorize instructions than during empathize or watch instructions. The empathize and watch conditions did not differ significantly on self-reported empathy.

analyses using regions commonly involved in empathy (dACC and AI), emotion (SA, amygdala, and rACC), and mentalizing (DMPFC, MPFC, and TPJ).

Table 1 shows a summary of regions that produced significant activations for each of the nine cells of our design and reveals a number of interesting patterns. Regions related to mentalizing (DMPFC, MPFC, and TPJ) produced reliable activations during empathize and watch instructions, but were not activated during memorize instructions. Somewhat surprisingly, the amygdala showed the same pattern. In contrast, dACC was reliably present during memorize instructions, but only appeared in two of the six remaining non-memorize blocks. Finally, SA activations were present during all nine trial types, and AI activations were present during eight of the nine trial types. Out of the 8 ROIs, the only the SA and AI were consistently activated across conditions. rACC was also observed in five of the nine trial types, but with no particular pattern with respect to emotion or attentional instructions.

Common activations during empathy for happiness, sadness, and anxiety

Our first goal was to identify core neural regions that were activated across different kinds of empathic experiences. To determine whether any neural regions were commonly recruited when trying to empathize with each of three different emotions, we used a conjunction analysis (Nichols et al., 2005) for the comparison of the empathize condition to the neutral condition for each of the three emotion types (happiness, sadness, and anxiety). This method only yielded clusters that were significantly active in each of the three contributing contrasts.

First, a contrast image was created for each emotion type that compared empathize instructions to the neutral condition (i.e., Happy Empathize > Neutral, Sad Empathize > Neutral, and Anxiety Empathize > Neutral). Then, a conjunction analysis of all three contrast images was used to identify neural regions that were commonly recruited when empathizing with the three emotions. This conjunction analysis across emotion types revealed common activity in MPFC, DMPFC, and amygdala, regions typically associated with mentalizing and emotion (see **Figure 3A**, **Table 2**). Slightly lowering the voxel extent for this contrast also revealed activation in SA (with the peak voxel at $x = 3$, $y = 2$, $z = 4$; $t = 3.51$; $k = 38$).

Similarly, the conjunction analysis across emotion types when watching others' emotional experiences (i.e., a conjunction of Happy Watch > Neutral, Sad Watch > Neutral, and Anxiety Watch > Neutral) produced common activations in a variety of regions related to social cognition (i.e., MPFC, DMPFC, TPJ, and pSTS), as well as in ventral AI and amygdala (see **Figure 3B**, **Table 2**). Lowering the voxel extent for this contrast once again revealed activation in SA (with the peak voxel at $x = 0$, $y = -4$, $z = -2$; $t = 3.31$; $k = 16$).

In contrast, when participants viewed the same kinds of emotional scenes but were focused on memorizing an 8-digit number, mentalizing-related regions were not commonly activated across emotion types. Instead, the conjunction of Happy Memorize > Neutral, Sad Memorize > Neutral, and Anxiety Memorize > Neutral yielded common activity in SA and in regions associated with controlled processes and salience detection: dACC and dorsal AI (see **Figure 3C**, **Table 2**). Taken together, these results suggest that regions related to mentalizing and emotion may be critical for generating empathic responses. However, cognitive load may disrupt activity in these core regions and reduce empathic responding.

Neural similarities and differences between empathizing and watching

To determine if reacting naturally (i.e., watching) and trying to empathize activated common neural regions, we ran additional conjunction analyses. For these analyses, we collapsed all empathize blocks into one condition and all watch blocks

Table 1 | Patterns of neural activity for each instruction type (compared to viewing neutral photos) within anatomically-defined regions of interest previously associated with empathy, emotion, and mentalizing.

	dACC	AI	Septal	Amygdala	rACC	DMPFC	MPFC	R TPJ
EMPATHIZE								
Happy			●	●		●	●	●
Sad		●	●	●	●	●	●	●
Anxiety	●	●	●	●	●		●	
WATCH								
Happy		●	●	●	●	●	●	●
Sad	●	●	●	●		●	●	●
Anxiety		●	●	●		●	●	●
MEMORIZE								
Happy	●	●	●		●			
Sad	●	●	●					
Anxiety	●	●	●		●			

Note. Cells were marked using a threshold of $p < 0.005$ and a 28 voxel extent which provides FDR corrected $p < 0.05$. Separate ROI masks were created for the septal area and amygdala. In these regions, marked cells are significant at $p < 0.005$ and a 3 voxel extent ($p < 0.05$ FDR corrected). For anterior insula and amygdala, cell are marked if a significant cluster appeared in either hemisphere.

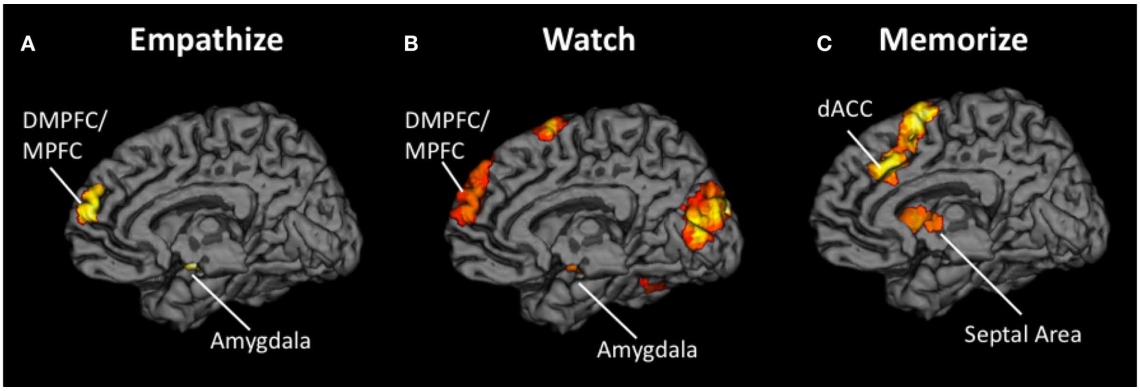

FIGURE 3 | Neural overlap during empathy for happiness, sadness, and anxiety using conjunction analyses for the contrasts (A) Happy Empathize > Neutral, Sad Empathize > Neutral, and Anxiety Empathize > Neutral (B) Happy Watch > Neutral, Sad Watch > Neutral, and Anxiety Watch > Neutral, and (C) Happy Memorize > Neutral, Sad Memorize > Neutral, and Anxiety Memorize > Neutral. In both the empathize and watch conjunction analyses, DMPFC and MPFC were two of the common neural areas across emotions. However, DMPFC and MPFC did not appear in the memorize conjunction analysis; instead, dACC and AI were two of the common neural areas across emotions.

Table 2 | Neural regions that were commonly activated during happiness, sadness, and anxiety for empathize compared to neutral, watch compared to neutral, and memorize compared to neutral.

Region	BA	Hemisphere	K	Coordinates			t
				x	y	z	
CONJUNCTION OF HAPPY EMPATHIZE > NEUTRAL, SAD EMPATHIZE > NEUTRAL, AND ANXIETY EMPATHIZE > NEUTRAL							
Medial prefrontal cortex/dorsomedial prefrontal cortex	10/9	R	70	6	59	13	3.86
Amygdala	–	R	61	18	−4	−11	4.41
		L	46	−21	−7	−11	5.01
CONJUNCTION OF HAPPY WATCH > NEUTRAL, SAD WATCH > NEUTRAL, AND ANXIETY WATCH > NEUTRAL							
Medial prefrontal cortex	10	R	421[1]	6	59	16	3.70
Dorsomedial prefrontal cortex	9/8	R	421[1]	3	56	31	3.93
Temporoparietal junction/posterior superior temporal sulcus	40	R	101	54	−43	16	4.30
Anterior insula	13	L	64[2]	−42	14	−17	3.79
Amygdala	–	R	49	18	−7	−14	4.33
Ventrolateral prefrontal cortex	47	L	64[2]	−45	29	−2	3.97
Dorsal premotor cortex	6	R	64	6	11	67	5.15
Fusiform	37	R	44	42	−55	−14	5.09
Occipital lobe	19/18	–	387	−6	−97	25	6.97
CONJUNCTION OF HAPPY MEMORIZE > NEUTRAL, SAD MEMORIZE > NEUTRAL, AND ANXIETY MEMORIZE > NEUTRAL							
Septal area	–	L	55	−3	−4	1	3.41
Dorsal anterior cingulate cortex	32	R	500[3]	3	29	31	4.42
Anterior insula	13	R	199	39	23	10	5.28
		L	223	−33	23	4	6.36
Dorsal premotor cortex	6	L	500[3]	−6	2	64	5.87

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

into one condition, regardless of emotion. We then created a contrast image that compared empathize instructions to the neutral condition (i.e., Empathize > Neutral) and another contrast that compared watch instructions to the neutral baseline (i.e., Watch > Neutral). A conjunction analysis of these two contrast images was then used to identify neural regions that were commonly recruited when trying to empathize or simply watch. This conjunction analysis showed activity in regions previously associated with social cognition, including the MPFC, DMPFC, VMPFC/rACC, TPJ, pSTS, and temporal poles, in addition to regions related to emotion, including SA, amygdala, and ventral AI (**Table 3** and **Figure 4**).

To identify differences between empathize instructions and watch instructions, we compared the empathize and watch conditions (**Table 4**). We did not find a large number of neural differences between the two instruction types, which is consistent with our finding that self-reported empathy was at similar levels for each instruction type. For the contrast Watch > Empathize, there was increased activation in some regions related to social cognition, namely DMPFC, precuneus, and pSTS. However, it appears that trying to empathize and watching naturally may have more neural similarities than differences.

Cognitive load effects

Next, we wanted to more directly test whether cognitive load (i.e., memorize blocks) would diminish the involvement of neural regions that were active when empathizing or watching naturally. Because we were primarily interested in the effect of cognitive load, the following analyses collapse all empathize blocks into one condition, all watch blocks into a second condition, and all memorize blocks into a third condition. To identify what regions were less active under load compared to actively empathizing, we compared empathize blocks (all emotion types) to memorize blocks (all emotion types) (see **Table 5**). For this contrast Empathize > Memorize, we found activations in regions typically associated with social cognition (i.e., MPFC, DMPFC, VMPFC, precuneus/posterior cingulate cortex, TPJ, pSTS, and temporal poles) and emotional arousal (i.e., amygdala) (see **Figure 5**). For the contrast Watch > Memorize, we observed activations in the same set of neural regions (see **Table 5**).

We also identified regions that were more active under load compared to empathizing (Memorize > Empathize) and more active under load compared to watching naturally (Memorize > Watch) (see **Table 6**). For both of these contrasts, dACC, AI, VLPFC, DLPFC, dorsal premotor cortex, and supplementary motor area were more active under load. In sum, putting

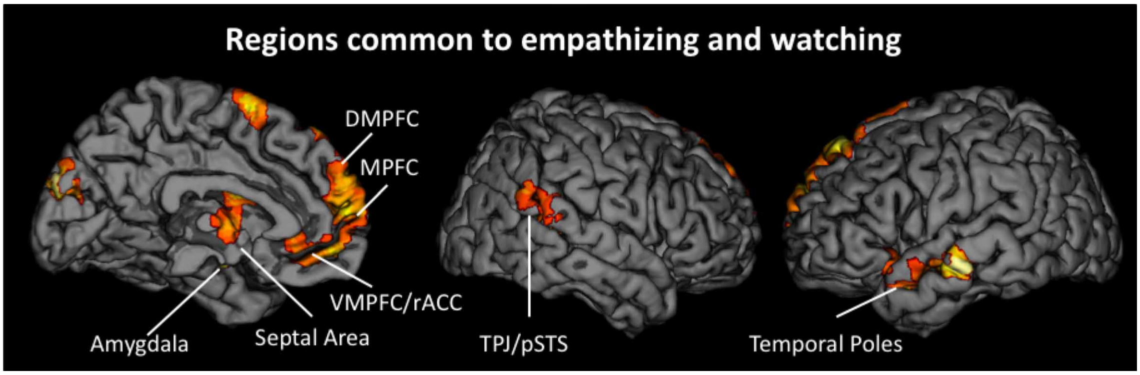

FIGURE 4 | Neural regions that were commonly activated during the empathize and watch conditions (collapsing across emotions) compared to neutral.

Table 3 | Neural regions that were commonly activated during empathize and watch (collapsed across happiness, sadness, and anxiety) compared to neutral.

Region	BA	Hemisphere	*k*	Coordinates			*t*
				x	*y*	*z*	
CONJUNCTION OF EMPATHIZE > NEUTRAL AND WATCH > NEUTRAL							
Medial prefrontal cortex	10	R	713^1	6	62	13	5.21
Dorsomedial prefrontal cortex	8/9	R	713^1	6	56	28	4.30
Ventromedial prefrontal cortex/rostral anterior cingulate cortex	11/32	L	713^1	−3	47	−11	4.51
Temporoparietal junction/posterior superior temporal sulcus	40	R	148	51	−40	10	5.20
Temporal poles/middle temporal gyrus	38/21	L	275^2	−54	2	−17	3.96
Septal area	–	R	150	3	−1	−2	4.03
Anterior insula	13	L	275^2	−42	14	−17	5.50
Amygdala/hippocampus	–	R	119	18	−7	−11	5.54
		L	275^2	−18	−10	−14	6.21
Dorsal premotor cortex	6	R	112	3	8	67	5.91
Occipital lobe	18/19	L	151	−3	−91	28	5.35

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

Table 4 | Neural regions that were more active for empathize compared to watch (collapsing across emotions), as well as neural regions that were more active for watch compared to empathize (collapsing across emotions).

Region	BA	Hemisphere	*k*	Coordinates			*t*
				x	*y*	*z*	
EMPATHIZE > WATCH							
Dorsal anterior cingulate cortex	32/24	L	289^1	−9	11	34	4.06
Supplementary motor area	6	R	289^1	9	−7	55	4.36
Putamen	–	L	59	−18	11	−8	4.43
Precentral gyrus	6	L	48	−21	−16	76	3.97
Postcentral gyrus	1/2	R	89	57	−22	55	3.39
WATCH > EMPATHIZE							
Dorsomedial prefrontal cortex	8/9	–	229	0	56	40	4.10
Precuneus	7/31	R	2870^2	6	−67	40	3.93
Posterior superior temporal sulcus/middle temporal gyrus	22	R	100	51	−43	−2	4.61
		L	158	−63	−40	1	4.67
Dorsolateral prefrontal cortex	8/9/10	R	788	45	35	37	6.07
Inferior parietal lobule/superior parietal lobule	40/7/39	R	726	42	−52	49	5.63
		L	706	−45	−52	40	4.95
Fusiform	37	R	2870^2	45	−55	−17	3.87
		L	2870^2	−42	−55	−20	3.68
Occipital lobe	18/19	R	2870^2	6	−79	1	4.28
Cerebellum	–	L	2870^2	−3	−82	−26	6.85

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

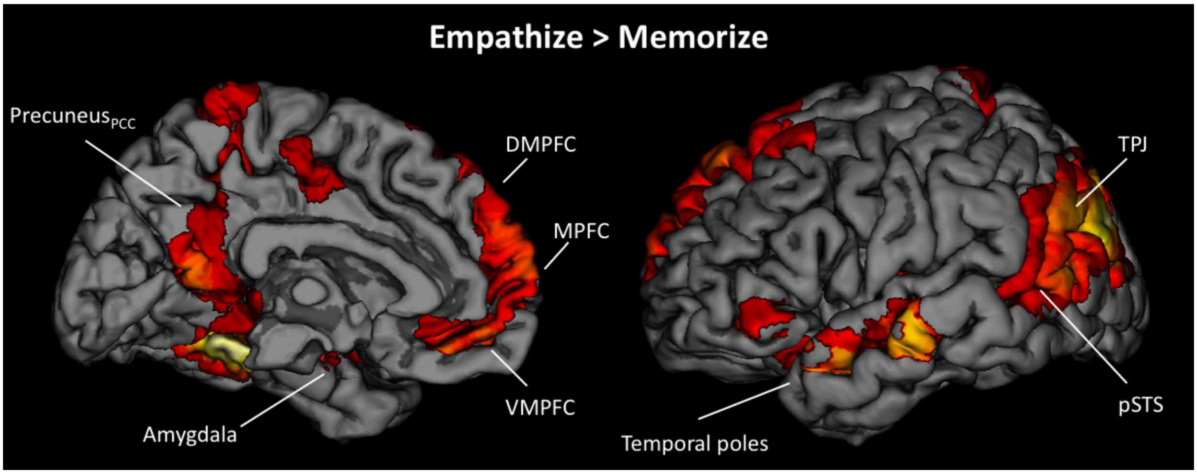

FIGURE 5 | Neural regions that showed reduced activity under cognitive load compared to empathizing (Empathize > Memorize).

people under cognitive load while looking at emotional stimuli may reduce activity in regions associated with social cognition and emotional arousal and increase neural activity in regions associated with attention and effort (**Table 7**).

Automaticity

Lastly, we examined what neural regions may be automatically engaged during empathy and remain active regardless of the attentional condition. Similar to previous analyses, we collapsed all empathize blocks into one condition, all watch blocks into one condition, and all memorize blocks into one condition. We then created a contrast image that compared empathize instructions to the neutral condition (i.e., Empathize > Neutral), another contrast that compared watch instructions to the neutral condition (i.e., Watch > Neutral), and a final contrast that compared memorize instructions to the neutral condition (i.e., Memorize > Neutral). Finally, a conjunction analysis of these three contrast images was used to identify neural regions that are engaged

Table 5 | Neural regions that were less active under cognitive load compared to empathize (collapsed across emotions) and less active under cognitive load compared to watch (collapsed across emotions).

Region	BA	Hemisphere	*k*	Coordinates			*t*
				x	*y*	*z*	
EMPATHIZE > MEMORIZE							
Medial prefrontal cortex	10	L	1197[1]	−6	62	1	4.03
Dorsomedial prefrontal cortex	8/9	R	1197[1]	3	56	28	5.87
Ventromedial prefrontal cortex	11	–	1197[1]	0	38	−14	6.40
Precuneus/posterior cingulate cortex	31	L	6903[2]	−6	−55	16	5.77
Temporoparietal junction/posterior superior temporal sulcus	22/39	R	6903[2]	57	−49	10	6.51
		L	6903[2]	−42	−70	22	6.53
Temporal pole/middle temporal gyrus	21/38	R	6903[2]	54	−1	−17	8.27
		L	6903[2]	−45	14	−23	6.23
Amygdala	–	R	6903[2]	21	−4	−17	6.61
		L	6903[2]	−21	−7	−17	5.53
Ventrolateral prefrontal cortex	46	R	45	54	38	10	5.37
Supplementary motor area	6	R	750[3]	3	−16	58	3.99
Inferior parietal lobule	40	R	113	57	−28	37	4.65
Hippocampus	–	R	6903[2]	30	−16	−14	6.60
		L	6903[2]	−30	−16	−14	6.21
Fusiform	37	R	6903[2]	24	−40	−14	9.99
		L	6903[2]	−24	−46	−11	10.84
Precentral/postcentral gyrus	6/4	R	750[3]	18	−43	70	4.78
Cerebellum	–	R	127	30	−79	−32	5.84
		L	137	−21	−79	−32	6.52
		L	212	−6	−52	−41	4.50
Occipital lobe	19	R	6903[2]	42	−79	25	12.50
		L	6903[2]	−42	−70	22	6.53
WATCH > MEMORIZE							
Medial prefrontal cortex	10	R	1728[4]	3	68	10	5.59
Dorsomedial prefrontal cortex	8/9	R	1728[4]	3	56	40	5.99
Ventromedial prefrontal cortex	11	L	1728[4]	−6	38	−14	5.52
Precuneus	7	R	171	9	−64	70	3.81
Temporoparietal junction/posterior superior temporal sulcus	22/39/40	R	9362[5]	57	−49	10	6.52
		L	9362[5]	−48	−70	19	6.54
Temporal poles	38	L	9362[5]	−54	2	−20	6.05
Amygdala	–	R	9362[5]	30	−10	−14	7.72
Ventrolateral prefrontal cortex	45/46/47	R	1728[4]	57	23	28	5.04
		L	9362[5]	−48	41	−8	6.51
Dorsal premotor cortex	6	L	1728[4]	−9	32	55	5.93
Hippocampus	–	R	9362[5]	27	−16	−11	7.87
Fusiform	37	R	9362[5]	36	−46	−8	7.10
		L	9362[5]	−30	−40	−14	7.89
Middle temporal gyrus	21/22	R	9362[5]	60	−7	−14	7.75
		L	9362[5]	−57	−16	−14	7.43
Angular gyrus	39	R	9362[5]	42	−70	25	8.01
		L	9362[5]	−48	−70	31	8.73
Occipital lobe	19	R	9362[5]	36	−70	7	6.68
		L	9362[5]	−33	−85	31	7.24
Cerebellum	–	L	9362[5]	−24	−79	−32	7.84

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

Table 6 | Neural regions that were more active under cognitive load compared to empathize (collapsed across emotions) and more active under cognitive load compared to watch (collapsed across emotions).

Region	BA	Hemisphere	*k*	Coordinates			*t*
				x	*y*	*z*	
MEMORIZE > EMPATHIZE							
Precuneus	7	R	2289^1	12	−64	40	6.05
		L	2289^1	−12	−64	52	4.64
Dorsal anterior cingulate cortex	32/24	R	2732^2	9	29	31	5.35
Anterior insula	13	R	249	36	17	10	6.09
		L	2732^2	−36	20	1	6.23
Ventrolateral prefrontal cortex	46/47	L	2732^2	−36	26	28	4.90
Dorsolateral prefrontal cortex	10	R	2732^2	33	53	22	6.72
		L	2732^2	−39	50	22	7.41
Inferior parietal lobule	40	R	406	48	−40	49	5.67
		L	2289^1	−48	−43	52	6.28
Dorsal premotor cortex/supplementary motor area	6	L	2372^2	−6	2	61	8.13
Precentral gyrus/inferior frontal gyrus	6/9	L	2732^2	−54	−7	49	6.40
Middle/superior frontal gyrus	6	R	72	21	8	64	4.45
Middle cingulate	23	–	151	0	−22	28	5.29
Occipital lobe	18	L	2289^1	−9	−76	4	10.62
Cerebellum	–	R	67	27	−67	−20	4.47
MEMORIZE > WATCH							
Precuneus	7	R	56	12	−67	40	4.03
		L	118	−9	−73	43	4.83
Temporoparietal junction	40	L	412^3	−51	−49	28	4.28
Dorsal anterior cingulate cortex	32/24	R	1111^4	6	26	31	5.97
Anterior insula	13	R	244	36	20	10	6.64
		L	1544^5	−30	20	4	7.09
Caudate	–	R	1544^5	12	8	−2	5.77
		L	1544^5	−6	5	10	3.71
Dorsolateral prefrontal cortex	10/9	R	389	30	41	37	7.71
		L	1544^5	−36	38	25	5.94
Ventrolateral prefrontal cortex		L	1544^5	−39	26	28	5.38
Inferior parietal lobule	40	L	412^3	−48	−40	49	4.92
Dorsal premotor cortex/supplementary motor area	6	L	1111^4	−6	2	61	11.85
Precentral gyrus/inferior frontal gyrus	6/9	L	1544^5	−48	−4	43	8.04
Postcentral gyrus	1/2	L	51	−60	−19	25	5.01
Middle cingulate	23	L	90	−3	−22	31	4.71

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

Table 7 | A summary of cognitive load effects that illustrates the relative increases and decreases in activation during empathize and watch compared to memorize (collapsed across emotions).

	dACC	AI	Septal	Amygdala	rACC	DMPFC	MPFC	R TPJ
Empathize > Memorize	↓	↓ *		↑		↑	↑	↑
Watch > Memorize	↓	↓		↑		↑	↑	↑

*Note. ↑ indicates a relative increase in activation for the ROI during empathize relative to memorize and watch relative to memorize. ↓ indicates a relative decrease in activation for the ROI during empathize relative to memorize and watch relative to memorize. *In addition to the AI cluster that was more active during memorize, a smaller cluster in AI was also more active during empathize compared to memorize.*

Table 8 | Neural regions that were commonly activated during empathize, watch, and memorize (collapsed across emotions) compared to neutral.

Region	BA	Hemisphere	k	Coordinates			t
				x	y	z	
CONJUNCTION OF EMPATHIZE > NEUTRAL, WATCH > NEUTRAL, AND MEMORIZE > NEUTRAL							
Septal area	–	R	123	3	−1	−2	4.01
Anterior insula	13	–	53	−39	14	−14	4.64
Dorsal premotor cortex	6	R	91	3	8	67	5.91
Occipital lobe	18/19	L	128	−3	−91	28	5.20

Note. BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; k refers to the cluster size (in voxels); x, y, and z refer to MNI coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively; t refers to the t-score at those coordinates (local maxima). Regions with ks that share a superscript originate from the same cluster.

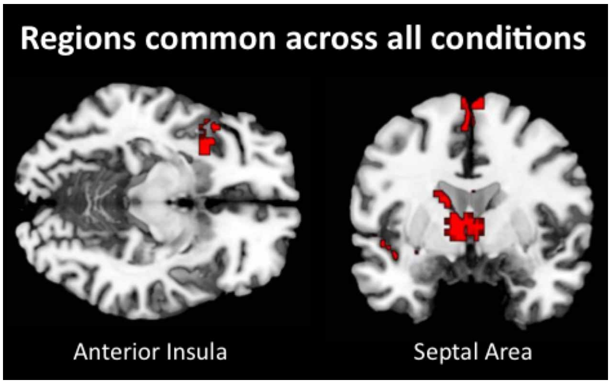

FIGURE 6 | Neural regions that were commonly activated during empathize, watch, and memorize (collapsed across emotions) relative to neutral.

during all three conditions. This conjunction analysis showed common activity in SA and ventral AI (**Table 8** and **Figure 6**), as well as the dorsal premotor cortex and occipital lobe. Thus, SA and ventral AI seem to be automatically engaged during empathy, regardless of attentional conditions.

DISCUSSION

The results of the present study begin to address several unanswered questions in the empathy literature. While most studies have examined neural processes during empathy for a single negative emotion, it is unclear whether these neural regions are specific to empathy for each negative emotion or critical for empathic processes more broadly. By measuring empathic processes across multiple emotions, we identified neural regions that are central to an empathic state. We also addressed other gaps in the current research by directly comparing the effects of several attentional conditions (i.e., watch, empathize, memorize) on empathic processes. More specifically, comparing neural responses during empathize and watch instructions allowed us to characterize what participants are actually doing when instructed to observe others (typical instructions in most previous studies). By including cognitive load instructions, we also identified which neural regions are automatically engaged during empathy and which neural regions may be disrupted by reduced attentional resources.

Across analyses, we find evidence for a core set of neural regions that support an empathic state (i.e., DMPFC, MPFC, TPJ, amygdala, AI, and SA). When participants observed or actively empathized with a target, we found relatively consistent activity in regions related to mentalizing (i.e., DMPFC, MPFC, and TPJ) across emotions. Conjunction analyses for each instruction type confirmed this pattern, showing DMPFC and MPFC activation when empathizing and DMPFC, MPFC, and TPJ activation when observing others. While studies on empathy for pain have consistently found dACC and AI activation, our results suggest that regions related to mentalizing may be core neural areas during empathy for both positive and negative emotions.

Previous research demonstrates that DMPFC, MPFC, and TPJ are some of the most consistently activated regions when thinking about the mental states of others (Spreng et al., 2009; Van Overwalle, 2009; Lieberman, 2010). TPJ activation often occurs when reasoning about temporary states such as the goals, intentions, and desires of other people (Saxe and Kanwisher, 2003; Van Overwalle, 2009; Young et al., 2010). Both DMPFC and MPFC are associated with inferring the enduring dispositions of the self and others (Van Overwalle, 2009). Because our task used a variety of emotional and situational contexts, participants probably thought about both the temporary states and enduring dispositions of targets. In addition, the stimuli depicted targets with varied gender, ethnicity, and age, experiencing events that the participants were both familiar and unfamiliar with. Thus, DMPFC may have been activated when participants contemplated targets who were dissimilar to themselves, while MPFC may have been activated when thinking about similar targets (Mitchell et al., 2006; Krienen et al., 2010). Overall, our results suggest that regions related to mentalizing are central to the experience of empathy, potentially helping us understand the varied emotional terrain of others' everyday experiences.

When participants observed or actively empathized with a target, we also found very reliable activity in the amygdala across whole-brain contrasts, as well as in the stricter conjunction analyses. The amygdala should play a central role in empathy because it is typically active when stimuli are motivationally relevant and emotionally impactful (Ewbank et al., 2009; Adolphs, 2010; Lindquist et al., 2012). Furthermore, amygdala activation is not emotion-specific and may be part of a distributed network that helps realize core affect (Lindquist et al., 2012). Thus, our results suggest that empathy for both positive and negative emotions may heighten emotional sharing and motivational relevance, leading to increased amygdala activation.

Interestingly, only ventral AI and SA were reliably activated across emotions and attentional conditions in whole-brain analyses, suggesting that these regions may be automatically engaged during empathy. In addition, a conjunction analysis across all attentional conditions further confirmed the automatic activation of ventral AI and SA during empathy. Our results suggest that the ventral anterior insula is a core neural region for empathy across multiple emotions and is not specific to empathy for pain (Singer et al., 2009). Ventral AI may be essential to empathic processes because it is often activated by the awareness of others' affective feelings (Wager and Feldman Barrett, 2004; Craig, 2009; Lindquist et al., 2012). For both autistic individuals and controls, poorer awareness of other's emotions is related to hypoactivity in the AI (Silani et al., 2008; Uddin and Menon, 2009). Therefore, previous work that shows AI activation during empathy for pain (Singer et al., 2004) is consistent with the idea that AI may reflect a heightened awareness of others' feelings. While the septal area has not often been associated with empathy, our analyses suggest that SA should be considered an automatic and core neural region for empathy. Both prosocial behavior and maternal caregiving activate the SA (Stack et al., 2002; Gammie, 2005; Krueger et al., 2007; Inagaki and Eisenberger, 2012), suggesting that SA activation may generally signal other-oriented feelings and behaviors. In addition, different analyses on this dataset have suggested that SA activation predicts daily prosocial behavior and may signal the intention to help others (Morelli et al., in press).

When comparing passively observing and actively empathizing, whole-brain contrasts showed very few neural differences and many common neural regions across these instruction types. Common activity occurred in core empathy-related regions (i.e., MPFC, DMPFC, and TPJ), social cognition-related regions, (i.e., VMPFC/rACC, pSTS, and temporal poles) and affect-related regions (SA, ventral AI, and amygdala). Also, self-reported empathy did not differ significantly between the empathize and watch conditions. Our results preliminarily suggest that observing others engages similar empathic processes as actively empathizing with others. Because these analyses capture group-level differences, future research should explore whether neural activity during these two instruction types may differ within each individual.

We also showed that cognitive load reduces the subjective experience of empathy, as well as decreasing neural responses in several core empathy-related regions (i.e., DMPFC, MPFC, TPJ, amygdala) and social cognition-related regions (i.e., VMPFC, precuneus, posterior cingulate cortex, pSTS, and temporal poles). This finding suggests that empathy for various emotions is not entirely automatic, extending previous findings that empathy for pain and sadness are not automatic (Gu and Han, 2007; Rameson et al., 2012) and challenging the assumptions of the Perception-Action Model (Preston and De Waal, 2002). Cognitive load also increased activation in dACC and dorsal AI when compared to each of the other conditions (neutral, watch, empathize). While dACC has been reliably implicated during empathy for pain, dACC was only consistently activated during cognitive load in the current study. Thus, dACC may not be universally activated by empathic processes across emotions. It is possible that activity in dACC and dorsal AI, as well as DLPFC and VLPFC, during cognitive load reflected the increased effort and attention needed to maintain the 8-digit number in memory (Blasi et al., 2006; Woodward et al., 2006; Mulert et al., 2007). Further, cognitive load differentially activated the dorsal portion of the AI, which is associated with cognitive control processes (Wager and Feldman Barrett, 2004). In contrast, the ventral portion of the AI, typically associated with emotional awareness, was indicated in the conjunction of the watch and empathize conditions. Alternatively, dACC and AI may be performing empathic functions that are amplified under cognitive load. The role of dACC and AI during cognitive load cannot be determined from this study alone and should be explored in future research.

LIMITATIONS AND CONCLUSION

One potential limitation of the current study design was the presentation of the watch condition in the first run, preceding the presentation of the other two conditions. Because the watch condition was meant to capture participants' completely spontaneous reactions to the emotional stimuli, we felt presenting it first was important for avoiding unwanted interference from the other instruction types. As is often the case, however, emphasizing ecological validity comes at the cost of experimental control, and this design produces an order confound. We attempted to minimize the effect of this cofound through careful pre-rating of the stimuli to insure all three conditions were otherwise as equivalent as possible. Follow-up studies in which all three conditions are intermixed will be useful in determining what, if any, effect the presentation order exerted upon the watch condition. A second limitation is that the neutral condition may not have been ideal. These photos did not directly show any faces and may not have controlled for the more detailed and varied emotional photos in the other conditions. Thus, when comparing the experimental conditions (i.e., empathize, watch, and memorize) to the neutral condition, some of the observed results—such as increased activity in the amygdala—may be due to general face processing.

In summary, the current study broadens our understanding of empathy by identifying core neural regions that underlie the empathic state. In addition, it demonstrates that empathic processes are not entirely automatic and may be disrupted by cognitive load. Lastly, the current study suggests that two key regions—the ventral AI and SA—are automatically engaged during empathy, even when attentional resources are reduced. By examining how attention impacts neural and subjective responses during empathy, we hope the current findings suggest potential ways to sustain empathy even in the face of everyday demands and distractions. Further, these findings indicate that attention impacts empathic processing and may play a role in empathic dysfunction in mental disorders such as autism.

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Vicarious pain while observing another in pain: an experimental approach

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Objective: This study aimed at developing an experimental paradigm to assess vicarious pain experiences. We further explored the putative moderating role of observer's characteristics such as hypervigilance for pain and dispositional empathy.

Methods: Two experiments are reported using a similar procedure. Undergraduate students were selected based upon whether they reported vicarious pain in daily life, and categorized into a pain responder group or a comparison group. Participants were presented a series of videos showing hands being pricked whilst receiving occasionally pricking (electrocutaneous) stimuli themselves. In congruent trials, pricking and visual stimuli were applied to the same spatial location. In incongruent trials, pricking and visual stimuli were in the opposite spatial location. Participants were required to report on which location they felt a pricking sensation. Of primary interest was the effect of viewing another in pain upon vicarious pain errors, i.e., the number of trials in which an illusionary sensation was reported. Furthermore, we explored the effect of individual differences in hypervigilance to pain, dispositional empathy and the rubber hand illusion (RHI) upon vicarious pain errors.

Results: Results of both experiments indicated that the number of vicarious pain errors was overall low. In line with expectations, the number of vicarious pain errors was higher in the pain responder group than in the comparison group. Self-reported hypervigilance for pain lowered the probability of reporting vicarious pain errors in the pain responder group, but dispositional empathy and the RHI did not.

Conclusion: Our paradigm allows measuring vicarious pain experiences in students. However, the prevalence of vicarious experiences of pain is low, and only a small percentage of participants display the phenomenon. It remains however unknown which variables affect its occurrence.

Keywords: vicarious pain, synaesthesia for pain, observation of pain, empathy, hypervigilance for pain

GENERAL INTRODUCTION

Viewing someone in pain has been suggested to elicit distress in observers (Goubert et al., 2005, 2009). In addition, several brain regions tapping into the affective-motivational properties of pain have been found to become activated when seeing someone else in pain (Jackson et al., 2005). Furthermore, studies have provided evidence that observing others' pain activates brain regions subserving the sensory-discriminative properties of pain (Bufalari et al., 2007). Intriguingly, observing pain in others may also give rise to a vicarious experience of pain. This experience has most often been described in patients with a history of intense, traumatic pain. For example, Giummarra and Bradshaw (2008) documented a case of vicarious pain in a woman who had an emergency caesarean section delivery because of a long and painful labor with obstruction. This woman reported the experience of "shooting pains from the groin that radiate down the legs" when told of another's traumatic experience. In another study with 74 phantom limb patients (Fitzgibbon et al., 2010a), 16% of the participants reported that observing or imagining pain in another person triggers their phantom pain. There is little research yet available on the occurrence of vicarious pain and underlying mechanisms (but see Fitzgibbon et al., 2012a,b). Most evidence stems from clinical studies, using self-report questionnaires, describing the phenomenon and research in amputees. Little is known whether vicarious pain experiences can be elicited in a more systematic way, for example by means of an experimental paradigm in a lab.

There is preliminary evidence that also individuals without traumatic pain experiences may feel pain by observing pain in others. Osborn and Derbyshire (2010) found that, when healthy volunteers were presented a series of images and video clips depicting painful events, almost 30% reported at least one pain experience. In a follow-up study, 10 of these vicarious pain responders were matched with 10 non-responders to take part in an fMRI study, and static images of painful events and emotional images not containing noxious events were shown. When observing the images of the painful events, vicarious pain responders showed higher activation of emotional (i.e., left and right insular) and sensory brain regions (i.e., secondary somatosensory cortex) associated with pain than non-responders.

The mechanisms and conditions that affect these vicarious experiences are largely unknown. Fitzgibbon and colleagues (2010b) proposed a framework to further our understanding of vicarious pain, which they dubbed "synesthesia for pain." They proposed several mechanisms to explain vicarious pain, amongst which empathy or processes underlying empathy, hypervigilance to pain, chronic prior pain and trauma. According to this model, vicarious pain is a maladaptive form of empathic processing. Empathy has been defined in various ways, but generally features the capacity to understand and respond to the unique affective experiences of another person (Decety and Jackson, 2006). The role of empathy in vicarious pain experiences is yet unclear. In the study of Osborn and Derbyshire (2010), a group of pain responders and non-pain responders were subsequently matched for trait empathy Interpersonal Reactivity Index (IRI); consequently no differences occurred between both groups regarding this trait. Undergraduate students who reported an actual noxious somatic experience in response to images or clips depicting noxious events scored higher on a measure of state empathy than non-vicarious pain responders. Although the pain responders displayed more state empathy evoked by the images and movie clips, this was not correlated with reported pain intensity. However, in two recent studies, no differences were found between amputees with vicarious pain, amputees without vicarious pain responses, and non-amputee controls on measures of empathic ability (Giummarra et al., 2010; Fitzgibbon et al., 2012b).

Prior trauma may be the modulating variable inducing hypervigilance to pain cues, according to the model of Fitzgibbon et al. (2010b). Hypervigilance for pain is an over-alertness to pain-related information, and is installed when pain or anticipated pain becomes a current concern (Crombez et al., 2005). As such, vicarious pain may be an exaggerating response to the anticipation of observed pain (Giummarra et al., 2010; Fitzgibbon et al., 2012c). Therefore, we may expect that participants high in hypervigilance for pain report more vicarious pain experiences independent of any pre-existence of chronic (prior) pain. As yet, the proposed underlying mechanisms remain largely untested (Fitzgibbon et al., 2010b).

The primary aim of the present study is to develop an experimental paradigm allowing the measurement of vicarious pain experiences in people who explicitly report vicarious pain in daily life. A secondary aim was to explore the role of two potential moderators, i.e., dispositional empathy and hypervigilance for pain. To address these questions we developed a paradigm inspired by the work of Banissy and Ward (2007) on vicarious touch. In a first experiment, pre-selected undergraduate students reporting vicarious pain in daily life (i.e., "pain responders") and a comparison group not reporting vicarious pain, were presented a series of videos showing hands being pricked, whilst receiving occasionally pricking experiences themselves in the same spatial location (congruent trials) or in the opposite location (incongruent trials) as the visual stimuli. Participants were instructed to report as rapidly as possible the spatial location of the administered somatosensory stimuli. First, we expected a higher frequency of vicarious pain during the experiment in the group reporting vicarious pain in daily life compared to the comparison group. In analogy with the study of Banissy and Ward (2007) in vicarious touch responders, we also expected that vicarious pain responders would be slower in incongruent relative to congruent trials. Second, we explored the effects and moderating role of dispositional empathy and hypervigilance to pain upon experiences of vicarious pain. In experiment 2, we aimed at replicating the findings of experiment 1, though with some procedural changes. Additionally, we explored the effect of the rubber hand illusion (RHI) upon vicarious pain, and differences between pain responders and controls in RHI experience. As pain responders experience bodily illusions in response to another in pain, we expect their experience of the rubber hand illusion to be more pronounced compared to controls.

EXPERIMENT 1

METHOD

Participants

Participants were recruited from a pool of approximately 682 undergraduate students from Ghent University who were invited to complete questionnaires screening for, amongst others, the experience of vicarious pain in daily life (November 2010 to January 2011). Specifically, participants were asked to indicate the extent to which they agreed with the question "Do you have the feeling experiencing pain when you observe another person in pain?" on a five point scale (0 = strongly disagree; 1 = disagree; 2 = neutral; 3 = agree; 4 = agree; 5 = strongly agree). This item was specifically developed for this study and was based upon the work of Banissy and colleagues (2009). Two-hundred fourteen students completed the screening questionnaires (31.38%). In line with Banissy and colleagues (2009), participants scoring 4 or higher (22.90%, $n = 49$) were invited to take part in the experiment. We also invited randomly 20 of those who scored 1 or lower. In total, thirty students (23 women, 7 men) agreed to participate. Mean age was 21.87 years ($SD = 5.99$, range: 18–49 years). All participants were Caucasian. Participants received either course credits for participation in this experiment ($n = 13$) or were paid ($n = 17$) 8 euro. Ethical approval was obtained from the Ethics committee of the Faculty of Psychology and Educational Sciences of Ghent University, Belgium.

Apparatus and stimuli

Visual stimuli. Visual stimuli consisted of 10 short videos with a duration of 3 s. Each video depicted a scene in which a left and right hand was presented, with one of the two hands being pricked by a sharp object (2000 ms after video onset). Five types of sharp objects were used across all videos, i.e., a safety pin, a needle, and three different syringes. Location of penetration (left vs. right hand) and type of sharp object were counterbalanced across videos. Videos were presented by INQUISIT Millisecond software (http://www.millisecond.com) on a Dell computer with a 19-in. CRT-monitor.

Somatosensory stimuli. Somatosensory stimuli were electrocutaneous stimuli (ES, bipolar, sinusoide, 200 Hz), delivered between thumb and index finger by two lubricated Medcat surface electrodes (1 cm diameter) of a constant current stimulator (DS5, Digitimer Ltd, Hertfordshire, UK). The duration of the ES was always 200 ms. The intensity of the electrocutaneous stimulus was individually determined. In a work up procedure, individuals were presented with stimuli of increasing intensity until a pricking sensation was reported. At the start the intensity was 0.25 mA, and increased by 0.25 mA for each next stimulus. Such procedure was performed for both the left and the right hand (used intensities: left: $M = 0.78$ mA, range: 0.25–1.5 mA; right: $M = 0.75$ mA, range: 0.25–1.5 mA).

Self report measures

To assess vicarious pain experiences in daily life, participants were asked to indicate the extent to which they agreed with the question "Do you have the feeling experiencing pain when you observe another person in pain?" on a five point scale (0 = strongly disagree; 5 = strongly agree). This question was used for the initial screening and read ministered during the lab experiment to classify participants in the pain responder group and the comparison group. At our university, the initial screening is anonymous and data from the screening can only be used to select participants but not for other research purposes.

Hypervigilance for pain was assessed by the Dutch version of the Pain Vigilance and Awareness Questionnaire (PVAQ; McCracken, 1997; Roelofs et al., 2003). This questionnaire consists of 16 items to be scored on a six-point scale (0 = never; 5 = always). The PVAQ consists of two subscales: attention to pain (e.g., 'I pay close attention to pain') and attention to changes in pain (e.g., 'I am quick to notice changes in pain intensity') (Roelofs et al., 2003). The questionnaire can be used in both clinical (McCracken, 1997; Roelofs et al., 2003) and non-clinical (McWilliams and Asmundson, 2001; Roelofs et al., 2002) samples. Higher scores are indicative of more vigilance to pain. The Dutch version of the PVAQ is reliable and valid (Roelofs et al., 2002, 2003). Cronbach's alpha for the present study was 0.89.

Dispositional empathy was assessed with the Dutch version of the (IRI; Davis, 1983; De Corte et al., 2007). The questionnaire contains 28 items and consists of 4 subscales: 'Perspective Taking' (i.e., cognitively taking the perspective of another, e.g., "I sometimes try to understand my friends better by imagining how things look from their perspective."), 'Fantasy' (i.e., emotional identification with characters in books, films etc., e.g., "When I watch a good movie, I can very easily put myself in the place of a leading character."), 'Empathic Concern' (i.e., feeling emotional concern for others, e.g., "I am often quite touched by things that I see happen.") and 'Personal Distress' (i.e., negative feelings in response to the distress of others, e.g., "When I see someone who badly needs help in an emergency, I go to pieces."). Each item is rated on a scale ranging from 1 ('does not describe me very well') to 5 ('describes me very well'). This questionnaire has shown to be reliable and valid (Davis, 1983; De Corte et al., 2007). Cronbach's alpha's in the current study were 0.78 (fantasy scale), 0.61 (empathic concern), 0.79 (personal distress) and 0.39 (Perspective Taking). The latter subscale was omitted from the analyses because of the low reliability score.

Intensity and the (un)pleasantness of the electrocutaneous stimuli were rated on eleven-point numerical rating scales (0 = 'not intense'; 10 = 'intense' respectively −5 = 'unpleasant'; +5 = 'pleasant').

Procedure

Preparation phase. Participants were informed that they would feel stimuli, varying in intensity and length, on their left, right or both hands during the experiment. After signing the informed consent, a pair of electrodes was attached to each hand. The skin at the electrode sites was first abraded with a peeling cream (Nihon Kohden) in order to reduce skin resistance. Subsequently, the stimulus intensity level was established for each hand. Questions measuring the (un)pleasantness and intensity of the somatosensory stimulus were administered. Participants were seated in front of a table, at about 60 cm away from the computer screen and were informed that different videos would be presented which they needed to watch attentively. Hands of the participants were covered by means of a box and placed on the table in front of the screen. Participants were told that when a somatosensory stimulus was administered on both hands, the intensity could vary across hands and that also trials without any stimulus would be included. In reality, only one fixed predetermined intensity was applied for each hand.

Experiment phase. Each trial began with a fixation cross (1000 ms duration) presented in the middle of the screen. Next, one of 10 different videos was presented. In two third of the trials, an electrocutaneous stimulus was delivered 2050 ms after video onset either on the left hand, the right hand, or on both hands of the participant. In line with Banissy and Ward (2007), the electrocutaneous stimulus was administered with a delay, which was 50 ms after the penetration of the sharp object in the observed hand. This resulted in the following trial types: (1) congruent trials, (2) incongruent trials, (3) trials in which no somatosensory stimuli were administered and (4) trials in which both hands of the participant received somatosensory stimuli. In congruent trials, somatosensory stimuli and visual stimuli were presented at the same spatial location (e.g., right). In incongruent trials, somatosensory stimuli and visual stimuli were presented in the opposite spatial location (e.g., left and right). The experiment started with 8 practice trials. The actual experiment phase consisted of three blocks of 64 trials, resulting in a total of 192 trials. There were 60 congruent trials, 60 incongruent trials, 60 trials without ES and 12 trials with ES at both hands equally divided over the three blocks. This latter trial type was added to make the response 'both' applicable and feasible. Visual stimuli were presented when ES was present or absent. Trial types were equally distributed across blocks. Order of trial types was randomized within each block. An overview of all trial types is presented in **Table 1**. During each trial, participants were requested to report whether a physical sensation was felt and indicate its location as quickly and accurately as possible by reporting aloud "left," "right" or "both." Reaction times were recorded by means of a voice key (see **Figure 1**). The experimenter coded the response by pressing the corresponding response button (left, right or both). The participant was instructed not to respond when no sensation was felt. In such situation a trial was considered completed when 2000 ms had elapsed after the video was ended. The completion of

Table 1 | An overview of all trial types (experiment 1 - experiment 2).

Reported site	Congruent trials				Incongruent trials				No tactile stimulation			
	Correct site	**Opposite site to visual and tactile**	**Both hands**	**No hands**	**Correct site**	**Opposite site (= visual site)** ***vicarious error***	**Both hands** ***vicarious error***	**No hands**	**Site congruent to visual** ***vicarious error***	**Opposite site to visual**	**Both hands**	**No hands**
EXPERIMENT 1												
%	93.27%	0.33%	2.07%	3.27%	90.40%	0.93%	3.00%	4.53%	1.40%	0.33%	0.20%	97.60%
EXPERIMENT 2												
%	94.00%	0.17%	0.42%	4.25%	92.00%	0.25%	1.42%	5.17%	0.67%	0.42%	0.00%	98.17%

Voice key errors are not included.

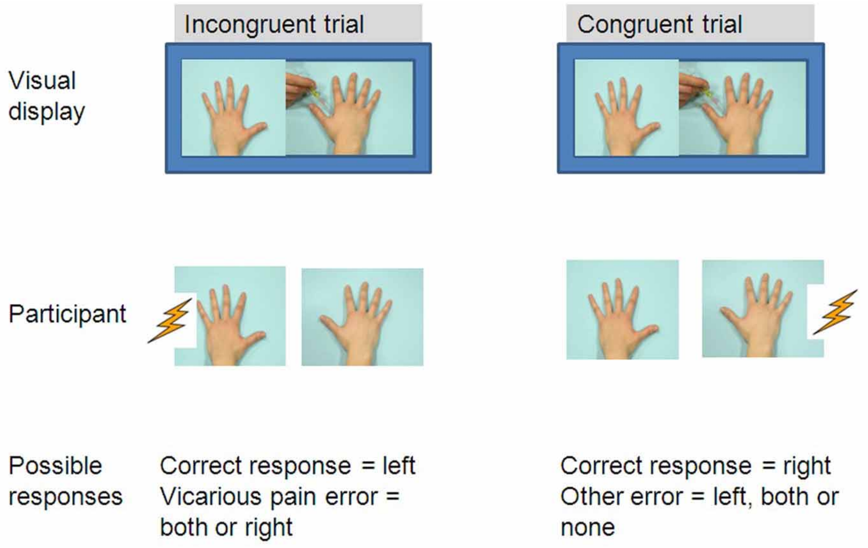

FIGURE 1 | Example of a possible trial.

the experiment took approximately 50 min. Vicarious pain errors were calculated from incongruent trials and from trials in which no ES was administered. A vicarious pain error was considered present when participants reported feeling a pricking sensation in the same spatial location as the visual stimulus without the administration of an actual ES at that location.

Post-experiment phase. After the experiment, participants were requested to fill out self-report scales measuring vicarious pain experiences in daily life, hypervigilance for pain (PVAQ) and empathic disposition (IRI).

Statistical analysis

Using the same criteria as during the screening, 14 participants were categorized in the pain responder group and 11 in the comparison group. Participants who did not fulfill these criteria at the moment of testing were excluded from analysis ($n = 5$).

To test the hypothesis that pain responders make more vicarious pain errors, count regression models were applied as the use of linear models is considered less appropriate when the frequency of responses has a skewed distribution that violates the normality assumption (e.g., Vives et al., 2006). Poisson regression is the basic model to analyze count data, but the variance of counts is often larger than the mean (overdispersion). The Negative Binomial (NB) regression, a Poisson regression with an overdispersion, may therefore better fit the data (e.g., Gardner et al., 1995). As count data may additionally exhibit a lot of zero counts, zero-inflated extensions of both models, called Zero-Inflated Poisson (ZIP) and Zero-Inflated NB (ZINB) models have been developed (see Karazsia and van Dulmen, 2010; Loeys et al., 2012). Deviance tests and Vuong test were used to select the best fitting count distribution for the dependent variable.

After the best fitting count model was chosen, several models were run. The first model contained the predictor ‘group’; the dependent variable was the number of vicarious pain errors. In subsequent analyses, participants’ characteristics were added as second predictor in the model to explore whether PVAQ respectively IRI (subscales) had a moderating role.

Dummy coding was used for the categorical variables and standardized z-scores for the continuous predictors. Regression coefficients are exponentiated (e^B) and called Rate Ratios (RRs). In percentages—100 × ($e^B - 1$)—RRs reflect the percentage decrease (RR < 1) or increase (RR > 1) in the expected frequency of vicarious pain errors for each standard deviation increase in the independent variable. R (version 2.15.1) was used to fit the count models.

To test whether participants in the pain responder group have higher hypervigilance and dispositional empathy scores compared with the comparison group, independent-samples t-tests were performed. To test whether pain responders show a larger congruency effect than non-pain responders (see Banissy and Ward, 2007), a 2 (congruency: congruent vs. incongruent) × 2 (group: comparison vs. pain responders) repeated measures ANOVA was performed, with congruency entered as within-subject variable and group as between-subject variable. Error trials and trials with responses faster than 200 ms or slower than 3 *SD* above the individual mean reaction time of each trial type were removed from RT analyses. These analyses were conducted with an $\alpha < 0.05$, using SPSS statistical software, version 21.0 for Windows.

RESULTS

Descriptive statistics

Mean scores, standard deviations and correlations of experiment 1 are presented in **Tables 2**, **3**. Because the variable (un)pleasantness did not have a normal distribution, Spearman correlations were computed for this particular variable (Kolmogorov-Smirnoff, $p < 0.05$). Mean age was 21.50 years in the pain responder group ($SD = 4.16$, range: 18–34 years) and 23.27 years ($SD = 8.76$, range: 18–49 years) in the comparison group. Of all participants, 27.3% indicated to have experienced an episode of chronic pain during their life (pain duration longer than 3 months). There was no significant difference between both groups [$t_{(20)} = -1.16, p = 0.26$]. In 2.7% of the incongruent trials and trials without any ES, vicarious pain errors were made (80 vicarious pain errors from a total of 3000 trials), mainly in the pain responder group (83.75% of all vicarious pain errors; $n = 67$). Two participants in the pain responder group were responsible for 66.25% of all vicarious pain errors (53 of a total of 80 vicarious pain errors). The number of vicarious pain errors did not differ across the 3 blocks (Kruskal-Wallis, $p = 0.12$). No difference was found between both groups in PVAQ scores [$t_{(23)} = -1.93, p = 0.07$] or empathy scores (subscales all $p \geq 0.10$).

Vicarious pain errors

The NB model was found to be the best fitting count model (χ^2 [1, $N = 25$] $= 149.26$, $p < 0.001$; V $= -1.33$, $p = 0.09$) to test the influence of group (pain responder vs. comparison group) upon the number of vicarious pain errors. In a first step, group was added as a predictor. Results showed that the number of vicarious pain errors significantly raised with 305% (RR $= 4.05$, $p = 0.04$; [95% CI: -0.02, 2.78]) when participants reported vicarious pain experiences in daily life (pain responder group) compared to the comparison group.

In order to explore the moderating role of individual differences in hypervigilance for pain (PVAQ) and dispositional empathy (IRI), additional models were run with PVAQ or IRI subscales entered as a second predictor and in interaction with group. A significant interaction was found between group and PVAQ ($p < 0.01$; [95% CI: -3.40, -0.57]). For pain responders, the

Table 2 | Mean scores and standard deviations of all measures (study 1).

	M (SD) pain responder group	M (SD) comparison group	M (SD) total group
1. RT incongruent trials	784.48 (118.44)	674.45 (74.34)	736.07 (114.06)
2. RT congruent trials	719.79 (136.86)	628.82 (70.88)	679.76 (119.84)
3. Intensity (0–10)	4.46 (1.66)	4.77 (1.65)	4.6 (1.63)
4. (Un)pleasantness	−1.43 (1.41)	−1.95 (0.76)	−1.66 (1.18)
5. PVAQ	39.62 (13.64)	30.0 (10.52)	35.39 (13.06)
6. EC	19.21 (3.38)	17.91 (3.75)	18.64 (3.53)
7. FS	21.29 (4.46)	19.00 (4.77)	20.28 (4.65)
8. PD	12.50 (6.16)	15.82 (3.34)	13.96 (5.30)

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RT, Reaction times.

Table 3 | Pearson/spearman correlations of all measures (study 1).

	2	3	4	5	6	7	8
1. RT incongruent trials	0.91**	−0.17	−0.05	0.03	−0.23	0.17	−0.51**
2. RT congruent trials	–	−0.24	−0.02	0.01	−0.32	0.09	−0.57**
3. Intensity (0–10)		–	−0.62**	0.41*	0.12	0.26	0.53**
4.(Un)pleasantness			–	−0.41*	0.22	−0.43*	−0.24
5. PVAQ				–	0.13	0.18	−0.07
6. EC					–	0.41*	0.17
7. FS						–	0.04
8. PD							–

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RT, Reaction times.

$^*p < 0.05$; $^{**}p < 0.01$.

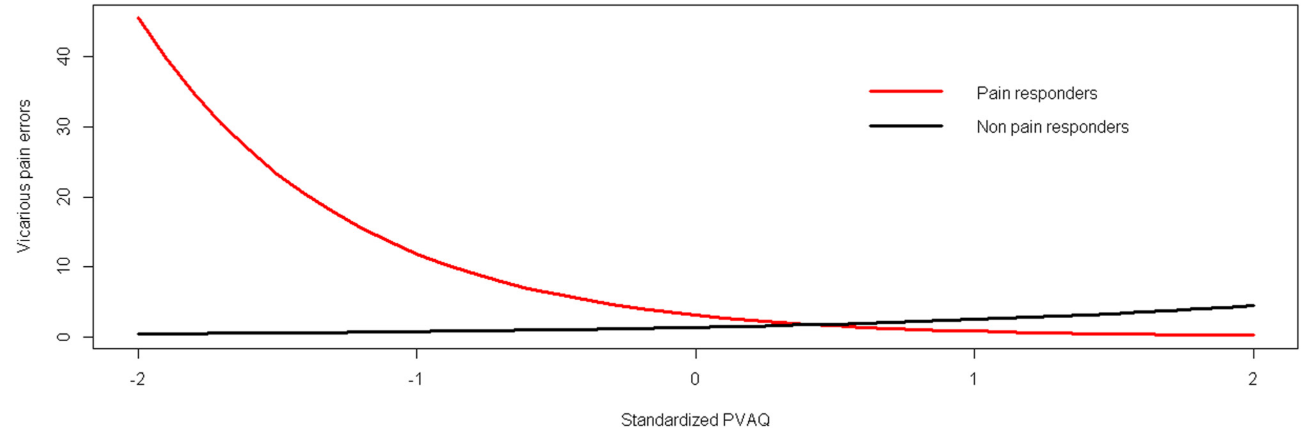

FIGURE 2 | The relationship between hypervigilance for pain (PVAQ) and vicarious pain errors as moderated by group (study 1).

probability of making vicarious pain errors decreased by 74% (RR = 0.26) for every standard deviation increase in hypervigilance for pain. For the comparison group, the probability of making vicarious pain errors increased by 79% (RR = 1.79) for every standard deviation increase in hypervigilance for pain (**Figure 2**). No main effect of hypervigilance for pain was found ($p = 0.28$).

Furthermore, no interaction was found between group and subscales 'fantasy' ($p = 0.22$), 'personal distress' ($p = 0.99$) and 'empathic concern' ($p = 0.61$). Also no main effects of these subscales were found (all $p > 0.44$).

Reaction times

A 2 (congruency: congruent vs. incongruent) × 2 (group: comparison vs. pain responder group) repeated measures ANOVA showed a main effect of group. In particular, the pain responder group was slower in both congruent and incongruent trials compared to the comparison group [$F_{(1,\ 23)} = 5.70$, $p = 0.03$]. Furthermore, also a main effect of congruency was observed [$F_{(1,\ 23)} = 29.84$, $p < 0.01$] indicating that all participants were faster on congruent than on incongruent trials. Contrary to expectations, no interaction was found between congruency and group [$F_{(1,\ 23)} = 0.89$, $p = 0.36$].

DISCUSSION

Current results indicate that our paradigm allows us to measure vicarious pain experiences in healthy students and revealed only a small percentage of vicarious pain errors. As the sample size of the first experiment was relatively small, a second experiment was performed to test whether the results could be replicated. Furthermore, a more stringent recruitment procedure was used than in experiment 1 where vicarious pain experiences in daily life were measured by means of only one item. As pain responders experience bodily illusions in response to viewing another's pain, an additional aim of the second experiment was to explore whether pain responders report a stronger rubber hand illusion experience than controls (Botvinick and Cohen, 1998). Finally, we also investigated whether the rubber hand illusion experience was related to participants' vicarious pain errors.

EXPERIMENT 2

METHODS

Participants

Participants were recruited from a pool of approximately 647 undergraduate students from Ghent University who were invited to complete several questionnaires (October to November 2011). One of these questionnaires intended to assess the experience of vicarious pain experiences in daily life by means of four items adapted from Banissy et al. (2009). Participants were asked to indicate on an eleven point scale (0–10; totally disagree—totally agree) the extent to which they agreed with the questions: "Do you feel pain in your own body when you see someone accidently bump against the corner of a table?", "Do you have the feeling experiencing pain when you observe another person in pain?", "Do you feel bodily pain when you observe another person in pain?" and "Do you feel a physical sensation (e.g., tingling, stabbing, …) when you observe another person in pain?". Completed questionnaires were available from 348 students (53.79%). As no standard cut-off for the presence of vicarious pain was available, we invited all participants who scored ≥ 6 on all questions (6.61%, $n = 23$). This cut-off preserves a balance between extreme values (inviting the highest scoring vicarious pain responders) and a minimum of pain responders to participate. We also invited randomly 20 of those who scored ≤ 1 on all questions.

In total, 24 undergraduates (23 women) agreed to participate. Their mean age was 19.17 years ($SD = 1.81$, range: 17–23 years). All participants, except one, were Caucasian. Participants received either course credits for participation in this experiment ($n = 21$) or were paid ($n = 3$) 8 euro. Ethical approval was obtained from the Ethics committee of the Faculty of Psychology and Educational Sciences of Ghent University (Belgium).

Design, apparatus and stimuli

The design, apparatus and stimuli, were similar as in experiment 1. The mean intensity of the somatosensory stimuli was 0.74 mA (range: 0.50–1 mA) for the left hand and 0.69 mA (range: 0.50–1mA) for the right hand.

Self-report measures

To assess vicarious experiences in daily life, participants were asked to indicate on an 11-point scale (0–10; totally disagree—totally agree) the extent to which they agreed with each of the four items, which were also used in the initial screening. This questionnaire was readministered during the procedure in the lab as the first screening was anonymous. Cronbach's alpha in the current study was 0.97.

Hypervigilance to pain (PVAQ; Cronbach's $\alpha = 0.91$) and empathic disposition (IRI; fantasy scale Cronbach's $\alpha = 0.84$, empathic concern Cronbach's $\alpha = 0.69$, personal distress Cronbach's $\alpha = 0.77$, perspective taking, Cronbach's $\alpha = 0.39$) were assessed in the same way as in experiment 1. As in experiment 1, the perspective taking subscale was omitted from the analyses because of the low reliability score.

Rubber hand illusion (RHI) experience was measured by means of nine items (e.g., 'It felt as if the rubber hand was my hand'; Botvinick and Cohen, 1998). Participants indicated the extent to which they agreed or disagreed on a 15 cm scale. Seven positions were marked ranging from strongly disagree (− − −) to strongly agree (+ + +). A total score for the RHI experience was based upon the sum score of all items (Cronbach's $\alpha = 0.79$).

Procedure

The first part of the procedure used in this experiment was identical to the applied procedure in experiment 1. Subsequent to the experiment, participants took part in a rubber hand illusion (RHI) test. The test was set up and conducted in line with previous RHI studies (Botvinick and Cohen, 1998). Participants were seated with their both arms placed upon a table. Their right hand was positioned next to a screen, outside the view of the participant. A right-handed life-sized rubber hand was placed on the table directly in front of the subject with its index finger 20 cm to the right of the participant's index finger. A black cape extending from their neck to the table obscured the view of their upper arms throughout the experiment. Participants were asked to focus on the rubber hand. Two small paintbrushes were used to stroke the participant's and rubber hand's index fingers during 3 min, synchronizing the timing of the brushing as closely as possible. After the RHI test, participants were requested to fill in a short questionnaire about their experience during the RHI test (see Botvinick and Cohen, 1998).

Statistical analysis

Participants were categorized in a pain responder group and a comparison group based upon the sum of their responses on the items measuring vicarious pain in daily life, administered during the experiment. As no cut-off was available, we considered to maintain all participants whose sum score was <15 ($n = 7$; comparison group) and those whose sum score was >25 ($n = 13$; pain responder group) as this cut-off preserves a balance between extreme values (the most extreme scoring vicarious pain responders) and a minimum of pain responders to analyze. Four participants scoring between 15 and 25 were excluded from the analyses.

To test the hypothesis that pain responders make more vicarious pain errors, we applied similar statistical analyses as those performed in experiment 1. Additional analyses were performed related to RHI. To investigate whether pain responders had a higher score on the questions measuring the RHI than the comparison group, we used a one sample t-test. We also explored whether the RHI experience was related to the number of vicarious pain errors in the behavioral paradigm.

RESULTS

Descriptive statistics

Mean scores, standard deviations and correlations for the second experiment are presented in **Tables 4**, **5**. The variables intensity and empathic concern did not have a normal distribution, therefore spearman correlations are indicated for these particular variables (Kolmogorov-Smirnoff, $p < 0.05$). The mean age of the participants in the pain responder group was 19.85 years ($SD = 2.03$, range: 18–23) and 18.29 years for the comparison group ($SD = 1.25$, range: 17–21 years). Of all participants, 52.6% indicated to have experienced an episode of chronic pain during their life (pain duration longer than 3 months). This was not significantly different between both groups [$t_{(17)} = -0.62$, $p = 0.54$].

In 0.88% of the trials, vicarious pain errors were made (21 vicarious pain errors from a total of 2400 trials), especially in the pain responder group (90.48% of all vicarious

Table 4 | Mean scores and standard deviations (study 2).

	M (SD) pain responder group	M (SD) comparison group	M (SD) total group
1. RT incongruent trials	711.07 (155.00)	685.51 (86.72)	702.12 (133.06)
2. RT congruent trials	681.10 (150.37)	651.05 (58.46)	670.59 (124.80)
3. Intensity	4.38 (2.31)	3.86 (2.46)	4.20 (2.31)
4. (Un)pleasantness	−1.81 (1.16)	−1.5 (1.08)	−1.70 (1.12)
5. PVAQ	42.23 (14.14)	42.00 (9.13)	42.15 (12.36)
6. EC	21.62 (2.02)	18 (4.58)	20.35 (3.51)
7. FS	20.85 (4.63)	19.57 (5.86)	20.40 (4.98)
8. PD	14.54 (4.99)	14.43 (5.22)	14.50 (4.94)
9. RHI	753.77 (206.04)	631.86 (199.73)	711.10 (207.29)

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RHI, Rubber Hand Illusion; RT, Reaction times.

Table 5 | Pearson/spearman correlations of all measures (study 2).

	2	3	4	5	6	7	8	9
1. RT incongruent trials	0.96**	−0.16	0.06	0.27	−0.12	0.18	−0.11	0.24
2. RT congruent trials	–	−0.07	0.10	0.33	−0.14	0.18	−0.10	0.23
3. Intensity		–	−0.61**	0.10	−0.18	0.17	0.24	0.16
4. (Un)pleasantness			–	0.01	0.02	−0.07	−0.21	0.11
5. PVAQ				–	0.28	0.23	0.47*	0.48*
6. EC					–	0.28	0.14	0.12
7. FS						–	0.06	0.39
8. PD							–	0.46*
9. RHI								–

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RHI, Rubber Hand Illusion; RT, Reaction times.
$^{*}p < 0.05$; $^{**}p < 0.01$.

pain errors, $n = 19$). Three pain responders were responsible for 76.19% of all vicarious pain errors (16 of a total of 21 vicarious pain errors). The number of vicarious pain errors did not differ across the three blocks (Kruskal-Wallis, $p = 0.75$). Furthermore, no significant difference was found between the pain responder group and the comparison group concerning the rubber hand illusion experience [$t_{(18)} = -1.28, p = 0.22$]. Also no differences were found between both groups regarding dispositional empathy scores (all $p \geq 0.60$) and hypervigilance for pain [$t_{(18)} = -0.04$, $p = 0.97$].

Vicarious pain errors

To investigate the impact of group (comparison vs. pain responder group) upon the number of vicarious pain errors, the NB-model was chosen as count model (χ^2 [1, $n = 20$] $= 27.84$, $p < 0.001$; V $= 1.71$, $p = 0.24$). The results of the NB regression testing showed that group did not influence the frequency of vicarious pain errors ($p = 0.17$).

In subsequent analyses, several models were run containing observer's characteristics such as PVAQ, subscales of the IRI and rubber hand illusion as a second predictor in the interaction to explore a moderating role. PVAQ did not significantly interact with group ($p = 0.86$), nor did the fantasy scale ($p = 0.44$), personal distress ($p = 0.55$), or rubber hand illusion ($p = 0.39$). Also no main effect was found of the PVAQ ($p = 0.57$), nor of the different subscales of the IRI (all $p > 0.24$) or RHI ($p = 0.34$).

Reaction times

A 2 (congruency: congruent vs. incongruent) × 2 (group: comparison vs. pain responder group) repeated measures ANOVA revealed no main effect of group; indicating that pain responders were not slower compared to the comparison group [$F_{(1,\ 18)} = 0.21$, $p = 0.66$]. Results did however reveal a main effect of congruency [$F_{(1,\ 18)} = 13.73$, $p = 0.002$], indicating that participants in general were faster on congruent than on incongruent trials. No interaction was found between congruency and group [$F_{(1,\ 18)} = 0.07, p = 0.80$].

DISCUSSION

In contrast to experiment 1, individuals reporting vicarious pain experiences in daily life did not report more vicarious pain errors in our behavioral paradigm than individuals from the comparison group. Although a negative association was observed between the number of vicarious pain errors and hypervigilance for pain in the pain responder group (see **Figure 3**), this effect proved to be non-significant. This may be due to a low sample size ($n = 20$). In that respect, it may however be that the results of both studies do not differ (Schmidt, 2010). To explore this issue further, we performed an analysis of the data combined from both experiments, and added an extra between-subject variable study (experiment 1 vs. 2).

OVERALL ANALYSES

RESULTS

Descriptive results

Mean scores, standard deviations and correlations of the pooled data are presented in **Tables 6**, **7**. As the congruent and incongruent RT as well as the self-report variables intensity, (un)pleasantness, personal distress and fantasy scale were not normally distributed (Kolmogorov-Smirnoff, $p < 0.05$) we reported Spearman correlations for these variables. To test whether both groups differed in hypervigilance and empathic concern, independent-sample t-tests were performed. Participants in the pain responder group were more empathic concerned compared to participants in the comparison group [$t_{(43)} = -2.33, p = 0.03$]. No difference was found between both groups in hypervigilance for pain [$t_{(43)} = -1.59, p = 0.12$]. For all analyses regarding reaction times, log10 transformation was used to normalize data.

Vicarious pain errors

To investigate the impact of group (pain responder vs. comparison group) upon the number of vicarious pain errors, the NB-model was again selected as best fitting count model (χ^2 [1, $n = 45$] $= 198.34$, $p < 0.001$; $V = -0.55$, $p = 0.29$). First, we checked whether study (experiment 1 vs. 2) had an impact upon number of vicarious pain errors. The relation between the number of vicarious pain errors and PVAQ ($p = 0.66$) and group ($p = 0.86$) was not dependent upon study (1 vs. 2). Also the interaction between the number of vicarious pain errors and study × group ($p = 0.33$) was not significant. Only a marginal main effect of study was observed, suggesting a slightly higher

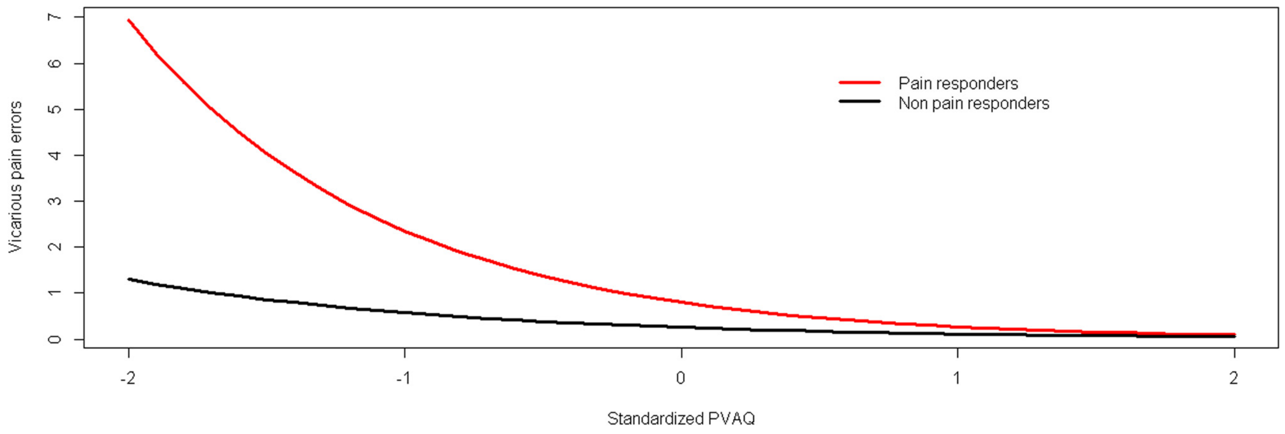

FIGURE 3 | The relationship between hypervigilance for pain (PVAQ) and vicarious pain errors as moderated by group (study 2).

Table 6 | Mean scores and standard deviations (overall analyses).

	M (SD) pain responder group	**M (SD) comparison group**	**M (SD) total group**
1. RT incongruent trials	749.14 (139.64)	678.76 (77.04)	720.98 (122.60)
2. RT congruent trials	701.16 (142.09)	637.47 (65.47)	675.69 (120.75)
3. intensity	4.43 (1.96)	4.42 (1.99)	4.42 (1.95)
4. (Un)pleasantness	−1.61 (1.29)	−1.78 (0.89)	−1.68 (1.14)
5. PVAQ	40.88 (13.68)	34.67 (11.43)	38.39 (13.06)
6. EC	20.37 (3.01)	17.94 (3.96)	19.40 (3.59)
7. FS	21.07 (4.46)	19.22 (5.06)	20.33 (4.74)
8. PD	13.48 (5.62)	15.28 (4.08)	14.20 (5.09)

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RT, Reaction times.

Table 7 | Pearson/Spearman correlations of all measures (overall analyses).

	2	**3**	**4**	**5**	**6**	**7**	**8**
1. RT incongruent trials	0.89**	−0.14	0	−0.14	−0.21	0.19	−0.37*
2. RT congruent trials	–	−0.13	−0.01	−0.15	−0.20	0.18	−0.44**
3. intensity		–	−0.68**	0.21	0.02	0.15	0.40**
4. (Un)pleasantness			–	−0.22	0.07	−0.28	−0.22
5. PVAQ				–	0.22	0.20	0.16
6. EC					–	0.38*	0.21
7. FS						–	−0.02
8. PD							–

PVAQ, Pain Vigilance and Awareness Questionnaire; EC, Empathic Concern; FS, Fantasy Scale; PD, Personal Distress; RT, Reaction times.
$^{*}p < 0.05$; $^{**}p < 0.01$.

prevalence of vicarious pain errors in the first study ($p = 0.06$). No interactions of study with any of the independent variables were found. To test whether pain responders make more vicarious pain errors compared to non-pain responders, group was added as a single predictor. The number of vicarious pain errors significantly raised with 282% (RR = 3.82, $p = 0.03$; [95% CI: 0.09, 2.54]) when participants reported vicarious pain in daily life (pain responder group) compared with the comparison group.

Additional analyses were run containing observer's characteristics such as PVAQ or subscales of the IRI as a second predictor in interaction with group to explore a possible moderating role. A significant interaction was observed between group and PVAQ ($p = 0.02$; [95% CI: −2.52, −0.05]). The size of the RR (0.96) demonstrated that the probability of making vicarious pain errors for the non-pain responders decreased by 4% for every standard deviation increase in hypervigilance for pain. For the pain responders, the probability of making vicarious pain errors decreased by 73% (RR = 0.27) for every standard deviation increase in hypervigilance for pain. The subscales of the IRI did not significantly interact with group ('fantasy scale,' $p = 0.26$; 'empathic concern,' $p = 0.68$; 'personal distress,' $p = 0.90$).

Reaction times

A 2 (congruency: congruent vs. incongruent) × 2 (group: pain responders vs. comparison) × 2 (study: first vs. second study) repeated measures ANOVA showed no main effect for group [$F_{(1, 41)} = 2.49$, $p = 0.12$] and for study [$F_{(1, 41)} = 0.30$, $p = 0.59$]. Overall, participants were faster on congruent than on incongruent trials [$F_{(1, 41)} = 39.60$, $p < 0.001$]. In contrast with expectations, no interaction was found between congruency and group [$F_{(1, 41)} = 0.16$, $p = 0.69$].

GENERAL DISCUSSION

Two experiments are reported, in which an experimental paradigm was used to assess the presence of vicarious pain experiences in healthy participants. Additionally, we explored the effects of some potential moderators proposed by Fitzgibbon et al. (2010b), i.e., dispositional empathy, hypervigilance to pain and also the tendency to experience the rubber hand illusion. In both studies, undergraduates were categorized in a pain responder group and a comparison group based upon reported vicarious pain experiences in daily life. They were presented a series of videos showing hands being pricked whilst receiving occasionally painful pricking sensations (electrocutaneous stimuli) themselves. In congruent trials, pricking stimuli and visual stimuli were applied to the same spatial location (e.g., right). In incongruent trials, pricking stimuli and visual stimuli were in the opposite spatial location (e.g., left and right). Participants were required to report as fast as possible where they felt a pricking sensation.

The main results can be readily summarized. In experiment 1, we found that the used paradigm was sensitive to measure vicarious pain experiences in healthy students. Findings indicated that participants who reported vicarious pain experiences in daily life made more vicarious pain errors during the experiment than participants of the comparison group. Furthermore, the probability of making vicarious pain errors decreased steeply for the pain responder group when they showed an increased level of hypervigilance for pain, whereas the probability of making vicarious pain errors increased for the comparison group when they showed an increased level of hypervigilance for pain. In experiment 2, however, findings of experiment 1 were not confirmed. No influence was found of the group to which participants belonged on the number of vicarious pain errors made during the experiment. Also no relationship was found between the level of hypervigilance for pain and the number of vicarious pain errors made. There was also no relationship between the number of vicarious pain errors and the rubber hand illusion experience. In order to explore the possible difference between both experiments, we opted to merge the data of both experiments. Results of these analysis showed that there was no difference in both experiments related to the findings. The overall results (i.e., of the merged data) were in line with findings of experiment 1 and indicated that (1) participants who reported vicarious pain experiences in daily life made more vicarious pain errors during the experiment than participants of the comparison group and (2) the probability of making vicarious pain errors decreased steeply for the pain responder group when they showed an increased level of hypervigilance for pain, while vicarious pain errors showed only a little decrease in the comparison group. For reasons of clarity, the discussion will mainly focus upon the combined findings.

First, our study reveals that undergraduates report vicarious pain experiences in daily life, albeit that the prevalence of pain responders was low. In experiment 1, the prevalence was 22.9%. In experiment 2, it was 6.61%. The difference in prevalence of self-reported vicarious pain experiences in daily life between both experiments is probably due to the use of a more stringent cut-off to categorize pain and non-pain responders compared to Experiment 1. Overall, the prevalence of vicarious pain found in the current study is low in comparison with the prevalence reported by Osborn and Derbyshire (2010), which was almost 30%. One reason for this difference may relate to the fact that the prevalence number in the present study was based upon self-report of vicarious pain experiences in daily life whereas the prevalence number reported by Osborn and Derbyshire (2010) was based upon report of participants who were shown images of people perceiving pain. It is worthwhile for future studies to combine both approaches and to recruit people based upon questions measuring vicarious pain in combination with showing participants video clips of painful situations to check whether they are feeling pain experiences. The variability in prevalence illustrates the need to have clear criteria to identify pain responders in future research.

Second, overall the experimental paradigm was successful in eliciting vicarious experiences of pain, in particular in those reporting vicarious pain experiences in daily life. The number of vicarious pain errors doubled in participants reporting vicarious pain in daily life (i.e., pain responder group) compared to the comparison group. However, it should be noted that the total number of vicarious pain errors was low, and only a few participants from the pain responders group accounted for the phenomenon. Future research may focus upon these few pain responders and investigate on which variables they differ from other participants. First, the low number of vicarious pain errors could be due to the fact that felt and seen stimuli may result in a different sensation. Indeed, it might be that the sensation experienced by the electrocutaneous stimulus differs too much from the sensation experienced when being confronted with images of a pricking sensation. Indeed, the more actual somatosensory sensations are alike to the vicarious experiences, the more vicarious errors may occur in our experimental paradigm. This may however only be achieved with vague somatosensory stimuli of low intensity. Interestingly, in the study of Osborn and Derbyshire (2010), the most frequent descriptor that was selected from the McGill Pain Questionnaire to describe vicarious pain was "tingling." Therefore, it would be interesting for future research to use tingling stimuli of a low intensity instead of electrocutaneous stimuli to investigate vicarious experiences. In line with this, pain responders in the study of Osborn and Derbyshire (2010) rated the average vicarious pain across all images rather low on a visual analogue scale ($M = 1.9$, $SD = 2.4$) ranging from 0 (no pain) to 10 (most pain imaginable). The experience of vicarious pain was dependent upon the content of the picture. In our study, the intensity of the ES were not rated as highly painful, since intensity ratings were on average around 4.4 on a 10-point scale (0 = not intense and 10 = intense), and unpleasantness ratings were on average −1.6 (−5 "unpleasant"; +5 "pleasant"). Our aim was to provide somatosensory stimuli that were not too painful and which induced experiences that were alike to the shown pricks. If somatosensory stimuli would be experienced too intense, it would be very easy to distinguish vicarious experiences from administered ES. With more intense ES, our prediction would be that no vicarious errors would occur. We included video clips showing hands being pricked. These videos depict less intense pain compared to the images and movies used in the study of Osborn and Derbyshire (2010). Vicarious pain may be elicited more easily when very intense pain is observed. The fact that pain responders in this study already experience vicarious pain during the mere observation of a subtle injury such as a needle prick is therefore very informative and interesting.

We explored the (moderating) role of several individual difference variables such as dispositional empathy, hypervigilance for pain and the degree to which the rubber hand illusion was experienced upon vicarious pain. Current findings do not provide support for the moderating role of dispositional empathy. Although the pain responder group was more empathic concerned, this had no influence upon the occurrence of vicarious pain errors. It might however be that, although dispositional empathy may not play a role as underlying mechanism in normal subjects reporting vicarious pain experiences, it might have an impact in individuals with prior chronic pain or trauma such as amputees, where vicarious experiences of pain are often experienced as more intense (Giummarra and Bradshaw, 2008; Fitzgibbon et al., 2010a). Also the degree in which the rubber hand illusion was experienced was not different for both groups. It had also no explanatory role in the experience of vicarious pain errors. In line with the model provided by Fitzgibbon and colleagues (2010b), we also explored whether the occurrence of vicarious pain errors was influenced by the degree of hypervigilance for pain. According to the theory of Fitzgibbon et al. (2010b), we expected pain hypervigilance to facilitate the production of vicarious pain errors as we expected pain responders to be overattentive to pain cues. As such, vicarious pain may be an exaggerating response to the anticipation of observed pain. Contrary to our expectations, more hypervigilance for pain was related to less vicarious pain errors in the group of pain responders, suggesting that hypervigilant participants were less misled by the visual stimuli. The same, albeit small, negative relation was found for the non-responder group. A possible explanation for this unexpected finding may relate to the fact that pain responders who are more focused upon the detection of somatic sensations experience less vicarious pain experiences. It is however unclear why hypervigilance for pain has a moderating role in making vicarious pain errors and how exactly this observer's characteristic prevents pain responders to make vicarious pain errors.

Taken all the literature together, there is preliminary evidence for vicarious pain experiences in response to observing pain in others (Fitzgibbon et al., 2010b). Until now there is little empirical investigation into this phenomenon. To date, the preliminary evidence regarding vicarious pain is primarily based upon anecdotal reports, and research in clinical populations with prior pain or trauma. Only little research is available on the conditions in which vicarious pain occurs and on the underlying mechanisms. Especially the role of empathy or processes underlying empathy have predominantly been investigated (e.g., Fitzgibbon et al., 2012a,b).

This study is one of the first to measure whether observers can feel pain themselves by observing pain in another individual measured by means of an experimental design. Insight into the conditions wherein pain is elicited by mere observation is of major significance for both the theory about pain as a biopsychosocial phenomenon and clinical practice. Theoretically, insight into the conditions and processes of vicarious pain is expected to fundamentally change the view about how pain is processed in the brain, demonstrating the important role of psychosocial variables (e.g., empathy, hypervigilance for pain), not only in the modulation (Van Damme et al., 2010) but also as cause of pain experiences in clinical and non-clinical populations. Further research is needed to investigate the underlying mechanisms of vicarious pain in a general population and in chronic pain patients. Also research is needed about the quality and intensity of the reported vicarious pain experiences and the difference between the reported vicarious experiences and the visual triggers (i.e., pain in another). Besides the neuroimaging and behavioral research, it would be interesting to explore whether vicarious pain experiences are also reflected in different patterns regarding psychophysiological measures (e.g., heart rate, skin conductance). Other possibilities are to show more intense painful images to enhance chances for vicarious pain errors to occur. Other studies have suggested that empathic responses are substantially influenced by whether or not one attends to the feelings of the target through the explicit imagination of the target's feelings (Jackson et al., 2006; Preston et al., 2007; Fan and Han, 2008). Future research may therefore consider using not only real life images and movies but also specific instructions to manipulate participants' empathic responses to investigate whether this impacts the occurrence of vicarious experiences.

A number of limitations deserve further consideration, each of which point to directions for future research. First, only few people reported vicarious pain experiences in daily life, resulting in a small sample size in these experiments. We tried to overcome this by additional analyses of the pooled data of the two experiments. Although sample sizes were small, the amount of pain responders who took part in the experiments were comparable to other studies who included participants reporting vicarious bodily sensations (Banissy and Ward, 2007; Osborn and Derbyshire, 2010). Second, for the second experiment, different cut-offs were used for initial screening and during the lab experiment to classify participants in the pain responder group and the comparison group to preserve a minimum of pain responders to analyze. This implies that participants scored the different questions not exactly the same over time. As the initial screening is anonymous at our university, data from the initial screening is not linked to specific individuals, which makes it impossible to compare both ratings in each individual. Future research is needed to investigate the reliability and stability of this phenomenon across time.

CONCLUSION

This new behavioral paradigm allowed measuring vicarious pain experiences in undergraduates. Vicarious pain experiences were found to be a rather rare phenomenon, elicited in only a subsample of participants reporting vicarious pain experiences in daily life. This behavioral paradigm is promising to investigate other underlying mechanisms (i.e., prior pain) of vicarious experiences of pain.

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Mirror-like brain responses to observed touch and personality dimensions

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The last years have shown a growing interest in research on the neural mechanisms for perceiving and understanding social interactions. Only very recently, a role for somatosensation in social perception has been suggested. Numerous studies reported vicarious responses in the primary somatosensory cortex (SI) and other areas merely when seeing others being touched. Moreover, it has been demonstrated that these vicarious somatosensory responses can be linked with inter-individual differences in empathy. However, beyond empathy other personality traits have been shown to interact with social perception and behavior. Here we tested if personality traits according to the Five-Factor-Model interact with vicarious activation in somatosensory brain regions. We conducted a functional magnetic resonance imaging (fMRI) study in which subjects viewed video clips showing simple non-painful touch to a hand and a control condition including the same visual and motion parts. Results revealed vicarious somatosensory activation when viewing the touched hand, as expected. Vicarious activation in SI showed a trend for a positive correlation with the personality trait openness to experience. Moreover, mirror-like responses in the insula were strongly correlated with the personality trait conscientiousness, suggesting links to processes of self-control. We conclude that vicarious brain responses to seen touch seem to interact with personality traits.

Keywords: somatosensory cortex, personality, touch, NEO-FFI, mirror network, fMRI

INTRODUCTION

In the last years numerous studies tried to reveal the neural mechanisms for perceiving and understanding social interactions (Cacioppo and Decety, 2011). Understanding of the conspecific's experiences is crucial for social behavior. According to the mirror neuron theory this understanding is accomplished by an internal simulation of other's experiences we are observing (Rizzolatti et al., 2001). Recent studies revealed mirror-like responses not only for actions, but also for touch. Thus, it has been shown that merely viewing touch involves the observers' somatosensory cortices. For example, Bufalari et al. (2007) reported that somatosensory evoked potentials (SEPs) were modulated by the observation of a touched hand. They found increased P45 amplitudes during pain observation (a needle penetrating a hand) and decreased P45 amplitudes during touch observation. Studies employing fMRI, magnetoencephalography, or transcranialmagnetic stimulation (TMS) support the results of vicarious somatosensory activation when observing touch (Keysers et al., 2004; Blakemore et al., 2005; Ebisch et al., 2008, 2011; Gazzola and Keysers, 2008; Schaefer et al., 2009; Pihko et al., 2010; Wood et al., 2010; Bolognini et al., 2012; Meyer et al., 2011; Kaplan and Meyer, 2012).

It has been argued that we perceive the social world differentially according to our personality traits. Consequently, recent studies suggest that mirror-like responses are linked with personality traits. For example, Fecteau et al. (2008) reported a relationship between mirror responses in the motor system and psychopathic personality traits. Avenanti et al. (2009) employed TMS to demonstrate that somatomotor responses to others' pain were influenced by the observers' empathy traits. In addition, several studies suggest that mirror-like responses in somatosensory brain regions are prone to interindividual differences. Osborn and Derbyshire (2010) report that when observing clips or pictures of injuries about one-third of participants experience feeling pain on the corresponding part of their own body, while the remaining two-thirds report negative feelings without a sense of somatic pain. A subsequent fMRI experiment revealed vicarious activity in SI and secondary somatosensory cortex (SII) associated with the images of injuries, but only in those participants who experienced localized vicarious pain.

Moreover, recent studies discuss an association for SI and empathy beyond the observation of painful stimulation. Ruby and Decety (2004) reported that empathy and perspective taking in complex social events are associated with activation in SI. Hooker et al. (2010) presented social scenes in an fMRI experiment and showed a correlation of somatosensory areas on the left postcentral gyrus with empathy. Gazzola et al. (2006) reported that a group of more empathic subjects compared with a group with lower empathy scores activated the mirror system (including the somatosensory cortices) more strongly. Our previous study supported these results by showing that mirror-like responses in SI during observation of simple nonpainful touch are linked with empathy (Schaefer et al., 2012a).

The above-mentioned studies refer to interindividual differences in vicarious somatosensory engagement only with regard to empathy. This makes sense in particular in studies examining somatosensory responses when witnessing painful stimulation. But recent studies showed interindividual differences in empathy even for participants observing stimuli not related to pain (e.g., Gazzola et al., 2006; Schaefer et al., 2012a). Based on these results one could hypothesize that vicarious somatosensory activations may also be affected by more general personality traits. This is supported by a recent study showing that personality may depend on primary somatosensory cortex activity. Using neuromagnetic source localization, this study demonstrated that the personality dimension extraversion predicted the strength of somatosensory brain responses when receiving non-painful touch (Schaefer et al., 2012b). The results support an earlier study reporting a relationship of extraversion with SI activity (Shagass and Schwartz, 1965). The relationship of the personality trait extraversion with primary somatosensory cortex activity can be explained by neurobiological assumptions of personality (e.g., Eysenck, 1967; DeYoung et al., 2010). Based on these results we here wanted to examine if somatosensory cortex activity elicited by merely observed touch is similarly prone to interindividual differences in extraversion. Since extraversion is related to the perception of social stimuli and the mirror neuron system is discussed as a neurobiological foundation of social perception, we hypothesized that interindividual differences in extraversion may also influence mirror-like responses in the brain. Thus, we tested if responses in somatosensory brain regions when seeing someone else being touched are affected by personality traits according to the Five-Factor-Model (FFM). The FFM is a factor-analytic approach describing the human personality in five core dimensions, which are extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience. Extraversion is displayed by a tendency to experience positive emotions and includes a high degree of sociability, assertiveness, and talkativeness. Neuroticism is linked to the tendency to experience negative emotions, involving anxiety, self-consciousness, and irritability. Agreeableness is linked to altruism, including traits such as cooperation, compassion, and politeness. Conscientiousness is reflected by being disciplined, organized, and achievement-oriented. Openness to experience involves active imagination, aesthetic sensitivity, attentiveness to inner feelings, preference for variety, and intellectual curiosity (Costa and McCrae, 1992).

In order to test our hypothesis we reanalyzed data from our previous fMRI study (Schaefer et al., 2012a), in which we presented video clips showing a hand receiving tactile stimulation with a paintbrush and as a control condition the same picture and motion parts, but without seeing the hand being stimulated (analogue to Keysers et al., 2004; Schaefer et al., 2009). We hypothesized that the vicarious activation of somatosensory brain regions during the observation of touch is linked with interindividual differences according to the FFM. Given the results of recent studies showing relationships of empathy with SI (Ruby and Decety, 2004; Gazzola et al., 2006; Hooker et al., 2010; Osborn and Derbyshire, 2010; Schaefer et al., 2012a), we expected an interaction of personality especially with vicarious activity in SI. More in detail, we assumed a relationship of extraversion with mirror-like responses in SI, because activity in SI has been linked with extraversion (Shagass and Schwartz, 1965; Schaefer et al., 2012b). Thus, we argue that the simulation of touch is similarly affected by the extraversion dimension as actual real touch. Based on previous results (Schaefer et al., 2012b) we hypothesized that more introverted participants should show stronger mirror-responses in SI.

Beyond mirror like responses in SI or SII, insula activation during observation of touch has been reported (Blakemore et al., 2005; Morrisson et al., 2011; Schaefer et al., 2012a). In addition, based on experiments investigating affective responses, numerous studies showed interindividual differences in insula activation (Mazzola et al., 2010; Guiliani et al., 2011; Banissy et al., 2012; Bauer et al., 2012). Furthermore, studies investigating the relationship between conscientiousness and learning suggest a link for this personality trait to self-related cognitions (e.g., Martocchio and Judge, 1997; Lee and Klein, 2002). For example, Martocchio and Judge (1997) suggested a model of two mediating constructs, self-deception and self-efficacy, which are hypothesized to mediate the relationship between conscientiousness and learning. Their findings indicated that conscientiousness was positively related to self-efficacy as well as to self-deception, whereas self-efficacy was positively and self-deception negatively linked to learning. However, both psychological constructs were linked to conscientiousness. Since these concepts can be described as self-related cognitions and the insula is known to represent self-awareness (Craig, 2009), sense of agency (Farrer and Frith, 2002) and sense of body ownership (Tsakiris et al., 2006), we hypothesized relationships of the insula with self-related personality dimensions (in particular, conscientiousness), whereas more social aspects of personality dimensions (extraversion, agreeableness) should not be related to insula activation when seeing someone else being touched.

MATERIALS AND METHODS

PARTICIPANTS

Seventeen out of the 22 participants that participated in the previous study (Schaefer et al., 2012a) were included in the current analyses. Two were discarded due to technical problems; one further participant was excluded due to poor data quality in the empathy questionnaire. In addition, the present study was unable to collect NEO-Five-Factor Inventory data from two further participants, resulting in a final N of 17 participants (nine females, mean age 26 years, range 23–39 years). All participants were right-handed native German volunteers with no neurological or psychiatric history. The study adhered to the Declaration of Helsinki and was approved by the local human subjects committee. Informed written consent was obtained from all subjects.

PROCEDURE

The stimuli consisted out of video clips depicting a right hand (egocentric viewpoint) and a moving paintbrush. There was one experimental condition (= touch observation condition), one control condition, and one additional condition to localize somatosensory brain regions (= real touch condition). The video clips (and the real touch condition) lasted for 18 s and were followed by resting periods of 15 s ± 3 s.

In the touch observation condition video clips showed a hand repeatedly being touched on the index finger by a paintbrush. In the control condition the paintbrush made identical motions as in the touch observation condition except that in the former, the brush stroked on the side of the index finger, but did not touch the hand (see **Figure 1**). In all conditions, a right hand was stimulated. The same visual stimuli and motion frequency (1/s) were applied in all video clips. The motion of the paintbrush was vertical in about 90 percent of all trials and horizontal in about 10 percent. Participants were required to press a key with their left hand to report the number of vertical strokes at the end of each video clip (analogue to Schaefer et al., 2009). Two fingers were used to indicate the number of vertical strokes. The key was custom-made and had two buttons. Participants were instructed to answer as soon as they saw the asterisk marking the beginning of the resting block. Yes and no buttons were randomized over the trials. The task was designed to ensure that subjects paid attention to the videos (analogue to Blakemore et al., 2005; Schaefer et al., 2009).

Visual images were back-projected to a screen at the end of the scanner bed close to the subject's feet. Subjects viewed the images through a mirror mounted on the birdcage of the receiving coil.

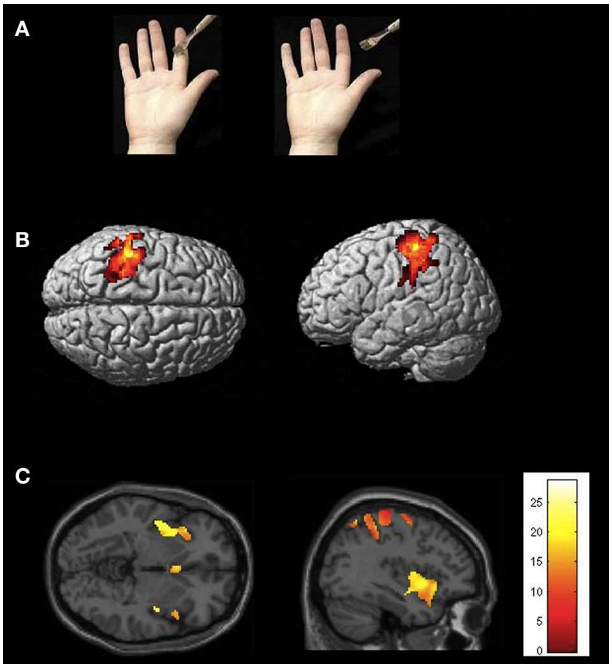

FIGURE 1 | (A) Conditions and types of stimuli used in the experiment. The picture on the left depicts the experimental condition (touch to a hand); the picture on the right shows the control condition (the paintbrush does not hit the depicted hand). **(B)** Statistical map showing common brain activation in left SI for receiving real touch (>resting baseline) and observing touch (>control) (random-effects analysis, $p < 0.05$, FWE corrected). **(C)** Statistical map demonstrating activation in insula (and other brain areas, masked with real touch > baseline). Areas of significant fMRI signal change are shown as color overlays on the T1-MNI reference brain.

In the real touch condition the participant's right hand was repeatedly touched by a paintbrush during the fMRI scan. Subjects were not able to watch the stimulation. The manner and frequency of brushing were identical to that shown in the touch observation videos. Participants were instructed to focus a fixation asterisk.

Each experiment consisted out of three runs. Each run included nine experimental and nine control blocks. In addition, three real touch blocks for localizing somatosensory brain areas were added to each run. Video stimuli and real touch stimulation were presented in a random order and were counterbalanced over the runs. The experiment lasted for about 45 min.

After the experiment, participants were asked to complete a German version of the NEO Five-Factor Inventory (NEO-FFI, Borkenau and Ostendorf, 1993). Furthermore, subjects completed a German version of the Interpersonal Reactivity Index (IRI, Davis, 1983), which is a 28-item self-report survey consisting out of four subscales: Empathic Concern (EC), Personal Distress (PD), Perspective Taking (PT), and Fantasy (F). EC describe a person's tendency to have feelings of sympathy and concern for others. PD measures the tendency to which someone feels a negative emotion. PT assesses the extent to which someone cognitively imagines a situation from the other person's point of view. The F subscale describes the tendency to project oneself into the place of fictional characters in books and movies. Results regarding the empathy measures were published in our previous study (Schaefer et al., 2012a).

fMRI DATA ACQUISITION AND ANALYSIS

The functional imaging was conducted by using a 1.5 T scanner (General Electrics Signa LX, Fairfield, Conneticut, USA) to conduct functional imaging (gradient echo T2-weighted echo-planar images; $TR = 2$ s, $TE = 35$ ms, flip angle = 80 degrees, FOV = 20 mm). Functional volumes consisted of 23 slices. Each volume comprised 5 mm slices (1 mm gap, in plane voxel size 3.125 × 3.125 mm). For anatomical reference a high-resolution T1-weighted structural image was collected (3D-SPGR, $TR = 24$ ms, $TE = 8$ ms).

Functional imaging used the technique of Statistical Parametric Mapping Software (SPM5, Wellcome Department of Imaging Neuroscience, University College London, London, UK). Prior to statistical analysis, the images were corrected for subject motion, spatially normalized to a standard anatomical space with a resampled voxel size of 3 mm (MNI, Montreal Neurological Institute template), and then spatially smoothed with a Gaussian kernel of 6 mm full-width half maximum.

Statistical parametric maps were calculated using multiple regression with the hemodynamic response function modeled in SPM5. We examined data on the individual subject level by using a fixed effects model (the three runs were concatenated for each subject). For each subject we calculated the contrast (blockwise) observing touch relative to control (t-test). The resulting parameter estimates for each regressor at each voxel were then entered into a second-level analysis. Functional analyses were based on the contrasts (t-tests) between observation of touch and the control condition, using random-effects models. To investigate common activations between real touch and the mere observation of tactile stimulation, the contrasts (observation of touch relative to control) were inclusively masked by the contrast of real touch minus resting baseline (at $p < 0.05$).

We report regions that survived correction for multiple comparisons over the whole brain [family-wise error (FWE) correction at $p < 0.05$]. We used the SPM Anatomy toolbox for anatomical interpretation of the functional imaging results (Eickhoff et al., 2005).

Scores of the personality traits were tested for possible correlations (Pearson) with the parameter estimates for voxels in the somatosensory region of interest (maximum peak in left SI for contrast touch observation relative to control condition, masked with real touch relative to resting baseline). Furthermore, we tested possible correlations with personality traits for left SII, left and right insula, and left premotor region (maximum peaks for touch observation relative to control, masked with real touch). Results of the correlation data were corrected for multiple tests (Bonferroni). Thus, considering five regions of interest and nine different scales (IRI and NEO-FFI), correlations with $p < 0.001$ were described as significant.

Behavioral responses were analyzed by comparing the task accuracy (stroke count) between experimental and control conditions (t-test). Task accuracy was defined as number of video clips in which participants correctly identified the number of vertical strokes. Furthermore, we tested task accuracy with personality dimensions (IRI and NEO-FFI) for significant correlations. The results were Bonferroni corrected for nine scales (IRI and NEO-FFI), thus, results with $p < 0.005$ were considered as significant.

Finally, we tested the behavioral responses (task accuracy) with BOLD signal changes in SI and insula (all correlations Pearson) (Bonferroni correction for two scales, $p < 0.025$).

RESULTS

NEO-FFI RESULTS

The mean value for extraversion was 29 ± 6 (mean ± standard deviation; range 15–36); for neuroticism 19 ± 9 (range 6–32); for openness to experience 32 ± 6 (range 21–41), for agreeableness 34 ± 5 (range 28–38) and for conscientiousness 33 ± 7 (range 17–46). There was a negative correlation between extraversion and neuroticism ($r = -0.74$, $p < 0.05$).

BEHAVIORAL RESULTS

The overall accuracy of the task performance during fMRI scanning was 80% (standard deviation ±15 %; across all conditions; mean for experimental condition: $79 \pm 15\%$; mean for control condition: $81 \pm 14\%$). There were no significant differences in subjects' performance (i.e., accuracy of stroke count) over the experimental conditions [touch observation, control condition: $t_{(16)} = -0.46$, $p = 0.65$]. Accuracy of the behavioral responses was not associated with personality dimensions (all $p > 0.10$). In addition, reaction times were not correlated with personality measures (all $p > 0.10$). None of our participants stated to have imagined the seen hand as the own hand.

IMAGING RESULTS

Analysis of the fMRI data showed that the contrast real touch relative to resting baseline yielded in activation of contralateral postcentral gyrus (SI), bilateral parietal operculum (SII/parietal ventral area), the precentral gyrus (BA4/6), the insula, the lateral temporo-occipatal cortex, the superior parietal /intraparietal cortex, and thalamus ($p < 0.05$, FWE corrected).

Brain regions overlapping with observed touch (touch observation > control, masked with real touch > resting baseline) showed significant activation in postcentral gyrus (SI/BA 2), SII, premotor cortex (BA44, BA6), SMA, ventral anterior (Deen et al., 2010) or mid (Taylor et al., 2009) insula, superior parietal lobe, superior temporal gyrus, and cerebellum (see **Figure 1** and **Table 1**).

Figure 2 shows scatterplots of brain responses (parameter estimates) in left SI with NEO-FFI scores of the five factors. We used the parameter estimates for the maximum activation (peak voxel) of the cluster in left SI, which has been assigned to BA2 (Eickhoff et al., 2005). Activity in SI correlated with openness to experience with a trend for significance ($r = 0.64$, $p = 0.006$), but not with any other personality measure (neuroticism: $r = -0.20$, $p = 0.44$; agreeableness: $r = -0.13$, $p = 0.62$; conscientiousness: $r = 0.19$, $p = 0.47$; extraversion: $r = 0.32$, $p = 0.21$).

Figure 3 depicts scatterplots of vicarious brain responses for observed touch in left anterior/mid insula (peak activation) and NEO-FFI scores of the five factors. Results revealed that activity in insula was strongly significantly correlated (negatively) with the personality factor conscientiousness ($r = -0.76$, $p < 0.001$). No other personality dimension revealed significant correlations with insula activation (neuroticism: $r = -0.06$, $p = 0.83$.; agreeableness: $r = -0.50$, $p = 0.04$; openness: $r = -0.01$, $p = 0.98$; extraversion: $r = -0.25$, $p = 0.33$).

Vicarious responses in SII, right insula or in premotor cortex failed to show any significant relationships with personality dimensions.

Table 1 | Results of random effects analysis (at $p < 0.05$, FWE corrected; L, left hemisphere; R, right hemisphere; masked with real touch > baseline) for contrast touch observation relative to control.

Contrast	Brain region	MNI coordinates	Peak *t*-value
Touch observation > control	L SI	−38, −36, 52	16.46
	L premotor cortex/BA44	−56, 8, 12	15.85
	L premotor cortex (BA6)	−28, −10, 60	20.36
	L precentral gyrus (BA6)	−54, 4, 38	11.34
	R SMA (BA6)	6, 14, 60	15.61
	L SMA (BA6)	−4, 4, 46	23.69
	L insula	−40, 2, −4	23.01
	R insula	44, 12, −6	16.48
	R SII/sup. temp. gyrus	58, −32, 22	12.90
	L SII	−54, −30, 2	9.45
	R sup. parietal lobe (BA7A)	22, −60, 64	15.05
	L sup. parietal lobe (BA7A)	−32, −60, 60	18.72
	L sup. temp. gyrus	−62, −42, 22	12.56
	Cerebellum	−8, −44, −31	22.80

The contrast control relative to touch observation failed to show any significant voxels.

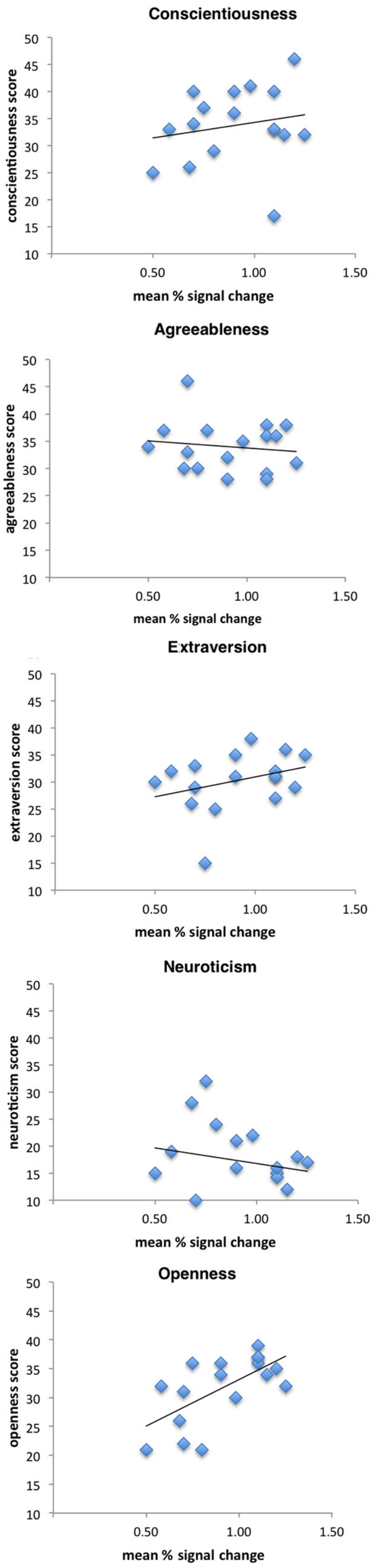

FIGURE 2 | Correlation scatterplots for personality dimensions openness to experience, agreeableness, extraversion, neuroticism, and conscientiousness of the FFM and left SI activation when observing a touched hand (see text for further details).

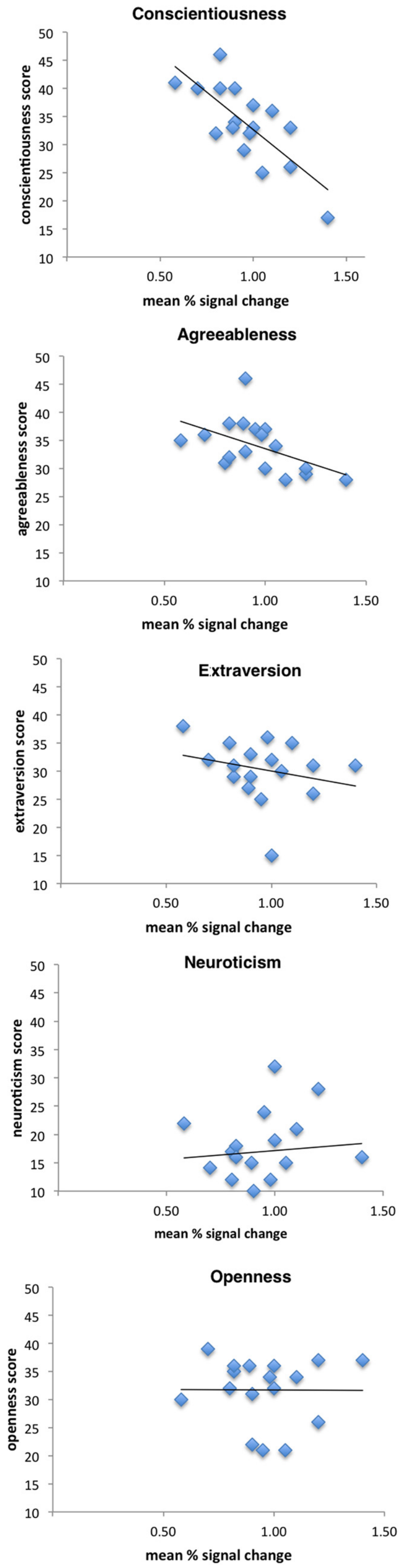

FIGURE 3 | Correlation scatterplots for personality dimensions and left mid insula activation when observing a touched hand. Results demonstrated a significant negative correlation with the personality dimension conscientiousness (see text for further details).

Furthermore, we tested if the five personality dimensions were related to the empathy subscales of the IRI. The empathy subscale PT, which has been shown to be linked with vicarious activation in SI in our previous study (Schaefer et al., 2012a), was correlated positively with openness to experience ($r = 0.38$), but failed to reach the level of significance ($p = 0.14$). Colinearity statistics revealed VIF (variance inflation factor) values of 1.1 for PT and openness. Since these values are relatively low, it seems unlikely that multicollinearity effects may have affected the correlation coefficient reported above. Further correlations revealed no significant results (PT with neuroticism: $r = 0.16$, with extraversion: $r = 0.06$, with agreeableness: $r = -0.44$, with conscientiousness: $r = 0.09$; PD with neuroticism: $r = 0.34$, with extraversion: $r = -0.28$, with openness: $r = -0.42$, with agreeableness: $r = -0.05$, with conscientiousness: $r = -0.04$; EC with neuroticism: $r = 0.34$, with extraversion: $r = -0.50$, with openness: $r = 0.03$, with agreeableness: $r = -0.20$, with conscientiousness: $r = 0.19$; F with neuroticism: $r = -0.009$, with extraversion: $r = 0.008$, with openness: $r = 0.44$, with agreeableness: $r = -0.06$, with conscientiousness: $r = 0.31$).

Furthermore, correlations between task performance and vicarious somatosensory activation in SI (and insula activation, respectively) revealed no significant correlations (analogue data analysis to the correlation analysis with personality dimensions).

We also correlated NEO-FFI personality dimensions with SI activation resulting from real touch. Results revealed a trend for a significant relationship with openness ($r = 0.61$, $p = 0.009$). Other personality dimensions were not linked to SI activity (extraversion: $r = -0.26$, $p = 0.31$; neuroticism: $r = 0.30$, $p = 0.23$; agreeableness: $r = -0.31$, $p = 0.61$; conscientiousness: $r = -0.11$, $p = 0.66$; PD: $r = -0.45$, $p = 0.08$; EC: $r = -0.00$, $p = 0.98$; F: $r = 0.43$, $p = 0.10$; PT: $r = 0.30$, $p = 0.26$).

DISCUSSION

Recent studies reported mirror-like responses in the somatosensory cortices when subjects witness the sensations, actions and somatic pain of others. Remarkably, it has been reported that these vicarious activations in SI are affected by interindividual differences in empathy (e.g., Schaefer et al., 2012a). The current study aimed to test if mirror-like responses in somatosensory brain regions are linked to personality dimensions beyond empathy. Results revealed no significant correlations of SI activity and personality dimensions, but a trend for significance for openness to experience. Mirror-like responses in insula were significantly (negatively) correlated with the personality trait conscientiousness.

Based on previous studies linking activity in SI with extraversion (Shagass and Schwartz, 1965; Schaefer et al., 2012b), we hypothesized that mirror-like responses in SI may similarly be associated with this personality dimension. Our results did not support this hypothesis. Moreover, SI activation for real touch expressed a negative correlation with extraversion, as expected, but failed to reach the level of significance. One explanation for this lack of significant relationship with real touch might be that we stimulated the right hand. Our previous study demonstrated significant correlations for SI with extraversion when touching the left hand. Touch to the right hand revealed a similar negative correlation, but this relationship was weaker and failed to reach the level of significance. The previous study explained this effect with a special role for the right hemisphere in processing social information. Furthermore, since neuromagnetic source imaging and BOLD responses do not measure exactly the same neurophysiological processes, they may not be fully comparable with respect to the activation level we report (dipole moments vs. signal change in BOLD response). In addition, different kinds of stimulation (pneumatically vs. paintbrush) on different sites of the hand were used. In general, correlational analysis of BOLD activity with behavioral responses should be done carefully, since behavioral tests often require many more participants than fMRI experiments usually provide (the same argument applies for correlations with neuromagnetic data). This seems to be in particular true for correlations with personality measurements. In order to address this question we here used conservative corrections for multiple tests (Bonferroni).

Is the lack of correlation between extraversion and seen touch driven by the lack of a significant correlation of extraversion with touch alone? We think that this is not likely because in contrast to touch alone (and our previous study), which expressed a negative correlation, the relationship for merely observed touch was positive. Thus, it seems that vicarious somatosensory responses in SI may be unaffected by the personality factor extraversion. Future studies are needed to examine if the observation of more complex social interactions may be linked to this dimension or if mirror-like responses in SI are independent of this personality factor. In addition, it should be tested if the observation of touch on a left hand would affect the relationship with the personality dimensions. Future research may also include further control conditions, for example, touch to animated relative to unanimated objects, which could refer more specifically to the social domain.

While our hypothesis of a correlation with extraversion was not confirmed, we found a positive correlation with a trend for significance between mirror-like responses in SI and openness to experience. Interestingly, SI activation during the real touch condition revealed a trend for a positive correlation with openness, too. However, both correlations failed to reach the level of significance. Thus, these results remain tentative and speculative. Future studies are needed to reveal if these trends point to meaningful relationships.

Why may openness to experience be related to vicarious touch? We speculate that both the correlations for observed as well as for real touch might be caused by attention effects, which is in accordance with the description of the openness personality trait (DeYoung et al., 2005). The reason why our previous study (Schaefer et al., 2012b) did not find any relationship with openness might be the different stimulation technique. While our previous study used an automatic pneumatic stimulation device, the current experiment used touch from a paintbrush moved by an experimenter. Recent results showed that the response in SI can be modified by affective information on the experimenter (Gazzola et al., 2012). Hence, the stimulation paradigm in the current study may have resulted in stronger attention to the stimulation, which seems to have driven the correlation with the personality dimension openness.

Previous studies already demonstrated that vicarious responses in somatomotor brain areas were affected by empathy (e.g., Schaefer et al., 2012a). So how is empathy related with the FFM? Several studies found interrelations between both the FFM and dispositional empathy. For example, Mooradian et al. (2011) report interrelations of the four empathy subscales of the IRI (Davis, 1983) with the FFM. The empathy subscale EC was closely related to agreeableness and PD closely linked to neuroticism. Perspective taking correlated with all five domains in the NEO-FFI, pointing to interstitial relationships to the five factors. Our results failed to show a significant correlation of the empathy subscale perspective taking (or of any other empathy subscales) with openness to experience, making it unlikely that empathy (perspective taking) rather than openness may have caused the correlation between SI and openness. Why were there no relationships between IRI and NEO-FFI in our study while other report correlations? Studies such as Mooradian et al. (2011) report results from a much bigger sample than our study, while our sample size may be typical for imaging studies. However, the low VIF values in our study make it unlikely that multicollinearity effects may have affected the correlation between openness and SI activity.

The current study reports mirror-like responses also for somatosensory brain regions beyond SI. Insula activation was closely associated (negatively) with the personality trait conscientiousness. Thus, the less the participant scored on the dimension conscientiousness, the more the insula was engaged while observing the touched hand. What is the role of the insula in our experiment? Since the insula is closely connected with ascending internal body signals, recent studies have proposed a role of the insula for the sense of self. For example, Modinos et al. (2009) let participants reflect upon their own personal qualities as compared to those of an acquaintance. Results revealed activation in left anterior insula uniquely associated with self-reflection. Karnath et al. (2005) suggested that the (postular) insular cortex is integral to self-awareness, in particular coding information on the subject's feeling of being vs. not being involved in a movement (similar Farrer and Frith, 2002). Thus, mirror-like responses in insula in our study seem to be linked to processes of self-awareness or -reflection. In order to differentiate between self and other a sense of self has to be maintained when mirroring (or simulating) seen touch. This seems to be warranted by the insula.

But how is the personality dimension conscientiousness related to this function? Conscientiousness has been described to reflect the tendency to inhibit impulses in order to follow rules. It is opposed to impulsivity and distractibility (Costa and McCrae, 1992; DeYoung et al., 2010). Thus, participants characterized by high impulsivity and distractibility seem to require strong insula activation in order to preserve a sense of self while observing the touched body part. In contrast, participants scoring high on conscientiousness are less impulsive or distractible. Consequently, those subjects may demand only little insula activation in this mirror experiment.

So far, only few studies examined neural correlates for conscientiousness. DeYoung et al. (2010) employed data from structural MRIs and linked conscientiousness with activity in the (lateral) prefrontal cortex, which has been related to the ability to plan and voluntary control of behavior. The authors explain this result with the association of conscientiousness with effective self-regulation at multiple levels of complexity. The results of the present study extend these results by demonstrating that conscientiousness also seems to be linked with functions of self-regulation in the insula during the simulation of observed touch to an alien body. We speculate that this interaction may be grounded on improved connections in the mirror network, on top-down processes (attention), or on both (Gazzola et al., 2006).

While we here argue for links between personality and vicarious somatosensory brain responses, alternative explanations for our results should also be taken into account. For example, one could argue that openness or conscientiousness may generally increase (or decrease, respectively) the cortical activation level. Nevertheless, since openness correlated only with activity in SI, not with any other clusters activated by the sight of touch, it seems unlikely that the association between openness and SI might be explained by a general increase of cortical activity. Similarly, conscientiousness corresponded only with insula activation (and this relationship was negative). Furthermore, task effects might explain our results. For example, participants scoring high on openness to experience simply may pay more attention to the task, resulting in stronger somatosensory responses. This objection might be supported by the fact that higher attention is one of the crucial features in people scoring high on openness. The objection of a possible link to task performance may be even stronger for subjects scoring high on conscientiousness, a personality trait that is known to be related to the ability to follow rules. However, we found no relationship of openness to experience or conscientiousness with the performance of the task. In addition, task performance was independent of BOLD activation in SI and insula. Furthermore, conscientiousness was negatively related with BOLD responses. Thus, it seems unlikely that task performance may have caused the relationship between personality and somatosensory response. In addition, the real touch conditions might have influenced the experimental and control conditions. This seems unlikely since we used relatively long blocks and resting periods. Furthermore, experimental and control conditions included a task, while the real touch condition was passive. However, we used the real touch condition only for localizing somatosensory brain areas. Last, motor responses due to button presses or effects of motor planning may have influenced our results. Thus, activity related to the planning and execution of the button press could have flown into the video conditions or the baseline. This activity could have created noise, which might even be related to personality measures in a systematic way. However, we believe that an influence is unlikely since participants used the left hand for button presses, while the video hand was a right hand. Furthermore, motor related activity should have affected both the touch as well as the non-touch conditions. Finally, response times were not correlated with personality measures.

Despite SI and insula, other brain regions known to be involved by viewing touch events did not show any relationships with personality traits. For example, SII and premotor region showed no significant relationship with personality. The lack of a correlation with vicarious premotor activity may be explained by the minimal motor content in our experimental paradigm (instruction to count the strokes of the paintbrush).

The present study examines relationships between mirror-like responses to observed touch and personality traits. However, based on the present data we feel unable to explain the direction of these correlations. Thus, it remains unclear if vicarious brain responses "cause" the parameter values of the personality traits or if the personality traits "produce" higher mirror-like responses. Future studies are needed to address these questions.

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The modulation of somatosensory resonance by psychopathic traits and empathy

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A large number of neuroimaging studies have shown neural overlaps between first-hand experiences of pain and the perception of pain in others. This shared neural representation of vicarious pain is thought to involve both affective and sensorimotor systems. A number of individual factors are thought to modulate the cerebral response to other's pain. The goal of this study was to investigate the impact of psychopathic traits on the relation between sensorimotor resonance to other's pain and self-reported empathy. Our group has previously shown that a steady-state response to non-painful stimulation is modulated by the observation of other people's bodily pain. This change in somatosensory response was interpreted as a form of somatosensory gating (SG). Here, using the same technique, SG was compared between two groups of 15 young adult males: one scoring very high on a self-reported measure of psychopathic traits [60.8 ± 4.98; Levenson's Self-Report Psychopathy Scale (LSRP)] and one scoring very low (42.7 ± 2.94). The results showed a significantly greater reduction of SG to pain observation for the high psychopathic traits group compared to the low psychopathic traits group. SG to pain observation was positively correlated with affective and interpersonal facet of psychopathy in the whole sample. The high psychopathic traits group also reported lower empathic concern (EC) scores than the low psychopathic traits group. Importantly, primary psychopathy, as assessed by the LSRP, mediated the relation between EC and SG to pain observation. Together, these results suggest that increase somatosensory resonance to other's pain is not exclusively explained by trait empathy and may be linked to other personality dimensions, such as psychopathic traits.

Keywords: pain perception, psychopathic traits, somatosensory resonance, shared representations, empathy

INTRODUCTION

Does vicariously experiencing someone else's pain help us understand and care about the distress this person might be feeling? Over the last decade, a large number of studies in healthy and clinical populations have used the representation of other people's pain as a means to investigate the different dimensions of empathy. The construct of empathy can be defined as the capacity to be in tuned with the affective experience of someone else. It involves, beyond a cognitive effort to understand and imagine someone else's state, a disposition to emotionally identify with other's feeling and to share their affective experience (Decety and Jackson, 2004; Kernberg, 2012a). Accordingly, this suggests that, at the brain level, multimodal neural networks are at play during empathic response. Early neuroimaging studies on pain observation have revealed a considerable overlap between cerebral regions involved in the direct experience of pain and its perception in others (e.g., Morrison et al., 2004; Singer et al., 2004; Jackson et al., 2005), suggesting the existence of a neuronal pathway implicated in the elaboration of representations that reflect our own responses to pain to understand how the pain of others feels (see Jackson et al., 2006; Lamm et al., 2011 for reviews). This shared neural representations between the perception of pain in self and other has been interpreted as the result of an automatic resonance mechanism (Jackson et al., 2006) that can be best described as the lower-level of a vicarious pain response on which higher order process operate to develop empathy (Han et al., 2009; Vachon-Presseau et al., 2011).

From initial clinical descriptions to contemporary taxonomies, psychopathy has been prototypically associated with severe emotional disturbances and empathy breakdown (Cleckley, 1941; Lilienfeld and Andrews, 1996; Hare, 2003). This personality disorder is better understood as a constellation of personality traits that encompass affective and interpersonal qualities along with behaviors reflecting a socially deviant lifestyle (Hare, 2003). Primary psychopathy has been designated as the heritable traits of emotional detachment commonly reported as a lack of compassion and guilt, callous misuse of others for personal gain and failure to form close interpersonal attachment (Levenson et al., 1995; Poythress and Skeem, 2006). Secondary psychopathy usually refers to poor behavioral control, hostility and antisociality

(Levenson et al., 1995). The majority of research on psychopathy has focused on samples of incarcerated male offenders, which has led to some pending interrogations about the generalizability of these results to community samples (Hall et al., 2004). Still, studies in non-incarcerated samples have gained in popularity, as the dimensional approach to personality disorders has obtained support from both clinical and research fields (for a review on the clinical perspective see Kernberg, 2012b).

Several transcranial magnetic stimulation (TMS; e.g., Avenanti et al., 2005), somatosensory-evoked potentials (SEP; e.g., Bufalari et al., 2007; Martínez-Jauand et al., 2012), magnetoencephalography (e.g., Cheng et al., 2008), functional magnetic resonance imaging (fMRI; e.g., Lamm et al., 2007; Saarela et al., 2007; Han et al., 2009) and somatosensory steady-state response (SSSR; e.g., Voisin et al., 2011a) studies have shown that brain regions processing the sensory dimension of first hand pain (i.e., somatosensory cortices) are also modulated by the observation of visual stimuli depicting body limbs in pain (Voisin et al., 2011a), painful facial expressions (Saarela et al., 2007), and even psychological painful scenarios (e.g., social rejection in Kross et al., 2012). Some studies have also demonstrated that this resonance mechanism can be modulated by individual factors such as state-reactivity (Avenanti et al., 2009), trait empathy (Avenanti et al., 2009; Vachon-Presseau et al., 2011) and callous-unemotional traits (Fecteau et al., 2008). The study of Fecteau et al. (2008), in which a community sample of men was exposed to visual stimuli depicting hands in painful and non-painful scenarios, was the first to show a positive correlation between suppression of motor evoked potentials (MEPs) and the score of their participants on the Coldheartedness subscale of the psychopathic personality inventory (PPI; Lilienfeld and Andrews, 1996). This result seemed counter-intuitive because increase sensorimotor resonance to the pain of others had been positively associated with self-reported empathy (Avenanti et al., 2009). However, it was also suggested that this automatic neural response could trigger distress (Decety, 2011) and threat related networks (Ibáñez et al., 2011), therefore advocating for an alternative or concomitant view to automatic pain resonance that simply implies arousal. This would also support the view that regulation processes of sensorimotor responses are required in order to respond empathically to the pain of others (Han et al., 2009). Together, these results suggest that sensorimotor resonance to the pain of others is not a direct path to empathy and further investigation on the role of psychopathic traits could be useful to better understand this relationship.

One question arising is how psychopathic traits influence the somatosensory resonance mechanisms involved in the perception of pain in others. To date, only one study has investigated the sensorimotor resonance to other's pain in a community sample of men with psychopathic traits (Fecteau et al., 2008). Although this TMS study has revealed intriguing and initially counterintuitive findings, it has mainly focused on the motor aspect of resonance. Previous studies have shown that seeing pain in others reduces somatosensory steady-state response (SSSR) to a non-painful stimulation (Voisin et al., 2011a) and that this reduction is specific to the frequency of the mechanical stimulation, reinforcing the idea that the modulation in SSSR reflects the inhibition (gating) of somatosensory activity by attention (Mayer et al., 2009). In order to gain understanding on the relationship between psychopathic traits and sensory resonance, we measured SSSR of participants exposed to clips depicting pain-evoking or neutral situations.

The aim of the present study was to investigate the somatosensory aspect of the resonance to other's pain in two groups of men selected from a large community: one group scoring very high and one group very low on a psychopathic traits measure [Levenson's Self-Report Psychopathy Scale (LSRP), Levenson et al., 1995]. Another objective of this study was to examine the relationship between the somatosensory response, self-reported empathy, and psychopathy. We used the modulation of the somatosensory response to a mechanical stimulation as a function of the visual stimuli depicting different levels of bodily pain (Voisin et al., 2011a) as a measure of somatosensory gating (SG). This response was subsequently compared with: (1) vicarious pain ratings, (2) the scores on a measure of trait-empathy [Interpersonal Reactivity Index (IRI), Davis, 1980] and (3) the scores on the LSRP (Levenson et al., 1995). We first expected to find lower scores on the affective subscale of the IRI in high psychopathic traits males compared to the low psychopathic traits ones. Taking into account that both the hypotheses of sensorimotor resonance mechanisms (Bufalari et al., 2007; Lamm et al., 2007) and arousal (Decety, 2011) might be at play during pain empathy, we also expected that participants with high psychopathic traits would have a greater SG to pain observation compared to individuals with low psychopathic traits. Finally, according to Fecteau et al. (2008) we posited that SG would be positively correlated with the affective and the interpersonal facets of psychopathy.

MATERIALS AND METHODS

PARTICIPANTS

Only males were invited to participate to this experiment because the prevalence of psychopathy in women is much lower than in men (e.g., Salekin et al., 1997; Jackson et al., 2002). One hundred and sixty four undergraduate right-handed male students were recruited across different Faculties of Université Laval, Québec, and asked to complete the LSRP (Levenson et al., 1995; see description below) in class. From this initial sample, and based on the distribution of the LSRP_Total scores, two sub-groups were invited to participate to an EEG protocol: 15 participants in the upper third (LSRP_High), and 15 participants in the lower third (LSRP_Low) (see **Table 1** for detailed characteristics

Table 1 | Mean age and scores on self-reports of psychopathy.

Groups	*N*	Age	LSRP_Total	PP1	PP2
		***X* (*SD*)**	***X* (*SD*)**	***X* (*SD*)**	***X* (*SD*)**
Whole sample	164	22.2 (2.75)	50.9 (6.31)	34.2 (5.6)	18.1 (3.2)
LSRP_Low	15	23.7 (2.9)	42.7 (2.94)***	27.7 (4.7)***	17.1 (2.9)**
LSRP_High	15	22.3 (1.44)	60.8 (4.98)***	38.8 (4.3)***	20.0 (4.3)**

$^{**}p < 0.01$, $^{***}p < 0.001$. PP1, primary psychopathy subscale; PP2, secondary psychopathy subscale.

of the sample). The LSRP_High total scores (60.8 ± 4.98) were significantly higher than the LSRP_Low scores [42.7 ± 2.94; $t_{(29)} = 12.12$, $p < 0.001$]. Participants reported having no history of neurological, pain-related, or psychiatric disorders, were not taking any medication, and had normal or corrected-to-normal vision. The participants received monetary compensation for their travel expenses to the laboratory and they each gave written informed consent. The study was approved by the Ethics Committees of the research center (CIRRIS-IRDPQ) and Université Laval.

MEASURES AND MATERIALS

Questionnaires

The LSRP (Levenson et al., 1995) is a 26-item self-reported measure of psychopathic traits developed for use in community samples. The LSRP assess primary and secondary psychopathy, two factors of the most predominant psychopathic measure, the Hare Psychopathy Checklist (PCL-R; Hare, 2003). Each item consists in a statement that the participant endorses on a 4-point Likert-type scale (1 = *disagree strongly* to 4 = *agree strongly*). The primary psychopathy subscale (PP1) consists in 16 items measuring an inclination to lie, a lack of remorse, callousness, and manipulativeness. The secondary psychopathy subscale (PP2) consists in 10 items measuring impulsivity, frustration tolerance, quick-temperedness, and lack of long-term goals.

The Davis' IRI (Davis, 1980) is a 28-item self-report instrument that assesses trait empathy, that is, one's own reactions to the observation of another's experiences. Each item is rated on a scale ranging from 1 (*does not describe me well*) to 5 (*describes me very well*). The IRI is composed of four subscales thought to reflect the affective and cognitive aspects of empathy: Empathic Concern (EC) and Personal Distress (PD), Fantasy (FS) and Perspective Taking (PT). The EC subscale measures experienced feelings of sympathy and compassion for others in distress. The PD measures self-oriented feelings of anxiety and distress in response to tense interpersonal situations. The FS scale measures the tendency to project oneself into fictional situations. The PT subscale measures the tendency to adopt the psychological point of view of others.

The situational pain questionnaire (SPQ; Clark and Yang, 1983) was used in order to evaluate how participants estimated their own sensitivity to pain. The discrimination scores P(A), indicate the extent to which subjects are able to differentiate painful scenarios from neutral, while the response bias scores B, indicate the degree to which the situations are considered painful (for details on the method see Danziger et al., 2006). The questionnaire consists in 15 events that are considered to be relatively painful and 15 non-painful events. Items are rated by using a numerical scale ranging from 1 (*not noticeable*) to 10 (*worst possible pain*).

Visual stimuli

Stimuli consisted in a series of 30-color pseudo-dynamic pictures depicting hands of male and female adults in three different conditions: Painful, Non-Painful, and Neutral situations. Specifically, each stimulus involved a sequence of three visual static pictures presented in a short sequence (750 ms + 250 + 1500 = 2500 ms) to create the illusion of a movement (similar to the task described in Decety et al., 2009; see **Figure 1**). Different types of pain (mechanical and thermal) inflicted to the hands were displayed. The No Pain stimuli showed hands in visually similar situations as in the Pain condition but without the painful consequence [i.e., the 3rd frame differed; e.g., a knife on the finger (Pain) vs.

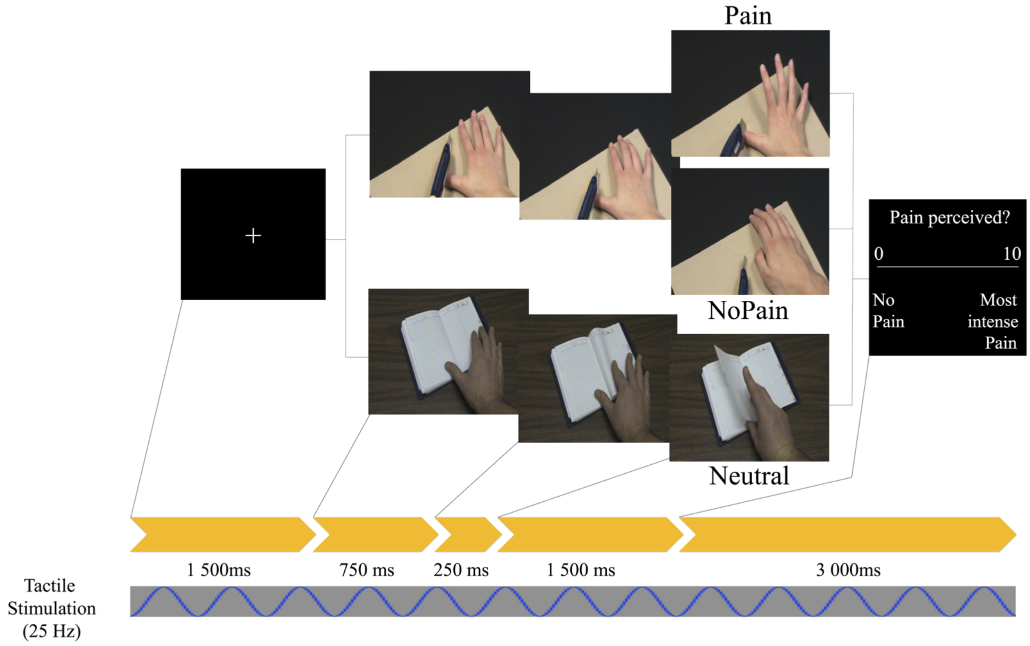

FIGURE 1 | Schematic of the experimental design depicting one trial. Timing in ms (below yellow arrows) corresponds to the duration of each picture. A light repetitive stimulation at a frequency of 25 Hz was continuously applied to the palm of the right hand throughout data acquisition.

a knife of the board (No Pain)]. Neutral stimuli showed hands in visually different situations devoid of any of the nociceptive elements found in the other two conditions (e.g., a hand grasping a set of keys or a tissue). We used a neutral condition to assess the possible priming effect of the nociceptive elements already found on the first picture of the Painful and Non-Painful conditions. The hands were shown from a maximum angle of 45° from the perspective of the observer, and all pictures were edited to show hands of same size and from approximately the same distance.

Tactile steady-state stimulation

Non-painful light repetitive (25-Hz) mechanical stimulations were continuously applied to the palm of the right hand using a custom-made vibrotactile stimulator similar to the one used in Voisin et al. (2011a,b). Compared to the previous stimulator, which targeted the ventral portion of the right index distal phalange, the one used in the current study stimulated the whole palm of the right hand.

EEG

EEG activity was acquired via $124 + 4$ Ag/AgCl electrodes contacting the scalp surface by way of saline-soaked sponges (HCGSN, Electrical Geodesic Inc., Oregon). The amplifier system used for EEG recordings was an EGI GES250 system (Electrical Geodesic Inc., Oregon). The sampling rate was 500-Hz, with acquisition reference at the vertex. Electrodes impedances were kept below 50 kΩ.

Electromyographic activity

In order to ensure that the modulation in SG was not due to muscle contraction of the right hand, electromyographic activity (EMG) was recorded in all participants using Ag-AgCl surface electrodes placed in bipolar configuration over the First Dorsal Interosseus (FDI) muscle. EMG was amplified and band pass filtered (20–1000 Hz). The Acknowledge software (Biopac System) was used to acquire surface EMG and events code. Online visual inspection of the EMG output and inter-block feedback to participants ensured that this muscle stayed relaxed during EEG data acquisition and that the energy contained in the 25-Hz band frequency was produced by the stimulation.

PROCEDURE

Participants took part in a 60 min EEG session. They were seated in an armchair with their right arm on an arm-rest while watching a 20″ (∼48 cm) LCD monitor positioned approximately at 85 cm. Stimuli were presented with a computer running the E-Prime software (Version 2.0, Psychology Software Tools, Inc.) to control the timing of the stimuli as well as the generation of event codes. Each trial began by a fixation cross (2500 ms), followed by a sequence of three static pictures (total time 2500 ms) successively presented, ending with visual rating scale (3000 ms) ranging from 0 (*no pain*) to 10 (*worst pain possible*) (see **Figure 1**). Subjects were told to refrain from blinking and performing head and jaw movements as much as possible during the presentation of fixation crosses and stimuli. After each scenario, participants were instructed to use the visual rating scale and verbally evaluate the level of pain that individuals would feel in each scenario via an intercom system as participants were seated in an audiometric room (Genieaudio Inc., Toronto). The experimental session consisted of six blocks of 30 trials lasting approximately 5 min each. The conditions were randomized and counter-balanced within each of the six blocks. Several practice trials were run prior to the experiment using other picture than those selected for the test trials. After the six experimental blocs, participants were asked to fill self-reported trait-empathy (IRI) and pain sensitivity (SPQ) questionnaires.

EEG DATA PREPROCESSING

All preprocessing was performed with the ELAB software developed at Centre de recherche en réadaptation et intégration sociale (CIRRIS) (Voisin et al., 2011a,b). ELAB is a series of Matlab routines allowing the control of the ELAN-Pack software developed at INSERM Brain Dynamics and Cognition team of the Lyon Neuroscience Research Center (Aguera et al., 2011). Raw data was first parsed into event, and indexed according to the type of the stimuli. Two faulty electrodes caused unreliable signal across all subjects and were removed from the analysis [electrodes 83 and 114 in the EGI system (HCGSN) corresponding to T10 and O2 in the 10–20 systems]. Then, a first rejection criterion was applied on the basis of any rating for a Painful stimulus <1, for a Neutral or Non-Painful stimulus >1 led to the rejection of the related-event, to ensure that further analyses would be made only on task-relevant data. Inspection of the data distribution enabled the selection of a series of criteria meant to detect blinks, muscle activity, and fast baseline shift. They were set to reject any sample that fell within 100 ms of one of these events: (1) the scalp potential exhibited variation over 200 μV within a 200 ms time window in the same electrode channel; (2) the energy content was more than 500 μV^2 in the 60–100 Hz band in the same electrode channel; (3) the scalp potential exhibited variation over 50 μV within a 10 ms time window in the same electrode channel; (4) the energy content was more than 1500 μV^2 in the 23–27 Hz band in the same electrode channel. The remaining data consisted of 77% of the original set. This remaining signal was submitted to a spherical spline interpolation process (Perrin et al., 1989), using Tikhonov regularization in order to reduce sensitivity to noise (Babiloni et al., 1998). This procedure allows the reconstruction of the signal of a noisy electrode based on the signal of the noise-free electrodes. Notably, this process poses a specific challenge as the rejected samples can be broadly distributed across time and electrodes so that a proper reconstruction has either to reject all samples each time a faulty electrode is found, or to reject all electrodes that included at least one rejected sample. Thus, any fixed method would have led to rejecting a large portion of the data. ELAB software allowed circumventing this problem by selecting, automatically for each trial, the set of electrodes that should enter the interpolation process so as to maximize the number of valid samples used. In the present experiment, the best solutions used a mean of 70% of the original samples (intersubject variability 48–93%) to reconstruct the signal. More precisely, the interpolation process was based on average on 77% of the 124 electrodes positioned on the scalp (intersubject variability 47–97%) and on average, 91% of the time bins (intersubject variability 68–99%). Once the signal was split-transformed, it was convoluted with complex Gaussian Morlet's wavelets (Tallon-Baudry and Bertrand, 1999) intended to extract the energy in the 25 Hz range (omega, 24–26; sigma, 3.6), representing the energy band in which the cortical response to the somatosensory stimulation used in the current study should be condensed. Mean 25 Hz range energy during the fixation cross (1000 ms before stimulus onset) was then computed, and any trial in which the baseline mean energy dispersion was over two standard deviation from the whole bloc mean energy was rejected (an average of one trial was rejected per subject, max rejection was two trials). No subject was rejected from analysis.

STATISTICAL ANALYSES

Behavioral data

Differences on mean pain ratings between conditions and groups were computed using a 3 (Conditions: Pain vs. NoPain vs. Neutral) × 2 (Groups: LSRP_high vs. LSRP_low) repeated measures analysis of variance (ANOVA). The relation between pain ratings and psychopathy scores (LSRPtotal, PP1, and PP2) were explored with Pearson correlations. In order to assess between group differences on the independent subscales of self-reported empathy (IRI), four independent sample *t*-tests were realized. Pearson correlations were then used to determine the relationship between empathy and psychopathy scores. Finally, group differences on pain sensitivity discrimination P(A) and bias scores (B) of the SPQ were tested with two independent sample *t*-tests.

EEG

A similar procedure as in Voisin et al. (2011a) was used to analyze the SSSR. First, epochs in all three conditions were averaged to delineate the regions of interest (ROI) for each group. Subtraction maps were then created by subtracting the baseline period (−1000:0 ms, the cross duration) from the first two pictures period (0:1000 ms). This procedure allows the visual identification of the electrodes in which SG was showing the greatest modulation during the first two pictures in comparison to baseline (fixation cross), for all conditions. Note that the maps were created from (1000 ms) time bins and statistical analyses were then all realized with more circumscribed 200ms time bins to increase accuracy. This initial analysis identified the following ROI electrodes [parietal electrodes 66, 67, and 71 in the EGI system (HCGSN) corresponding to P3 in the 10–20 systems] on which the remaining of the analyses was done.

Prior to test the *non-specific initial gating* (i.e., not imputable to the observation of pain), defined as the mean energy (mA/m3) difference between Fixation Cross Baseline (−200:0 ms) and Gating period (600:800 ms) (see Voisin et al., 2011a), Cross Baseline stability was verified using a 3 (Conditions: Pain vs. NoPain vs. Neutral) × 2 (Groups: LSRP_high vs. LSRP_low) repeated measures ANOVA. To investigate initial gating effect, mean energy during Gating period (600:800 ms) and Cross Baseline (−200:0 ms) were compared for each condition using simple *t*-tests against H_0 (i.e., absence of gating). Second, *pain anticipation* [(Pain = Nopain) > Neutral] was tested by comparing mean energy ratios between the three experimental conditions during the Gating period (600:800 ms) with a one-way repeated measures ANOVA [Gating period × Conditions (3: Pain vs. NoPain vs. Neutral)]. Third, Pain Gating was assessed using ratios [(Second Picture Baseline - 3rd Picture Pain Gating)/Second Picture Baseline] by comparing painful and non-painful conditions for each participant in order to verify the specific modulation imputable to the onset of painful conditions using a 2 (Conditions: Pain vs. NoPain) × 2 (Groups: LSRP High vs. LSRP Low) repeated measures ANOVA. The 3rd Picture Gating period (1100:1700 ms) was divided in three (200 ms) time bins. Separated analysis was performed on each time bin. All the analyses were done with an alpha level set at 0.05 and corrected with Bonferroni procedure for multiple comparisons.

Mediation analysis

As sensorimotor resonance was previously found to be positively associated with scores on Coldheartedness subscale (Fecteau et al., 2008), which reflect a lack of empathy and sensibility toward others, and conversely positively correlated with trait-empathy (Avenanti et al., 2009), we sought to explore the indirect effect of primary psychopathy on the relationship between self-reported empathy and SG to pain. This was tested using the bootstrapping method developed by Preacher and Hayes (2004, 2008; see Simple Mediator model). This non-parametric method overcomes limitations of the Baron and Kenny's (1986) causal steps and Sobel's test that are conservative and not likely to detect indirect effects in smaller samples. Moreover, this method has the benefit of not assuming normality of the sampling distribution of the indirect effect and allows testing of mediating effect (Preacher and Hayes, 2004). The SPSS macro developed by Preacher and Hayes (2008) provides the strength of direct effects of independent and mediating variables. Preacher and Hayes (2004) also stated that it is possible to find a significant indirect effect even if there is no evidence of a significant total effect (path c, see **Figure 7**). Point-estimate of the indirect effect and 95% bias corrected confidence intervals (BC) were computed based on a 5000 bootstrap resample. In order to conclude for the presence of a mediating effect, the 95% BC confidence interval must not include zero, thus suggesting that the value of the indirect effect is significantly different from zero. Note that the relatively small sample in the current study suggests caution in drawing inference from the mediation analysis.

RESULTS

BEHAVIORAL RESULTS

Analyses performed on pain intensity ratings confirmed the expected significant effect for the main effects of Condition [$F_{(1,\ 28)} = 160.7$, $p < 0.001$] whereas no significant effect was observed for Group [$F_{(1,\ 28)} = 0.21$, $p = 0.657$] nor their interaction [$F_{(1,\ 28)} = 1.19$, $p = 0.283$]. *Post-hoc* pair comparisons showed that mean pain ratings for painful scenarios (4.9 ± 0.362) differed significantly from non-painful (0.002 ± 0.001; $p < 0.001$) and neutral scenarios (0.03 ± 0.021; $p < 0.001$) whereas no difference has been found between the latter two ($p = 0.143$). As illustrated in **Figure 2A**, between-group analyses showed no significant differences for the mean ratings in the pain condition (LSRP_High: 5.1 ± 0.441; LSRP_Low: 4.5 ± 0.473). To compare the differences between LSRP_Low and LSRP_High participants on trait empathy, independent *t*-test on each IRI subscale were used and revealed no significant between-groups difference on three of the four subscales [PT: $t_{(29)} = 2.3$, $p = 0.142$; F: $t_{(29)} = 0.562$, $p = 0.47$; D: $t_{(29)} = 0.962$, $p = 0.344$]. **Figure 2B** shows the only subscale (EC) for which a significant difference between both groups was found [LSRP_Low: 19.6 ± 3.7; LSRP_High: 14.1 ± 4.9; $t_{(29)} = 10.9$, $p = 0.003$]. Over all participants, the correlations showed a significant negative relationship between the EC subscale and the LSRP_total score ($r = -0.561$, $p = 0.001$), as well as between the EC subscale and the PP1 subscale ($r = -0.560$, $p = 0.001$; **Figure 2C**) indicating an inverse relationship between affective empathy and psychopathic traits. Between-group analyses on the pain sensitivity responses indicated no significant differences for the discrimination [PA: $t_{(29)} = 0.21$, $p = 0.668$] nor the bias scores of the SPQ [B: $t_{(29)} = 1.9$, $p = 0.184$].

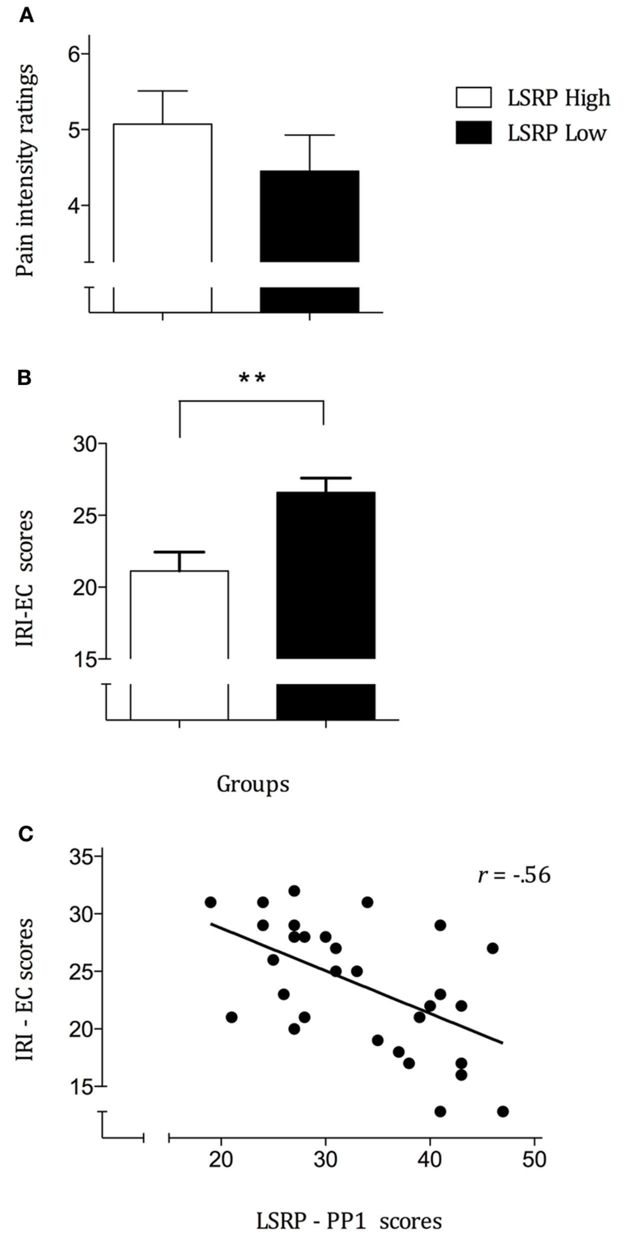

FIGURE 2 | (A) Mean pain ratings for each group indicating an absence of significant difference ($p = 0.35$) between LSRP_High and LSRP_Low; **(B)** Self-reported Empathic Concern (EC) scores significantly differed between LSRP_High and LSRP_Low group; **(C)** Negative correlation between primary psychopathy (PP1) scores and empathic concern scores. $^{**}p < 0.01$.

EEG RESULTS

General gating effect

EEG data showed that the maximal change in SG during the visual presentation of the first two stimuli was over the parietal cortex controlateral to the stimulated hand for both experimental groups. As illustrated in **Figure 3**, subtraction maps (First two pictures − Fixation cross) indicated a strong decrease in left caudal part of the parieto-central region [electrodes 66, 67, 71 in the EGI system (HCGSN) corresponding to P3 in the 10–20 systems] for both groups. A decrease in the 25 Hz energy band was also found in the same region during the presentation of static stimuli depicting hand in painful and non-painful situations in previous EEG studies using a similar protocol (Voisin et al., 2011a,b,c). Statistical analyses were then restricted to this region specifically showing SG.

In order to assess baseline stability during the Cross Baseline period (-200:0 ms) prior to the first picture onset, a 3 (Conditions: Pain vs. NoPain vs. Neutral) × 2 (Groups: LSRP_Hihg vs. LSRP_Low) repeated measures ANOVA was conducted. No significant effect was observed neither for main effects of Condition [$F_{(1,\ 28)} = 0.06, p = 0.812$] or Group [$F_{(1,\ 28)} = 1.71, p = 0.201$] nor their interaction [$F_{(1,\ 28)} = 0.31$, $p = 0.583$], reducing the chance that the Cross Baseline period could be the source of subsequent differences.

Figure 4 shows the decrease in the 25 Hz energy band irrespective of the experimental conditions stabilizing 600–800ms after the first picture onset. To investigate this general gating effect, mean energy ratios during Gating period (600:800 ms) and Cross Baseline (−200:0 ms) were compared for each condition using simple t-tests against H_0 which is the absence of gating (ratio = 0). On average, modulation amplitude reached.19, corresponding to 19% of Cross Baseline raw amplitude. Contrasts

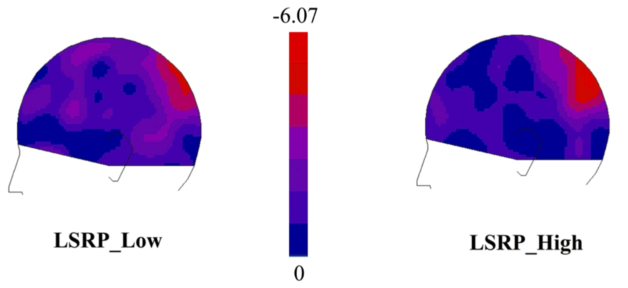

FIGURE 3 | Subtraction maps created to identify the ROI electrodes [66-67-71, in the EGI system (HCGSN) corresponding to P3 in the 10–20 systems] in which the somatosensory gating (SG) was showing the greatest modulation during the first two pictures (0:1000 ms) in comparison to the Cross Baseline (−1000:0 ms).

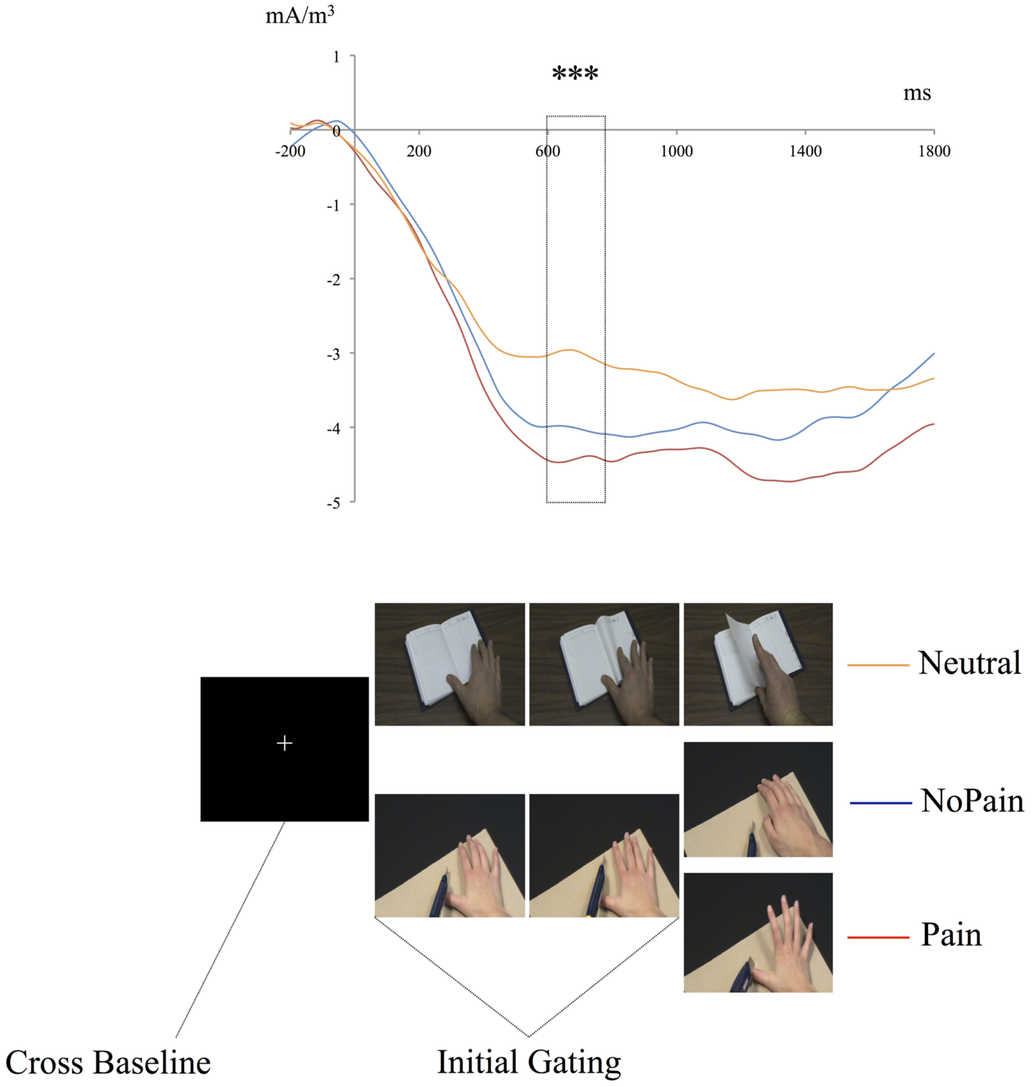

FIGURE 4 | Time course of the mean energy (mA/m^3) of the somatosensory steady-state response (SSSR) during the presentation of the pseudo-dynamic stimuli. The mean energy of the somatosensory gating (SG) during the first two pictures [initial gating (600:800 ms)] was significantly different from mean energy during the Cross Baseline (−200–0 ms) for each condition and for all participants. The magnitude of the SG during the initial gating (600:800 ms) was significantly greater in the Pain and NoPain conditions compared to the Neutral condition. $^{***}p < 0.001$.

between Baseline and Gating period were all statistically significant [NoPain: ratio $= 0.21 \pm 0.03$; $t_{(29)} = 5.9$, $p < 0.001$; Pain: ratio $= 0.23 \pm 0.02$; $t_{(29)} = 7.8$, $p < 0.001$; Neutral: ratio $= 0.14 \pm 0.02$; $t_{(29)} = 4.0$, $p < 0.001$], confirming that the observation of the stimuli depicting hands, irrespective of the condition, triggered changes in sensory processing of somatic information in the observer.

Pain anticipation effect

To assess the possible effect of pain anticipation, mean energy ratios were compared between the three experimental conditions during the Gating period (600:800 ms). A significant effect was found for Conditions [$F_{(1,\ 28)} = 6.8$, $p = 0.014$] but not for Groups [$F_{(1,\ 28)} = 1.3$, $p = 0.262$]; the interaction was not significant [$F_{(1,\ 28)} = 1.2$, $p = 0.294$]. Paired comparisons for Conditions showed that Neutral significantly differed from Pain ($p = 0.013$) and NoPain ($p = 0.043$) whereas the latter two did not ($p = 0.891$).

Pain observation effect

In order to assess Pain Gating, a baseline period was set during the second picture (800:100 ms) for the Pain and NoPain conditions. The stability of this baseline was tested by comparing mean energy for both condition using a 2 (condition: Pain vs. NoPain) × 2 (groups: LSRP Low vs. High) repeated measures ANOVA. No significant effect was observed for the main effects of Condition [$F_{(1,\ 28)} = 0.27$, $p = 0.612$] or Group [$F_{(1,\ 28)} = 2.6$, $p = 0.121$] nor their interaction [$F_{(1,\ 28)} = 0.05$, $p = 0.833$], confirming that Second Picture Baseline would not account for later differences.

Mean energy ratios were subsequently compared between Pain and NoPain conditions for both groups during the third picture period (1100:1700 ms) through three (200 ms) time bins (see **Figure 5**). 2 (condition: Pain vs. NoPain) × 2 (groups: LSRP Low vs. High) repeated measures ANOVA were conducted on the same three time bins. During the (1100:1300 ms) period, main effects of Condition [$F_{(1,\ 28)} = 3.8$, $p = 0.063$] and Group [$F_{(1,\ 28)} = 2.8$, $p = 0.114$] did not reach statistical significance. Still the effect of interaction between both Condition and Group was significant [$F_{(1,\ 28)} = 4.8$, $p = 0.042$]. *Post-hoc* analyses revealed a significant difference between Pain and NoPain Conditions only for the LSRP_High ($p = 0.014$; LSRP_Low: $p = 0.863$). Throughout the (1300:1500 ms) period, no significant effect was observed for main effects of Condition [$F_{(1,\ 28)} = 2.1$, $p = 0.163$] or Group [$F_{(1,\ 28)} = 3.5$, $p = 0.074$]. However, a significant interaction was found [$F_{(1,\ 28)} = 6.2$, $p = 0.024$]. *Post-hoc* analyses in each group showed a significant difference between Pain and NoPain Conditions for the LSRP_High group ($p = 0.001$), but not for the LSRP_Low group ($p = 0.563$). For the (1500:1700 ms) period, no significant effect was found for main effects of Conditions [$F_{(1,\ 28)} = 0.8$, $p = 0.382$] or Group [$F_{(1,\ 28)} = 3.8$, $p = 0.074$] nor their interaction [$F_{(1,\ 28)} = 3.2$, $p = 0.081$].

CORRELATION BETWEEN THE BEHAVIORAL AND THE EEG RESULTS

In order to assess the linear dependence between the modulation of SG during pain observation and psychopathic traits, Pearson correlations were used. The analyses performed on the mean energies ratios for the pain picture [Second Picture Baseline (800:100 ms) − Third Picture maximal Gating (1300–1500 ms)/Second Picture Baseline] pointed out some positives associations with LSRP scores. As illustrated in **Figure 6**, strong positive correlations were found between SG during pain observation and LSRP_Total scores ($r = 0.518$, $p = 0.003$; **Figure 6A**), and PP1 scores ($r = 0.516$, $p = 0.004$; **Figure 6B**). However, the relationship between SG and the PP2 scores did not reach statistical significance ($r = 0.29$, $p = 0.122$). No significant correlation was found between SSSR and any of the IRI subscales (PT: $r = 0.15$, $p = 0.431$; F: $r = -0.06$, $p = 0.763$; EC: $r = -0.21$, $p = 0.284$; D: $r = 0.03$, $p = 0.861$). Finally, no significant relationship was found between SG during pain observation and Pain ratings ($r = 0.11$, $p = 0.562$).

THE INDIRECT EFFECT OF PRIMARY PSYCHOPATHY

Figure 7 presents the results of the mediation model of direct and indirect effects. The model aimed at testing the interplay between

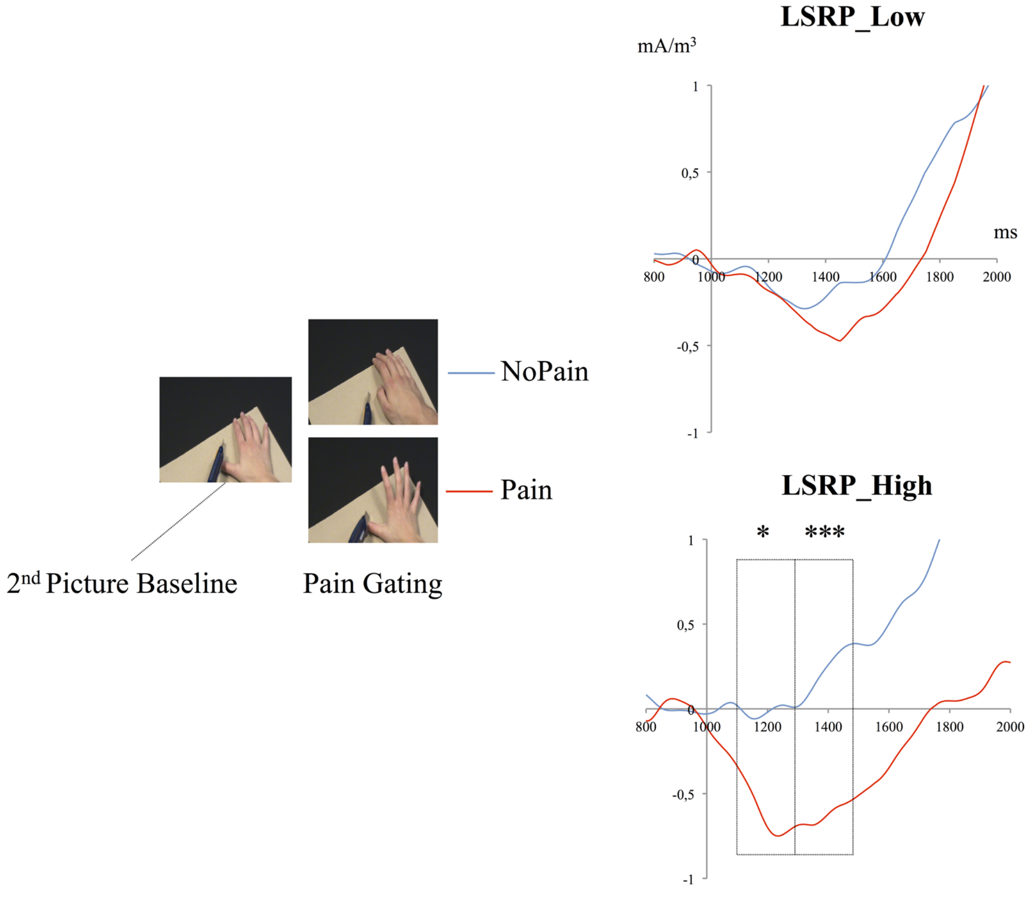

FIGURE 5 | Time course of the mean energy (mA/m³) of the SG during the presentation of the third picture (i.e., the picture where the painful contact occurred or not). The mean energy ratios during the (1300:1500 ms) and (1500:1700 ms) periods were significantly different from that of the Second Picture Baseline (800:100 ms) only in the LSRP_High group. $^{*}p < 0.05$, $^{***}p < 0.001$.

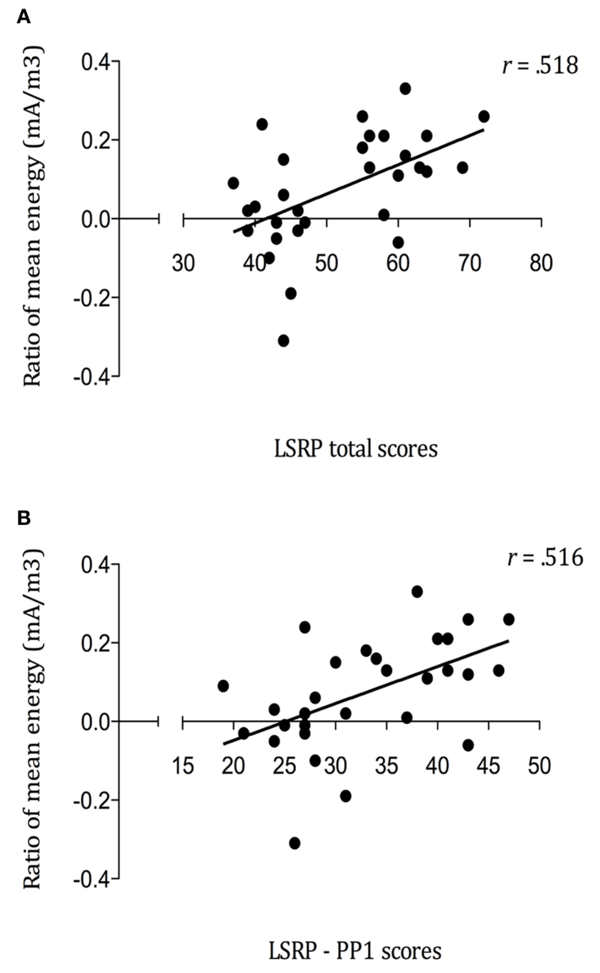

FIGURE 6 | Positive correlations between mean energy (mA/m^3) ratios during Pain Gating (1300–1500ms) and (A) self-reported psychopathy total scores ($p = 0.003$); (B) primary psychopathy (PP1) subscale scores ($p = 0.004$).

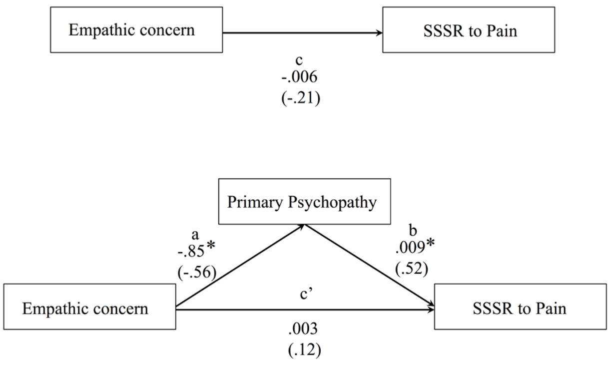

FIGURE 7 | Illustration of the direct effects of the bootstrap mediating model predicting SG to pain observation ($N = 30$) using the 5000 bootstrap samples. Path values represent both unstandardized regression coefficients (bold) and standardized regression coefficients (in brackets). $^*p < 0.05$.

empathy and psychopathy during somatosensory resonance. The results indicated that the total effect of EC on SG to pain (path c) remained non-significant but changed its direction (path c') after introducing primary psychopathy as a mediator. Point-estimate of the indirect effect of EC on SSSR to pain through primary psychopathy was -0.0091 with a 95% BC confidence interval of -0.0200 to -0.0039. Because zero was not in the confidence interval, we can conclude that there is a significant indirect effect [R^2 for the mediating model $= 0.277$, $F_{(2, 27)} = 5.16$, $p = 0.013$], suggesting that primary psychopathy is a mediator of EC predicting SG to the pain of others. This suggests that psychopathic traits in community individuals contribute to the relation between the affective empathy and somatosensory resonance during pain observation in others.

DISCUSSION

The goal of this study was to assess changes in somatosensory processing during pain observation in a group of male college students with respect to self-reported empathy and psychopathic traits. Generally, the observation of pseudo-dynamic stimuli depicting hands in Painful and Non-Painful scenarios produced a modulation of the SG response to a mechanical stimulation of the right hand in both high and low psychopathic traits groups. Modulation of the SG was maximal in a parieto-central region contralateral to the stimulated hand. This corroborate previous finding using a similar design (Voisin et al., 2011a) and parallel results showing that observing the body improves tactile performance and modulates SEP (e.g., Taylor-Clarke et al., 2002; Morrison et al., 2007; Cardini et al., 2011). Interestingly, SG specific to pain observation was statistically significant only for the LSRP_High group. Overall, this SG was also positively correlated with affective and interpersonal aspect of psychopathy. Moreover, EC scores were significantly lower in this group compared to LSRP_Low, suggesting that increase somatosensory resonance to other's pain is not exclusively explained by components of affective empathy and may be linked to other personality traits, such as psychopathy. In fact, results from the mediation analysis indicated that primary psychopathy might play a role of mediator in the relation between EC and SSSR to pain.

SELF-REPORTED EMPATHY NEGATIVELY CORRELATED WITH PSYCHOPATHIC TRAITS

Our behavioral results showed that LSRP_High and Low groups did not differ in their subjective evaluation of pain intensity. This result seems to be in line with previous works reporting that both healthy and conduct disorder adolescents displaying psychopathic traits judged painful stimuli as similarly more painful (Decety et al., 2009) and that pain ratings in juvenile offenders characterized by high and low callous-unemotional traits did not differ (Cheng et al., 2012). The significant difference found between High and Low LSRP groups on IRI-EC subscale adds to the inconsistent findings regarding differences in self-reported empathy among psychopathic and their respective comparison groups. If negative correlations between self-reported empathy and psychopathic traits have been more consistently reported (Sandoval et al., 2000; Jolliffe and Farrington, 2004; Mahmut et al., 2008), some studies have failed to show differences on IRI subscales when comparing psychopathic offenders with non-psychopathic offenders with antisocial personality disorder and community samples (Book and Quinsey, 2004; Dolan and Fullam, 2004). Indeed, psychopathy and antisocial personality disorder might be conceived as dimensional constructs (Marcus et al., 2006), hence reducing the possibility to found between group differences on empathy. Besides, the use of self-report empathy with correctional sample may offer limited efficacy as deception, manipulation and grandiose sense of self-worth are at the core of psychopathic manifestation. In the current study, the significant difference found on IRI-EC subscale might be attributed to the composition of the non-forensic sample, as low score on antisocial deviance were found in both groups. The absence of between-group difference in PT is also congruent with current conceptions that psychopathic individuals are seen as having a reduced sensibility to other's distress instead of an incapacity to adopt the psychological perspective of others (Dolan and Fullam, 2004; Blair, 2006).

THE SOMATOSENSORY GATING WAS STRONGER WHEN PAIN WAS ANTICIPATED

The results of the present study also showed that the increase in the magnitude of SG was more important in the first two pictures for Pain and NoPain conditions compared to Neutral condition. This suggests that contextual dependent effect of the nociceptive elements found in the former conditions might account for the difference in the mean levels of energy. They also support the assumption that whenever our attention is directed to the somatic cause of pain (Bufalari et al., 2007; Lamm et al., 2007), somatosensory processes are engaged by the observer, allowing him or her to create a cerebral representation of others' painful experience by assigning a *quantitative sense of pain* (Keysers et al., 2010). These results might also be explained by possible pain anticipation. It was previously shown that anticipation of pain in others triggered fear-potentiated startle reflex (Caes et al., 2012) thus potentially modulated the SG to pictures containing nociceptive components. In addition, the study of Caes et al. (2012) demonstrated that startle reflex was blunted in participants depicting higher psychopathic traits. Yet, the current study did not show a significant difference between high and low psychopathic traits group on SG to pain anticipation. The stronger SG found during the first two pictures in which the nociceptive component was displayed compared to neutral pictures indicated a specific change in somatosensory activity during pain anticipation.

PSYCHOPATHIC TRAITS FACILITATED PAIN-RELATED SOMATOSENSORY RESONANCE

To our knowledge, this is the first study to show that pain observation modulates SG to a greater extend in male college students with high scores on self-reported psychopathy compared to participants with low scores. Other studies have, however, accumulated evidence supporting enhanced somatosensory response to other's pain in male adolescent with high psychopathic traits (Decety et al., 2009; Chen et al., 2012). Specifically, adolescents with conduct disorders and psychopathic traits showed greater sensorimotor resonance for neural response to pain perception compared to healthy adolescents (Decety et al., 2009). Furthermore, young offenders with high callous-unemotional traits showed stronger *mu* suppression (10 Hz) compared to the low ones during pain observation (Cheng et al., 2012). Together, these results are in accordance with our findings, suggesting a greater sensorimotor resonance to other's pain in samples characterized by a reduced capacity for empathy and compassion toward other's distress. This speaks for a more complex link between empathy for pain and resonance than the direct relationship previously proposed, and argue for the contribution of regulation mechanisms allowing prosocial reactions (Decety and Jackson, 2004; Singer et al., 2004; Vachon-Presseau et al., 2012).

Our results also parallel findings from previous studies reporting that SEP elicited by tactile stimulation were modulated by negative emotional stimuli in healthy adults (Montoya and Sitges, 2006) and that the aversion felt during observation of others' pain is negatively correlated with the magnitude of sensorimotor response to others' pain (Avenanti et al., 2009). This is also in line with findings from Decety et al. (2009) who showed greater responses in regions dedicated to affective and sensory components of pain perception in conduct disorders adolescent with psychopathic traits. Specifically, connectivity analysis demonstrated stronger activation of amygdala and striatum together with reduced response in orbitofrontal cortex, suggesting that seeing pain in others did not generate distress in these adolescents but could have led to pleasant feelings. All together, these results suggest that the presence of high psychopathic traits can attenuate the effect of negative emotional arousal caused by the observation of pain in others, thus increasing attention to the sensory components of the stimuli displayed.

Another interesting result consists in the positive correlations found between SG during pain observation and LSRP_Total scores, as well as between SG to pain observation and PP1 subscale scores, which support and extend the findings of Fecteau et al. (2008). As previously demonstrated, participants who scored higher on a specific psychopathic traits subscale (Coldheartedness) showed greater corticospinal inhibition (Fecteau et al., 2008). Interestingly, this subscale measures the absence of deep feeling of guilt and empathy, reflecting the tendency to lack of caring for others (Lilienfeld and Andrews, 1996), all referring to the affective and interpersonal dimension of psychopathy, namely primary psychopathy. However, the negative correlation between empathic concern (IRI-EC) and SG to pain observation did not reach significance. Still, a negative relationship was confirmed between IRI-EC and the PP1 subscale. The fact that the correlations found between the SSSR modulation to pain and both LSRP_total and PP1 subscale are similar (total: $r = 0.518$; PP1: $r = 0.516$) and the absence of significant relation with the PP2 subscale is interesting. These findings suggest that affective and interpersonal aspects of psychopathy constituted the principal factor explaining the modulation of the somatosensory gating. As it might be expected in a community sample study, the PP2 scores resulting from the evaluation of social deviance were low in both groups but still differed significantly; the scores were not comparable to those of incarcerated samples. Nevertheless, results from a community sample indicated that the PP1 factor is more related to high narcissism and prototypical psychopathy compared to the PP2 factor, which tend to be associated with a broad range of personality disorders (Miller et al., 2008).

PRIMARY PSYCHOPATHY MEDIATED THE LINK BETWEEN EMPATHY AND SOMATOSENSORY RESONANCE

Results from the Simple Mediator model confirmed the mediating role of primary psychopathy on empathic concern in predicting SG to pain observation. One plausible hypothesis that could account for the absence of significant direct relation between empathic concern and SG to pain observation is the interaction of the suppressor effect revealed by the negative correlation between empathic concern and primary psychopathy with the facilitator effect of primary psychopathy on SG to pain observation. The findings from the mediation analysis could help interpreting the divergent relationship found between enhanced sensorimotor resonance and trait-empathy (Avenanti et al., 2009), as well as between resonance and cold-heartedness traits (Fecteau et al., 2008). The results show that psychopathic traits mediated the relation between empathic concern and SG, arguing against the assumption of a straight path between sensorimotor resonance and empathy. This finding is important because it suggests that psychopathic traits in healthy individuals could explain the great inter-individual variability in sensory resonance when decoding pain in others. Further studies will need to dissect the affective and interpersonal qualities that might best contribute to the mediating role of primary psychopathy.

LIMITATIONS AND FURTHER STUDIES

Some limitations can be pointed out with respect to the proposed interpretation of the findings. First, the use of somatosensory steady-state and time-frequency analysis offer more precision in the frequency domain compared to event-related potential (ERP) and peak to peak analysis but this come with a cost in terms of temporal resolution, as reflected by the use of relatively long time bins (200 ms) in the analyses. Subtle changes in SG relative to temporal dynamics of pain perception might thus have been missed with this method. For instance, the effect of psychopathic traits on pain anticipation was previously shown in a study using ERP with young offenders by assessing early negative arousal (Cheng et al., 2012). Second, the use of extreme scores on the LSRP to form experimental groups may have contributed to the absence of significant SG to pain observation in the LSRP_Low group. Even if this remains speculative, some personality traits and/or emotional factor such as higher negative arousal than individuals in the mid-range of LSRP scores could account for the absence of significant SG during pain observation in the LSRP_Low group. However, mean scores on the PD subscale did not significantly differ between groups and the direction of the relation between negative arousal and sensorimotor response to other's pain needs to be clarified (Meng et al., 2013). Therefore, the present results should be interpreted with regards to the direction of the effect instead of its magnitude. Indeed the more robust outcomes, explaining the largest proportion of the variance, were the correlation between LSRP_total/PP1 scores and SG to pain observation suggesting that a dimensional approach might be more appropriate to understand somatosensory resonance with respect to psychopathic traits.

In the current study, the correlation between pain ratings and SG to pain observation was not statistically significant. However, prior studies on pain perception have shown significant positive correlations between sensorimotor processing and evaluations of pain intensity (e.g., Avenanti et al., 2005; Bufalari et al., 2007; Valeriani et al., 2008; Betti et al., 2009). This suggest a multifaceted relationship between sensorimotor resonance and evaluation of others' bodily feelings, suggesting that somatosensory response may not be exclusively related to the intensity of the pain perceived but also to the arousal generated by the stimuli (Bolognini et al., 2013). Future studies will need to clarify the likely interaction of affective arousal on somatosensory processing.

CONCLUSION

This study demonstrated that observing pain in others triggered somatosensory gating to a greater extends in college male students with high psychopathic traits compared to students with low psychopathic traits. It provides additional evidence on the relationship between personality traits associated with affective and interpersonal dimensions of psychopathy and somatosensory resonance to other's pain. The mediation effect found for psychopathic traits thus gives insight into the complex relationship between trait empathy and somatosensory processing of other's pain. The current study also contribute to extend the growing body of literature on psychopathic correlates in non-incarcerated samples trying to depict a sharper representation of the affective-related alterations observed in these individuals, thus supporting a dimensional approach of psychopathy.

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Beta event-related desynchronization as an index of individual differences in processing human facial expression: further investigations of autistic traits in typically developing adults

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The human mirror neuron system (hMNS) has been associated with various forms of social cognition and affective processing including vicarious experience. It has also been proposed that a faulty hMNS may underlie some of the deficits seen in the autism spectrum disorders (ASDs). In the present study we set out to investigate whether emotional facial expressions could modulate a putative EEG index of hMNS activation (mu suppression) and if so, would this differ according to the individual level of autistic traits [high versus low Autism Spectrum Quotient (AQ) score]. Participants were presented with 3 s films of actors opening and closing their hands (classic hMNS mu-suppression protocol) while simultaneously wearing happy, angry, or neutral expressions. Mu-suppression was measured in the alpha and low beta bands. The low AQ group displayed greater low beta event-related desynchronization (ERD) to both angry and neutral expressions. The high AQ group displayed greater low beta ERD to angry than to happy expressions. There was also significantly more low beta ERD to happy faces for the low than for the high AQ group. In conclusion, an interesting interaction between AQ group and emotional expression revealed that hMNS activation can be modulated by emotional facial expressions and that this is differentiated according to individual differences in the level of autistic traits. The EEG index of hMNS activation (mu suppression) seems to be a sensitive measure of the variability in facial processing in typically developing individuals with high and low self-reported traits of autism.

Keywords: alpha, beta, mu, EEG, ERD, autism, emotion

INTRODUCTION

The study presented here was undertaken in order to examine the usefulness of measuring EEG sensorimotor reactivity to examine individual differences in emotional facial processing. For half a century, it has been known that suppression of the dominant resting rhythm in the EEG over sensorimotor areas accompanies not only movement execution but also movement observation (Gastaut, 1952; Gastaut and Bert, 1954). This rhythm, most commonly known as mu (but also referred to as the Rolandic or wicket rhythm) has two contributing bandwidths: an 8–12 Hz component oscillating at alpha frequencies and a 12–20 Hz low beta band component, perhaps reflecting contributions from primary somatosensory cortex and motor cortex, respectively (Hari, 2006; Avanzini et al., 2012). A substantial amount of experimental work has established that movement execution is associated with suppression of the mu oscillatory activity over the sensorimotor cortex: at rest, the mu bandwidths show a synchronized activity, leading to high-amplitude oscillations. This synchronized activity is functionally distinguishable from the dominant occipital alpha activity. When a movement is executed, this synchronized activity is suppressed and this suppression is thought to reflect active processing in sensorimotor areas (Pfurtscheller and Lopes da Silva, 1999). Such suppression is often referred to as desynchronization or event-related desynchronization (ERD), particularly when it is measured in relation to a pre-stimulus baseline (or reference) period (Pfurtscheller and Aranibar, 1977).

Gastaut and colleagues' investigation of mu activity demonstrated that not only did mu desynchronize to movement execution but also to imagining and observing movements (Gastaut, 1952; Gastaut and Bert, 1954). The findings pertaining to movement observation were under-explored for several decades until the discovery of so-called "mirror neurons" in monkeys in the 1990's (Di Pellegrino et al., 1992; Rizzolatti et al., 1996). Research then turned to looking for human analogs of mirror neurons using various neuroimaging and other psychophysiological techniques. Mirror neurons were originally described as cells in monkey area F5 (an analog of the inferior frontal gyrus in humans and also later in parietal lobule) that fire not only when the animal makes a specific movement but also when it observes that movement (Rizzolatti and Craighero, 2004). Work in humans using fMRI (e.g., Iacoboni et al., 1999, 2005; Molnar-Szakacs et al., 2006), transcranial magnetic stimulation (TMS; Fadiga et al., 1995; Enticott et al., 2010; Sartori et al., 2012), depth electrode recording (Mukamel et al., 2010), and EEG/MEG (e.g., Hari et al., 1998; Nishitani and Hari, 2000; Muthukumaraswamy and Johnson, 2004a,b; Kilner et al., 2009) have since shown the existence of a similar observation-execution matching system that has been labeled the human mirror neuron system (hMNS) as this does not necessitate the existence of "mirror neurons" per se in humans, just a functionally similar mechanism. In this context, it is the EEG/MEG research that has drawn on the work of Gastaut and colleagues to explore the links between mu suppression and the hMNS. Not only has mu-suppression been shown to be a useful indicator of action-observation pattern matching (in that suppression accompanies both action-execution and action-observation) but that it also closely matches other measures of the putative hMNS. For instance, mu-suppression to the observation of hand movements has been shown to closely mirror fMRI BOLD activation in areas analogous in humans to mirror neuron areas in primate studies (Perry and Bentin, 2009). In this context, mu-suppression has also been shown to be modulated by the laterality of the presentation stimulus (i.e., it is driven by the side of the screen on which an observed movement occurs), to be consistent with the reactivity of mirror neurons in area F5 in monkeys (Kilner et al., 2009) and to be dynamically modulated similarly in both action observation and action performance (Press et al., 2011). Accordingly, mu-suppression during action observation is interpreted as an index of activity in the hMNS (Pineda, 2005, 2008; Kilner et al., 2009). Indeed, whereas until recently, mu-suppression during action-observation has been thought to result from post-synaptic modulation from mirror neurons in premotor cortex (Rizzolatti and Craighero, 2004; Pineda, 2008), recent evidence of so-called "M1 view" cells in primary motor cortex with mirror neuron-like properties (Dushanova and Donoghue, 2010) suggests that mu-suppression may be a more direct measure of hMNS than was previously believed, as M1 may itself be a part of the hMNS (Press et al., 2011).

The notion of a hMNS has been used as an argument for the biological mechanisms underlying theories of embodied cognition such as simulation theory. Simulation theory posits that we understand the behaviors and emotions of others by activating similar neural processes in ourselves to those at play in the person observed (Gallese and Goldman, 1998; Gallese, 2009). This has been particularly investigated in relation to how we understand the facial expressions of others. Many studies have found fMRI evidence for common neural activation during both the execution and perception of facial expressions, particularly in areas associated with the hMNS (e.g., Carr et al., 2003; Leslie et al., 2004; Hennenlotter et al., 2005; van der Gaag et al., 2007). This has been strengthened by TMS studies showing that performance on a facial emotion processing task correlates with TMS-induced motor evoked potentials (thought to be an index of hMNS activity; Enticott et al., 2008) and that disrupting pre-SMA activity with TMS impairs the recognition of happy faces (Rochas et al., 2012). To date, although it has been known for some time that mu suppression is sensitive to oro-facial movements (Muthukumaraswamy et al., 2004a), little work has been carried out using EEG to gauge mu reactivity to facial emotion processing. However, a handful of studies report findings that suggest that the use of mu suppression may be useful in this context. For instance, Moore et al. (2012) report mu ERD to both happy and disgusted faces, with an earlier response to disgust and a longer, more extensive response to happy faces. Similarly, decreased beta power (akin to increased beta ERD) has been observed to painful stimuli during the observation of emotional compared to neutral expressions (Senkowski et al., 2011). One other study has also reported a difference between beta reactivity over central electrodes (sensorimotor areas) to angry and happy faces; with increased beta power in the angry condition (Guntekin and Basar, 2007). In addition, Pineda and Hecht have shown that mu suppression is positively correlated with a social-perception task (matching facial expressions based on the eye region alone) but not with a social-cognitive task (judging intentions and beliefs of others), suggesting that the hMNS may be involved in the former behavior but not the latter (Pineda and Hecht, 2009).

With regard to action observation, the use of EEG to measure mu suppression has been useful in terms of discovering clinical and individual differences in sensorimotor (and possible hMNS) activation. Clinically both schizophrenia (McCormick et al., 2012) and autism (Oberman et al., 2005; Bernier et al., 2007) have been associated with abnormal mu reactivity, although much debate remains regarding the robustness and interpretation of these results (Raymaekers et al., 2009; Fan et al., 2010; Puzzo et al., 2011). In terms of individual differences, the level of expertise (Behmer and Jantzen, 2011), amount of learning (Marshall et al., 2009), and degree of habituation (e.g., in smokers; Pineda and Oberman, 2006) have been shown to affect mu suppression. Sex differences have also been observed (Cheng et al., 2008; Silas et al., 2010), along with altered mu reactivity according to the degree of empathy (Perry et al., 2010; Woodruff et al., 2011; Cooper et al., 2012) and the level of autistic traits (Puzzo et al., 2010). However, to date, no studies looking at mu reactivity to facial emotion processing have found any individual differences. Of the three studies to look in this area, two did not investigate individual differences (Guntekin and Basar, 2007; Senkowski et al., 2011) and one, investigating the influence of the level of empathic traits, found no differences between those scoring high and low for empathy (Moore et al., 2012). Given the lack of research in this area and the evidence for the usefulness of mu suppression as an index of individual differences in action observation mechanisms, we undertook to explore its application for investigating the neural mechanisms of facial emotion processing. Specifically, we were interested in examining whether emotionally charged facial expressions (positive, negative, and neutral) modulate the sensorimotor reactivity induced by hand movement observation. In addition, given the debate in the autism literature, we were interested in testing whether or not this reactivity would vary according to the level of self-reported autistic traits in typically developing adults. The benefits of using such a population include, the availability of larger numbers of potential participants, the lack of certain possible confounds such as medication and the potential to gain insight into the boundaries of the disorder (Hirsch and Weinberger, 2003). Indeed, in the last decade, autism spectrum disorder (ASD) classifications have changed, so that now, facets of autism are seen as an extreme end of the behavioral traits observed in the normal population

(Baron-Cohen et al., 2001; Constantino and Todd, 2003, 2005). Thus, investigating autistic traits in a typically developing population is useful both for the insight it may provide into autism per se and also into how these traits are manifest in the population as a whole.

METHOD

PARTICIPANTS

Initially, 80 participants completed the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001). From this sample, two groups were formed comprising of 10 high scorers (high AQ group; seven female) and 10 low scorers (low AQ group; six females). The high AQ group was comprised of those scoring ≥22 and the low AQ group scoring <11 (Almeida et al., 2010). Thus, the number of participants in the EEG part of the study was 20 (mean age = 25.4 years). The mean AQ score was 23.9 (*SD* = 2.28) for the high group and 7.6 (*SD* = 1.43) for the low group. All participants gave written informed consent and the study was approved by the University of Essex Ethics Committee.

MATERIALS

The AQ was used to assess the degree to which adults from a normal population have traits typically associated with ASD (Baron-Cohen et al., 2001). The questionnaire comprises of 50 questions, each item in the AQ scores one point if the participant's answer is an autistic-like answer. Participants' scores can range from 0 to 50, with higher scores associated with high traits of autism.

This experiment was part of a larger study looking at social gestures, and for the purposes of this experiment, videos containing actors opening and closing their right hands with three different facial expressions were used (see **Figure 1**). For each condition (happy, neutral, angry), four actors were filmed (two female) wearing dark clothes against a dark back-drop, and seated in the center of the screen. The actors' hands were held in front of their chests so that both the hand movement and the facial expression were clearly visible. The actors opened and closed their hands at a rate of 1 Hz, holding their fingers and thumbs straight. Thus, in total, there were 12 different video clips that constituted one block. Six blocks were run in total with the presentation of the video clips randomly ordered at the start of each block. Each video lasted 3 s with a 3 s inter-trial interval. Stimuli were presented using Superlab software (Cedrus Corporation, San Pedro, CA) on an Apple PowerMac (2 GHz PowerPC G5; Apple Inc., Cupertino, CA).

EEG DATA ACQUISITION

EEG data were recorded with Neuroscan 4.4 acquisition software and SynampsII amplifiers using a 64 channel Quick-Cap arranged according to the international 10–10 system (Compumedics, Melbourne, Australia). Eye movements were recorded using teo facial electrodes—above and below the left eye. Impedances for all electrodes were reduced to below 10 kOhm before the start of each session. All data were continuously sampled at 1000 Hz with a bandpass filter of 0.15–200 Hz and a 50 Hz notch filter. Online EEG data were referenced to a point midway between Cz and CPz, and grounded midway between Fz and FPz.

EEG DATA PREPARATION

Following visual inspection of the data, noisy data blocks were rejected. Bad electrodes were excluded on a participant by participant basis (electrode C2 was excluded from one high AQ participant and one low AQ participant; electrode Oz was excluded from three high AQ participants). Ocular artifact rejection was carried out using the Neuroscan Edit transform (derived from Semlitsch et al., 1986) followed by a second, automatic artifact rejection sweep, with exclusion parameters set at ±75 mV. In order to calculate event-related desynchronization/synchronization (ERD/S), the data were epoched from −1500 to 3500 ms around the start of each video clip and the following steps were performed using the event-related band-power transform in Neuroscan Edit 4.4 (Compumedics, Melbourne, Australia): the data underwent complex demodulation and concurrent filtering (zero phase-shift, 24 dB roll-off, envelope computed) into the EEG bandwidths of interest: alpha (8–12 Hz) and low beta (12–20 Hz). It was trimmed (1000 ms from each end, to remove filter warm-up artifacts) and averaged. A reference interval of −500 to 0 ms was used to calculate the percentage change between the active period (500–2500 ms) and it, using the classic method adapted from Pfurtscheller and colleagues (e.g., Pfurtscheller and Aranibar, 1977; Pfurtscheller and Lopes da Silva, 1999): ERD% = (R−A) / R × 100, where R = power in the reference interval and A = power in the active or task phase. Thus, desynchronization and synchronization are expressed as a percentage of activity relative to the reference interval (NB, using this formula ERD produces positive scores and ERS negative). In order to reduce the number of multiple comparisons, the electrodes were collapsed within each hemisphere, resulting in two variables: left central (C5, C3, C1) and right central (C6, C4, C2).

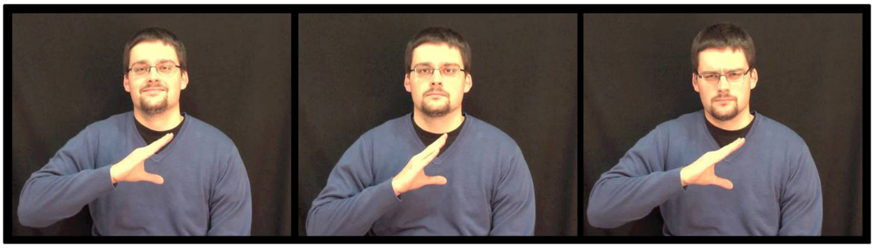

FIGURE 1 | Stills taken from stimulus video of one actor portraying from left to right: happy, neutral, and angry facial expressions.

DESIGN

This experiment was a mixed factor design with two repeated-measures factors: emotional expression (happy, neutral, angry) and hemisphere (left, right) and one between-subjects factor: AQ group (high AQ, low AQ). In order to check that our findings were due to mu activity (i.e., deriving from sensorimotor areas) and not related to occipital alpha we also employed Oz as a control site. For Oz data, there was only one repeated measures factor (emotional expression). The dependent variables for all ANOVAs were the ERD/S values in the alpha and low beta bandwidths. Thus, two mixed measures ANOVAs were carried out for each scalp location (central alpha, central low beta, occipital alpha, and occipital low beta). In order to explore interactions, planned comparisons used one-way ANOVAs to examine between subjects differences and paired students' t-tests for repeated measures differences.

RESULTS

CENTRAL SITES (C5, C3, C1, C2, C4, C6)

Low beta band

No main effects for emotion, hemisphere or group were observed ($ps > 0.187$). A strong interaction was observed between emotion and group [$F_{(2,\ 36)} = 9.38$; $p = 0.001$; $\eta_p^2 = 0.343$]. As can be seen in **Figure 2**, this was driven by greater low beta ERD to happy than both angry and neutral expressions in the low AQ group [$t_{(9)} = 2.867$; $p = 0.019$; 95% CI = 2.83 to 24.04 and $t_{(9)} = 3.327$: $p = 0.009$; 95% CI = 2.22 to 11.69, respectively] and by greater low beta ERD to angry than to happy expressions in the high AQ group [$t_{(9)} = 2.497$; $p = 0.034$]. There was also significantly more low beta ERD to happy faces for the low than for the high AQ group [$t_{(18)} = 2.221$; $p = 0.039$; 95% CI = 0.94 to 34.02]. No other two- or three-way interactions were significant ($ps > 0.154$).

Alpha band

No main effects for emotion, hemisphere or group were observed ($ps > 0.459$) but there was a significant interaction between emotion and hemisphere [$F_{(2,\ 36)} = 3.492$; $p = 0.041$; $\eta_p^2 = 0.162$]. As can be seen in **Figure 3**, greater alpha ERD was observed for happy than for angry expressions in the left hemisphere [$t_{(19)} = 2.847$; $p = 0.01$; 95% CI = 3.57 to 23.4]. Also, for happy expressions, alpha ERD was greater in the left than in the right hemisphere [$t_{(19)} = 2.51$; $p = 0.021$; 95% CI = 2.28 to 25.26].

OCCIPITAL SITE (Oz)

Data from three participants (all high AQ group) were omitted due to noise on the Oz electrode. No main effects or interactions were observed in either bandwidth ($ps > 0.071$). This suggests that our findings for the central sites were indeed due to mu activity and not to occipital alpha.

DISCUSSION

This study sought to examine the usefulness of mu suppression when investigating individual differences in emotional facial processing. Specifically, we investigated whether alpha and low beta ERD over sensorimotor areas would differ according to both the degree of autistic traits of the observer and the facial expression of the observed subject (i.e., the person "doing" the actions). Our main finding was that in the low beta band from central sites (overlying primary motor areas), whereas those scoring high in autistic traits (high AQ group) showed greater low beta ERD to angry compared to happy expressions, those with low AQ scores

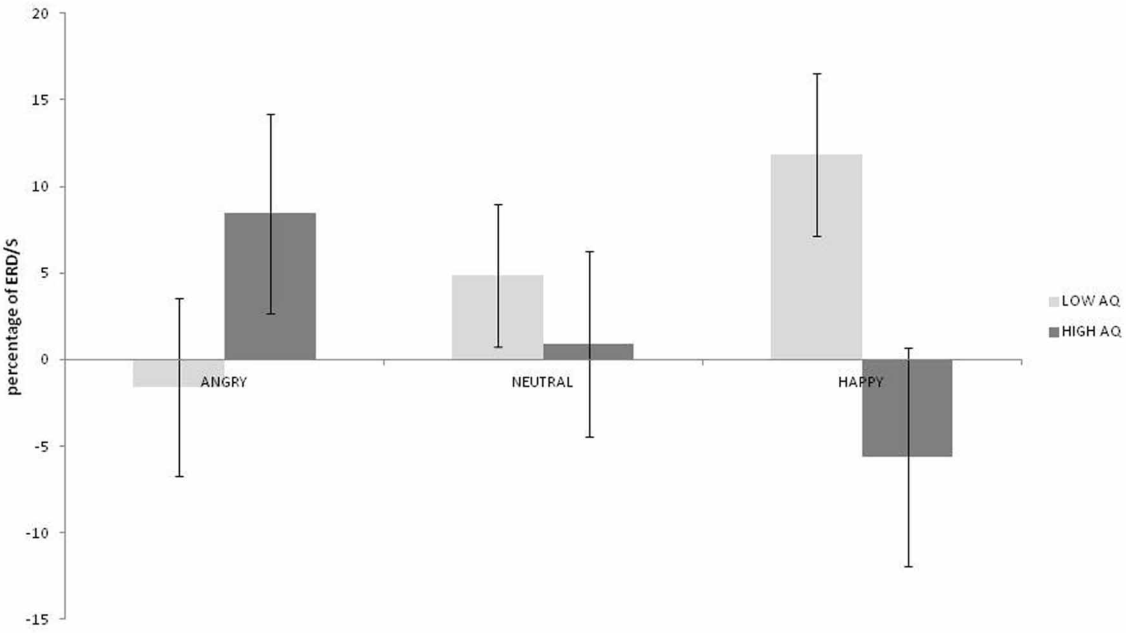

FIGURE 2 | Low beta ERD percentage-change over central sites for low and high AQ groups during angry, neutral, and happy conditions (positive values indicate ERD, negative scores indicate ERS).

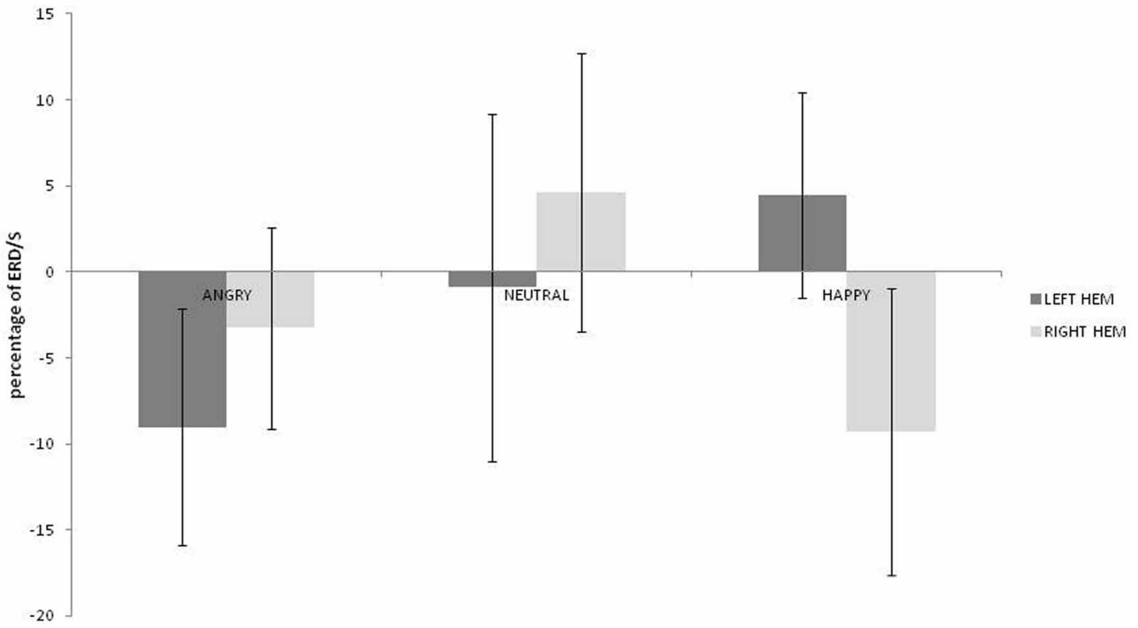

FIGURE 3 | Alpha ERD percentage-change over central sites for left and right hemispheres during angry, neutral, and happy conditions (positive values indicate ERD, negative scores indicate ERS).

showed the opposite effect (greater ERD to happy than either angry or neutral expressions). Also, the low AQ group had greater low beta ERD to happy faces than the high AQ group. In the context of action observation, mu suppression is regarded as a reliable index of hMNS activation (Muthukumaraswamy and Johnson, 2004b; Pineda, 2005, 2008; Kilner et al., 2009). In the present study, mu suppression to action observation was modulated by the facial expression of the actor making the hand movement. Consequently, our results suggest that those with higher levels of autistic traits have greater hMNS activation to negative facial expressions (anger) and those with low levels have greater hMNS activation to positive ones (happy). Additionally, when viewing happy expressions, the low AQ group showed greater hMNS activation than the high AQ group. This differentiation according to the level of autistic traits may also help to explain the discrepancy in findings in the previous studies examining mu reactivity in facial processing (Guntekin and Basar, 2007; Moore et al., 2012) as such individual differences were not taken into account in these studies.

It is interesting, and perhaps surprising, that we did not find any differences between AQ groups in the alpha bandwidth or indeed, much in the way of alpha ERD to the stimuli presented, regardless of AQ group. Many previous studies, investigating action observation have shown alpha to be suppressed during the observation of movement (e.g., Muthukumaraswamy and Johnson, 2004a,b; Oberman et al., 2007; Perry and Bentin, 2009) and some have reported differences in this suppression between people with autism and control groups in alpha (Oberman et al., 2005; Bernier et al., 2007). This alpha suppression is typically interpreted in terms of the internal simulation of the movement in the observer. The reason for our lack of findings in this bandwidth is unclear. It is possible that the nature of the stimuli presented may have altered the response (e.g., the relatively small area of the visual scene taken up by the moving hand). Also, with the inclusion of the emotional faces, there is more to take in and potentially more to simulate. It may be that the addition of faces to the stimuli usually presented in such protocols (i.e., moving hands) has a differential modulating effect on the two mu components (alpha and low beta) and that would suggest a different functional role for them both in the simulation process. For instance, it has been suggested that changes in alpha may reflect activation of primary somatosensory cortex, whereas those in beta might indicate motor cortex activity (Hari, 2006; Avanzini et al., 2012) and therefore the results from the current study might reflect relatively greater motor cortex and less somatosensory activation in response to the stimuli. The differential functions of the mu bandwidths in action observation and emotional recognition is an interesting question that merits further investigation.

Returning to our main results in the lower beta band, a superficial interpretation might lead one to expect that those scoring high for autistic traits should be worse at recognizing happy faces (possibly as a result of less emotional resonance with positive emotions). However, a recent meta-analysis of emotional facial processing in autism suggests that while there may be a difficulty in recognizing emotions in autism, recognition of happiness is only marginally impaired (Uljarevic and Hamilton, 2012). However, it should be noted there were problems in this analysis resulting from a lack of viable control stimuli (e.g., neutral faces) and that much of the studies analyzed used still images as opposed to more ecologically valid moving images. In contrast, and in line with our results, recent psychophysiological findings do show an atypical response to happy faces in adolescents with autism and their siblings (Spencer et al., 2011) and individuals scoring highly on autism spectrum personality traits (Gayle et al., 2012). Specifically, Gayle and colleagues found a reduced EEG mismatch negativity response to happy but not sad images in those scoring highly on the AQ. Spencer's group found that fMRI BOLD responses to happy faces were significantly reduced compared to neutral expressions in both those with autism and their siblings but that this effect was not seen for fearful expressions; this BOLD response was observed in the fusiform face area and putative "social brain" areas, particularly the superior temporal sulcus (STS). These findings were interpreted in terms of impaired emotional reactivity in autism (Spencer et al., 2011) and argued to be consistent with diminished approach motivation and positive affect and to underlie the general negative experience of social interactions in ASD (Gayle et al., 2012). Additionally, Gayle and colleagues suggested that a reduced response to positive expression is not surprising (as it is consistent with negative social interaction), but that reduced response to negative expressions would be (as it would be consistent with positive social interaction). Our results of both decreased reactivity to happy expressions and increased reactivity to angry faces in the high AQ group fit well with this interpretation and provide even more rationale for negative social experience in ASD. The finding of increased reactivity to angry faces is also compatible with previous reports of preserved "anger superiority effect" in Asperger's syndrome (Ashwin et al., 2006).

The previous findings of decreased STS BOLD response to happy faces in ASD (Spencer et al., 2011) is interesting in relation to our present findings of decreased mu desynchronization for the high AQ group for happy faces. There is a question as to whether previous findings of decreased mu suppression to action observation in ASD reflect a problem with the core hMNS or whether it is a reflection of inefficient upstream modulation by a faulty STS (Puzzo et al., 2009). The STS can be included in descriptions of an extended hMNS (e.g., Pineda, 2008) and has been shown to be involved in several mentalizing tasks and biological motion processing (Allison et al., 2000; Spencer et al., 2011). Given that individuals with ASD show an impairment in motion perception (Dakin and Frith, 2005) and that the level of autistic traits correlates with STS structure and function (von dem Hagen et al., 2011) it is plausible to suggest that observed problems in core hMNS areas (and their associated behaviors) might stem from abnormal input from the STS (information passes from the STS to the inferior parietal lobe and then on to the inferior frontal gyrus; Pineda, 2008). This is an issue that needs to be addressed in future research.

Another issue that warrants further investigation is that of how an individual with average levels of autistic traits would react to the protocol used in this experiment. In this paper we have reported the cortical reactivity (in the form a mu ERD) of both high and low AQ scorers. We have found a strong interaction between emotional expression and AQ group, with opposite effects according to group. However, it is unknown as to whether the mu-ERD of an average AQ scorer would more resemble that of a high or low scorer or be intermediate between the two. Common sense might suggest that average scorers will be like low scorers but given that the "anger superiority effect" is also seen in typically developing individuals (e.g., Ohman et al., 2001) it is entirely plausible that the mu ERD of average scorers might resemble the pattern of results shown by high AQ scorers. In such a scenario, the findings presented here of low AQ scorers' increased mu reactivity to happy expressions and decreased reactivity (indeed ERS: event-related synchronization) to angry faces could be viewed as the more atypical reaction and might be indicative of increased empathic ability in this group. However, a recent review paper has suggested that the findings of an anger superiority effect in the general population may be an artifact of the stimuli used and that in fact, there is a tendency toward a "happiness superiority effect" (Becker et al., 2011), in which case, it is arguable that it is the low AQ group who are producing more typical responses. Clearly more work is warranted in this field, both in terms of typical and atypical development.

Another issue and possible limitation of the present study, was our use of only three emotional expressions (anger, happiness, and neutrality) with two of these (anger and happiness) being somewhat extreme. We chose not to explore other, arguably more subtle, emotions as we were primarily interested in testing the usefulness of mu-ERD in detecting individual differences in responses to emotional facial expressions. The data presented in this study goes some way to establish its value and sets the scene for further investigations into the more subtle aspects of facial processing, particularly in ASD. Other issues to be explored include, did our use of somewhat fixed facial expressions (albeit, on a moving person), influence the results. There is some evidence, for example, that individuals with ASD do better on tasks with slow dynamic facial expressions rather than static images (e.g., Gepner et al., 2001; Tardif et al., 2007). The potential for high temporal resolution in ERD/S measures puts it in a good position to answer such questions. Also, the degree to which different facial muscles are involved in different facial expressions may also have had an effect on our findings. If (as in ASD), our high AQ group was only focusing on certain parts of the faces they were presented with, then this may have had an effect on the amount of beta ERD elicited. Future work needs to investigate this possibility through the use of isolating various aspects of the expressions whilst measuring mu-suppression, preferably with the concomitant use of eye-tracking techniques.

Although not directly related to the main aims of the present study, it is also interesting to note the findings pertaining to the interaction between emotion and hemisphere in the alpha band. To recap, we found ERD to happy faces over the left hemisphere in contrast to ERS (alpha synchronization) in the right hemisphere. Additionally, we found that this ERD to happy faces in the left hemisphere was significantly different to the left hemisphere alpha activation to the angry faces (which also took the form of ERS). This suggests that hMNS activation is greater in the left hemisphere to happy faces and is intriguingly consistent with theories of hemispheric laterality in approach-avoidance actions (e.g., Maxwell and Davidson, 2007). However, at present it is unclear what alpha ERS represents in this context. It is plausible that, as in other contexts (e.g., memory and attention), alpha ERS may represent an active inhibition of cortical processing (Cooper et al., 2003; Klimesch et al., 2007) but at present this remains speculative and much more work is needed in this area to understand the possible balance between activation and inhibition in the hMNS and how this may be reflected in oscillatory activity in the mu bandwidths. What can be seen from our results as a whole, is that low beta activation may be a more sensitive index of hMNS activation than alpha. This is consistent with previous work from our lab with regard to biological motion (Puzzo et al., 2011) and extends the usefulness of this approach to the measurement of individual differences in emotional facial processing.

In summary, we sought to examine the usefulness of measuring mu reactivity (changes in alpha and low beta oscillations over sensorimotor cortex) to examine individual differences in emotional facial processing. We found that those scoring highly for autistic traits had greater low beta ERD to angry than to happy faces. Those with low AQ scores exhibited the opposite pattern (greater low beta ERD to happy than angry faces) and also showed greater low beta ERD to happy faces than high scorers did. We interpret these findings in the context of the general negative experience of social interactions in ASD and propose that the measurement of mu reactivity in emotional face processing is a useful tool that facilitates the differentiation of both affective stimuli and individual differences in the level of autistic traits.

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Walking a fine line: is it possible to remain an empathic physician and have a hardened heart?

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Establishing an empathic physician–patient relationship is an essential physician skill. This chapter discusses the sexually dimorphic aspects of the neural components involved in affective and cognitive empathy, and examines why men and women medical students or physicians express different levels of empathy. Studies reveal levels of medical student affective or cognitive empathy can help reveal which medical specialty a student will enter. The data show students or physicians with higher empathy enter into specialties characterized by large amounts of patient contact and continuity of care; and individuals with lower levels of empathy desire specialties having little or no patient contact and little to no continuity of care. Burnout and stress can decrease the empathy physicians had when they first entered medical school to unacceptable levels. Conversely, having a too empathetic physician can let patient conditions and reactions interfere with the ability to provide effective care. By learning to blunt affective empathic responses, physicians establish a certain degree of empathic detachment with the patient in order to provide objective care. However, a physician must not become so detached and hardened that their conduct appears callous, because it is still important for physicians, especially those in specialties with a large amount of patient contact, to use empathic communication skills.

Keywords: empathy, vicarious, cognitive, affective, burnout, medical, students, BEES

WHY IS PHYSICIAN EMPATHY IMPORTANT?

How a physician interacts with patients impacts how the patient views the physician. Patients desire an empathic physician who listens and expresses an understanding of their medical condition. Empathy is a highly desirable professional trait, since empathic communication skills promote patient satisfaction, establishes trust, reduces anxiety, increases adherence to treatment regimens, improves health outcomes, as well as decreasing the likelihood of malpractice suits (Butow et al., 1997; Levinson et al., 1997; Roter et al., 1997; Brownell and Coté, 2001; Glaser et al., 2007; Del Canale et al., 2012). A physician may possess competent diagnostic skills, yet be considered by patients as "ineffective" because the physician misses the link between patient satisfaction and adherence to medical instructions and empathy. Being empathic not only benefits the patient, it also has a positive impact upon the physician who can be more effective and provide better care (Di Blasi et al., 2001). Empathic physicians are happier in their workplace, have more enjoyment seeing patients, are less likely to succumb to severe burn-out, and may be more clinically-competent (Suchman et al., 1993; Davis, 1996; Hojat et al., 2002a; Kataoka et al., 2012). Yet, as discussed in section How Physician Stress and Burnout Impacts Empathy, work-related stressors influence how physicians relate to patients.

WHAT IS EMPATHY?

Empathy is a multidimensional trait with many factors contributing to its development and expression (e.g., see Eisenberg, 2005). Empathy is not sympathy or pity where you favor or feel sorry for another, respectively. There have been numerous attempts to define empathy, but embedded in all of the definitions are the concepts that empathy combines aspects of thinking and feeling. Although the distinction can be considered somewhat blurred, empathy can be divided into two main definitions or types: affective (vicarious) and cognitive (imaginative; Engelen and Röttger-Rössler, 2012). Affective empathy is "an individual's vicarious emotional response to perceived emotional experiences of others"; whereas cognitive empathy is "an individual's ability to imaginatively take the role of another so as to understand and accurately predict that person's thoughts, feelings and actions" (Mehrabian et al., 1988). The first definition reflects an innate emotional response, i.e., a "gut reaction," while the second definition reflects a learned ability to imagine and intellectualize or "role-play."

In this chapter the term "affective empathy" is equal to vicarious, innate or emotional empathy, and "cognitive empathy" is equal to imaginative empathy or affective theory of mind (ToM).

Regardless of the definition you prefer, a physician has to "feel into" the patient and consider, either emotionally and/or cognitively, the patient is their counterpart in a particular situation. There is no reason to debate if the affective or cognitive aspect of empathy is most important within physicians, since it is how the physician interacts via verbal communication and body language that is important to the patient. Larson and Yao (2005) consider empathy expressed by physicians to be an "emotional labor," where physicians can either use "deep acting" (i.e., method acting) to generate consistent affective and cognitive reactions to a patient, or "surface acting" to forge empathic behavior in the absence of cognitive or affective reactions to the patient.

Being considered empathetic by the patient makes the physician more sociable and able to engage in meaningful therapeutic interactions benefiting both the patient and the physician. This becomes especially important when physicians have to correctly interpret facial or non-verbal expressions of pain behavior (Goubert et al., 2005). To do this, the physician needs to reflect, via perspective-taking, upon their vicarious empathic state, orchestrated by more primitive brain regions (e.g., insula, anterior cingulate cortex and amygdala), and then make an appropriate emotional response (Hadjistavropoulos et al., 2011). As discussed later, neocortical regions modulate the vicarious feelings, e.g., the prefrontal cortex (PFC) and temporoparietal junction (Lamm et al., 2007).

EMPATHY SCALES REVEAL SEXUAL DIMORPHISM

Using the Balanced Emotional Empathy Scale (BEES; Mehrabian, 1996), the degree of affective empathy has been shown to consistently differ between the sexes with women having higher BEES scores, i.e., showing greater degrees of affective empathy, than men (Mehrabian et al., 1988; Newton et al., 2000, 2008a,b; Shapiro et al., 2004; Dehning et al., 2012). The Jefferson Scale of Physician Empathy (JSPE; Hojat et al., 2001), which measures cognitive empathy, gives variable results on whether there is a consistent female > male sex difference (Hojat et al., 2002a,b; Kataoka et al., 2009; Rahimi-Madiseh et al., 2010; Beattie et al., 2012; Suh et al., 2012). Other scales that measure cognitive empathy show women generally report higher levels of empathy than men (Diseker and Michielutte, 1981; Mestre et al., 2009; Neumann et al., 2011; Dehning et al., 2012). This chapter will focus on studies using the BEES and the JSPE. Regarding any survey instrument, there is the caveat that the BEES and JSPE only reveal the self-reported "trait empathy," which can differ from the "state empathy" representing the actual affective or cognitive state of mind expressed during a specific encounter.

EMPATHY, PROSOCIAL BEHAVIOR, AND MORAL DEVELOPMENT

Although there is some debate on how empathy contributes to prosocial behavior, the consensus is prosocial behavior is linked to, or augmented by, empathy (Singer and Lamm, 2009). Studies by Eisenberg and colleagues have confirmed the link between empathy and the willingness to help others (Eisenberg and Fabes, 1990; Eisenberg, 2005, 2007). An individual who exhibits a high degree of prosocial behavior as a young child, will continue to exhibit prosocial behavior as a young adult (Eisenberg et al., 1999; Eisenberg, 2005)—the age at which most people enter into undergraduate medical education.

Moral reasoning is correlated with empathy, because those individuals who display empathy-related responding (even at preschool age) show a higher level of moral reasoning and reduced use of hedonistic reasoning as adults (Eisenberg et al., 1991; Eisenberg, 2005, 2007). Being a physician demands a high degree of moral judgment, yet medical school can stunt moral growth and increase cynicism (Self et al., 1993; Feudtner et al., 1994; Hafferty and Franks, 1994; Testerman et al., 1996; Patenaude et al., 2003). Accordingly, numerous studies have shown the erosion of physician affective and cognitive empathy, a decrease in numerous attitude measurements, and an increase in derogatory remarks and cynicism toward patients which can be exacerbated after entering clinical rotations, residencies or the workforce (Testerman et al., 1996; Bellini et al., 2002; Griffith and Wilson, 2003; Woloschuk et al., 2004; Dyrbye et al., 2005; Newton et al., 2008a,b; Hojat et al., 2009). This erosion can have a negative impact on both the physician and patient if the physician dislikes the patient and displays unprofessional behavior. An example of professional behavior erosion would be the frustration a physician feels who has repeated interactions with a non-compliant patient who is compromising their health by not adhering to the physician's advice. Thus, if a certain degree of empathy is not inherently present, the physician may not have the ability to suppress their true negative emotions in order to rationally and calmly, once again, explain the need for the non-compliant patient to practice a healthier life-style. (As discussed in the next section, there is a large cognitive component via higher CNS centers used to modulate the initial, vicarious empathic response.) Therefore, low levels of empathy can lead to a decreased ability to respond to others in distress in an appropriate emotional fashion, and to externalize and verbalize problems (Hastings et al., 2000; Zhou et al., 2002). The advantage of being empathetic and prosocial is that it reduces and/or inhibits aggressive actions toward others (Mehrabian and Epstein, 1972; Miller and Eisenberg, 1988).

The ability to express prosocial behavior and empathic concern, ostensibly reducing aggressive interactions, is not restricted to humans. A review of several studies show rodents respond in a prosocial fashion to another's distress (Mogil, 2012); emphasizing this ability is an evolutionarily conserved positive trait. It is interesting to note that much like humans, where women report higher degrees of empathy than men (Mehrabian et al., 1988; Newton et al., 2008a,b), female rats were much more likely to release a trapped cage mate than male rats (Bartal et al., 2011).

AFFECTIVE AND COGNITIVE EMPATHIC RESPONSES USE DIFFERENT CNS SITES

Over the past several decades considerable research has been devoted to elucidating the central nervous system (CNS) sites activated during empathic responses to various controlled situations—especially reactions to pain paradigms. Several recent, excellent review articles (e.g., Singer, 2006; Decety, 2011; Bernhardt and Singer, 2012; Walter, 2012) go into detail about empathy-activated CNS sites. However, a brief review of the different sites involved in affective vs. cognitive empathy, and how this relates to the sexually dimorphic empathic response, is provided.

Studies measuring affective empathy (Fan et al., 2011; Lamm et al., 2011; Bernhardt and Singer, 2012; Walter, 2012) have shown the anterior insula (AI) and the anterior and dorsal midcingulate cortex are the most consistently activated sites. Other sites include the inferior frontal gyrus (IFG), amygdala, periaqueductal gray (PAG), and the secondary somatosensory cortex.

Affective empathy sites differ from those used for ToM and cognitive empathy, which include the temporoparietal junction, superior temporal sulcus, dorsomedial PFC, ventromedial PFC, and the posteromedial parietal cortex.

Walter (2012, see Figure 1) proposes the existence of a "low road and a high road" to empathy. The low road corresponds to affective empathy where there is an automatic (i.e., visceral) response to the state of another, especially when pain or suffering is being observed. The low road for affective empathy uses the AI, mid-cingulate cortex, amygdala, secondary somatosensory cortex, and the IFG, with the AI and mid-cingulate cortex most consistently activated. These affective empathy sites utilize different portions of the CNS than the high road that corresponds to cognitive ToM. Cognitive ToM uses the temporoparietal junction, superior temporal sulcus, dorsomedial PFC, and posteromedial cortex. Both affective and cognitive ToM pathways communicate with each other via the ventromedial PFC which enables the cognitive empathic expression. Therefore, the ventromedial PFC appears to be the linchpin where crosstalk and processing of CNS inputs from the cognitive ToM and affective empathy regions are combined for the modulation of the cognitive empathic response to the emotional state of the other. Evidence that the ventromedial PFC is responsible for the expression of cognitive empathy comes from patients with ventromedial PFC lesions who have an impairment of expressing cognitive empathy, yet are still able to complete cognitive ToM tasks (Shamay-Tsoory and Aharon-Peretz, 2007). Another study showed patients with a ventromedial PFC lesion had impaired cognitive but not affective empathy measures, whereas the opposite was found for patients with an IFG lesion who had lower affective but not cognitive empathy scores (Shamay-Tsoory et al., 2009).

The high and low roads for the expression of empathy are similar to the "bottom-up vs. top-down" neural processing that occurs for empathic expression (see Decety and Lamm, 2006; Singer and Lamm, 2009). The bottom up, affective empathy can be modified by top-down cognitive ToM informational processing for the generation of the cognitive empathic response. To have a cognitive empathic response the observer must use higher CNS processing, via cognitive ToM regions, to put what the other is going through into an emotional context. This cognitive empathic reaction to the situation of another can then influence an affective empathic response, and vice versa, an initial affective empathic response actives higher CNS regions modulating cognitive empathy. Therefore, the affective aspect of empathy can be modified by higher order executive functioning to make the individual less dependent on their affective empathy inputs.

GENETIC CONDITIONS AND LESION STUDIES SUBSTANTIATE DIFFERENT CNS REGIONS ARE USED TO EXPRESS AFFECTIVE AND COGNITIVE EMPATHY

The above section revealed that different CNS regions are used to express either affective or cognitive empathy. As further proof, a number of studies [along with the aforementioned lesion studies by Shamay-Tsoory et al. (2009) and Shamay-Tsoory and Aharon-Peretz (2007)] have examined how the expression of empathy is altered in individuals who have suffered various CNS lesions. An fMRI study by Danziger et al. (2009) showed individuals with the rare condition of congenital insensitivity to pain still have affective and cognitive CNS regions responding to observed pain, even though these individuals have never felt pain themselves. Observed pain activated the anterior mid-cingulate cortex and the AI in both congenital insensitivity to pain patients and control individuals. The study also showed that BEES scores (measuring affective empathy) in the congenital insensitivity to pain group was significantly, positively correlated with the activity of the ventromedial PFC and anterior cingulate cortex. Danziger et al. (2006) also showed the posteroventral cingulate cortex of the congenital insensitivity to pain patients was significantly correlated with BEES scores when examining facial expressions of pain, such that the stronger the CNS activity for observing pain, the higher the BEES score. Therefore, the intensity of their empathic response was correlated with their degree of affective empathy. In contrast, the control group showed no correlation between the facial expressions and BEES scores. These studies reveal affective empathic behavior can be expressed even when a person has not directly experienced the pain of another. Therefore, physicians should have the ability to "feel into" and have an affective empathic response for patients in pain, and for patients on whom they will inflict pain or prescribe a painful procedure, even though they have not experienced that pain themselves.

Patients who have had traumatic brain injuries (TBI), which involve prefrontal regions and their connections to the limbic system, have changes in cognitive and affective empathy. In a study by Wood and Williams (2008), TBI patients showed twice as many low affective empathy scores when compared to controls. The data revealed men had lower BEES scores than women, and women with TBI had significantly more low BEES scores than the normal female population. Interestingly, there was no relationship between the severity of the TBI and BEES scores. Thus, even a minor head injury can alter affective empathy as much as a more severe TBI.

SEXUAL DIMORPHISM FOR PAIN PLAYS A ROLE IN AFFECTIVE EMPATHY SEXUAL DIMORPHISM

Because observing pain in others elicits an empathic response, Lamm et al. (2011) performed a meta-analysis to determine the empathic cortical regions used when observing pain in others. Results show the bilateral AI and the anteromedial and posteroanterior cingulate cortical regions are consistently activated when observing pain; importantly these same regions are also activated when the observer is experiencing pain themselves. A review by Bernhardt and Singer (2012) indicates the AI and the anterior and mid-cingulate cortex are involved in eliciting the affective empathic response to pain, and these same regions also receive afferents carrying nociceptive information. Therefore, the expression of affective empathy is linked to the pain axis/matrix.

The pain axis/matrix involves CNS regions bringing nociceptive inputs from the periphery to higher cortical regions to be perceived as pain. This axis includes afferents sending nociceptive information into the dorsal horn of the spinal cord or the trigeminal nucleus. The nociceptive information is sent to the thalamus to be relayed to the postcentral gyrus. The thalamus also sends nociceptive afferents to the insular and anterior cingulate cortex, the IFG and PAG: areas processing the affective components of pain and the same regions already implicated in affective empathy (Rainville, 2002; Singer et al., 2004).

In rats, portions of the pain axis are sexually dimorphic. In the spinal cord, the dimorphism extends from the numbers of dorsal root ganglion neurons sending afferent information into the dorsal horn (male > female) to the qualitative and quantitative amounts of various neurotransmitters and receptors used to relay nociceptive inputs to the spinal cord or thalamus (Newton et al., 1990; Newton, 1992; Mills and Sengelaub, 1993; Newton and Tate, 1996; Phelan and Newton, 2000). In this regard, male rats have more of the neurotransmitters to suppress nociception within the spinal cord than female rats (e.g., enkephalin and galanin); whereas, there is no sexual dimorphism for the neuropeptides involved in sending nociceptive inputs into the spinal cord (e.g., substance P and calcitonin gene-related peptide).

The sexual dimorphism has now been shown to extend to regions involved in affective empathy. For example, the PAG has extensive connections with the insular cortex, medial PFC, anterior cingulate cortex, and amygdala (Linnman et al., 2012). Human fMRI studies show sex differences exist in the activation of various cortical regions involved with affective empathy, such that men have a greater PAG connectivity to the insula and PFC than women, and women have a greater PAG connectivity to the mid-cingulate cortex than men (Kong et al., 2010). Other studies have shown men have greater pain-induced activation of the insular cortex than women; whereas women have a greater activation of the medial PFC (Derbyshire et al., 2002; Straube et al., 2009).

Somatic or visceral nociceptive inputs also activate the autonomic nervous system (ANS), and a recent study has shown sex differences in the parasympathetic response of the amygdala, with women having a greater activation than men (Nugent et al., 2011). The ANS connections with the amygdala, insula, and anterior cingulate cortex are well known and these regions are activated in a sexually dimorphic fashion during highly emotional situations (Critchley, 2005). Therefore, the affective component of empathy recruits the same brain regions involved in the cortical modulation of the ANS. For example, the sympathetic activation of the AI and cingulate cortex is characteristic of the activation of these regions by painful stimuli and strong emotions (Singer et al., 2004; Critchley, 2005). Indeed, the representation of autonomic and visceral responses, especially within the right AI, causes the autonomic inputs to become consciously available in order to influence emotional empathic reactions. Further proof the ANS is involved in empathy is pupil size varies when viewing sad faces. Those individuals with higher empathy scores have a greater pupillary response than individuals with lower empathy scores (Harrison et al., 2007). Also, individuals with primary autonomic failure have significantly attenuated BEES scores as compared to age and gender-match controls (Chauhan et al., 2008).

HOW DOES THE PHYSICIAN RESPOND TO PAIN AND DISPARATE TRAITS IN THEIR PATIENTS?

How is a physician, who is supposed to have an empathic connection with the patient, respond to the pain being described by the patient, or to the pain they will inflict with a medical procedure? How does the physician deal with the non-compliant patient, where the physician feels the patient will not follow directions; or a patient who is culturally, morally or ethnically different than them? Some physicians have been known to call difficult patients as “heartsink patients,” a descriptive term that accurately describes the unempathetic response physicians have toward these patients (McDonald and O’Dowd, 1991).

Many times a patient comes to a physician because of pain, or a physician has to perform or prescribe interventions that may be painful. The study by Singer et al. (2004) showed that when a painful stimulus was applied to another person, the affective component of pain was activated in the observer, especially the bilateral AI and rostral cingulate cortex. Furthermore, a person will have an even stronger cortical response to another’s pain if they have experienced the pain themselves (Lamm et al., 2010). Therefore, how does a physician cope with the pain of others and not become too empathetic which can lead to compassion fatigue, ineffective care, stress, and anxiety (Figley, 2002; Dyrbye et al., 2005; West et al., 2006; Pejušković et al., 2011)? For example, will a surgeon who performs painful procedures on patients be better able to perform the surgery if they have a reduced amount of affective empathy as compared to a family or internal medicine physician who does not perform as many, or as severe, painful procedures? Research may shed light on this question. CNS regions used to elicit empathic responses differ according to whether the observer is looking at facial expressions, which displays emotional-communicative information, vs. the limbs (Gu and Han, 2007; Han et al., 2009; Vachon-Presseau et al., 2012). Perhaps physicians who are in specialties with high amounts of patient contact, e.g., family practice and internal medicine, who are constantly looking at the patient’s facial expressions, may have a greater empathic response than physicians who perform painful procedures, e.g., general surgeons or orthopedists, but do not have to look at the patient’s face while performing surgery. Indeed, the ability to detect the intensity of another’s pain is most highly correlated with the degree of the facial response of the one in pain (Gu and Han, 2007; Saarela et al., 2007; Han et al., 2009; Hadjistavropoulos et al., 2011).

In 2007, Cheng et al. showed physicians who are experts at practicing acupuncture keep a detached perspective while performing a procedure they know causes pain to the patient. Compared to novice physicians and controls, there was a significantly reduced activation of the AI, anterior cingulate cortex and PAG; but an increased activation in the medial and superior PFC and the temporoparietal junction in the expert physicians. These data suggest expert physicians are using cortical regions involved in emotion regulation and ToM to suppress the affective empathy pathway associated with the pain matrix. Furthermore, the expert physicians used significantly lower ratings on the visual analog pain intensity scale for the pain they were inflicting on their patients than the novice and control participants. These results were verified by Decety et al. (2010) who showed internal medicine physicians, in contrast to control participants, used cortical regions controlling executive functions and self-regulation, i.e., dorsolateral and medial PFC and temporoparietal junction, to inhibit the activation of the empathic pain matrix involving the dorsal anterior cingulate cortex, AI, and PAG. Once again, these physicians rated painful stimuli as significantly less painful than the controls. Both of these studies show a clear blunting of the physician's affective empathy by executive cortical regions.

In 2008, Han et al. and Fan and Han (2008) showed a sex difference in the empathic response to observing pain using event-related brain potentials. Their studies showed both men and women have a short-latency empathic response over the frontal lobe to seeing painful pictures, but a long-latency empathic response over central-parietal regions. Placing these data in the context of physicians shows three things. First, there are two CNS responses to empathy, a short-latency response corresponding to affective empathy, and a long-latency response that underpins the later cognitive empathic response to pain in others. Therefore, feeling into the patient occurs first and elicits an affective empathic response, which is then cognitively modified. Second, although there was no sex difference in the short-latency CNS regions activated by affective empathy, only women showed a strong positive correlation between the activation of these regions with their subjective rating of pain in others. Men showed no such correlation. Thus, the degree of the affective empathic response in women is more strongly determined by the degree to which they subjectively feel how much the patient is suffering. Third, the sex difference in the long-latency, cognitive empathic response suggests women have stronger top-down attentiveness in controlling their affective empathy than men; i.e., women physicians evaluate the painful condition of the patient more intensively than male physicians.

The studies by Han et al. (2008) and Fan and Han (2008) were expanded by Decety et al. (2010) who showed a distinct top-down regulation of the affective empathic response in physicians. This top-down (high road) regulation serves to inhibit the bottom-up, affective perception of pain in others via modulation of the PAG by the anterior cingulate cortex (Valet et al., 2004). Since men have a greater number of connections from the insular cortex and PFC to the PAG than women (Kong et al., 2010); this suggests men may have a greater capacity to blunt affective inputs from the PAG than women.

The above studies indicate experienced physicians are using cognitive processes to modulate the affective component of empathy. However, this begs the question if a novice, i.e., a medical student or beginning resident, has the emotional capacity to engage the neural mechanisms to promote detached concern? If not, they may become emotionally over-involved when feeling into the patient, leading to a potential deterioration of effective patient management. This is especially concerning since the PFC does not reach maturity until the mid-20s (e.g., Sowell et al., 1999), and many medical students begin their medical training in their early 20s when they are expected to empathically reassure worried patients (Epstein et al., 2007). The sex differences in the neural processing of empathy for pain (Han et al., 2008) may confound the ability for both male and female physicians to reach an equivalent level of detached concern, yet still use cognitive (role-playing) empathy to maintain effective physician–patient communication. Thus, will the innate amount of affective empathy possessed by a medical student impact how they will communicate with patients, and even determine if they want to be in a specialty having a large degree, or almost no, patient contact?

THE PHYSICIAN AND THE NON-COMPLIANT PATIENT

Regarding a non-compliant patient, an inference can be made to the study by Singer et al. (2006) where they evaluated the perceived fairness of others by using the Prisoner's Dilemma Game. For both men and women there was no sexual dimorphism in the activation of brain regions corresponding to affective empathy (anterior cingulate cortex, AI, and PFC). For both sexes, the more empathic the person, the greater the fMRI activation of the aforementioned regions. However, a sex difference was observed when the Prisoner's Dilemma Game was carried out with an "unfair" person. In this instance, men had significantly reduced empathy-related responses when observing an unfair person receiving pain; however, this reduction was not seen in the women observers. Thus, women showed no significant difference when comparing the results between painful trials for fair or unfair individuals. In the context of medicine, this infers male physicians may not be as empathic toward an "unfair," non-compliant patient as female physicians. Indeed, the 2006 Singer study showed men had an increased activation of brain reward regions correlated with a desire for revenge. This suggests male physicians, especially those with low empathy, may not treat the non-compliant patient as effectively as female physicians or male physicians with higher empathy. Less effective care may be provided in order for the physician to feel the self-satisfaction the non-compliant patient is responsible for their own misery/decreased health by ignoring medical advice (Squier, 1990).

HOW DO PHYSICIANS RESPOND TO DISPARATE PATIENTS?

How do physicians empathically-relate to individuals who are disparate from themselves, e.g., those of a different race or culture or, e.g., the morbidly obese? Physicians who feel angry with patients and yet find these feelings unacceptable, face barriers on how to relate to the patient's perspective. A study by Lamm et al. (2010) demonstrates an observer looking at a person who is responding in a painful, but incongruent fashion to a harmless stimulus (touching the hand with a Q-tip) activates the same empathic neural regions involved with feeling the pain themselves, i.e., bilateral AI, medial, and anterior cingulate cortex. In contrast, a procedure that would be considered painful for the observer, but not for the patient, recruited CNS regions involved with the self-other distinction and ToM cognitive control, e.g., dorsomedial PFC and right inferior frontal cortex (Mitchell et al., 2006; Decety and Lamm, 2007). These studies indicate physicians should have the cognitive ability to adopt the perspective of a patient dissimilar to themselves and communicate in an empathic fashion. But the ability to do so depends upon the recruitment of CNS regions controlling the affective component of empathy. Therefore, the response to pain in others not like ourselves depends upon the top-down regulation of the bottom-up routes of empathy (e.g., Decety and Lamm, 2006; Lamm et al., 2008). This top-down adaptability enables the physician to understand and emote to the feelings of a patient who is in a situation the physician has not experienced, e.g., a female physician empathizing with a male patient reluctant to have a rectal exam, or any physician relating to someone who has suffered seizures or broken bones, when they themselves have never experienced these traumatic events.

The above positive aspects of a physician being able to establish an empathic relationship with the disparate patient need to be tempered with other results. Can physicians reliably empathize with patients toward whom they naturally feel little or even negative emotions, when it has been shown that empathic responses in the anterior cingulate cortex and AI are influenced with perceived group membership and racial bias? The activation of these empathic regions are reduced when the person observes others different than themselves (Xu et al., 2009; Avenanti et al., 2010; Hein et al., 2010). Therefore, a physician has to be consciously aware of any bias within themselves, e.g., negative feelings for obese patients (Huizinga et al., 2009), and be prepared to cognitively inhibit the affective empathic bias. This becomes especially important when dealing with patients in pain. A study by Drwecki et al. (2011) showed empathy played a role in the quality of pain treatment nurses offered to African Americans or European Americans, such that African Americans received less effective pain management. On a positive note, the study suggested "perspective-taking" intervention could be used to help ameliorate the treatment disparities (see Batson et al., 1997). Therefore, incorporation of this technique into student and physician training can make them aware of this inherent nature to discriminate.

Considering that most physicians participate in a health care team when dealing with patients, it becomes important to question whether interactions with team members who are more empathetic than the physician can influence the physician's behavior. Three examples of increasing prosocial behavior include a study by Drwecki et al. (2011) who showed nurses were more empathetic toward patients in pain, regardless of race, than controls. Another was third year medical students watching exemplary team behavior in the operating room. This made the students more aware of the need to comfort patients and to cooperate and respect other healthcare professionals (Curry et al., 2011). Finally, "human factors" training during surgical clerkships resulted in students being more likely to ask a nurse's perspective on an action plan and increased student–patient communication (Cahan et al., 2010).

DO SEXUALLY DIMORPHIC LEVELS OF AFFECTIVE AND COGNITIVE EMPATHY DETERMINE WHAT MEDICAL SPECIALTY A STUDENT WILL SELECT?

Although many studies demonstrate sex differences in affective and cognitive empathy among medical students or physicians, few studies have examined medical student empathy changes over time, or have correlated levels of empathy with student or physician specialty choice. Elucidating how empathy is involved with specialty choice becomes important when examining the correlation of empathy with medical student or physician coping skills and the stress of treating patients who are in pain.

Several past studies have suggested certain personality traits of medical students can be used to help predict what medical specialty the student will practice (Rezler, 1974; Hojat et al., 1998; Batenburg et al., 1999). The recent longitudinal affective empathy study by Newton et al. (2008a,b), which surveyed the 2001–2004 graduating classes at the University of Arkansas for Medical Sciences, clearly showed affective empathy levels can indicate what specialty a medical student desires to practice. During the longitudinal empathy study, medical students selected, out of a possible 23 choices, what specialty they would like to enter each time they took the BEES. Newton et al. (2000, 2008a,b) broke the specialties into two different classifications: "core" and "non-core." There are five core specialties, each characterized by a large degree of patient contact and continuity of care: family and internal medicine, general pediatrics, obstetrics and gynecology (Ob/Gyn), and psychiatry. Non-core specialties (e.g., radiology, emergency medicine, anesthesiology, pathology, surgery) are characterized by low or no patient contact and little or no continuity of care.

At the beginning of the senior year, students with the highest BEES scores desired to enter the core specialties vs. those students with lower BEES scores who desired to enter the non-core specialties. These data can be further broken down by gender. After completing the first three years of undergraduate medical school, women who wanted to enter core specialties had a 13.0% drop in BEES scores compared to their BEES score obtained during orientation to medical school (i.e., base line data). Yet women who desired to enter non-core specialties had more than a twofold larger drop in BEES scores (29.3%) compared core women. By the start of the senior year, core-selecting men had a 25.8% reduction in BEES scores, and non-core men dropped by 38.7%. All of these declines are significantly different from the BEES scores obtained during freshman orientation. These data show students who desire to enter core specialties with a large amount of patient contact and continuity of care better maintain their affective empathy than students who want to enter non-core specialties, and the rate of decline in core BEES scores was half that of their non-core classmates.

It is interesting to note the largest drops in BEES scores occurred after the completion of the first basic science year of medical school and the first year of clinical rotations (Newton et al., 2008a). It was hypothesized a drop in BEES scores would occur after completing the first basic science year of medical education, and the authors suggested the reason is the students may be suffering from traumatic deidealization (Kay, 1990). The drop in BEES scores after finishing the first year of clinical rotations was unexpected. The authors had expected BEES scores of third year (junior) students to either stay stable or rise because the students were obviously excited about being finished with "book work" and could now start clinical rotations and see patients. The significant drop in affective empathy while seeing patients was disconcerting, since the students were supposed to be learning how to establish an empathic physician–patient relationship rather than decreasing their affective empathy. The drop in affective empathy levels after completing the first year of clinical rotations may be attributed to the severity of cases seen in a tertiary care hospital and/or the lack of positive physician role models. An ongoing analysis of the above data (Newton et al., 2008a) suggests students with high freshman BEES scores, who say they desire to enter non-core specialties, shift to selecting core specialties by the time they take the BEES at the beginning of their senior year. The opposite is true for students who have low BEES scores obtained during orientation and want to enter a core specialty; they tend to shift to non-core specialties (manuscript submitted).

A study using the JSPE to look at specialty preference in relation to cognitive empathy (Hojat et al., 2005) gave results similar to the BEES data (Newton et al., 2000, 2008a,b). This study showed that freshmen medical students who desired to enter primary care specialties (e.g., family and internal medicine, and pediatrics) scored higher on the JSPE than students who wanted to enter technology- or procedure-based specialties (e.g., orthopedics, ophthalmology, radiology, pathology, neurosurgery). Their results showed no sex differences in cognitive empathy scores when compared to desired medical specialty. Results from this study were confirmed by two other studies (Tavakol et al., 2011; Chen et al., 2012).

Hojat et al. (2002a) also examined physician cognitive empathy using the JSPE. Physicians in psychiatry had the highest JSPE scores, but they were not significantly higher than physicians in internal medicine, pediatrics, emergency medicine, and family medicine. Physicians with the lowest JSPE scores were in orthopedic surgery, neurosurgery, radiology, and anesthesiology. The JSPE data showed no sex differences among the physicians. The difference between the BEES and JSPE results may be a reflection of the two different types of empathy being measured, or that the BEES data came from medical students, whereas the JSPE was used to survey physicians.

AFFECTIVE EMPATHY vs. RESIDENCY MATCH

It is telling when BEES scores, obtained at the beginning of the senior year of undergraduate medical school, are compared to the medical specialty the students actually entered upon graduation (Newton et al., 2008b). For specialties with an $n \geq 7$ graduates, the BEES scores of the five core specialties ranked in the top six specialties. In rank order, they were Ob/Gyn, general pediatrics, psychiatry, family medicine, anesthesiology (a non-core specialty), and internal medicine. Even though senior BEES scores were lower when compared to the BEES scores obtained during freshman orientation to medical school (vide supra), each of the core specialties still maintained an "average" amount of affective empathy when compared to the normal population. (The average rating is equivalent to the 50th percentile on the bell-shaped curve of BEES scores; Mehrabian, 1996). Therefore, senior students who better maintained their BEES scores, and by inference had the smallest decreases in affective empathy, matched into the core medical specialties characterized by a large degree of patient contact and continuity of care. Almost all non-core specialties had BEES scores lower than the population norm. The non-core specialties ranked as having "slightly low" affective empathy (31st percentile; −0.5 s.d.) were, in descending order of BEES scores, diagnostic radiology, medical pediatrics, ophthalmology, general surgery, urology, and emergency medicine. Non-core specialties ranked as "moderately low" (16th percentile, −1.0 s.d.) were students entering into pathology and orthopedic residencies.

There were several specialties where the number of students who entered them was low enough ($n \leq 6$) that only a trend average could be established. Graduates entering into dermatology, radiation oncology, and physical medicine residencies had an "average" BEES score; while preventive medicine and nuclear medicine were rated as "moderately low." Otolaryngology ranked as "very low" (7th percentile; −1.5 s.d.), and plastic surgery and neurosurgery were ranked as "extremely low" (2nd percentile; −2.0 s.d.). The only specialty to rank above "average" was neurology, which was "slightly high" (69th percentile, +0.5 s.d.). (A possible reason for the slightly high BEES score for entering neurology residents is that several of our neurologists are outstanding role models, have won "Humanism Awards" and have a large teaching role.)

The above affective empathy data suggest medical students are self-selecting their specialty choice according to their intrinsic level of affective empathy. Thus, students with the higher BEES scores, who enter into core specialties with a large degree of patient contact and continuity of care, may demonstrate a better bedside manner than those students entering into non-core specialties with little patient contact. In other words, students with higher BEES scores may maintain more of their innate ability to more effectively communicate with their patients in an empathic fashion than those students who select specialties with little patient contact. (This is not to say that all physicians, regardless of their specialty, need to practice empathic communication skills.) It appears the students are aware of their own innate level of affective empathy and enter into the specialties where they are most comfortable with the level of patient contact. Anecdotally, we all either know, or have heard, about physicians in certain specialties having a more brusque bedside manner than physicians in other specialties. The affective empathy study by Newton et al. (2008b) provides some empirical data to support the anecdotal observations, since graduates entering into surgical specialties (general surgery, orthopedic surgery, neurosurgery, plastic surgery) have affective empathy scores 0.5–2.0 s.d. lower than the population mean. Other studies support the observation surgical specialties may have a preponderance of less empathic physicians (Hall et al., 2002; Levinson et al., 2006; Duberstein et al., 2007). However, because women generally have better physician/patient skills than men (Bylund and Makoul, 2002; Mast et al., 2007) and higher BEES scores (Newton et al., 2000, 2008a,b), and because more women are entering surgical specialties formerly dominated by men, the decreased level of affective empathy displayed by physicians in these surgical specialties may be improved by the recent increased presence of normally more empathic women.

Related to the above suggestion, various interventions have helped to increase physician prosocial behavior by learning to respect members of a health care team (many of which are women) and to improve communication skills with team members and patients (Cahan et al., 2010; Curry et al., 2011). However, do these interventions have the same degree of success on all the various specialty fields? The aforementioned studies focused on operating room interactions; yet most interactions take place outside the operating room. Is it possible the cognitive modulation of the vicarious physician empathy can be influenced with whom they interact? To what extent does emotional contagion (see Singer, 2006) and mirror neurons in humans (Baird et al., 2011) play a role in a physician's ability to react in a more empathic, prosocial fashion? These questions become even more complicated with the sex differences in the human mirror-neuron system (female > male for pars opercularis and inferior parietal lobe volumes; Cheng et al., 2009). It remains to be determined if a physician can become more empathic if surrounded by team members displaying empathic behavior, and if women will potentially have a greater positive response than men.

HOW PHYSICIAN STRESS AND BURNOUT IMPACTS EMPATHY

Recent studies clearly show being a medical student, resident, or physician is stressful (Dyrbye et al., 2006; West et al., 2006; Nettleton et al., 2008; Pejušković et al., 2011), and women generally have a more adverse response to medical profession stressors than men (Lloyd and Gartrell, 1981; Hojat et al., 1999; Lindfors et al., 2009; Backović et al., 2012). Some degree of stress is found in any profession, and a certain amount of stress can be motivating for some individuals, but physicians exhibit greater burnout from stressors than the general population (Shanafelt et al., 2012). The stressors include, among other things, workload, exposure to patient death/suffering, ethical conflicts, the hidden curriculum and poor role models (e.g., Hafferty and Franks, 1994; Figley, 2002; Dyrbye et al., 2005; Haglund et al., 2009). These stressors, if not managed adequately by the medical student or physician can lead to substance abuse, suicide, increased cynicism, medical errors, impaired competency, burnout, depression, a sense of lack of accomplishment, as well as influencing specialty choice (Dyrbye et al., 2005, 2006; West et al., 2006; Pejušković et al., 2011). Additional studies show cognitive and affective empathy are blunted by these stressors (West et al., 2006; Thomas et al., 2007; Koehl-Hackert et al., 2012). Taft et al. (2011) reveal there is a sexual dimorphism in the strategies used to address stress and burnout. Women use more emotion-based coping skills, whereas men use more problem-focused skills. Over reliance on emotional coping skills was a significant predictor of increased psychological distress and decreased self-efficacy.

Stress can exacerbate emotional responses. Over arousal due to an excessive affective empathic response tends to make a person self-focus and experience personal distress (Wood et al., 1990a,b). A physician's excessive empathic response to a patient can decrease their ability to care for the patient, because the physician focuses on their own vicarious response to the patient's medical situation vs. being attentive to the needs of the patient. So, a physician who is predisposed to becoming overly empathetic to negative situations needs the ability to control their empathic response in order to remain effective. There are two ways a person can become empathically over-aroused: either by the temperament they are born with, which modulates the intensity and quality of their empathic response, or their ability (or inability) to self-regulate their empathic/emotional response. The latter has been termed "effortful emotion-related regulation" where a person modulates the intensity and duration of their expressed emotional behavior in order to accomplish their goals (Eisenberg and Morris, 2002). This emotion-related regulation involves effort, where the person deliberately down-regulates their negative emotions and activates appropriate behavior toward another, even if they really don't want to do so. Yet, the capacity to control temperament and emotional responses varies with the individual. Thus, the temperament of the individual, along with their ability to regulate their emotions contributes to individual differences in empathic capabilities (Eisenberg, 2005). Therefore, a physician needs the ability shift attention away from negative affective inputs they are truly feeling and express their empathic response to the patient in an adaptive manner. This inhibiting mechanism involves the anterior cingulate gyrus which is involved in affective empathy (Rothbart and Bates, 1998). Individuals who have more executive control over cognitive functions should be better able to control their empathic response and less likely to experience personal distress and depression when compared with people who have less executive control over their empathic response (Zalewski et al., 2011).

It is revealing when one compares the rate of physician burn out with trait empathy via BEES and JSPE scores (Hojat et al., 2002b; Newton et al., 2008b; Shanafelt et al., 2012). For the core specialties, the BEES scores dropped while the students progressed through medical school but still remained in the "average" range as described by Mehrabian (1996). Yet among these five core specialties, there was a considerable amount of physician burnout (Shanafelt et al., 2012). Internal and family medicine physicians had burnout rates of 54 and 50%, respectively. Ob/Gyn was close behind with a 46% burnout rate; psychiatry and general pediatrics, which had the lowest burnout rate, fared better with burnout rates of 40 and 35%, respectively. Non-core specialties with BEES scores ranked as "slightly low" (−0.5 s.d. lower than the population norm) had burnout rates that ranged from the highest level of 65% (emergency medicine) to 45–40% (diagnostic radiology, general surgery, ophthalmology, urology, medical pediatrics). The two specialties ranked as "moderately low" (−1.0 s.d.), orthopedics and pathology, had burnout rates of 47 and 37%, respectively. When comparing these BEES data with JSPE scores, any core specialty having an "average" BEES score was associated with a JSPE score of over 120 (JSPE range: 20–140), whereas most remaining specialties had JSPE scores <120.

So how does a physician in a specialty with a high burnout rate still maintain an "average" amount of affective empathy? It's possible core physicians who are in the front line of primary care (family and internal medicine) are more efficient at using ToM and cognitive empathy skills to more effectively blunt their affective empathy so the burnout they are experiencing does not further decrease their average-ranked BEES scores into lower rankings which are −0.5 to −2.0 s.d. off the population norm. In other words, the core physicians with higher JSPE scores are presumably better able to maintain empathic role-playing communication with their patients, even though they have burnout rates at or above 50%. However, the conundrum is cognitive control over affective inputs takes an emotional toll on physicians and contributes to higher rates of burnout—especially for women (Lloyd and Gartrell, 1981; Hojat et al., 1999; Lindfors et al., 2009; Backović et al., 2012). Those physicians in non-core specialties, who theoretically do not need to display or use as many cognitive empathy skills with their patients, have cognitive empathy JSPE scores lower than physicians in core specialties. These non-core physicians may not feel the need to communicate effectively with their patients and therefore do not need to go through the emotional labor to role-play an empathic response to the patient.

Clearly, additional research is needed to elucidate the interactions of affective and cognitive empathy with burnout and stress, especially regarding how a physician actually reacts to patients (i.e., state empathy) vs. their trait empathy.

SHOULD PHYSICIANS HAVE A HARDENED EMPATHIC HEART?

Physicians frequently deal with the emotional burden of life, death, and patients in pain during their practice, yet still have to relate to patients in an empathic manner. There are several ways a physician can respond to this burden. A physician can be empathically neutral and perform what needs to be done to the patient without feeling grief, regret, or other difficult emotions. Alternatively, detached insight could be used to communicate with and treat the patient. This detachment, orchestrated by ToM and cognitive empathy, blunt the affective empathy pathways allowing the physician to respond to the patient with role-playing behavior. Accomplishing this may be more difficult than it sounds, since displaying role-playing empathy for the patient, while feeling affective empathy which is different from what you really want to express, leads to an empathic dissonance within the physician. It takes considerable effort for the physician to put forward an empathic front for the patient, especially when the physician has a negative emotional reaction to the patient that causes personal distress. Many physicians find maintaining an empathic relationship with patients is not an easy task and can be likened to an emotional labor. Just as one example, there are complex biopsychosocial interactions needed to interpret the degree of an individual's pain and to respond with an appropriate level of empathic support (Hadjistavropoulos et al., 2011).

So is it necessary for a physician to have a hardened heart? Being too empathetic can leave the medical personnel vulnerable to the negative consequences of a patient's medical condition (Badger et al., 2008). An over empathic physician risks over-identifying with their patients, whereby emotional responses from the patient can threaten medical objectivity. Therefore, a certain amount of emotional detachment from the patient is necessary or else the physician lets the affective empathy bring about feelings within themselves that detracts from their ability to effectively manage the medical situation. Yet, on the other end of the empathic spectrum, a total detachment from the patient by a physician who appears not to care or is callous, does not establish the empathic connection the patient desires and expects.

For those physicians entering core, patient-oriented specialties, maintaining an average level of affective empathy, while having higher cognitive empathy skills would be beneficial in maintaining a positive physician–patient rapport. However, this level of empathy would not necessarily benefit physicians entering non-core specialties, since they deal with patients with more intrusive techniques—even if ordered by a core physician. Allowing too much affective empathy to overwhelm non-core physicians as they perform surgeries, endoscopic exams, or diagnose patient pathologies, would potentially lead to ineffective treatment of the patient as the physician pays more attention to their own affective inputs vs. concentrating on the patient. Therefore, for the non-core specialty physician, having a lesser amount of affective empathy should result in less effort to maintain a reasonable detachment from the patient and enable more efficient patient care.

Ultimately, the answer to the question is—"Yes"—physicians need to harden their heart, but like most things in life the answer is not "black or white." Empathic shades of gray are needed depending on the physician's specialty and their innate levels of affective and cognitive empathy. Assuredly, the most emotionally difficult task for the physician is to moderate the degree to which they harden their hearts. Physicians walk a fine empathic line to ensure they can relate to the patient without becoming too hardened themselves.

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Mom feels what her child feels: thermal signatures of vicarious autonomic response while watching children in a stressful situation

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Maternal attunement with an infant's emotional states is thought to represent a distinctive feature of the human primary bond. It implies the mother's ability of empathizing with her child in order to fulfil the child's needs in an immediate and appropriate manner. Thus, it is particularly involved in stressful situations. By assuming that maternal attunement embodies a direct sharing of physiological responses with the child, we compared the autonomic response of mothers observing their own distressed child with those of other women observing an unknown child involved in an ecological distressful condition (mishap paradigm). The hypothesis was that the adult's response was more attuned with the child's response in the former group than in the latter group. The autonomic response was non-invasively evaluated through the recording of the thermal facial imprints by means of thermal infrared (IR) imaging. Nine mother-child dyads and 9 woman-unknown child dyads were studied. We found marked similarities between the facial temperature dynamics of women and children along the experimental procedure, thus providing evidence for a direct emotional sharing within the adult-child dyad. The evidence for common dynamics in the time course of the temperatures was assessed through correlation analysis and, nevertheless, resulted stronger in the mother-child dyads than in the other women-child dyads. In addition, temporal analysis showed a faster response in mothers than in other women, thus confirming our study hypothesis. Besides confirming the extraordinary capability of IR imaging to preserve ecological context in the study of social or non-verbal interactions, these results suggest that maternity appears to potentiate the emotional attunement with the child. Although based on preliminary results, this study opens new perspectives in the study of the factors modulating vicarious socio-emotional processes.

Keywords: emotion, vicarious responses, emotional sharing, mother-child synchrony, mother-child bond, autonomous nervous system, IR thermal imaging

INTRODUCTION

Maternal attunement with a child is a key element of secure attachment relationships (Bowlby, 1958). A mother who is capable to share affect with her child, to empathize with his/her emotional needs and to appropriately respond to his/her requests, allows the infant to perceive a sense of being accepted and recognized, which facilitates social adjustment and a positive psychological functioning (Bowlby, 1958). Conversely, the lack of such a sensitivity could lead to less favorable outcomes in the child's subsequent development (Sullivan et al., 2011). Although there is a general agreement on the importance of maternal attunement, little is still known about the biological basis of that ability.

Maternal attunement with offspring is especially involved when mothers are facing infants' distress. As shown by a large amount of empirical evidence, mother's alertness and arousal increase because of the baby's distress signals (Swain et al., 2007), allowing to immediately provide the help needed for the infant's recovery (Bell and Ainsworth, 1972; Frodi and Lamb, 1978; Mills-Koonce et al., 2007). As found by neuroimaging research, watching a child's emotional expressions specifically activates some brain regions, like the anterior insula, the amygdala and the mirror neuron system (Rizzolatti et al., 2001; Gallese et al., 2004). This activation occurs mostly when a mother observes her own child rather than an unknown child (Iacoboni et al., 1999; Lenzi et al., 2008). Since the anterior insula is considered the relay between the action representation (mirror neuron system) and the emotional processing (limbic system) (Lenzi et al., 2008), the above activation could relate to the mother understands of her own child's distress signal, probably to the aim of responding successfully and appropriately. Particularly, the infant's crying—the most powerful distress signal—activates the same brain regions involved in attention, emotional attachment and in the process of integrating autonomic states with social behavior (Seifritz et al., 2003; Swain et al., 2007, 2008; Kim et al., 2010; Swain, 2011; Swain et al., 2011). The infant's distress also elicits autonomic responses in the own mother. In particular, blood pressure as index of aversive stimuli, heart rate as attentional and defensive response, and skin conductance as index of arousal, increase in mothers witnessing their infant's crying (Frodi and Lamb, 1978).

Beyond the ability to provide the right intervention in distressing situations, synchronization of the mother's responses to the infant's signals in typical dyadic interactions can be considered a key aspect of sensitive parenting, as it implies the promptness of the mother response (Bell and Ainsworth, 1972) and the adaptation moment by moment to the child's emotional states (Noriuchi et al., 2008; Guedeney et al., 2011). Repeated experience of well-synchronized and appropriate interactions allow mother and child to become sensitive to each other's physiological and behavioral cues (Fleming et al., 1999; Feldman, 2007; Feldman et al., 2011, 2012) and capable to perceive the other's behaviors as a response to their own behavior, which contributes to the formation of a unique bond between them (Stern, 1985; Mogi et al., 2011).

The autonomic nervous system seems to represent an elementary mechanism supporting emotional synchrony between mother and infant. According to Porges (1998, 2003a,b), the emergence of parenting behavior in mammals is linked to the development of the Polyvagal system (Feldman and Eidelman, 2007). In his opinion and with reference to the human realm, the decrease of heart-rate variability due to vagal-tone suppression in response to a stressful event (Porges, 2003a,b) would facilitate complex behaviors such as attention, orientation and the maintenance of calm states, which are required for early formation of secure social bonds and for achieving the more advanced coordination of social signals that underlie human interpersonal interactions. Supporting that hypothesis, research on early infancy found that the mother's and her child's vagal tone are inter-related (Feldman et al., 2010), thus suggesting that the degree of parasympathetic control during social engagement is shaped by co-regulatory processes. As suggested by Feldman (2007); Feldman et al. (2012), biological synchrony in interpersonal interactions shows online sensitivity to the partners' ongoing behavior.

The physiological side of the mother-infant bond has been typically observed in stressful situations. Mother's and infant's cortisol reactivity were found to be strictly associated in the still-face paradigm, an interactive situation eliciting some degree of stress in infants (Haley and Stansbury, 2003; Feldman et al., 2010), and while playing a challenging- for-the-child game (Sethre-Hofstad et al., 2002). All together, these findings provide prototypical examples of the bio-behavioral synchrony underlying interactions, as suggested by Feldman (2007). Accordingly, an autonomic-visceral synchrony between mother and child was found in our previous study (Ebisch et al., 2012), showing a significant parallelism between mothers' and children's facial temperature variations when mothers observed their own children involved in a stressful situation. Since skin temperature is mediated by the autonomous nervous system and varies in response to emotional stimuli originated from external environment (Anbar, 2002; Merla and Romani, 2007; Nakanishi and Imai-Matsumura, 2008; Shastri et al., 2009; Nhan and Chau, 2010; Kuraoka and Nakamura, 2011), that study showed for the first time a direct sharing at the autonomic level between mother and child associated with an experience of affective attunement.

The present study aimed to deepen the results found by our previous one (Ebisch et al., 2012). In that study we demonstrated autonomic thermal synchrony in mother-child dyads when the mother watched her own child experiencing a stressful situation elicited by the mishap paradigm (Cole et al., 1992). Thermal autonomic responses were assessed through the use of high-resolution thermal infrared (IR) imaging (Merla and Romani, 2007). In the present study, using the same paradigm of the previous study, we compared the thermal autonomic responses between two groups of dyads: mother-her own child dyads and women-unknown child. Since, according to previous research (Seifritz et al., 2003; Swain et al., 2007, 2008), the experience of one's own child distress seems to influence the women's reactions to the infant's emotional needs, we expected to find different autonomic responses, on either the intensity or the time scale, across the groups. Specifically, we hypothesized that the former group of dyads would attune more than the second group, thus showing a stronger shared response. Alternatively, the two groups could exhibit the same physiological response, thus suggesting that the such a response to the child's distress is a general reaction, independently of the specific bond with the distressed child. Moreover, according to evidence for the contingency of maternal responses as one of the specific characteristics of maternal sensitivity (Feldman, 2007; Feldman et al., 2012), we expected to find more ready and prompt responses in the first group of dyads.

METHODS AND MATERIALS

PARTICIPANTS

Fourteen children (seven male, age 39–45 months) participated in the study. All of the children were born at term and had a typical psychological and physical development. The adult sample was composed of eighteen women divided in two groups: the first one included nine mothers (age 25–43) who watched their own child during the experiment ("mothers," M); the second sample was composed of 9 women (age 23–38) ("other woman," OW). Four of these had preschool children not participating to the study, while the other five were not mother. The data about six out of nine mother-child dyads were included in our previous study (Ebisch et al., 2012). The two groups of women were matched for socio-economical status and study degree. Inclusion criterion for adult subjects was the absence of any overt physical, psychiatric or psychological disease. All participants were asked to refrain from heavy physical activities and consumption of coffee, cigarettes and vasoactive substances for at least 2 h prior to the measurements, and to avoid cosmetics on their faces at the moment of the experiment. The study was approved by the Local Ethics Committee. Written informed consent was obtained from all the participants in agreement with the Declaration of Helsinki.

PROCEDURE

Prior to testing, each subject was left to acclimatize for 10–20 min to the experimental room and to allow the neutral condition skin temperature to stabilize. The recording rooms were set at standardized temperature (23°C), humidity (50–60%) without direct ventilation. The subjects sat comfortably on a chair during both the acclimatization and the measurement periods, without any restriction of body movements. Before the start of the experiment, the children underwent an adequate familiarization period to ease the psychological habituation to the setting and the experimenter, first in presence of their mothers, then followed by neutral interaction with the experimenter alone. During neutral interaction between the experimenter and the child, some toys were presented to allow the child to feel at ease and to get used to play with the experimenter.

After the neutral interaction with the experimenter, the children were exposed to a potential stressful experience, elicited by the "Mishap Paradigm" (Cole et al., 1992). More specifically, children were invited to play with a toy, which was previously manipulated to break in the child's hands when playing with it, thus suggesting that the child accidentally broke the toy. The toy was introduced by the experimenter as her own favorite. Distinct phases could be distinguished in the paradigm: (1) "presentation" (the experimenter demonstrated the toy); (2) "playing" (the child played with the toy, while the experimenter left the room for 1 min); (3) "mishap" (child "broke" the toy); (4) "re-entry" of the experimenter (the experimenter did not say anything for 30 s and merely looked at the broken toy); (5) "soothing" of the child (the experimenter cheerfully indicated that the toy could be fixed and that the breaking was not the child's fault).

In order to perform the analyses, the above mentioned phases were grouped in conditions. The neutral interaction defined the "neutral condition"; the presentation and playing phases together formed the "intermediate condition"; the mishap, re-entry and soothing phases together formed the "experimental condition."

The "mothers" and the "other women," naive about the specific content of the experiment, were invited to silently observe the children-experimenter interaction through a one-way mirror from a separated room. It was possible that two women (one for each group of dyads) watched at the same child together, though they could not see each other or interact as a screen was placed between them.

Facial thermal images for all of the subjects were recorded along the whole experimental procedure (acclimatization, neutral, intermediate, and experimental conditions).

MATERIALS

Thermal IR imaging was performed by means of three digital thermal cameras FLIR SC660 (640 × 480 bolometer FPA, sensitivity: <30 mK @ 30°C). The acquisition frame rate was set to 15 Hz for each thermal camera.

Two remote-controlled video-cameras (Canon Vc-C50iR) were used to film the child for the behavioral analysis. Video-signals were sent to two video-recorders (BR-JVC) and mixed by a Pinnacle system (Liquid 6). Subsequently, the movies were processed through a specialized software (Interact Plus, Mangold) that allows to code behavior in synchrony with the ongoing movies of the children during the experiment. The toy presented to the children in the "Mishap Paradigm" was a black and white robot with a height of approximately 20 cm. When turning on the robot with a switch on its back, it started to walk and play music. Both hands of the robot could be opened and closed by means of pressing/relieving a button. One of the hands of the robot were prepared to break when manipulated by the child. The robot could be repaired only by the experimenter. The toys presented during neutral interaction between the experimenter and the child were a puzzle, a magic wand and 3-D book.

DATA ANALYSIS

BEHAVIORAL DATA ANALYSIS

Following from the notion that different combinations of relevant signs in a mishap situation may be indicative of guilt (Barrett et al., 1993; Kochanska et al., 1995), we coded the presence or absence of the child's reactions into five categories (see **Table 1**): *gaze and eye*, *bodily tension*, *arms*, *repair, and verbalizations* (Barrett et al., 1993; Kochanska et al., 2002; Mills, 2003;

Table 1 | Expressive features coded for the scoring of child reactions.

Category	Features	Description
Gaze and face[a,b]	Gaze aversion	The child stares into space, or toward the oblique low, or toward another insignificant object (excluding the broken toy and the experimenter).
	Lip rolled-in	Lower lip rolled-in; corners of mouth drawn.
Bodily tension[b]	Bodily avoidance	The child backs up while looking at the experimenter; or moves away from her, toward insignificant object, after focusing on her.
	Hunched shoulders	Relaxed or hunched shoulders.
	Head lowered	Head hanging or tilted forward.
Arms[b]	Arms across body	Arms across the midline, held close to the body (e.g., hugging the body).
	Covering, touching face	The child covers or touches all or part of the face.
	Fingers in mouth	Putting a finger or fingers in mouth.
Repair[c]	Trying to repair the object	The child tries to repair, to fix the toy or he/she manipulates it. It is not coded as repair if the action is meant to play.
Verbalizations[b,c]	Confession	The child admits to have broken the toy e.g., saying "I broke it" or "I pulled this piece off."
	Negative self-evaluation	The child judges him/herself negatively, e.g., saying "I am not able to play" or "I can't do it."

[a] *Barrett et al., 1993; Barrett, 2005.*

[b] *Mills, 2003.*

[c] *Tangney and Fischer, 1995; Stipek, 1995; Lewis et al., 1998; Kochanska et al., 2002.*

Barrett, 2005). The duration of the phases was similar among children [$M = 35.86$ ($SD = 17.54$) seconds in playing; $M = 62.21$ ($SD = 14.52$) seconds in mishap; $M = 48.86$ ($SD = 16.44$) seconds in re-entry], and there were no cases of distress so important to reduce the duration of the phase in a relevant way for the appearance of the behaviors to code. Thus, in playing, mishap and re-entry of experimenter, overall distress response was coded on a 4-point scale [(1) child was not affected in any way; (2) child appears middle distressed as evidenced by one or two signal coded; (3) child appear distressed as evidenced by three or four signal coded; (4) child is strongly distressed as evidenced by five signal coded]. Behaviors were coded with the software INTERACT 8.

Comparisons were made between the playing, mishap and re-entry phases, because in these phases the children were engaged with the same object and that made more reliable the coding of their behaviors.

Reliability

Two observers coded all the children for each phase and Kappa's ranged from 0.72 to 0.80 (all $p < 0.05$).

THERMAL DATA ANALYSIS

A visual inspection of the changes in facial thermal imprints in all subjects was performed to qualitatively investigate the autonomic responses of the women and the children throughout the experiment. This analysis was followed by a quantitative estimation of temperature variations of the nasal tip. Referring to the literature about thermal signature of emotions (Shastri et al., 2009; Nhan and Chau, 2010; Kuraoka and Nakamura, 2011), the nasal tip has been proved to be associated with the activation of the sympathetic nervous system by emotional and distressing stimuli (Roddie, 1963; Merla and Romani, 2007; Nakanishi and Imai-Matsumura, 2008; Shastri et al., 2009; Nhan and Chau, 2010; Kuraoka and Nakamura, 2011; Ebisch et al., 2012). More precisely, temperature decrease of the nasal tip is related to sympathetic alpha-adrenergic vasoconstrictor activity and the reduction of this vasomotor effect is related to the thermal recover due to the vasodilatation effect.

Thermal signals have been extracted through the use of tracking software, developed with homemade Matlab algorithms (The Mathworks Inc., Natick, MA). The tracking algorithm is based on the 2-D cross-correlation between a template region, chosen by the user on the initial frame, and a similar ROI in a wider searching region, expected to contain the desired template in each of the following frames (Tangherlini et al., 2006). In this way it is possible to automatically extract the thermal signals in defined regions of interest during the whole experiment. The extracted thermal data have been filtered subsequently with a low-pass filter ($f_{\text{cut}-\text{off}} = 0.2\,\text{Hz}$), to eliminate breathing effects (Ebisch et al., 2012).

A comparison was made between the neutral, the intermediate, and the experimental conditions. Because the mishap paradigm is an ecological situation the duration of the conditions depended on the children spontaneous behaviors. Therefore, the timing of the experiment presented some variations within subject. The mean duration of neutral condition was 134.62 ($SD = 80.21$) s. The mean duration of the intermediate condition was 139.104 ($SD = 115.097$) s. For the experimental condition the mean duration was 222.327 ($SD = 55.79$) s.

STATISTICAL DATA ANALYSIS: INDIVIDUAL DYADS

The thermal signals of the nasal tip for all the subjects were transformed in z-scores. A repeated measures (3×3) ANOVA was performed on the mean nasal tip temperature of the three conditions for all subjects. The conditions (neutral, intermediate, and experimental) were set as within-subject factor. The groups (children, mother, other women) were set as between-subject factor. Pairwise multiple comparisons between conditions were adjusted for multiple comparisons by means of Bonferroni correction. The goal of this analysis was to control the autonomic response of the subjects during the entire paradigm. In particular our hypothesis was that there were no differences in autonomic response of the subjects between neutral and intermediate condition. On the contrary, it was hypothesized that the autonomic response in the experimental condition was significantly different, compared with both the neutral and the intermediate condition. Besides, we wanted to investigate if this autonomic response changed according to the specific group of the subjects. Pearson correlation coefficients among the time courses of the temperature signals were calculated for each women-child dyad and for the neutral and the experimental condition. Correlation coefficients were then transformed according to Fisher's distribution (r to z transform) and a t-test was performed to evaluate whether significant differences could be found between conditions (neutral and experimental) and groups of dyads in the two conditions.

A cross-correlation like analysis on each dyad's temperature signals during the experimental condition was also performed to test which delay between the signals corresponded their highest correlation value. For this purpose, Pearson correlation coefficients were computed by delaying the woman's signal with respect to the child's signal with 10, 20, 30, 40 s. For each group, the mean values of the delays corresponding to the highest dyad correlation were computed. A Mann–Whitney U-test was performed to assess possible differences between the two groups of dyads regarding the distributions of time delays maximizing the correlations.

As the "other women" group included four mothers, explorative descriptive analyses on the "other women" subgroups were performed to preliminarily investigate possible differences between other mothers and non-mothers. Pearson correlation coefficients were calculated on the individual dyads level for the other mothers and non-mothers subgroups. Furthermore, the temporal modulation of the signal was explored for the two subgroups.

GROUP ANALYSIS

Since the experiment duration depended on the child's behavior, signal resampling was performed to compare the three conditions and the three groups (children, mother, other women). Each temperature signal was resampled in order to obtain 300 data points for each condition, equally spared across the time duration of the condition (for the experimental condition, 120 samples were included for the mishap phase, 60 for the re-entry phase and

120 for the soothing phase). The resampled z-score temperatures where then averaged for the groups, thus providing an average time course for each group and condition.

RESULTS

BEHAVIORAL RESULTS

Behavioral analyses showed that all children experienced an increase of distress in response to the mishap. Specifically, the repeated-measures ANOVA indicated that the children reacted in a different way in the playing, mishap and re-entry of experimenter phase [$F_{(1,\ 13)} = 10.95$; $p < 0.05$]. There was an evident increase of distress signs in both the mishap and experimenter re-entry phase, compared with playing ($t = 4.37$, $p < 0.01$; and $t = 3.31$, $p < 0.01$, respectively). No significant evidence of difference in distress signs was found comparing the mishap and the experimenter re-entry phases. **Table 2** reports the results of the behavioral analysis.

VISUAL ANALYSIS OF FACIAL THERMAL IMPRINTS

A visual inspection of the facial thermal imprints was performed to investigate the presence of appreciable signs of autonomic responses in the mothers, the other women and the children throughout the experiment. The qualitative results resembled those already found in our previous work (Ebisch et al., 2012).

A representative example of the facial thermal imprints of one mother-other woman-child triad is shown in **Figure 1**. As to the child, no appreciable modulations were detected regarding the facial skin temperature distribution between the neutral condition and the intermediate condition. However, after the mishap a sympathetic reaction could be observed, reflected by a sudden and wide-spread decrease of face temperature, especially in the nasal tip as previously found in human as well as macaques (Kistler et al., 1998; Merla and Romani, 2007; Nakanishi and Imai-Matsumura, 2008; Shastri et al., 2009; Nhan and Chau, 2010; Kuraoka and Nakamura, 2011; Ebisch et al., 2012). The decreased skin temperature in the nasal tip likely reflects peripheral vasoconstriction due to the alpha-adrenergic activity. These sympathetic responses gradually decrease after the re-entry of the experimenter. During the soothing phase, the temperature of the nasal tip soon increased, likely reflecting a withdrawal of the sympathetic alpha-adrenergic vasoconstrictor effect. Moreover, the nasal tip temperature presented an over-response, compared to the neutral condition value.

Concerning the mother, no appreciable modulation of skin temperature distribution was detected during the intermediate condition. After the mishap as well as after the re-entry of the experimenter, the same thermal variations observed in the child could be appreciated in the mother. During the soothing phase, the mother showed a gradual and generalized increase of facial temperature, re-establishing the neutral condition state. Moreover, like the child, she showed an over response of the nasal tip temperature, compared to the start of the experiment.

Finally, the other woman did not show any signal modulation between neutral condition, intermediate condition, and mishap. During the experimenter re-entry, there was a cooling of the nasal tip, however, milder (using the same temperature scale and image contrast) than that showed by the child and the mother. In the soothing phase the other woman showed a recovery of the nasal tip temperature to the initial neutral condition value.

COMPARISONS OF AUTONOMIC RESPONSES BETWEEN GROUPS AND CONDITIONS

An ANOVA (3 × 3) was performed on the re-sampled z-score mean temperatures of the nasal tip. A significant within-subject effect was found for condition [$F_{(2,\ 29)} = 5.70$; $p < 0.01$]. Bonferroni adjusted pairwise comparisons on the within-subject factor "condition" showed no significant difference between neutral and intermediate condition ($p = 1$). There was a significant difference between the neutral and the experimental condition ($p < 0.05$) and between the intermediate and the experimental condition ($p < 0.05$). The condition × group effect was not significant [$F_{(2,\ 29)} = 0.58$; $p = 0.68$]. These results suggest that the experimental condition, but not the intermediate condition induced a significant modulation on autonomic response in all three groups (i.e., children, mothers and other women), compared with the neutral condition.

CORRELATION ANALYSIS

Table 3 shows the Pearson correlation coefficients calculated for all the dyads in the neutral condition and in the experimental condition. As we were interested in studying the attunement of the autonomic responses of the mothers with those evoked by the distressful condition in the child, the non-distressful intermediate condition was not included in the correlation analysis. Pearson correlation coefficients were found to be statistically significant

Table 2 | Means and standard deviation of the categories in all phases coded.

Categories	*N*	Phases					
		Playing		Mishap		Re-entry	
		Mean	*SD*	Mean	*SD*	Mean	*SD*
Gaze and face	14	0.57	0.51	0.86	0.36	0.71	0.47
Bodily tension	14	0.14	0.36	0.36	0.50	0.50	0.52
Arms	14	0.21	0.42	0.29	0.47	0.29	0.47
Repair	14	0	0	0.64	0.50	0.43	0.51
Verbalizations	14	0	0	0.21	0.43	0.21	0.43
Total scores	14	1.71	0.47	2.42	0.51	2.28	0.61

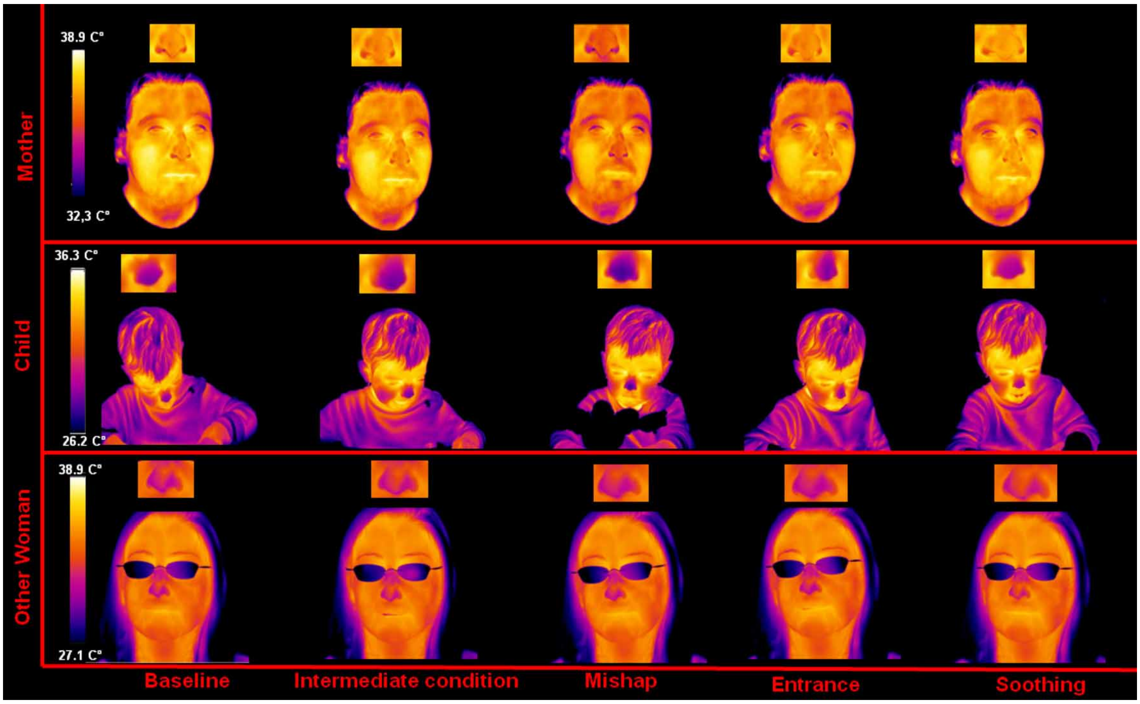

FIGURE 1 | Facial thermal imprints of one of the mother-other woman-child triads.

Table 3 | Pearson correlation coefficient for all the dyads.

Dyad	Type of dyad	Neutral condition	Experimental condition
1	M-C	0.53*	0.67*
2	M-C	0.51*	0.76*
3	M-C	−0.51*	0.71*
4	M-C	0.49*	0.84*
5	M-C	0.86*	0.91*
6	M-C	−0.64*	0.94*
7	M-C	−0.61*	0.28*
8	M-C	0.86*	0.97*
9	M-C	0.06*	0.23*
10	OW-C	−0.12*	0.24*
11	OW-C	0.26*	0.58*
12	OW-C	−0.77*	−0.03*
13	OW-C	−0.85*	0.82*
14	OW-C	0.35*	−0.38*
15	OW-C	−0.24*	0.75*
16	OW-C	0.29*	0.40*
17	OW-C	0.93*	0.71*
18	OW-C	−0.32*	0.54*

*In the column type of dyad M-C, mother-child dyads; OW-C, other women-child dyads. *p < 0.001.*

(all $p < 0.001$). With respect to the mother-child dyads group, the mean coefficient value resulted $r_{\text{mean}} = 0.17$ ($SD = 0.60$) during the neutral condition and during the experimental condition it increased up to a mean value of $r_{\text{mean}} = 0.70$ ($SD = 0.27$). The t-test on the Fisher-transformed r-values showed a significant difference in the correlation coefficient between neutral condition and experimental condition in the mothers-child dyads group ($t = -3.32$, $df = 8$, $p < 0.05$).

With respect to the other woman child-dyads, in 5 out of 9 cases there was an increase of correlation in the experimental condition, compared with the neutral condition. The mean value of the neutral condition correlation was $r_{\text{mean}} = -0.05$ ($SD = 0.57$), while the mean value in the experimental condition was $r_{\text{mean}} = 0.40$ ($SD = 0.39$). The t-test showed no differences between neutral condition and experimental condition in this second group ($t = -1.64$, $df = 8$, $p = 0.14$).

The comparison between the two groups suggested that there was no significant difference regarding correlation coefficients in the neutral condition ($t = 0.76$, $df = 16$, $p = 0.45$). Instead, the t-test yielded a significant difference between the two groups in the experimental condition ($t = 2.19$, $df = 16$, $p < 0.05$), reflecting a higher mean correlation in the mother group, compared with the other women group.

Finally, an explorative descriptive analysis was performed in order to assess the differences in correlation coefficient between other mothers-child dyads and non-mother-child dyads belonging to the other women group. The mean correlation in the other mother-child dyads was $r_{\text{mean}} = 0.16$ ($SD = 0.58$) for the neutral condition and $r_{\text{mean}} = 0.60$ ($SD = 0.58$) for the experimental condition. In the non-mother-child dyads the mean correlation is $r_{\text{mean}} = 0.16$ ($SD = 0.58$) for the neutral condition and $r_{\text{mean}} = 0.25$ ($SD = 0.47$) for the experimental condition.

TEMPORAL ANALYSIS OF THE RESPONSES

Table 4 shows the Pearson correlation coefficients for the thermal signal of the nose tip of adult and child for the experimental condition, in both the groups of dyads. In order to evaluate whether the maximum value of the correlation varied along the time course of the experimental phase, i.e., to evaluate possible delayed responses, and whether such eventual delays differed between the two groups of dyads, we computed the Pearson correlation coefficients by delaying the woman's signal with respect to the child's one with 10, 20, 30, 40 s, like in a cross-correlation analysis. The largest delay with respect to which we report the cross-correlation results is 40 s, since a higher delay did not maximize the correlation value in any dyads (see **Table 4**).

The average value of the maximum correlation coefficients for the mothers-child dyad group was $r_{\text{mean}} = 0.81$ ($SD = 0.21$), corresponding to an average delay of 7.8 ($SD = 13.94$) s.

One mother-child dyad (dyad #6) reached its maximum correlation value at a 40-s delay, even though its correlation coefficient was already larger than 0.67 and significant at 0 time delay. By excluding this dyad from the group, the average value of the highest correlation coefficients did not change, but there was a significant decrease of the mean delay in which r-value is maximized in the mother-child dyads. Excluding mother-child dyad number six reduced the average delay to 3.75 s ($SD = 7.44$).

The average value of the maximum correlation coefficients for the other woman-child dyad group was $r_{\text{mean}} = 0.57$ ($SD = 0.42$), corresponding to an average delay of 26.7 ($SD = 20.0$) s. The Mann–Whitney U-test on the delay levels showed a significant difference between the two groups ($U = 14$, $p < 0.05$), even when taking into account the dyad #6 in the mother-child dyad group.

Although aware of the small size of the sample, an explorative analysis was performed on the other women group, by dividing it in two subgroups: other mothers (i.e., mothers watching not their own child) and non-mothers. The mean of the maximum correlation coefficients in other mother-child dyads was $r_{\text{mean}} = 0.64$ ($SD = 0.21$), whereas the mean of the delays was 20 s ($SD = 23.09$). In the non-mother-child dyads the mean of maximum correlation was $r_{\text{mean}} = 0.52$ ($SD = 0.56$) with an average delay of 32 s ($SD = 17.88$).

GROUP ANALYSIS OF CORRELATION

Figure 2 shows the groups' average signal. The correlation coefficients were calculated among the three average signals, for the their whole time course and for each condition. For the whole time course signal, the correlation coefficient value for the mother-child dyads was $r = 0.88$ ($p < 0.001$), while it resulted $r = 0.84$ ($p < 0.001$) for the other women-child dyads. The Pearson coefficient values did not differ between the two groups in the experimental condition (mother—child: $r = 0.89$ $p < 0.001$; other women—child: $r = 0.90$ $p < 0.001$).

DISCUSSION

The present study focused on the physiological expression of the emotional attunement of mothers to their own children. We compared the autonomic response, measured through the nose tip temperature, of a group of mothers while watching their own child engaged in a stressful situation with that of another group of women observing unknown children in the same situation. According to the exiting literature, reporting increased behavioral responses and higher neural activation in mothers watching their own distressed child, we expected that

Table 4 | The table shows the Pearson correlation coefficient for all dyads for synchronous and shifted signals.

No.	Type of dyads	Delay				
		No delay	**10 s**	**20 s**	**30 s**	**40 s**
1	M-C	0.24*	**0.96***	0.94*	0.92*	0.90*
2	M-C	**0.28***	0.24*	0.21*	0.19*	0.16*
3	M-C	**0.97***	0.34*	0.41*	0.5*	0.58*
4	M-C	**0.82***	–0.34*	–0.35*	–0.39*	–0.29*
5	M-C	0.76*	0.72*	**0.94***	0.47*	0.92*
6	M-C	0.67*	0.76*	0.78*	0.83*	**0.85***
7	M-C	**0.71***	0.63*	0.44*	0.19*	–0.03*
8	M-C	**0.84***	0.74*	0.50*	0.13*	–0.20*
9	M-C	**0.91***	0.89*	0.69*	0.64*	0.69*
10	OW-C	0.75*	0.79*	0.84*	0.88*	**0.91***
11	OW-C	**0.40***	0.30*	0.28*	0.14*	–0.17*
12	OW-C	**0.71***	0.67	0.68*	0.62*	0.35*
13	OW-C	0.51*	0.28*	0.35*	0.45*	**0.55***
14	OW-C	0.24*	0.60*	0.68*	0.71*	**0.74***
15	OW-C	**0.58***	0.51*	0.49*	0.49*	0.47*
16	OW-C	0.28*	0.48*	0.60*	0.68*	**0.74***
17	OW-C	0.55*	–0.52*	–0.53*	–0.52*	**–0.46***
18	OW-C	0.82*	0.79*	0.86*	0.88*	**0.98***

*In the column type of dyad M-C, mother-child dyads; OW-C, other women-child dyads. *p < 0.001. Bold value indicates maximum correlation coefficient for the dyad.*

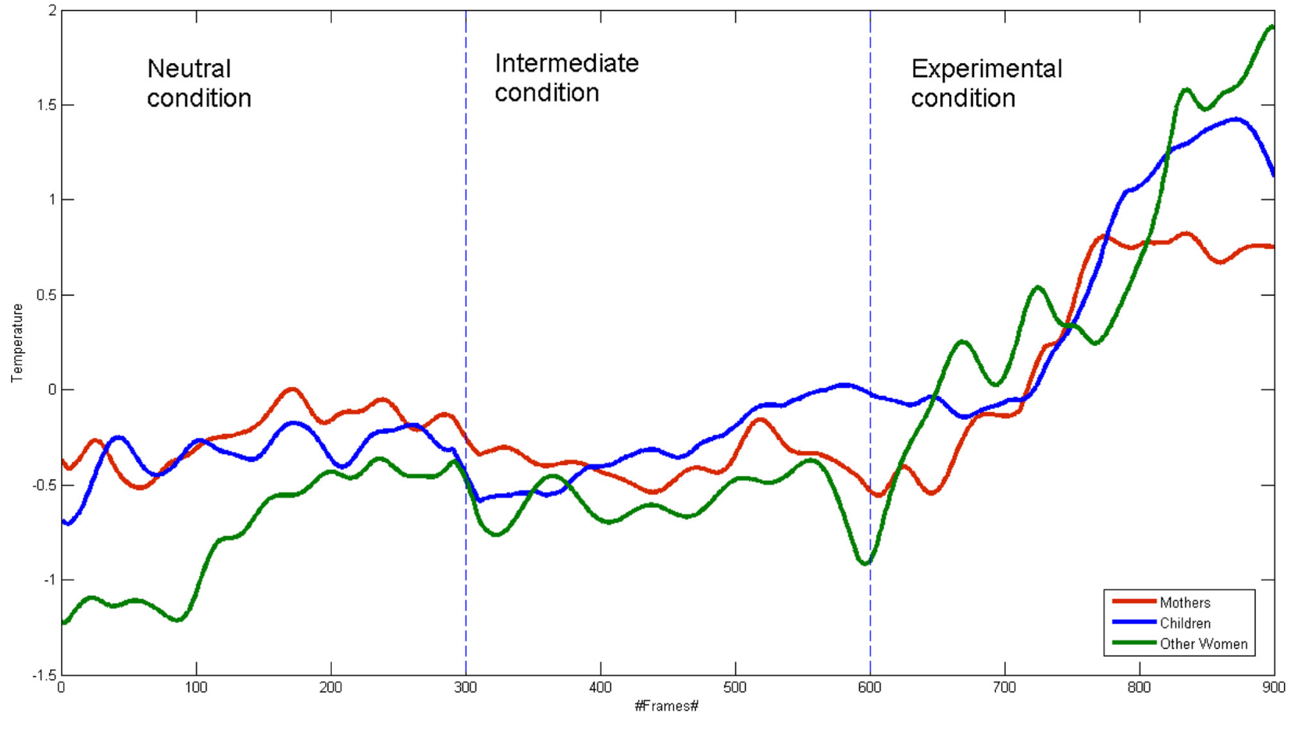

FIGURE 2 | Mean signals of mothers, other women and children for all the conditions.

the two groups would have presented differences with respect to either the intensity and/or the timing of their physiological reactions. Our results indicate that, for both groups of women, the considered autonomic response significantly changed during the experimental condition with respect to the neutral one. The emotional attunement resulted slightly stronger and much faster in the mother-child group than in the other women-child group.

Specifically, according to the hypothesis that the emotional attunement with another person embodies a direct sharing of visceral-autonomic responses (Konvalinka et al., 2011), we found that the time course of the nose tip temperature confirmed that adult women shared such an autonomic response with child exposed to a distressful situation, independently of parenting relations with the child. When analyzing the single adult-child dyad response, the two groups of dyads differed. The autonomic responses stronger correlated during the experimental condition with respect to the neutral condition for all of the mothers-child dyads, while the same did not always happen in the other women group.

Moreover, the highest cross-correlation coefficient values between the time courses of the adult-child dyad signals during the experimental condition were found at a very short or null delay for the mother-child group, whereas a much longer delay characterized the other women-child group.

Group average correlation coefficient values did not significantly differ between the two groups. This result may rise an apparent discrepancy between the results found at a group level and at a single dyad level results. Such a mismatch likely depends on the procedure used to perform the group analysis, which emphasized the shared signals modulations within the dyads. As the experiment was designed to maximally preserve the natural and ecological context, there were no a priori limits or timing for the time duration of the phases' time duration. Therefore, it was not possible to adopt a unique common time frame the whole at the group level.

The last finding suggests that the emotional promptness to one's own child's distress is a distinct feature of maternal attitude, thus confirming at a physiological level the largely confirmed results found at a behavioral level (Stern, 1974, 1999; Brazelton et al., 1974; Beebe and Lachman, 1988; Tronick, 1989; Trevarthen, 1993; Fleming et al., 1999; Trevarthen and Aitken, 2001; Feldman, 2007; Feldman and Eidelman, 2007; Papousek, 2007; Feldman et al., 2012). Since such a faster promptness for emotional vicarious processes seems to characterize maternal responses, our results further suggest to consider it as a basic mechanism for organizing early mother-child interactions. The faster autonomic response of the mothers supports the idea that the Autonomic Nervous System plays a fundamental warning role for the mother with respect to the child's emotional shift (Frodi and Lamb, 1978; Gunnar and Donzella, 2002). This signal would modulate an embodied and pre-reflective sensitivity that helps the mother to immediately recognize any shift in the child's emotional needs, as well as to promptly soothe the child when distressed (Mills-Koonce et al., 2007).

The explorative, qualitative analysis within the other women group suggested interesting preliminary information about possible differences between mothers and not mothers looking unknown children. The small size of the sample does not allow drawing any conclusion, but our results suggest to investigate further whether the other mothers may have a stronger autonomic attunement with child and a faster response than non-mothers. Such a result would be in accordance with previous fMRI data showing different responses in brain regions involved in the attachment and in the integration of autonomic states with social behavior to infant negative emotions between the mothers and non-mothers (e.g., hypothalamic–midbrain–limbic–paralimbic–cortical circuits) (Seifritz et al., 2003; Feldman, 2007; Swain et al., 2008).

The present study crucially extends the results obtained by our previous work (Ebisch et al., 2012) where, using the same paradigm, we provided consistent evidence for a synchrony in emotional response of mothers watching their own distressed child. Following that evidence, the present study tested in a larger sample the hypothesis that the above synchrony was modulated by the bond between the woman and the child. Therefore, a control group of "other women" was recruited and compared with the "mother" group. A key improvement, from a methodological point of view, in the present work is represented by the use of a novel technique for extracting the thermal signal in predefined region of interest. The tracking algorithm allowed for an extraction of the signals that, despite the movements of the subjects, was objective over the entire experimental session, thus providing a stable and more accurate evaluation of temperature variations, together with an increased number of processed frames per condition. The extraordinary potentialities of thermal infrared imaging in this field of research have been further confirmed by this study, as we were able to record physiological measures of the vicarious reactions without interfering with the subjects' spontaneous behavior.

Our study present some limitations that should be addressed. Firstly, the sample size is somewhat small. Therefore, our results should be considered preliminary, but suggestive of new insights in the study of the body communication between adults and children. Larger sample would be desirable, even though it has to be recognized that is it difficult, and somehow complex, to involve young children with their parents in a physiological study on children's distress. However, we plan to enlarge the sample size. The choice of preserving the ecological context determined the needs for the rejection of a not irrelevant number of dyads because of the excessive movements of the child that caused a artifacts that our tracking software could not fix. In addition, it determined the impossibility for a obtaining a group average signal.

To conclude, the findings show that the child's distress evocates in the observing women a spontaneous autonomic response, which could reflect an emotional sharing ability, stronger and faster in the mothers. Therefore, our study supports the hypothesis that the maternal bond can modulate the promptness of the adult's response to the child's needs.

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Men perform comparably to women in a perspective taking task after administration of intranasal oxytocin but not after placebo

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Oxytocin (OT) is thought to play an important role in human interpersonal information processing and behavior. By inference, OT should facilitate empathic responding, i.e., the ability to feel for others and to take their perspective. In two independent double-blind, placebo-controlled between-subjects studies, we assessed the effect of intranasally administered OT on affective empathy and perspective taking, whilst also examining potential sex differences (e.g., women being more empathic than men). In study 1, we provided 96 participants (48 men) with an empathy scenario and recorded self-reports of empathic reactions to the scenario, while in study 2, a sample of 120 individuals (60 men) performed a computerized implicit perspective taking task. Whilst results from Study 1 showed no influence of OT on affective empathy, we found in Study 2 that OT exerted an effect on perspective taking ability in men. More specifically, men responded faster than women in the placebo group but they responded as slowly as women in the OT group. We conjecture that men in the OT group adopted a social perspective taking strategy, such as did women in both groups, but not men in the placebo group. On the basis of results across both studies, we suggest that self-report measures (such as used in Study 1) might be less sensitive to OT effects than more implicit measures of empathy such as that used in Study 2. If these assumptions are confirmed, one could infer that OT effects on empathic responses are more pronounced in men than women, and that any such effect is best studied using more implicit measures of empathy rather than explicit self-report measures.

Keywords: oxytocin, empathy, perspective taking, sex differences, self-report

INTRODUCTION

Oxytocin (OT) is a highly conserved neuropeptide and an accumulation of its receptors are found in the amygdala (Loup et al., 1991). The amygdala is a structure that is part of the limbic system, associated with social behavior and emotion processing (Phelps and LeDoux, 2005), or more broadly with "relevance detection" (Sander et al., 2003). OT is involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, and thus affects processes such as birth and breast-feeding in females and sexual mating, attachment and bonding in both sexes (see Carmichael et al., 1987, 1994; Carter, 1992; Altemus et al., 1995; Meston et al., 2004; Vignozzi et al., 2008). OT is also proposed to have anxiolytic effects (Uvnäs-Moberg, 1997; Heinrichs et al., 2003). Thus, OT acts centrally and peripherally as a central neurotransmitter/neuromodulator and a peripheral hormone in both males and females (Carter, 1998; MacDonald and MacDonald, 2010).

In line with its anatomical and functional properties, OT is involved in human interpersonal information processing and behavior such as in enhancing prosocial judgments and behavior. For example, OT as compared to placebo administration (1) yielded higher trust in others (Kosfeld et al., 2005), (2) increased perceived attractiveness and trustworthiness of unfamiliar faces (Theodoridou et al., 2009), (3) increased charitable donations (Barraza et al., 2011), (4) promoted positive inferences about others' mental states (Domes et al., 2007), and (5) facilitated the identification of emotions regardless of valence (Lischke et al., 2012). Pointing to OT influences in clinical populations, individuals with autism benefited from OT administration by showing enhanced affective speech comprehension (Hollander et al., 2007), "mind-reading" (Guastella et al., 2010), and processing of social signals and social feedback (Andari et al., 2010). Likewise, in patients suffering from psychotic symptoms, OT administration improved performance in theory of mind tasks and perceptions of trustworthiness (Pedersen et al., 2011).

Given OT's role in interpersonal information processing and behavior, it can be assumed that it also plays a role in empathy, that is, the ability to understand another's emotional perspective and to be personally affected by it in a way that mirrors the feelings of the individual (Eisenberg and Miller, 1987). Empathy is crucial to successful interpersonal skills and relations (Miller and Eisenberg, 1988; Batson, 1991; Eisenberg et al., 2002). According to most models, empathy consists of at least two components (Gladstein, 1983; Mahrer et al., 1994; Kerem et al., 2001). The first component accounts for the cognitive effort involved in considering another's viewpoint (i.e., perspective taking), and the second concerns vicarious emotional affective empathy (Davis, 1983; Hoffman, 2000; Blair, 2005), herein referred to as "affective empathy." Both are required for normal "empathic ability" (Davis, 1983; Duan and Hill, 1996; Cialdini et al., 1997) and are shown to be related (Thakkar et al., 2009; Mohr et al., 2010; Thakkar and Park, 2010; Gronholm et al., 2012) and modulated by individual difference variables and personal experiences (Mohr et al., 2010; Cooper and Mohr, 2012).

To date, examination of OT's role in empathy has been associated with two main pitfalls. Firstly, most studies have used self-report questionnaires, which lack accuracy and are prone to socially desirable responding Tierney and McCabe, 2001; Kämpfe et al., 2009; Gerdes et al., 2010; Taras et al., 2010. Secondly, research findings have been mixed, painting a rather unclear picture (Zak et al., 2007; Singer et al., 2008; Bartz et al., 2010; Hurlemann et al., 2010). On the one hand, studies show that OT administration enhances self-reported emotional (but not cognitive) empathy (Hurlemann et al., 2010) as measured by the Multifaceted Empathy Test (MET; Dziobek et al., 2008) as well as empathic accuracy (Bartz et al., 2010), that is, the ability to accurately rate others' feelings when they narrate emotional events, in particular in listeners that are not socially proficient. Also, OT as compared to placebo administration enhanced perspective taking ability and generosity toward others in an economic game; i.e., more money was transferred to partners after having imagined their perspective and considered their reaction to an offer (Zak et al., 2007). On the other hand, OT versus placebo administration exerted a null effect on emotional empathic responses to a romantic partner's pain, i.e., on self-reported unpleasantness ratings when considering the partner's experience of painful hand stimulation (Singer et al., 2008). These inconsistent findings may either be due to OT and empathy being unrelated, or problems with the self-report measurement of empathy. We here consider these possibilities.

In two independent studies, we used comparable double-blind placebo-controlled between-subject designs to assess healthy individuals' empathy as a function of nasal OT administration. In study 1, we provided participants with a vignette in which a person's unfortunate plight was described. Participants rated their empathic feelings toward the individual (see e.g., Coke et al., 1978; Batson et al., 1989; Mikulincer et al., 2001); thereby directly linking the self-reported empathic response to an individual's plight. In study 2, we used a more implicit strategy by assessing reaction times for perspective taking in a computerized task. In this task, participants see back-facing and front-facing human figures sequentially on the computer screen and have to match the own perspective with the one of the figure (e.g., Mohr et al., 2010; Thakkar and Park, 2010; Gardner et al., 2012). Matching the own body position with that of a front-facing figure is cognitively more challenging than matching it with a back-facing figure as reflected in enhanced reaction times (see **Figure 1A**). This task has been used to examine various questions on cognitive functioning such as those underpinning different forms of mental rotation (Ratcliff, 1979; Zacks et al., 1999), cognitive correlates of out-of-body experiences (Blanke et al., 2005; Easton et al., 2009; Braithwaite et al., 2011) and schizotypy (Mohr et al., 2006; Easton et al., 2009), to evaluate learning (Bailey et al., 2007), and spatial compatibility effects (Gardner and Potts, 2011). Empirical evidence showed that at least part of task performance variance is modulated by empathy. For instance, in this 3^{rd} person perspective taking task (3PP-task) increasing self-reported empathy scores are negatively correlated with response speed (Thakkar et al., 2009) in women but also positively correlated with greater accuracy (Thakkar and Park, 2010) and reaction times (Mohr et al., 2010), in particular for individuals reportedly using a social rather than a spatial perspective taking strategy (Gronholm et al., 2012). Thus, if OT enhances empathy, irrespective of the assessment format chosen, we would expect that increased OT availability enhances individuals' empathy in both studies, leading to higher empathic concern ratings in study 1 and potentially faster reaction times in study 2. Yet, if explicit, self-report measures of empathy bias desirable responding, the effect of OT might not be observed in study 1, with the 3PP task in study 2 producing more pertinent results, at least statistically.

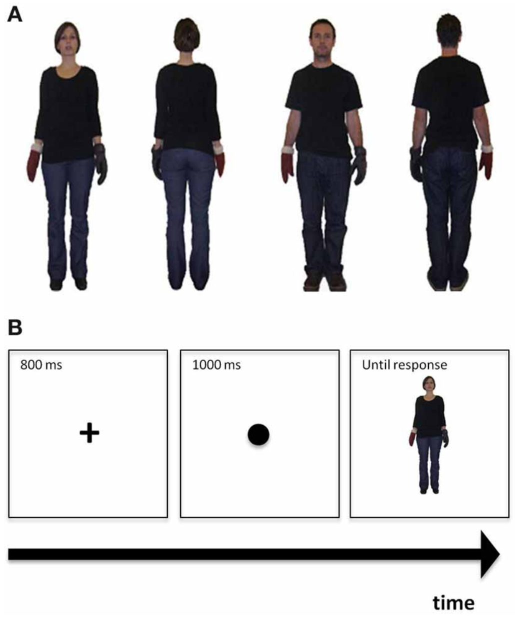

FIGURE 1 | (A) Examples of figures used in the perspective taking task. From left to right: The first two frames illustrate front- and back- facing female figures, while the remaining two frames depict front- and back-facing male figures. **(B)** Demonstration of the perspective taking task procedure: The cross is presented first, followed by the coloured dot, followed by the figure.

In addition to these hypotheses, we considered the role of participant sex. Some studies of OT effects support an enhancing role of OT for interpersonal behavioral responses in both sexes (for evidence of absence of sex-dimorphic effects of OT see Ditzen et al., 2009; Theodoridou et al., 2009, 2011; Alvares et al., 2010; Rockliff et al., 2011), but others yield direct evidence for potential sex-specific effects of this neuropeptide Fischer-Shofty et al., 2013; Theodoridou et al., 2013; for a recent review on the role of sex in individual responses to OT see MacDonald, 2012). It is worth noting that studies that have reported effects of OT specifically on empathy and/or perspective taking either recruited only men (Zak et al., 2007; Bartz et al., 2010) or found that OT selectively affected men (Hurlemann et al., 2010). In light of the above inconsistent evidence (Ditzen et al., 2009; Hurlemann et al., 2010), we considered the possibility that OT might exert sex-specific effects on empathy and perspective taking and tested an equal number of women and men.

MATERIALS AND METHODS

PROCEDURE COMMON TO BOTH STUDIES

In both studies, we conducted two sessions: a baseline session performed by participants at home and a laboratory session for which participants came to the University. Before participation in either session we obtained written informed consent from each participant. We only tested participants who met our inclusion criteria: being a fluent English speaker, not having consumed any medication, or having any other medical reason why they should not receive OT. In the case of female participants, they could not be pregnant, or if post-birth, should not be breastfeeding. The research protocol in both studies was approved by the Faculty of Science Human Research Ethics Committee at the University of Bristol. We recruited participants through poster advertisement in and around university buildings and sent emails to various departments and posted on the university's jobs website. In the baseline session, participants provided demographic information (e.g., age, sex) and filled in self-report questionnaires such as the Major Depression Inventory (MDI; Bech, 1997); results from these measures can be found in Theodoridou et al. (2009) and Theodoridou et al. (2013). Participants sent the completed questionnaires to the experimenter.

In the laboratory session at the local university, approximately one week later, participants were tested individually. They were instructed to abstain from alcohol, caffeine, and nicotine for 24 h before testing and from food and drink (except water) for 2 h before testing. When they arrived in the laboratory, each participant signed an informed consent form. The session lasted up to 2 h, with the actual task battery being assessed in the first 60 min after the waiting period, and the remaining time being used to guard for potential side effects. At the very beginning, participants were told that they would first receive a small dose of OT or a near identical looking and smelling placebo before being tested in various tasks. Information was also given about possible side effects associated with OT administration and participants were informed that they had the right to withdraw from the study at any time. In a double-blind procedure, participants were randomly assigned to self-administer a small intranasal dose of either 24 IU OT (Syntocinon Spray, Novartis, 3 puffs per nostril, each puff containing 4 IU OT), or placebo (containing the same ingredients, but OT, to the OT nasal spray). After a waiting period of 25–30 min, participants completed the task battery including the empathy vignette task (Study 1) and the 3PP-task (Study 2). Tasks were presented in two blocks, randomized in order. In study 1, the empathy scenario task was administered either 35 or 55 min after drug administration. In study 2, the 3PP-task was completed either 35 or 60 min after drug administration (see Theodoridou et al., 2009, 2011, 2013 for additional results from these studies). This time window is likely sensitive to OT effects; Gossen et al. (2012) showed that OT reaches its peak plasma level at approximately 30 min after a dose of 26 IU intranasal OT. Also note that the present protocol has led to established methods and findings in our laboratory before (see Theodoridou et al., 2009, 2011, 2013).

In the laboratory sessions, we also assessed current mood, wakefulness, and calmness with the short form of the Multidimensional Mood State Questionnaire (Steyer et al., 1997). This 6-point scale consists of 15 items with answers ranging from "definitely not" to "extremely." In Study 1, this measure was completed once, whereas in Study 2, it was completed twice, immediately before drug administration and immediately before testing. After testing, participants were instructed to guess the substance they had received[1]. Finally, participants were debriefed and offered either a monetary reward of £15 or experimental credit (or chocolate in a few instances).

STUDY 1

Participants

Of the 96 participants (mainly students, mean age: 21.4 years, age range: 18–40 years), 51 (25 males) received OT, and 45 received placebo (23 males). As reported in our previous study (Theodoridou et al., 2009), any drug effect, sex effect, or interaction cannot be explained by participants' current affect, wakefulness or calmness. Likewise, independent samples *t*-tests showed no significant differences between drug groups in depression and trait anxiety (see Theodoridou et al., 2011 for details).

Empathy task

Emotional reactions to another person's plight were assessed using a procedure similar to that employed previously (e.g., Coke et al., 1978; Batson et al., 1989; Mikulincer et al., 2001). More precisely, the experimenter read out a brief story about the plight of a university student who had recently lost her parents in a car accident. The full story read as follows: "*Anna is 21 years old studying, on a full-time basis at the University of Bristol. A month ago her parents and older sister got killed in a car accident. At the moment she is desperately trying to take care of her surviving younger brother and sister while trying to finish her last year of BSc studies. If she does not complete her degree, she will not be able to earn enough money to support her brother and sister and will have to put them up for adoption. What is more, Anna has no relatives that can help her out.*" Immediately afterwards, the experimenter read out 10 adjectives (taken from Batson et al., 1989; see below), each of which participants verbally rated on a 7-point visual analog scale according to how they felt while listening to the story (1—not at all felt, 7—very strongly felt). Participants were asked to bear in mind that the student was a mere acquaintance to them. We stressed this point because we wished to examine the effect of OT on prosocial behavior toward non-intimate others to avoid ceiling effects due to emotional closeness to the main character of the story. A digital voice recorder (Olympus; VN-2100PC) was used to record responses in this task.

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[1] As reported in previous studies on results obtained from this population, participants could not predict the treatment they received (see Theodoridou et al., 2009, 2013).

Half of the adjectives tap on empathic concern (i.e., other-oriented emotional empathy at the plight of others): *sympathetic*, *soft-hearted*, *compassionate, tender, moved*, and the other half tap on feelings of personal distress (i.e., self-oriented emotional reactions at the plight of others): *alarmed*, *grieved, distressed, upset, and disturbed*. We calculated mean scores for empathic concern responses and personal distress responses, separately (range of scores 1–7 with higher scores reflecting greater empathic concern and personal distress, respectively) to account for the possibility that these two dimensions are differently influenced by OT and/or sex. For instance, OT might increase empathic concern for a person in need and/or attenuate feelings of personal distress (Batson et al., 1987). OT might act anxiolytically (Carter et al., 2001; Heinrichs et al., 2001, 2003; Cardoso et al., 2012; de Oliveira et al., 2012; for reviews see Meyer-Lindenberg et al., 2011; Striepens et al., 2011; MacDonald and Feifel, 2012) decreasing discomfort and concern for one's own self.

STUDY 2

Participants

Of the 120 participants (mainly students, mean age: 22.4 years, age range: 18–44 years), 60 (30 males) received OT, and 60 received placebo (30 males). As in study 1 (Theodoridou et al., 2009), we observed no influence of drug and/or sex on participants' current affect, wakefulness, or calmness. In more detail, following Domes et al.'s (2007) procedure, we calculated difference scores on the different mood measures affect, wakefulness and calmness for time 1 (pre drug administration) and time 2 (30 min post drug administration) by subtracting Mood at time 2 from Mood at Time 1. Thus, positive values reflect better mood at time 1 and negative values reflect better mood at time 2. We performed a multivariate ANOVA (MANOVA) on these difference scores with drug (OT, placebo) and participant sex (male, female) as between-subjects variables. There was no effect of drug on change in affect, $F_{(1,\ 116)} = 0.02$, $p = 0.90$, wakefulness, $F_{(1,\ 116)} = 0.04$, $p = 0.85$, and calmness, $F_{(1,\ 116)} = 0.06$, $p = 0.80$. Similarly, no effect of participant sex was found on change in affect, $F_{(1,\ 116)} = 0.10$, $p = 0.75$, change in wakefulness, $F_{(1,\ 116)} = 0.02$, $p = 0.90$, and change in calmness, $F_{(1,\ 116)} = 1.71$, $p = 0.19$, and no significant drug × participant sex interactions (all $ps > 0.1$).

Perspective taking task

Picture preparation. To make figures more realistic, we here refrained from using schematic drawings used before (Mohr et al., 2010, in press; Cooper and Mohr, 2012) and took photographs of an adult man and an adult woman of approximately the same height instead, both dressed in jeans and black T-shirts (see also Thakkar et al., 2009; Thakkar and Park, 2010). The photographs showed these adult models standing upright with the arms slightly outstretched to the right and left (see **Figure 1A**). Each of them was photographed in this same position from the front and the back. For each picture taken, the models were always wearing a black glove on the one hand and a brown glove on the other hand. The side of the black glove was once on the right and once on the left for both front-facing and back-facing positions. This counterbalancing resulted in eight possible photographs that were all of the same size (237 × 239 pixels), cropped and set against a white background (see **Figure 1A** for representative examples). For single trials, a centrally placed fixation cross appeared first for 800 ms followed by a centrally presented dot (diameter = 1.5 cm) for 1000 ms that was black in half of the trials and light brown in the remaining trials. After the disappearance of the dot, one of the pictures was presented centrally (visual angle $\approx 5°$ width $\times\ 6.1°$ height) until a response was provided, that is, the task was self-paced.

Task procedure. First, participants received the written instruction that the following task would assess their empathic ability. The exact instruction was as follows: "*This is a test of your ability to see the world from another person's perspective. Performance on this test reflects empathetic ability. Empathy is a social skill that is defined as being able to identify with, and understand what another person is perceiving, and to respond appropriately.*" This instruction was based on previously used instructions (Massa et al., 2005) and was included to ensure that the task was introduced as a test of empathic abilities. Participants then received both a written and a verbal instruction to imagine being in the other person's shoes. Specifically, the instruction was: "*Imagine you are in the person's body position. If the coloured circle is black, indicate which hand the black glove is on. If the coloured circle is brown, indicate which hand the brown glove is on. If the glove would be on your own left hand, press key '1.' If the glove would be on your own right hand, press key '5.' Please respond as quickly and accurately as possible, but always aim to take the other person's perspective first.*" Following task instructions, a slide with the demonstration of the task procedure was presented for 6000 ms (see **Figure 1B**). Each picture was presented 10 times resulting in 80 experimental trials. The task was preceded by eight practice trials. We assessed the number of correct responses and the reaction times for correct responses.

DATA ANALYSIS

In Study 1, data from one participant was excluded because this person responded especially slowly (average response time: 18 s). We also excluded scores (ratings) that were two standard deviations above or below the mean (1.51% of the data). A MANOVA test was carried out on mean empathic concern ratings and mean personal distress ratings, with drug (OT, Placebo) and participant sex (male, female) as between-subjects variables. One-sample *t*-tests were also performed on the key dependent variables in study 1, namely, mean empathic concern and personal distress ratings against the chance value of 3.5. Further one-sample *t*-tests were carried out, on the empathic concern ratings and on the personal distress ratings separately for the sexes in each drug group.

In Study 2, reaction times shorter than 200 ms and longer than 5000 ms were considered to be outliers and were dropped (Harris et al., 2002; Mohr et al., 2010). Incorrect trials were also discarded. The data of five participants were discarded because their error rates (ranging from 27.5% to 48.75%) were more than two standard deviations above the mean (Mean error rate = 7.84%, *SD* = 8.24). A mixed model ANOVA was carried out on the mean RT data, with drug (OT, placebo) and participant sex (male, female) as between-subjects variables, and target sex (male, female), position (front, back) as repeated measures. No statistical analyses were performed on accuracy data as the average error rate (%) after removal of the five outlying cases was very low (Total Mean = 6.59%; OT Mean: 6.68%; Placebo Mean: 6.49%). Pairwise *post-hoc* comparisons were based on Newman-Keuls tests. In both studies, we performed univariate ANOVA tests to examine potential age differences between the two drug groups and the two sex groups. The alpha level for all the statistical test results reported henceforth was set to 5% (0.05).

RESULTS

STUDY 1: OT AND RATINGS OF ADJECTIVES SUBSEQUENT TO AN EMPATHY SCENARIO

Participants

The ANOVA on age showed no significant main effects [drug: $F_{(1,\,92)} = 0.33$, $p = 0.57$, participant sex: $F_{(1,\,92)} = 0.003$, $p = 0.96$] and no significant interaction, $F_{(1,\,92)} = 0.01$, $p = 0.91$.

Adjective ratings

The MANOVA showed that OT (vs. placebo) had no effect on empathic concern, $F_{(1,\,90)} = 0.16$, $p = 0.69$, or personal distress ratings, $F_{(1,\,90)} = 0$, $p = 0.99$. A significant main effect of participant sex was found for empathic concern ratings, $F_{(1,\,90)} = 4.18$, $p = 0.04$, with females self-reporting greater empathic concern ($M = 5.30$, $SD = 0.99$) than males ($M = 4.93$, $SD = 0.77$). No effect of sex was found on personal distress scores, $F_{(1,\,90)} = 1.91$, $p = 0.17$. We did not observe any significant interactions [largest interaction effect: $F_{(1,\,90)} = 1.41$, $p = 0.24$][2].

When comparing the two adjective rating scores against chance level (3.5), the one-sample *t*-tests showed that the mean empathic concern rating ($M = 5.12$; $SD = 0.90$) was significantly higher than chance level, $t_{(93)} = 17.38$, $p < 0.001$, as was the mean personal distress rating ($M = 3.83$; $SD = 1.27$), $t_{(93)} = 2.52$, $p = 0.01$. The same conclusion could be drawn when performing the same comparisons for the two sexes in each drug group, separately (see **Table 1** for detailed results). The opposite conclusion could be drawn when performing the same comparisons for mean personal distress ratings, i.e., the mean adjective ratings scores were not different from chance level, apart from higher scores in female participants in the placebo group (see **Table 1**).

STUDY 2: OT AND PERSPECTIVE TAKING

Participants

The ANOVA on age showed no significant main effects [drug: $F_{(1,\,116)} = 0.87$, $p = 0.35$, participant sex: $F_{(1,\,116)} = 1.11$, $p = 0.29$] and no significant interaction, $F_{(1,\,116)} = 0.02$, $p = 0.89$.

Reaction time analysis for the 3PP-task

The ANOVA on mean reaction times for correct decisions showed a significant main effect of figure position, $F_{(1,\,111)} = 124.03$, $p < 0.001$, with front-facing figures eliciting longer reaction times ($M = 1122.53$, $SD = 346.86$) than back-facing figures ($M = 913.93$, $SD = 255.64$). In addition, the main effect of figure's sex, $F_{(1,\,111)} = 31.68$, $p < 0.001$, indicated that participants responded faster to female figures ($M = 994.69$, $SD = 271.36$) than to male figures ($M = 1040.09$, $SD = 304.05$). The main effects of drug, $F_{(1,\,111)} = 1.8$, $p = 0.18$, and participant sex, $F_{(1,\,111)} = 1.35$, $p = 0.25$, were both not significant[3].

Table 1 | Mean empathic concern ratings and their difference from chance level (3.5) for the two sexes in each drug group.

		Empathic concern	*t* (*p*-value)	Personal distress	*t* (*p*-value)
OT	M	4.93 (0.64)	10.93 (<0.001)	3.80 (1.01)	1.47 (0.15)
	F	5.23 (0.89)	9.82 (<0.001)	3.86 (1.46)	1.24 (0.23)
P	M	4.93 (0.91)	7.39 (<0.001)	3.49 (1.18)	−0.04 (0.97)
	F	5.39 (1.10)	8.03 (<0.001)	4.16 (1.35)	2.30 (0.03)

Notes: standard deviations are in parentheses; OT, oxytocin; P, placebo; M, Male; F, Female; OT Male df = 23; P Male df = 21; OT Female df = 25; P Female df = 21.

We found significant 2-way interactions between figure position and participant sex, $F_{(1,\,111)} = 9.03$, $p = 0.003$, and figure position and target sex, $F_{(1,\,111)} = 10.3$, $p = 0.004$, and a significant 3-way interaction between drug, target sex, and participant sex, $F_{(1,\,111)} = 5.7$, $p = 0.02$. *Post-hoc* comparisons on these significant interactions showed for the figure position by participant sex interaction that male participants had faster reaction times than female participants for the front-facing condition ($p = 0.04$) (see **Figure 2A**). The same comparison for the back-facing condition was not significant ($p = 0.92$). Moreover, reaction times were significantly faster in the back- than front-facing condition for both male ($p < 0.001$) and female participants ($p < 0.001$). *Post-hoc* comparisons on the figure position by target sex interaction showed that female figures were responded to faster than male figures in the back-facing condition ($p < 0.001$) and front-facing condition ($p = 0.04$) (see **Figure 2B**). In addition, reaction times for back-facing figures were significantly faster than for front-facing ones for both male and female targets (all *ps* < 0.001).

Finally, to further elucidate the significant drug, target sex, and participant sex interaction, we performed 2-way ANOVAs, for the OT and the placebo group separately, with figure sex as a repeated measure and sex as a between subject-factor. The ANOVA for the OT group only showed the significant main effect on figure sex, $F_{(1,\,56)} = 11.88$, $p = 0.001$, i.e., that reaction times were faster for female than male figures. The main effect of sex, $F_{(1,\,56)} = 0.14$, $p = 0.71$, and the interaction, $F_{(1,\,56)} = 1.96$, $p = 0.17$, were both not significant (**Figure 2C**). The ANOVA for the placebo group, however, showed in addition to the main effect of figure sex, $F_{(1,\,54)} = 24.58$, $p < 0.001$ (male figures > female figures), a main effect of participant sex, $F_{(1,\,54)} = 6.34$, $p = 0.01$. Male participants responded faster than female participants

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[2] No effect of task order (task administered 35 min vs. 55 min after drug intake) was found when it was added as a covariate to the MANOVA ($p > 0.05$).

[3] When task order (task administered 35 min after drug intake, task administered 60 min after drug intake) was added to the above ANOVA as a covariate no effects involving task order were found (all *ps* > 0.05).

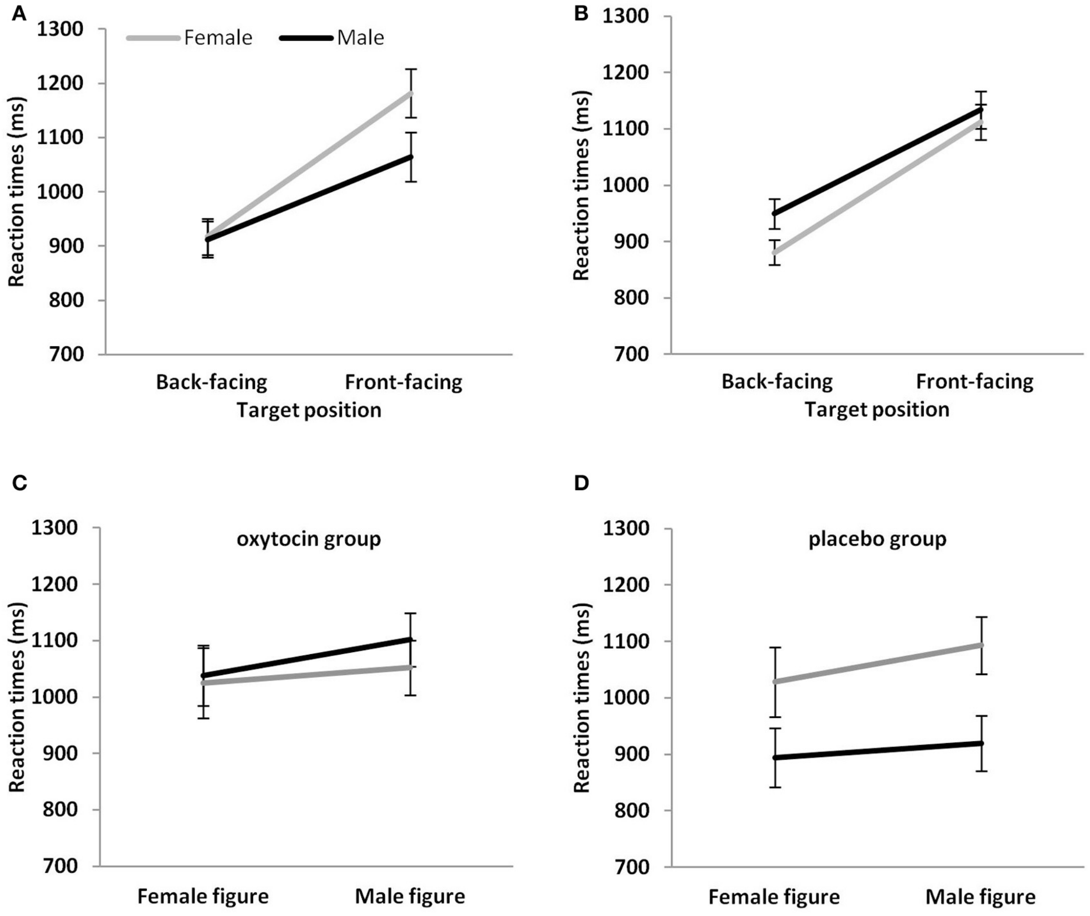

FIGURE 2 | Mean reaction times (A) of male and female participants to target figures in the back- and front-facing position, (B) to male and female target figures in the back- and front-facing position, (C) of male and female participants to target figures in the OT group and (D) the placebo group. Vertical bars indicate standard errors.

(**Figure 2D**). Finally, the interaction was significant, $F_{(1,\ 54)} = 4.25$, $p = 0.04$. *Post-hoc* comparisons showed that reaction times were faster for female than male figures in female ($p < 0.001$) and male ($p = 0.045$) participants. Moreover, male as compared to female participants showed a significant reaction time advantage for male figures ($p = 0.02$) that was only a statistical trend for female figures ($p = 0.08$).

DISCUSSION

In two independent double-blind, placebo-controlled between-subject design studies we investigated whether the consumption of a single dose of OT affected the ability to empathize with another individual's unfortunate plight (Study 1) and the ability to mentally take the perspective of another person (Study 2). In study 1, we provided participants with a scenario designed to elicit empathy [modified version used by Coke et al. (1978); Batson et al. (1989)] and assessed two levels of self-reported empathy (empathic concern and personal distress) by having participants rate empathy relevant adjectives. In study 2, we recorded reaction times in a computerized 3PP-task to assess empathy more implicitly (e.g., Thakkar et al., 2009; Mohr et al., 2010, in press) and to also avoid the response biases often associated with self-report measures (Kämpfe et al., 2009). Given that OT has been previously shown to enhance interpersonal processes and behavior (for reviews see MacDonald and MacDonald, 2010; Bartz et al., 2011; Guastella and MacLeod, 2012); including empathy (Hurlemann et al., 2010) and related phenomena such as "mind-reading" (Domes et al., 2007; Guastella et al., 2010), we hypothesized that OT as compared to placebo administration would result in enhanced empathic responses (study 1) and speeded perspective taking (study 2). We also considered that this enhancement might be more prominent in study 2, because response biases associated with self-report measures might override the OT effect in study 1. Our main findings were that (1) the adjective ratings in study 1 (empathy scenario) did not reveal higher empathic responses in the OT as compared to the placebo group, and (2) sex differences in the 3PP-task (male over female participant advantage, in particular for male figures) observed in the placebo group were absent in the OT group. Before discussing these results and additional task findings, we would like to mention that neither study 1 nor study 2 found effects of OT administration on affect, wakefulness and calmness, indicating that the above reported behavioral effects of OT could not be attributed to or mediated by changes in mood. These findings are in agreement with previous studies that have reported null effects of OT on mood (Kosfeld et al., 2005; Domes et al., 2007; Fischer-Shofty et al., 2010; Lischke et al., 2011).

OT AND EMPATHY RATINGS WHEN EXPOSED TO THE PLIGHT OF AN UNKNOWN PERSON

In study 1, the OT and placebo group provided comparable adjective ratings after hearing about an unknown person's plight. By inference the two groups reported comparable empathic reactions and personal distress when rating these adjectives. Contrary to previous findings supporting the role of OT in prosocial and affiliative behavior (Kosfeld et al., 2005; Theodoridou et al., 2009; Barraza et al., 2011), our results suggest that OT may not play a role in the experience of affective empathy. However, given that to be empathetic is a socially desirable trait and that participants spoke aloud their answers to the experimenter, we can assume that our methodology was prone to self-report biases (e.g., see Tierney and McCabe, 2001; Kämpfe et al., 2009; Gerdes et al., 2010; Taras et al., 2010). Our findings indicate that participants seemed inclined to provide high scores in these ratings: the average empathic concern rating was 5.12, thus, biased toward the highest possible score of seven. Our results show that this mean rating was significantly different to chance level 3.5 (i.e., mid-scale point), and that our female participants' self-reports of empathy deviated more strongly from this chance level than did male participants' self-reports. What is more, the rating of 5.12 appears high compared to values obtained in previous studies using similar (but not identical) designs, and in which seven was also the highest possible value [e.g., see Batson et al., 1988, studies 1 and 3 (3.81 and 3.88, respectively); Batson et al., 1989, study 2 (4.44 and 5.79)]. Consistent with sex differences observed by Batson et al. (1988, 1989), women scored higher in empathic concern than men (see also Baron-Cohen and Wheelwright, 2004; Hurlemann et al., 2010). As for personal distress ratings, the mean value here was lower than the value in a comparable study (e.g., in Batson et al., 1988, study 2). Given the overall caution with regard to self-report measures in this domain (Baron-Cohen and Wheelwright, 2004; Kämpfe et al., 2009), we suggest that empathic concern adjectives might tap onto sex stereotypes regarding emotions, i.e., women being more caring and higher in sympathy than men (Plant et al., 2000). By inference, such stereotypes may trigger stronger response biases and desirable responding than personal distress adjectives.

Importantly, our results show no effect of drug administration on personal distress or empathic concern. Therefore, our findings fail to provide evidence for an anxiolytic and prosocial effect of OT, respectively, in the context of affective responses to an individual's plight. It is worth noting that in line with previous relevant studies (Batson et al., 1988, 1989; Mikulincer et al., 2001) we only tested affective responses to a *woman's* plight. Future studies should balance out for possible sex-specific effects and include a male target, although a faster reaction toward women is generally likely (see Lewin and Herlitz, 2002; Cellerino et al., 2004; Mohr et al., 2010) in line with our finding of speeded responses to female figures in study 2.

To further understand the influence of sex on the link between OT effects on empathic abilities we tested an equal number of women and men. Studies in which individuals were provided with audio tapes narrating the plight of a needy person showed that women reported higher levels of empathy than men for the needy person (Batson et al., 1988, studies 1 and 3), and that reports of empathy for the needy person were relatively high (Batson et al., 1988, studies 1 and 3; Batson et al., 1989, study 2). Such sex differences in self-reports of empathy have often been documented, but could reflect a female tendency toward more socially appropriate responding relative to men (Eisenberg and Miller, 1987). In our study we did indeed observe that females' self-reports of empathy deviated more strongly from chance level than did males self-reports. However, no differential effect of OT was found in men's and women's self-reported empathy.

OT AND REACTION TIMES IN A COMPUTERIZED 3PP-TASK

In study 2, we found that speed of response in the drug groups interacted with figure sex and participant sex. We observed that sex differences in the placebo group were absent in the OT group. More precisely, in both drug groups, we found that people responded faster to female than male figures. In the placebo group, we additionally observed that men responded faster than women, and that this sex difference was statistically significant for male figures and a statistical trend for female figures. Given that these sex differences are absent in the OT group, we infer that OT might have sex-dimorphic effects on this measure of perspective taking ability, an inference that is in line with a recent review by MacDonald (2012). The observation that male participants in the OT group responded as slowly as female participants in the OT group could further indicate that men adopted a comparable perspective taking strategy to the one used by women. This conjecture assumes that the women in our study, irrespective of whether they have received OT or placebo, adopt a relatively more time-consuming social perspective taking strategy when completing the 3PP-task as compared to the men in the placebo group. Evidence for this suggestion comes from research indicating that women experience greater rotational costs for front-facing figures (reflected in increased reaction times and decreased accuracy) than men when performing a 3PP-task (Mohr et al., 2010). In addition, further studies on computerized perspective taking ability indicate that social strategies might be more prevalent in women and object-based spatial strategies more prevalent in men, and that women find the 3PP-task more effortful, as reflected in lower accuracy rates (Kaiser et al., 2008). The link between faster reaction times and self-reported empathy seems to be most evident for women (Mohr et al., 2010), while no role of sex is reported in two further studies (Thakkar and Park, 2010; Gardner et al., 2012). Finally, studies using a similar (but not identical) perspective taking task to ours showed that women with high affective empathy scores are slower on perspective taking (Thakkar et al., 2009; but also see Thakkar and Park, 2010).

If OT fosters social perspective taking in men, we could expect in future studies that a higher than normal OT availability may facilitate men's tendency to step into another person's shoes, a fundamental component of empathy (e.g., see Kaiser et al., 2008; Thakkar et al., 2009; Gardner et al., 2012). The present conclusion is relevant to empathy and OT researchers as it suggests that OT's beneficial effects might not be general but nuanced (Bartz et al., 2011), i.e., affecting men more strongly than women, at least in the context of social perspective taking. Alternatively, such beneficial OT effects might be evident in those who are less socially proficient, which men are thought to be (see also Bartz et al., 2010).

We suggest that the above findings on OT effects in men are not an artifact of overall or aberrant performance in our study population, because we replicated previous behavioral findings using slightly modified versions of the current 3PP-task. Firstly, reaction times were faster for back-facing than front-facing pictures (see also e.g., Arzy et al., 2007; Mohr et al., 2010, in press; Thakkar and Park, 2010; Cooper and Mohr, 2012) indicating that participants performed mental transformations. This finding is in line with previous reports regarding the mental rotation of objects (Shepard and Metzler, 1971; Wohlschläger and Wohlschläger, 1998), body parts (Cooper and Shepard, 1975; Parsons, 1987; Bonda et al., 1995; Petit et al., 2003; Seurinck et al., 2004), and perspective taking tasks (e.g., Kaiser et al., 2008; Rilea, 2008) which report longer reaction times when the position of a stimulus (or own current body position) does not match the position of the target stimulus. Moreover, mental perspective transformations for female figures were faster than those for male figures, an advantage that was specific to back-facing figures, supporting previous observations (see Mohr et al., 2010).

CONCLUSIONS AND POSSIBILITIES

Two studies examined the differential effects of OT on empathic responses, once using self-report ratings after having heard the story of an unknown person's unfortunate plight (study 1) and once using reaction times in a computerized 3PP-task (study 2). The major findings were that while OT as compared to placebo administration did not enhance self-reported empathic concern toward others (study 1), it showed that a male over female advantage in the 3PP-task that was evident in the placebo group was absent in the OT group (study 2). This finding is suggestive of a potential strategy change (purportedly more social than spatial performance strategy, see rationale in more detail above) in men after consuming OT as compared to placebo. Such a facilitation of social perspective taking might already be present in women, regardless of which of the two drugs were consumed. Thus, additional OT availability might affect men but not women in the 3PP-task. This conjecture, if supported in the future, might be relevant to sub-populations low in appropriate social abilities, such as individuals with alexithymia, social anxiety disorder, and schizophrenia (Caldwell et al., 2009; Guastella et al., 2009b; Bartz et al., 2010; Feifel et al., 2010; Rubin et al., 2010; Luminet et al., 2011; Pedersen et al., 2011; Hall et al., 2012) as it has already been shown in autism spectrum disorders (Andari et al., 2010; Guastella et al., 2010).

Given the conjectural nature of our conclusions, future studies should verify the strategy participants employ in the 3PP-task, e.g., examine whether women are slower because they use a social perspective strategy while men (at least without pharmacologically enhanced OT availabilities) use a spatial perspective taking strategy (Gardner et al., 2012; but also see Gronholm et al., 2012). Indeed, one could also reason that OT administration hindered a spatial strategy that might have been favored by men, without having to necessarily facilitate a social strategy. While this possibility cannot be excluded, we consider our initial explanation to be more likely because men and women seemingly used different strategies in perspective taking including mental rotation (e.g., Weiss et al., 2003; Kaiser et al., 2008), and women with higher self-reported empathy were found to slow down in perspective taking, presumably because they are using a social strategy that is also more time-consuming (Thakkar et al., 2009). However, it should be noted here that other studies have shown better perspective taking to be linked to faster reaction times (e.g., Mohr et al., 2010; Thakkar and Park, 2010). Given that the above studies assessed empathy via self-report and that such approaches are problematic, we propose that future studies would benefit from using more objective measures of empathy (e.g., actual behavioral observations and/or facial mimicry) to examine whether higher empathy is associated with slower or faster reaction times.

Another potential explanation of the above finding is that OT administration generally slows men down. It should be noted that whilst OT administration has been shown to slow men down in contexts other than spatial processing, such as during approach-avoidance motor responses to emotional faces (Theodoridou et al., 2013) and identification of fearful faces (Di Simplicio et al., 2009), it has not been found to have a slowing effect on approach-avoidance motor responses to non-social stimuli (Theodoridou et al., 2013), early processing (i.e., detection speed) of angry, and happy faces (Guastella et al., 2009a) and recognition of emotional faces (Fischer-Shofty et al., 2010). Therefore, it seems unlikely that OT administration generally slows men's speed of response.

Importantly, the sex differences and the interaction with drug group were observed in a task that was introduced as a task that assesses empathy. Future research could introduce the task as one that assesses mental rotation (see also Massa et al., 2005 for instruction effects), to test whether drug effects are influenced by such context effects. This would provide us with some further insight regarding task expectancies, and their interaction with drug treatment. In any case, we suggest that the 3PP-task was powerful at showing drug by sex interactions because such reaction time measures are difficult to manipulate/see through relative to a self-report task, thereby rendering our participants less able to guess our specific experimental hypotheses. This advantage might also explain why no drug effect or drug by sex interaction was observed in study 1, in which participants are actively asked to rate their feelings toward an unfortunate person in the presence of the experimenter. We suggest that response biases such as social desirability and stereotyping come strongly into play when using such paradigms, resulting in artificially elevated scores and commonly observed sex differences (women having higher scores than men) when using self-report measures (see for example Massa et al., 2005; Wraga et al., 2007). Furthermore, this is unlikely to be the case when using implicit measures such as the current perspective taking task (Mohr et al., 2010, in press; Thakkar and Park, 2010; Gardner et al., 2012). Thus, our findings indicate that more implicit measures such as the current 3PP-task might be better suited to assessing empathy, and that any effects of empathy-related processes whether cognitive or neurochemical (such as OT in the present case) might emerge more consistently when using measures that are less response bias prone.

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A transcranial magnetic stimulation study of the effect of visual orientation on the putative human mirror neuron system

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Mirror neurons are a class of motor neuron that are active during both the performance and observation of behavior, and have been implicated in interpersonal understanding. There is evidence to suggest that the mirror response is modulated by the perspective from which an action is presented (e.g., egocentric or allocentric). Most human research, however, has only examined this when presenting intransitive actions. Twenty-three healthy adult participants completed a transcranial magnetic stimulation experiment that assessed corticospinal excitability whilst viewing transitive hand gestures from both egocentric (i.e., self) and allocentric (i.e., other) viewpoints. Although action observation was associated with increases in corticospinal excitability (reflecting putative human mirror neuron activity), there was no effect of visual perspective. These findings are discussed in the context of contemporary theories of mirror neuron ontogeny, including models concerning associative learning and evolutionary adaptation.

Keywords: mirror neurons, transcranial magnetic stimulation, electromyography, associative learning, action observation, visual perspective

INTRODUCTION

Mirror neurons are a class of motor neuron that are active during both the performance and observation of behavior. Fortuitously discovered in macaque monkeys (di Pellegrino et al., 1992), an analogous "mirror neuron system" (MNS) has since been established in humans (Rizzolatti and Fabbri-Destro, 2010). From a theoretical perspective, it has been widely suggested that the MNS facilitates action understanding and other aspects of social cognition. This has been labeled the "adaptation model" of the MNS, as it suggests that mirror neurons have been selected for throughout evolution because they confer a survival and reproductive advantage (e.g., recognition of negative emotions including fear and disgust, development of interpersonal relations, child rearing, formation of complex social systems) (Gallese and Goldman, 1998; Rizzolatti et al., 2001; Meltzoff and Decety, 2003; Rizzolatti and Craighero, 2004; Bertenthal and Longo, 2007; Lepage and Theoret, 2007; Heyes, 2010). Indeed, there is evidence to suggest a link between social cognition and MNS activity among healthy individuals (Enticott et al., 2008b; Pfeifer et al., 2008; Lepage et al., 2010), while mirror neuron activity is often reduced among disorders involving impaired social cognition (e.g., autism, schizophrenia; Oberman et al., 2005; Dapretto et al., 2006; Enticott et al., 2008a,b).

Given a proposed link to interpersonal understanding, there has been some interest in the degree to which a mirror neuron response is modulated by the perspective from which an action is presented (e.g., self/egocentric vs. other/allocentric perspective). For instance, a number of transcranial magnetic stimulation (TMS) studies have investigated effects of manipulating visual orientation during the observation of hand movements. Maeda et al. (2002) showed, using intransitive movement stimuli, that simple finger and thumb movements from an egocentric perspective elicited far greater putative mirror neuron activity than movement from an allocentric perspective. Using TMS to investigate visual orientation, Alaerts et al. (2009) found that viewing right-handed intransitive actions induced a greater mirror response from an egocentric perspective, but viewing left-handed intransitive actions induced a greater mirror response from an allocentric perspective. By contrast, however, Theoret et al. (2005) did not find an effect of visual orientation (egocentric vs. allocentric) during intransitive hand action observation among their healthy control participants. Although using techniques that are generally unable to be employed in humans, Caggiano et al. (2011) found that the majority of mirror neurons in macaque F5 were "view-dependent," responding to one of three different viewpoints.

The present study used TMS and electromyography (EMG) to investigate corticospinal excitability (CSE) whilst observing hand actions (putatively reflecting mirror neuron activity) from egocentric and allocentric perspectives. Importantly, and in contrast to previous studies, this study employed transitive action stimuli, which we have previously demonstrated is more reliably associated with a putative mirror response (Enticott et al., 2010).

MATERIALS AND METHODS

PARTICIPANTS

Participant demographic data is presented in **Table 1**. Twenty-three participants with no self-reported history of psychiatric or neurological illness were recruited by advertisement at Monash University and The Alfred (a teaching hospital in Melbourne,

Table 1 | Participant demographics.

n	23
Gender (M:F)	13:10
Age (Years)	23.09 (3.75)
Age range (Years)	18–31
Formal education (Years)	15.91 (1.41)
Handedness (L:R)[a]	4–19

[a] *Assessed using the Edinburgh Handeness Inventory (Oldfield, 1971).*

Australia). Prior to the experiment, participants were screened to ensure they met TMS safety standards (Wassermann, 1998). Participants were compensated $25 for their time and travels. The study was approved by the Alfred Hospital Ethics Committee and the Monash University Human Research Ethics Committee. Participants provided written informed consent prior to participation in the study.

MATERIALS

Short video clips depicting either a static hand or a hand grasping a mug were used to measure putative MNS activity. We elected to use only a static hand control as our previous research has indicated that additional control stimuli (e.g., static hand with object, pantomimed grasp) do not significantly modulate CSE (Enticott et al., 2010). Stimuli were presented from both egocentric (i.e., self) and allocentric (i.e., other) perspectives.

Screen shots of the videos are displayed in **Figure 1**. Participants were shown two blocks of videos each consisting of 40 video clips (80 in total, 20 of each condition: static egocentric, active egocentric, static allocentric, active allocentric). Each block of videos ran for 5 m 05 s, and there was a short break (2–3 m) between blocks. All clips were 4 s in length, appearing in a quasi- randomized sequence with a 2 s gap (black screen) between each.

PROCEDURE

Using a 70 mm figure-of-eight coil, single pulse TMS was administered to the scalp at the left primary motor cortex (M1; scalp location resulting in largest motor-evoked potential from the right first dorsal interosseous, FDI). Resting motor threshold (RMT) was defined as the minimum stimulation intensity that evoked a peak-to-peak MEP of >50 μV in at least three out of five consecutive trials.

MEP data were recorded from right FDI via EMG using self-adhesive electrodes. This signal was amplified by the PowerLab/4SP (AD instruments, Colorado Springs, CO, USA) and sampled via a CED Micro 1401 mk II analog-to-digital converting unit (Cambridge Electronic Design, Cambridge, UK). Participants viewed the video presentations seated 120 cm away from a 56 cm widescreen LCD monitor positioned at eyelevel in a comfortable reclining chair.

Participants were administered a TMS pulse (120% RMT) during each video clip and their MEP was recorded. A light sensor placed on the top right-hand corner of the LCD monitor was used to control the timing of the TMS pulse. In order to activate the light sensor, a 4 cm × 4 cm white-square was embedded within the clips [i.e., in the top right hand corner of the screen for a period of 1 frame (40 ms)] at two time intervals (i.e., "early" at the 2 s mark and "late" at the 3 s mark). Two time-points were used to minimize anticipation of the TMS pulse. This was also in accord with previous research illustrating that MEP amplitude corresponds significantly to finger aperture of grasping actions (Gangitano et al., 2001, 2004), and that MEP is greatest 60–90 ms after the onset of a finger movement (Lepage et al., 2010). The embedded white square time-locked the TMS pulse to each video clip through a 5 V TTL pulse delivered via a BNC connector. A second trigger was sent from the TMS stimulator upon activation of the pulse to the EMG device to initiate MEP recording.

DATA ANALYSIS

Participants' median CSE values were then indexed to provide a ratio of change between the "grasp" versus "static" conditions (i.e., median CSE amplitude for "grasp" conditions/median CSE amplitude for "static" conditions × 100; be they "early" or "late" respectively) This is referred to as the MEP-Ratio. This is a common approach whereby an MEP-Ratio above 100% reflects putative mirror neuron activity (Enticott et al., 2012a). The use of median (rather than mean) valuesis also consistent with our previous research (e.g., Enticott et al., 2010, 2012a,b), and is intended to minimize the influence of transient increases in CSE than can

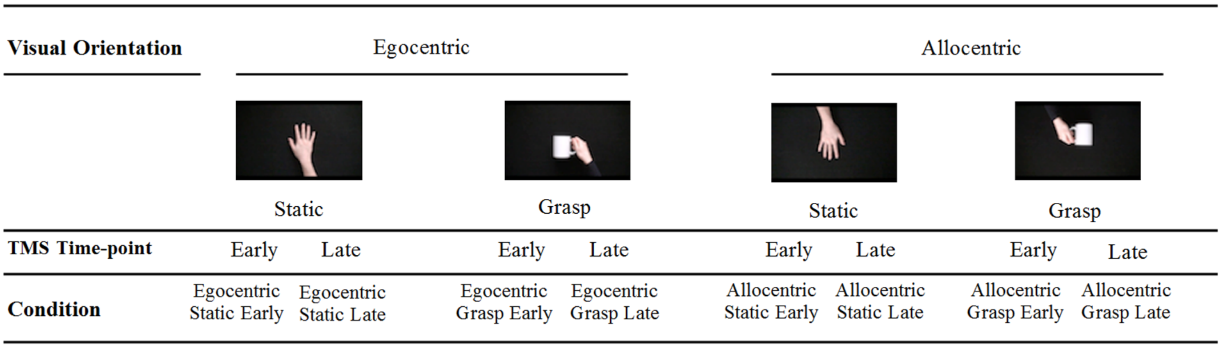

FIGURE 1 | Stimuli presented during TMS administration.

occur during the early stages of a TMS experiment (Schmidt et al., 2009).

The distributions of MEP-Ratio datawere examined for extreme outliers (±3 standard deviations from the mean) in each condition. One participant was omitted due to consistently outlying data. Based on recommendations within the statistical literature (e.g., Tabachnick and Fidell, 1996), the remaining extreme outliers were reduced to one value above the next highest data point to minimize their influence. There were two extreme outliers in the Egocentric-Early condition, one in the Allocentric-Early condition and three in the Allocentric-Late condition. Finally, to satisfy the assumption of normality, the square root of the MEP-Ratio was derived and used for analysis.

We conducted a 2 (timepoint: early vs. late) × 2 (viewpoint: egocentric vs. allocentric) repeated-measures ANOVA to compare the MEP-Ratio across the four action observation conditions (i.e., egocentric-early, egocentric-late, allocentric-early and allocentric-late). For all analyses, sphericity was violated and a Greenhouse-Geisser correction was used.

RESULTS

MEP-Ratio results are presented in **Figure 2**, and raw MEP amplitudes (although not subject to inferential analyses) are presented in **Figure 3**. A one-sample t-test for action observation conditions combined revealed a significant increase above 100% ($M = 105.98$, $SD = 13.60$), $t(22) = 2.11$, $p = 0.047$, suggesting that, consistent with previous research, action observation produced the expected increase in CSE above static hand observation. There was no significant interaction between viewpoint and time-point, $F(1{,}22) = 2.43$, $p = 0.133$, $\eta_p^2 = 0.10$. Similarly, there was no difference in CSE between the egocentric and allocentric viewpoints, $F(1{,}22) = 0.73$, $p = 0.403$, $\eta_p^2 = 0.03$, nor was there a difference between the early and late TMS pulse time-points, $F(1{,}22) = 2.61$, $p = 0.120$, $\eta_p^2 = 0.11$.

While there was an overall MEP-Ratio increase above 100%, this was not uniformly found across the four individual conditions (egocentric-early: $t[22] = 2.26$, $p = 0.034$; egocentric-late: $t[22] = 0.06$, $p = 0.950$; allocentric-early: $t[22] = 0.78$, $p = 0.442$; allocentric-late: $t[22] = 1.16$, $p = 0.260$). Accordingly, it might be argued that this fails to provide sufficient evidence of a mirror response to the stimuli across all conditions. In an attempt to address this concern, we conducted a subsequent analysis involving only those 15 participants who displayed, overall, a facilitation effect (i.e., mean MEP-Ratio > 100%). The range of mean overall MEP-Ratios for this subgroup was 103–138% (compared with 85–99% for those excluded from this analysis), while 14 of the 15 participants in the subgroup also displayed a MEP-Ratio of >110% in at least one of the two viewpoint conditions. This was justified on the theoretical basis of the paradigm (i.e., a score >100% indicating a mirror neuron response), and was intended to determine whether a sample that show consistent facilitation effects would reveal the same pattern of results as the broader sample.

Based on our findings, which revealed no effect of timepoint for either the full sample or subgroup (see below), the two time points were averaged for each condition. One-sample t-tests indicated that these participants displayed a significant increase in MEP-Ratio for egocentric ($M = 111.60\%$, $SD = 14.14$), $t(14) = 3.18$, $p = 0.007$, and a near significant increase for allocentric ($M = 113.71\%$, $SD = 25.19$), $t(14) = 2.11$, $p = 0.053$.

A subsequent 2 (timepoint: early vs. late) × 2 (viewpoint: egocentric vs. allocentric) repeated-measures ANOVA with this subgroup revealed no effect of viewpoint, $F(1{,}14) = 0.01$, $p = 0.928$, $\eta_p^2 = 0.001$, or timepoint, $F(1{,}14) = 0.26$, $p = 0.617$, $\eta_p^2 = 0.02$, and no interaction effect, $F(1{,}14) = 0.25$, $p = 0.619$, $\eta_p^2 = 0.02$.

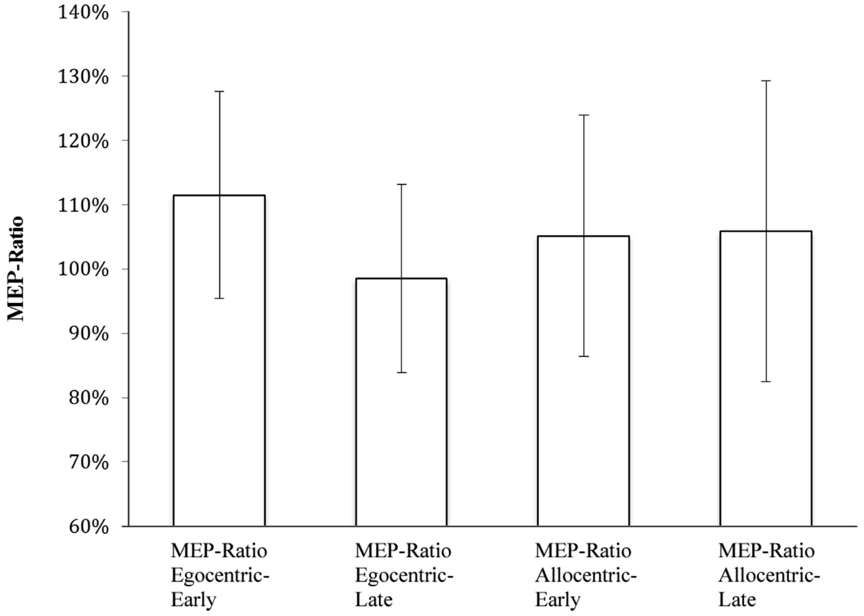

FIGURE 2 | MEP-Ratios for video presentation conditions.

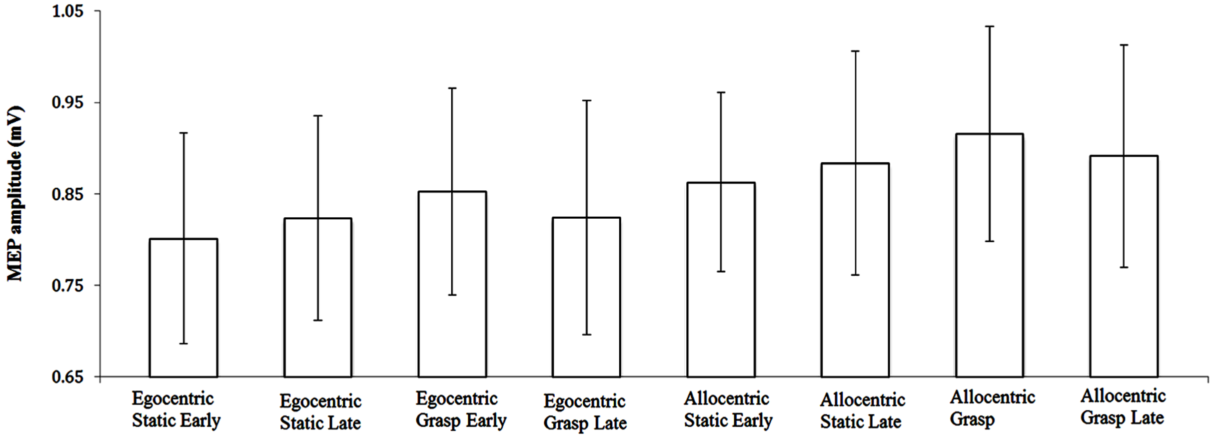

FIGURE 3 | Raw MEP amplitude (±SE) for video presentation conditions.

DISCUSSION

The current study was designed to examine whether there were differences in the putative mirror neuron response when viewing the same action from different visual perspectives. There did not appear to be an effect of visual orientation on MEP-Ratio, our measure of putative mirror neuron activity. Although a failure to demonstrate consistent facilitation effects means that we must be careful in interpreting these data, these findings are inconsistent with some previous studies assessing the effect of visual orientation on a TMS-induced mirror neuron response (e.g., Maeda et al., 2002; Alaerts et al., 2009). There are, however, a number of differences between these studies and ours, including the use of transitive stimuli in the current study (which we have demonstrated is more reliably associated with corticospinal facilitation; Enticott et al., 2010). It may transpire, for example, that different mechanisms underlie the mirror response to transitive and intransitive movements (for example, different populations of mirror neurons that result in differences in motor CSE), similar to what was found among macaques by Caggiano et al. (2011). It should be noted, however, that Kraskov et al. (2009) showed, among macaques, that 73% of mirror neurons that responded to a transitive action also responded to an equivalent intransitive action. Alternatively, motor CSE during transitive movements may result from a combination of mirror neuron (responsive to biological motion) and canonical neuron (responsive to motion but also objects) activation, again raising the possibility of a different pattern of motor CSE.

From a theoretical perspective, mirror neurons are often seen from an evolutionary perspective, where a genetic component is necessarily assumed, and often a relatively minimal role is attributed to sensorimotor experience. By contrast, a more recent model suggests that mirror neurons are not of evolutionary importance, but rather a product of associative learning that takes place during sensorimotor processing (e.g., visual and motor activity, such as during the observation of one's own hand movement; Cook et al., 2010; Cooper et al., 2013). The strongest evidence for such a model demonstrates that relatively limited sensorimotor training can significantly modulate putative human mirror neuron activity (Haslinger et al., 2005; Catmur et al., 2007; Capa et al., 2011; Wiggett et al., 2011). Proponents of this "association model" suggest that mirror neurons have not evolved to facilitate action understanding (Heyes, 2010; Cook et al., in press).

The association models might predict that mirror neuron activity should be enhanced for those associations that are more strongly established (Heyes, 2010). Similarly, the more an action stimulus represents a strongly held association, the greater the mirror neuron response. One example of association that would produce mirror neurons involves hand-eye coordination. Typically, hand actions involving affordances (e.g., grasping a mug) are visually monitored by the individual performing the action. This ensures simultaneous activation of both visual and motor neurons, which allows the formation of an association where, eventually, activation of visual neurons is sufficient to produce activation of some motor neurons (i.e., mirror neurons; Casile et al., 2011). For instance, hand-eye coordination is clearly embedded within an egocentric (i.e., self) viewpoint. Thus, under the association model, it could be conceived that actions viewed from an egocentric perspective should elicit a more pronounced mirror response, as this perspective is more common for synchronous visual-motor activity and therefore has stronger associations.

Although these data seem thereforeinconsistent with this aspect of the association model, it is not clear whether they are necessarily consistent with the adaptation model. As noted, an adaptation account maintains that the MNS has evolved to serve the needs of action understanding and related social cognitive abilities. Thus, it might be argued that any system designed to facilitate this behavioral understanding should process visual stimuli comparably across all orientations, as the essential meaning to be derived is the same. In this respect these results might be seen as compatible with no preference for specific perspectives, as is clearly the case here. Alternatively, it might be argued that the adaptation model should favor the allocentric perspective in order to understand others' behavior, which is inconsistent with the current findings. Reconciliation of the adaptation model with previous research illustrating training effects (Haslinger et al., 2005; Catmur et al., 2007; Capa et al., 2011; Wiggett et al., 2011) is similarly difficult.

There is, however, an alternative interpretation within the associative learning model that could account for the current findings. Proponent of this theory, which is based on the associative learning literature (including the Rescorla-Wagner model of conditioning, which concerns the strength of prediction for one cell firing together with another; Cooper et al., 2013), might suggest that there are ceiling effects to the formation of visuomotor associations when events are no longer novel or surprising. By adulthood, there may have been sufficient experience to allow visuomotor associations across the various visual perspectives. While this will require further research and theoretical development, under this model it is conceivable that we should see equivalent mirror neuron activation across differing perspectives.

There are several limitations to this research. Perhaps most importantly, there was a great deal of variability across our data, and not all of the individual conditions displayed a significant facilitation effect. Although the results held when investigating a subset of participants who displayed facilitation, it remains that we must interpret these data cautiously. These data ultimately do not allow us to draw firm conclusions about the influence of visual perspective at this point. Another limitation concerns the ecological validity of the video presentations. In order to maintain experimental control, grasping actions needed to remain consistent throughout the video clips. Due to technical constraints, the most tenable solution was to film the stimuli from above, appearing egocentrically orientated. This camera setup allowed for an allocentric orientation to be created by flipping and rotating the original clips. While all effort was made to maintain proper ecological validity (including preventing the mug from appearing upside down), it is conceivable that some participants may have had concerns with the realism of stimuli from the allocentric orientation, particularly with the perceived orientation of the mug. Nevertheless, our approach was consistent with other studies of mirror neurons and visual perspective (Maeda et al., 2002; Theoret et al., 2005; Alaerts et al., 2009). From a theoretical perspective, the association model would predict an increased mirror response with a stimulus that more closely approximates stored associations; accordingly, even if not a true allocentric representation, the stimuli used in the current study provide such an approximation. We will, however, attempt a more ecologically valid methodology in any subsequent research (e.g., simultaneous filming of a single action from different perspectives).

In summary, when examining the effect of egocentric and allocentric orientated goal-directed visual stimuli, measures of MEP-Ratio (i.e., putatively reflecting mirror neuron activity) did not appear to differ across perspectives. It is unclear, however, whether or not these findings are consistent with current models of mirror neuron ontogeny, and this area will require further theoretical and empirical investigation.

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Mechanisms of self-other representations and vicarious experiences of touch in mirror-touch synesthesia

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In recent years several studies have documented a near-universal tendency to vicariously represent the actions and sensations of others (e.g., see Keysers and Gazzola, 2009 for review). For example, observing another person experiencing pain activates neural regions involved in experiencing pain (e.g., Singer et al., 2004; Avenanti et al., 2005) or observing somebody being touched recruits regions of the somatosensory cortex involved in experiencing touch (e.g., Keysers et al., 2004, 2010; Ebisch et al., 2008; Schaefer et al., 2012). For most of us, these vicarious representations are implicit and do not lead to overt sensations of the observed events (e.g., we do not feel pain when observing pain to others). There are, however, a small number of individuals who do experience overt somatic sensations when observing others' tactile experiences (Ward et al., 2008; Osborn and Derbyshire, 2010; Fitzgibbon et al., 2012; Banissy, 2013). For example, in mirror-touch synesthesia observing touch or pain to others evokes a conscious tactile sensation on the synesthetes' own body (Banissy and Ward, 2007; Holle et al., 2011). This opinion piece seeks to discuss potential neural mechanisms that contribute to the developmental form of mirror-touch synesthesia (for descriptions of acquired forms of mirror-touch/pain synesthesia see Fitzgibbon et al., 2012; Goller et al., 2013), and the important role that self-other representations may have on vicarious experiences of touch in mirror-touch synesthesia.

Approximately 1.6% of individuals experience developmental mirror-touch synesthesia and there are at least two spatial subtypes (Banissy et al., 2009; also see White and Aimola Davies, 2012). In the more common subtype, the synesthetic experience is evoked as though looking in a mirror (i.e., observing touch to the left side of the face evokes tactile sensations on the right side of the synesthete's face). In the less common, anatomical subtype, the synesthetic experience is mapped anatomically (i.e., observing touch the left side of the face evokes tactile sensations on the left side of the synesthete's face)[1]. For each subtype, their experiences are reported to be automatic, enduring, and present since childhood (Banissy and Ward, 2007; Holle et al., 2011).

While several studies have examined cognitive and perceptual characteristics of mirror-touch synesthesia (e.g., Banissy and Ward, 2007; Banissy et al., 2009, 2011; Holle et al., 2011; White and Aimola Davies, 2012; Aimola-Davies and White, 2013), there has been relatively less research that delineates the neural mechanisms that contribute to developmental mirror-touch. One common suggestion is that developmental mirror-touch synesthesia may be a function of atypical cortical excitability within neural regions supporting normal somatosensory mirroring. That is, brain regions that are generally recruited when observing touch to others are over excitable in mirror-touch synesthesia leading to observed touch evoking overt tactile sensations. For example, Blakemore and colleagues (2005) reported the first case of developmental mirror-touch synesthesia in a functional neuroimaging study where they compared neural activity in a single mirror-touch synesthete ("C") to a group of control participants. Using fMRI Blakemore and colleagues investigated the neural systems underlying C's synesthetic experience by contrasting brain activity when watching videos of humans relative to objects being touched (the latter did not evoke synesthesia) in "C" and in 12 non-synesthetic control subjects. In controls, a network of regions was recruited during the observation of touch to a human relative to an object (including primary and secondary somatosensory cortex, premotor regions, and the superior temporal sulcus). Similar brain regions were also activated during actual touch, indicating that observing touch to another person activates a similar neural circuit as actual tactile experience—the mirror-touch system. "C" recruited a similar network of regions, but showed hyperactivity in many of these regions (including the primary and secondary somatosensory cortices). This hyper-activity was interpreted as the neural correlate of C's synesthesia, with the suggestion that C's overt experiences of touch when observing touch to others may be a function of hyper-excitability of normal somatosensory mirroring mechanisms (Blakemore et al., 2005).

While hyper-excitability of somatosensory mirroring mechanisms may be a correlate of mirror-touch synesthesia, precisely what contributes to mirror-touch synesthetes showing increased cortical excitability within the mirror-touch system when observing touch to others is

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[1] These two spatial frames of reference are consistent with neurophysiological findings in primates documenting anatomical and mirrored spatial frames of reference that mediate bimodal visual-tactile cells in the macaque parietal cortex. These cells respond when the monkey is touched and when the monkey observes touch to the same body part of someone else (Ishida et al., 2009).

somewhat elusive. It is not the case that the somatosensory system is hyper-excited in some global (i.e., context-free) sense. For instance, in a recent group fMRI study (Holle et al., under revision) there was evidence of hypo-excitability (in mirror-touch synesthetes relative to the control group) within somatosensory regions when observing touch to dummy faces. The latter stimuli do not tend to elicit synesthetic touch. As such the activity within the somatosensory network seems to be differently modulated (or gated) in synesthetes relative to controls.

In controls, behavioral evidence from an interference paradigm involving real touch (to one's own face) and the sight of touch (to an observed face) shows that visuo-tactile interference is greatest when self-other similarity is greater; for instance, in terms of visual appearance or even political opinions (e.g., Serino et al., 2008, 2009). One plausible suggestion is that faulty self-other monitoring mechanisms may lead to a disinhibition of normal somatosensory mirror mechanisms in individuals with mirror-touch synesthesia (Banissy et al., 2009; Fitzgibbon et al., 2012). In line with this, recent findings indicate that observing touch to others not only evokes overt tactile sensations in mirror-touch synesthetes, but also elicits changes in mental representations of the self (Maister et al., 2013). In that study the "enfacement illusion" was used to examine self-representations in developmental mirror-touch synesthesia. In the typical enfacement illusion participants are shown a series of images of morphed faces containing varying proportions of the participants face or an unfamiliar other, and are asked to indicate the extent to which the face looks like the self. They then view a video in which another person is being touched that is in synchrony and congruent with felt touch that is delivered to the participants face. This synchronous mapping between observed and felt touch leads participants to report an increase in perceived similarity between the other and themselves. That is to say that after experiencing synchrony between observed and felt touch, the images that participants had initially perceived as containing equal quantities of self and other became more likely to be recognized as the self (i.e., they show a self-other blurring where they begin to incorporate more of the other into representations of themselves—Tsakiris, 2008; Tajadura-Jimenez et al., 2012). For mirror-touch synesthetes, this self-other blurring was shown to occur in the absence of felt touch being applied to their own face, implying that simply viewing touch to others evokes a change in self-representations in mirror-touch synesthesia (Maister et al., 2013).

Potential candidate neural regions that may mediate a relationship between self-other processing and neural activity in the mirror-touch system include the inferior parietal lobule, temproparietal junction (TPJ), and anterior insula (see Northoff et al., 2011 for review of brain areas involved in representing and distinguish self from other). In the context of mirror-touch synesthesia, regions of particular note are the anterior insula and TPJ. In the functional neuroimaging study by Blakemore et al. (2005) the only brain region that was shown to distinguish between synesthete "C' and the control group was neural activity in the anterior insula. The anterior insula has been linked to self-other processing in several domains, including self-face recognition (e.g., Devue et al., 2007), body ownership (e.g., Tsakiris et al., 2007), and perspective taking (e.g., Ruby and Decety, 2001). It is also known to have structural connections with neural regions involved in the mirror-touch system, including the secondary somatosensory cortex (Mesulam and Mufson, 1985): in this context it is notable that although our recent neuroimaging study of a group of mirror-touch synesthetes did not observe functional differences in the anterior insula (Holle et al., under revision), we did see cortical excitability differences localized to the secondary somatosensory cortex, which may be mediated by functional connectivity with the anterior insula.

A further candidate that may contribute to atypical self-other processing in mirror-touch synesthesia is the TPJ. The TPJ is also commonly linked to self-other representations, including agency discrimination (e.g., Farrer and Frith, 2002), perspective taking (e.g., Aichhorn et al., 2006), empathy (e.g., Völlm et al., 2006), and the online control of representations between self and other (e.g., Santiesteban et al., 2012). Recent findings indicate that mirror-touch synesthetes show structural brain differences relative to controls within the right TPJ (namely, reduced gray matter volume; Holle et al., under revision), suggesting broader cortical difference in mirror-touch synesthesia beyond regions involved in vicarious somatosensory mirroring. This area may therefore also contribute to atypical self-other processing in mirror-touch synesthesia (e.g., Aimola-Davies and White, 2013; Maister et al., 2013), which in turn may modulate somatosensory mirroring in mirror-touch synesthesia.

In a broader context, it is also interesting to consider the extent to which differences in cortical mechanisms related to self-other processing may contribute to broader traits observed in developmental mirror-touch synesthesia. For example, we have previously reported that developmental mirror-touch synesthetes show heightened levels of emotional empathy relative to controls (Banissy and Ward, 2007), and it is fairly clear to see how a blurring between the self and other may be useful in facilitating this capacity. However, one may also ask whether there may be circumstances where atypical self-other monitoring may lead to less beneficial consequences. One prediction may be that developmental mirror-touch synesthetes will show reductions in capacities that are dependent on their ability to engage online control of the representations of the self or other (e.g., agency discrimination). This remains to be determined with future studies. What is clearer, however, is that it would seem unlikely that alterations in self-other processing would lead solely to mirror-touch synesthesia; rather one would expect that mirror-touch synesthesia may be one of a constellation of traits associated with atypical mechanisms of self-other representation.

In sum, individuals with mirror-touch synesthesia experience tactile sensations on their own body when simply observing touch to others. While the majority of explanations related to this condition have focused around hyper-active somatosensory mirroring, relatively less has focused on the important role that self-other processing may play in modulating somatosensory mirroring mechanisms. Despite this, there is growing evidence to suggest atypical self-other representations in mirror-touch synesthesia and further work is needed to determine the relationship between neural regions involved in self-other processing and the mirror-touch system, in both mirror-touch synesthesia and typical adults.

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Feeling the pain of others is associated with self-other confusion and prior pain experience

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Some chronic pain patients and healthy individuals experience pain when observing injury or others in pain. To further understand shared pain, we investigated perspective taking, bodily ownership and tooth pain sensitivity. First, participants who reported shared pain (responders) and those who did not (non-responders) viewed an avatar on a screen. Intermittently, 0–3 circles appeared. Sometimes the participant's and avatar's perspective were consistent, both directly viewed the same circles, and sometimes inconsistent, both directly viewed different circles. Responders were faster than non-responders to identify the number of circles when adopting a consistent perspective. Second, participants sat with their left hand hidden while viewing a rubber hand. All participants reported an illusory sensation of feeling stroking in the rubber hand and a sense of ownership of the rubber hand during synchronous stroking of the rubber and hidden hand. The responders also reported feeling the stroking and a sense of ownership of the rubber hand during asynchronous stroking. For experiment three, participants with either low, moderate, or high tooth sensitivity observed a series of images depicting someone eating an ice-popsicle. Low sensitivity participants never reported pain. In contrast, moderate and high sensitivity participants reported pain in response to an image depicting someone eating an ice popsicle (4 and 19% of the time, respectively) and depicting someone eating an ice-popsicle and expressing pain (23 and 40%, respectively). In summary, responders have reduced ability to distinguish their own and others' visual perspective and enhanced ability to integrate a foreign arm into their bodily representation. The tendency to share pain is also enhanced when an observed pain is commonly experienced by the observer. Shared pain may therefore involve reactivation of pain memories or pain schema that are readily integrated into a self perspective and bodily representation.

Keywords: pain, empathy, illusion, vicarious, sensitivity

INTRODUCTION

A significant number of patients with phantom limb pain report pain in response to the observation of injuries or other thoughts and images associated with pain (Giummarra and Bradshaw, 2008; Fitzgibbon et al., 2009, 2010; Giummarra and Moseley, 2011) and some patients report feeling touch when observing others being touched (Goller et al., 2013). Normal control populations also report feeling pain when observing images or videos of others' injuries (Osborn and Derbyshire, 2010) and some normal subjects also report feeling touch sensations when observing another person being touched (Banissy et al., 2009). Thus, there is evident capacity for shared sensory experience, including physically painful experience, that extends beyond a shared emotional empathic response (Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005, 2006) or a metaphorical shared pain experience (Eisenberger et al., 2003; MacDonald and Leary, 2005). The mechanisms behind such shared physical experiences remain uncertain and here we investigate the influence of visual perspective taking, bodily ownership, and prior pain experience.

Visual perspective taking refers to the ability to predict what another person sees (Michelon and Zacks, 2006). Increased ability to process information in the first person perspective relative to the third person perspective suggests that visual perspective may play a crucial role in the representations of self and the representations of other (Jeannerod and Anquetil, 2008). Successful social interaction requires inferring the visual and mental perspectives of others. The ability to infer what another person can see implies disengaging from the self visual perspective and adopting the visual perspective of another (Samson et al., 2010). Self perspective is considered as a default egocentric bias that is corrected or inhibited when trying to understand others (Keysar and Henly, 2002). Studies have shown that some participants can suppress self perspective more quickly, suggesting that some individuals more readily adopt the perspective of others (Epley et al., 2004; Samson et al., 2005). Here it is hypothesized that individuals who report feeling pain in response to seeing others' injuries, known as pain responders, will have fewer processing constraints from a first to third person perspective and thus will map across visual perspectives more quickly and easily relative to non-pain responders who never report feeling pain in response to seeing others' injuries.

A way of exploring bodily ownership is to utilize the rubber hand illusion (Botvinick and Cohen, 1998). The rubber hand illusion is induced when a participant sits with their hand and arm hidden by a partition while viewing a rubber hand and arm in an anatomically appropriate position such that their hand and arm could be in the position of the rubber hand and arm. The experimenter then synchronously strokes both the hidden hand and the rubber hand. Within a few minutes, most subjects report that the stroking sensation no longer feels as if it is coming from their hidden real hand but is actually emanating from the observed rubber hand. This illusory sensation and feeling of ownership over the rubber hand is thought to come about through multisensory integration of visual, tactile, and proprioceptive information (Haggard and Tsakiris, 2005). After establishing the illusion, "injuring" the rubber hand by bending back a finger causes an elevated skin-conductance response (Armel and Ramachandran, 2003), although skin-conductance is a general measure of arousal and so may not be linked to a feeling of threat or pain. Threatening the rubber hand with a knife, however, activates regions of the brain associated with anticipated pain (Ehrsson et al., 2007). A noxious stimulus can also result in pain mislocated into the rubber hand (Capelari et al., 2009; Mohan et al., 2012). Pain evoked by someone else's injury seems to involve a misattribution of threat from the location of the observed injury to the same location on the observer (Osborn and Derbyshire, 2010). Thus, it is hypothesized that pain responders will have stronger illusory sensation and feeling of ownership over the rubber hand during the rubber arm illusion compared with non-responders.

The role of prior pain experience when sharing pain through observation has been explored in several reports on phantom limb pain (Fitzgibbon et al., 2009, 2010). Phantom limb patients have reported experiencing heightened phantom pain when observing, thinking about, or inferring the pain of another. At least sometimes the pain is linked to the patient's particular history. For example, one patient experienced pain in his lower limb stumps when observing someone walking barefoot (Fitzgibbon et al., 2009). Following a particularly distressing and painful emergency caesarean section, another patient reported shooting pains from the groin that radiated down the legs when hearing about others' trauma (Giummarra and Bradshaw, 2008). These case studies imply that shared pain experience might reactivate prior or ongoing pain sensations. Here it is hypothesized that participants with high tooth sensitivity will be more likely to report a shared pain experience when viewing someone expressing pain while consuming an ice popsicle than participants without tooth sensitivity. Tooth sensitivity is a common dental problem characterized by short, sharp pain from the teeth in response to a variety of stimuli often including cold stimuli (Addy, 1992). Thus, tooth sensitive participants were considered a convenient population to test the possibility that shared pain experience can involve reactivation of previous pain.

The three studies described here will provide insight into mechanisms of shared pain experience. Specifically, it is possible, but yet to be demonstrated, that shared pain involves readily taking the perspective of another person, which may be indexed by more rapid orientation to the visual perspective of others (experiment one); readily mapping the location of injury of another to the self, which may be indexed by stronger sense of mislocating sensation into a rubber arm (experiment two); and readily integrating the observed pain of another into a personal historical schema, which may be indexed by activation of tooth pain in those with and without tooth sensitivity (experiment three).

MATERIALS AND METHODS

EXPERIMENT ONE

Twenty six self selecting participants (3 males; mean age = 19; range = 18–21) provided informed consent and took part in experiment one for course credit. All participants were examined in a single session by a female experimenter. Participants observed a series of images or videos depicting injury and rated any pain responses (Osborn and Derbyshire, 2010). If a participant reported pain they were asked additional questions to explore the nature of the pain experience and to ensure that feelings of unpleasantness or visceral reaction were clearly discriminated from somatic signs of noxious experience. Further questions included: "How long did the pain sensation last?," "How would you describe the pain sensation you felt?," "How did it feel?," "Have you previously experienced a similar kind of pain following an injury or other problem?," and "Do you get this type of pain in everyday life or when you watch a movie?" The investigator asked additional questions to clarify the nature of the experience as somatic, rather than just visceral or emotional, when necessary. Those responding to at least one image or video with a pain response that was not just an emotional or "gut" reaction were assigned as a responder to yield ten responders and sixteen non-responders.

All participants then took part in a reaction time experiment involving an avatar viewed on a computer screen surrounded by three virtual walls (following the design of Samson et al., 2010). A female avatar was used for female participants and a male avatar for male participants. At intermittent intervals, 0–3 circles were presented either on the wall facing the avatar or on the wall facing away from the avatar (**Figure 1**).

The participant could always see the number of circles. In half of the trials the avatar was observing the same number of circles as the participant such that the avatar's and the participant's perspective were consistent. In the other half of the trials the avatar observed a different number of circles to the participant such that the avatar's and the participant's perspective were inconsistent. The position of the avatar was randomized for each trial. Prior to seeing the room, participants were cued to adopt either their own perspective, which was written as "you," or the perspective of the avatar, which was written as "he" or "she" as appropriate. For half of the trials the participants adopted the perspective of the avatar and for the other half they adopted their own perspective. After viewing the screen for 750 ms, participants were asked to identify the number of circles on the wall from their adopted perspective (self or other) as quickly as possible. There were 96 trials in total. Time taken to press the button was automatically recorded. Reaction times 2.5 standard deviations outside the mean were removed as outliers.

EXPERIMENT TWO

Fifty two new self selecting participants (all females; mean age = 20; range 18–22) provided informed consent and took part in experiment two for course credit. All participants observed the images or videos depicting injury, as before, and 19 reported pain to at least one image or video (responders).

All participants then took part in a test of the rubber hand illusion. A purpose built partition and cover allowed each participant to sit with their left arm and hand hidden from view. All participants wore a yellow rubber glove on their right hand and were seated with their arms resting on a table in front of them. The partition obscured their view of their left arm and hand and the gloved rubber arm and hand was placed on the visible side of the partition positioned where the participant indicated it felt natural, "as though my own left arm could comfortably be resting there." Two experimental conditions, synchronous stroking of the participant's left hand and the rubber hand and asynchronous stroking of the participant's hand and the rubber hand then followed and continued for 1 min. The order of conditions (synchronized or asynchronized stroking) was randomized across participants. Immediately after finishing each condition, the participant was asked to fill out the Botvinick and Cohen (1998) questionnaire. The Botvinick and Cohen (1998) questionnaire includes eight items describing perceptual qualities associated with the rubber arm illusion. The first three items have been previously demonstrated as highly correlated with the rubber hand illusion (Botvinick and Cohen, 1998). Participants were asked to what extent they agreed or disagreed with each statement from 3 (strong agreement that the sensation or experience was felt) to −3 (strong disagreement).

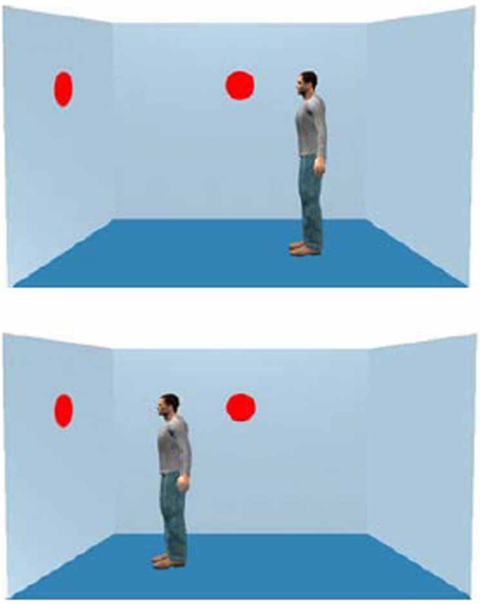


FIGURE 1 | The figure shows two dots and an avatar observing two dots (top), consistent with the participant's viewpoint or observing one dot (bottom), inconsistent with the participant's viewpoint.

EXPERIMENT THREE

Sixty-three new participants (7 males; mean age 20; range 18–21) were recruited by advertisement from the University of Birmingham and surrounding area. All participants provided consent. Participants completed a "teeth sensitivity" questionnaire which included the following items: "how much pain do you feel when you eat cold foods (0 = none, 10 = most pain imaginable)," "how sensitive do you think your teeth are (0 = not at all, 10 = extremely)," and "do you receive treatment for sensitive teeth (Y/N)." Participants who scored 15 or above and who reported receiving treatment for teeth sensitivity were categorized as high sensitivity ($n = 20$). Participants who scored 10 or below and who reported not receiving treatment for sensitive teeth were categorized as low sensitivity ($n = 21$). The remaining participants were categorized as moderate sensitivity ($n = 22$).

Participants viewed a series of six images of a male or female face depicting three conditions: expressing pain, eating an ice-popsicle and not expressing pain and eating an ice-popsicle and expressing pain (see **Figure 2**). The final image was expected to elicit a greater frequency of pain in participants with tooth sensitivity. The image expressing pain alone was intended to control for evoked pain independent of tooth sensitivity similar to previous studies (Osborn and Derbyshire, 2010) and the image not expressing pain and eating an ice-popsicle controlled for the influence of observing an act that could cause the observer pain. The images were presented for three seconds and then the participants were asked if they felt any sensation of pain while viewing the image. It was emphasized that the pain should be felt in the body and general feelings of unpleasantness or unease should not be recorded as painful (following Osborn and Derbyshire, 2010). Participants who reported pain also rated the intensity of their pain using a visual analogue scale (VAS) (anchored at 0 for no pain and at 10 for most pain imaginable) and the short-form McGill Pain Questionnaire (MPQ). All participants completed the Interpersonal Reactivity Index (IRI) to assess trait empathy and rated their empathic feelings (state empathy) toward the person in each image using a numerical rating scale from

FIGURE 2 | The figure shows the images used for experiment three. On the left is pain alone, in the middle is the ice popsicle alone and on the right is pain with the ice popsicle.

zero (indicating no compassion, warmth, or sympathy toward the depicted person) to 10 (indicating the most compassion, warmth, or sympathy imaginable).

RESULTS

EXPERIMENT ONE

Figure 3 shows the reaction times for the consistent and inconsistent trials, when adopting a self or other perspective, for the responder and non-responders separately. Participants were faster across groups and conditions for the consistent trials. The difference between consistent and inconsistent trials when adopting a self perspective, however, was greater for the responders compared to the non-responders. In contrast, the difference when adopting an other perspective was greater for the non-responders compared with the responders. Prior to analysis, the data were examined for violations of normality including skewness and violations were not exceptional (measures of skewness ranged from 0.1 to 1.0). The data were also tested for equality of variance and no violation of unequal variance was evident ($p = 0.48$). Thus, a 2 (consistent/inconsistent) × 2 (self/other perspective) × 2 (responder/non-responder) ANOVA was used to formally assess the data. The ANOVA confirmed a main effect of consistency [$F_{(1, 24)} = 28.6$, $p < 0.001$] a consistency by perspective interaction [$F_{(1, 24)} = 12.6$, $p < 0.01$] and a trend toward a three way interaction of consistency, perspective and group [$F_{(1, 24)} = 3.7$, $p = 0.07$]. No other effects reached or trended toward significance.

Post-hoc paired t-tests were used to explore the interaction of consistency with perspective and revealed significant differences between consistent and inconsistent trials when adopting the self ($t = 2.9$, $p < 0.05$) and other ($t = 6.4$, $p < 0.001$) perspective in responders but only when adopting the other perspective in non-responders ($t = 5.4$, $p < 0.001$). No other differences reached significance.

EXPERIMENT TWO

Prior to analysis, the Botvinick and Cohen questionnaire data were examined for violations of normality including skewness and violations were not exceptional (measures of skewness ranged from −0.75 to 0.04). The data were also tested for equality of variance and a violation of unequal variance was evident ($p < 0.001$) and so corrected degrees of freedom were implemented. The data were first examined with a 2 (synchronous/asynchronous stroking) × 8 (question) × 2 (responder/non-responder) ANOVA for formal assessment. The results revealed significant heterogeneity across questions [$F_{(4.7, 230)} = 22.7$, $p < 0.001$] as well as a significant main effect of synchronicity [$F_{(1, 49)} = 5.4$, $p < 0.05$]. Question one ("It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched") received the highest score and question eight ("It felt as if my real hand were turning rubbery") the lowest score. Scores were higher during synchronized compared with asynchronized stroking. The interactions of question with group and question with condition were significant [$F_{(4.7, 230)} = 2.3$, $p < 0.05$; $F_{(4.9, 242)} = 2.4$, $p < 0.05$] but there was no significant three-way interaction of question, condition and group [$F_{(4.9, 242)} = 1.8$, $p = 0.11$]. No other effects reached, or approached, significance.

The data were explored further by analyzing the three critical questions relating to feeling the stroking of the brush, feeling the stroking being caused by the touch of the brush on the rubber hand, and feeling ownership of the rubber hand, using a 2 (synchronous/asynchronous stroking) × 3 (question) × 2 (responder/non-responder) ANOVA. The results are illustrated in **Figure 4**.

From **Figure 4** it can be seen that the responders tend to have greater responses than non-responders, largely because the responder scores remained high even during asynchronous stroking. Formal analysis confirmed the main effect of group [$F_{(1, 50)} = 5.8$, $p < 0.05$], synchronicity [$F_{(1, 50)} = 4.3$, $p < 0.05$] and question [$F_{(2, 100)} = 3.6$, $p < 0.05$] as well as a significant interaction of synchronicity with group [$F_{(1, 50)} = 3.6$, $p < 0.05$] and synchronicity with question [$F_{(2, 100)} = 9.7$, $p < 0.001$] but no three way interaction of synchronicity, question, and group

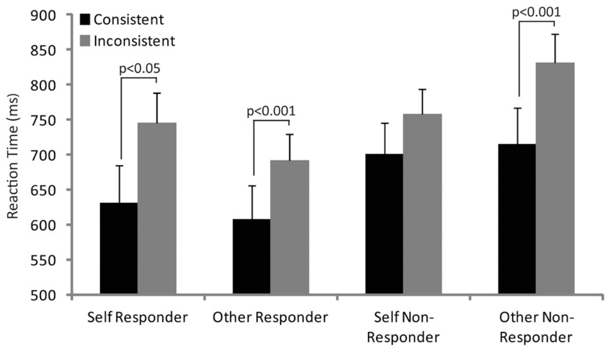


FIGURE 3 | The figure shows the reaction times in responders and non-responders during consistent and inconsistent trials when adopting self and other perspective. *Post-hoc* significant differences are indicated.

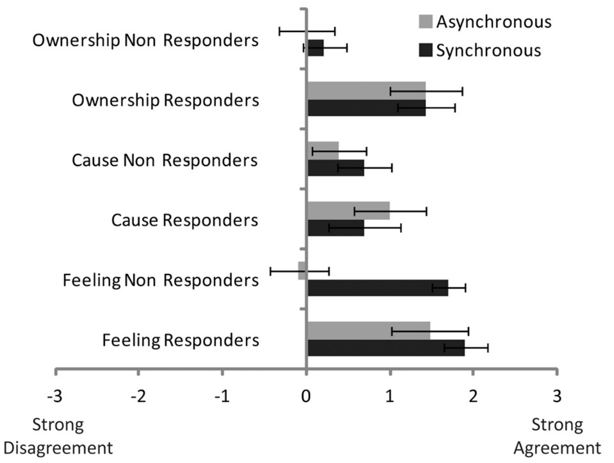


FIGURE 4 | The figure shows the group mean ratings for feeling the touch of the brush on the rubber hand ("Feeling"), reporting the touch to be caused by the brush ("Cause") and feeling as if the rubber hand was the participant's hand ("Ownership").

$[F_{(2,\,100)} = 2.1,\ p = 0.11]$. No other effects reached, or came close, to significance.

EXPERIMENT THREE

High sensitivity participants reported more pain in the presence of the ice-popsicle than the other two groups. The low sensitivity participants never reported pain (see **Table 1**). A series of χ^2 analyses revealed a significant effect of group for pain responses to the pain without ice popsicle picture $[\chi^2_{(2)} = 7.4,\ p < 0.05]$, the no pain with ice popsicle picture $[\chi^2_{(2)} = 19.1,\ p < 0.001]$ and the pain with ice popsicle picture $[\chi^2_{(2)} = 30.2,\ p < 0.001]$.

The mean VAS pain ratings for each group in response to each class of image are shown in **Figure 5**. The data were analyzed using a 3 (group—high, moderate or low sensitivity) × 3 (image—pain without ice popsicle, no pain with ice popsicle or pain without ice popsicle) × 2 (gender—male or female picture) ANOVA. The main effects of group and image were significant $[F_{(2,\,60)} = 3.7,\ p < 0.05;\ F_{(2,\,120)} = 9.1,\ p < 0.001]$ and so was the interaction of image with group $[F_{(4,\,120)} = 2.6,\ p < 0.05]$. *Post-hoc* pairwise comparisons revealed significantly ($p < 0.05$) greater pain in the moderate sensitivity group compared with the high and low sensitivity groups for the pain without ice popsicle picture. Both the high and moderate sensitivity groups reported significantly greater pain compared with the low sensitivity group for the pain with ice popsicle picture. No other differences reached significance.

Out of the 79 pain reports, 74 were reported in the teeth, face, or head (two were reported in the lower back, two in the right foot and one in the chest). The pain was typically described as sharp (used 57 times), shooting (39), aching (36), and throbbing (30). Trait empathy was similar across groups (high = 78, moderate = 79, low = 83) but state empathy differed according to group as shown in **Figure 6**. State empathy data were formally analyzed using a 3 (group—high, moderate or low sensitivity) × 3 (image—pain without ice popsicle, no pain with ice popsicle or pain without ice popsicle) × 2 (gender—male or female picture) ANOVA. The main effects of group and image were significant $[F_{(2,\,60)} = 7.2,\ p < 0.01;\ F_{(2,\,120)} = 67.7,\ p < 0.000]$ and so was the interaction of image with group $[F_{(4,\,120)} = 3.8,\ p < 0.01]$. *Post-hoc* pairwise comparisons revealed significantly ($p < 0.05$) higher ratings in the moderate sensitivity compared with low sensitivity group for the pain without ice popsicle picture; higher ratings in the high sensitivity group compared with moderate and low sensitivity groups and higher ratings in the moderate sensitivity compared with the low sensitivity group for the pain with ice popsicle picture; and higher ratings in the high and moderate sensitivity groups compared with the low sensitivity group for the no pain with ice popsicle picture. No other differences reached significance.

DISCUSSION

Three experiments, involving different samples of participants who do (responders) and do not (non-responders) report directly

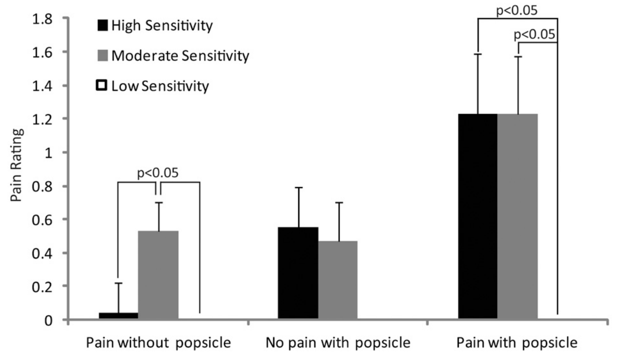


FIGURE 5 | The figure shows the mean VAS pain ratings for each tooth sensitivity group in response to each image type. *Post-hoc* significant differences are indicated.

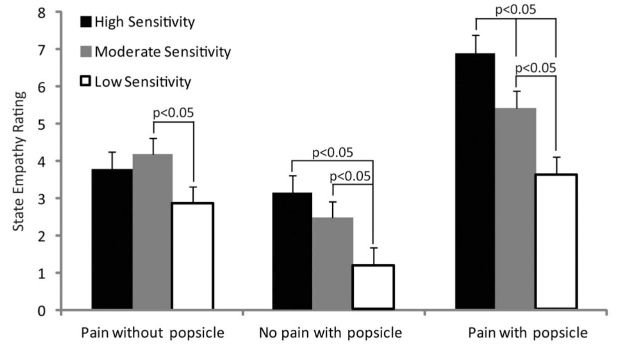
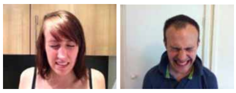
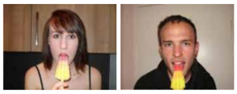
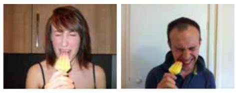


FIGURE 6 | The figure shows the mean state empathy ratings for each tooth sensitivity group in response to each image. *Post-hoc* significant differences are indicated.

Table 1 | Shows the number of times participants in the high, moderate (Mod) and low sensitivity groups responded with or without pain for the three image conditions.

	Pain without ice-popsicle			**No pain with ice-popsicle**			**Pain with ice-popsicle**		
									
	High	**Mod**	**Low**	**High**	**Mod**	**Low**	**High**	**Mod**	**Low**
Pain	4	9	0	15	4	0	32	20	0
No pain	76	79	64	65	84	64	48	68	64

sharing others' pain, were conducted to further understand the mechanisms of shared pain experience. Experiment one provides evidence that all participants suffer interference from someone else's visual perspective even when explicitly instructed to adopt their own perspective, which replicates previous findings (Samson et al., 2010). Experiment one, however, also provided evidence for greater interference effects when adopting the perspective of the other compared with the self and this was driven in part by reduced interference when adopting a self perspective. This reduced interference was especially noticeable for the non-responders although the critical three-way interaction only trended toward significance. Experiment two provides evidence for a stronger integration of the rubber arm into bodily representation for responders compared with non-responders. Experiment three provides evidence that being a pain responder is increased if the observed pain is congruent with a current pain sensitivity. Specifically, people with high and moderate tooth sensitivity were significantly more likely to report pain when observing an image of someone biting into an ice-popsicle, especially if the person expressed pain while biting. In combination, these findings suggest that responders can more readily adopt the perspective of others, more readily integrate foreign body parts into their own body schema and more readily experience pain when observing a behavior that has caused them pain in the past.

The visual perspective taking task used here required the participants to make inferences about what another can or cannot see (Newcombe, 1989). Correctly inferring what another can see requires the viewer to inhibit their egocentric viewpoint and adopt the other's visual perspective. This inhibition of egocentric or self viewpoint can also contribute to understanding the thoughts and feelings of others by reducing the influence of the predominant, egocentric, self perspective (Vogeley et al., 2001). Inhibiting the self-perspective and adopting another's mental perspective is considered an essential part of empathic understanding (Davis, 1980). Imagining a "self" perspective while viewing someone in pain, for example, may aid confusion between self and other perspectives (Lamm et al., 2007).

Visual perspective taking does not necessarily require any inference regarding the mental state of the other (Newcombe, 1989; Aichhorn et al., 2006). Inferring the mental state of another and then sharing that state, as is the case with empathy, may involve subjectively adopting the cognitive perspective of the other to understand what he or she is thinking. There is a distinction between the ability to shift visual perspective, which is a low level skill, and the ability to empathize by thinking what someone else is thinking or feeling what someone else is feeling. Presumably lower level skills, including automatic visual perspective taking, contribute to higher level skills, including empathy (Samson et al., 2010). It is possible that the low level mechanism of visual perspective taking contributes to the emotional experience of empathy for another in pain, which correlates with vicarious sensation of both touch and pain (Singer et al., 2004; Banissy and Ward, 2007), but that at least some components of empathy remain independent of vicarious sensation.

Pain responders reported similar experiences of the rubber hand illusion in the asynchronous stroking as the synchronous stroking condition. Previous research has demonstrated an attenuation of the illusion during asynchronous stroking, stronger than observed here in the responders (Botvinick and Cohen, 1998; Ehrsson et al., 2005; Tsakiris and Haggard, 2005; Tsakiris et al., 2006; Makin et al., 2008; Moseley et al., 2008; Aspell et al., 2009). Although aspects of the rubber hand illusion can be generated with asynchronous stroking, synchronous stroking is considered as particularly important for generating feelings of ownership over an external body part (Makin et al., 2008; Tsakiris, 2010). Here, reports of body ownership during asynchronous stroking suggest that strong correlations between tactile and visual input are less important for ownership over another person's hand for pain responders.

It is possible that visual information dominates tactile information in driving feelings of ownership for responders. Previous research has demonstrated that viewing a body other than one's own tends to activate a visual simulation mechanism that rapidly readies the somatosensory system to experience observed physical events (Longo et al., 2011; Cardini et al., 2011, 2012, 2013). Pain responders might be at the extreme end of this tendency, partly explaining their experience of pain in response to someone else's injury but possibly also explaining why responders were equally affected by congruous as by incongruous stroking. It is possible, at least for responders that simply viewing the rubber hand in an anatomically appropriate position resulted in rapid somatotopic integration sufficient to compensate for the incongruent tactile stimulation that followed. Some participants did spontaneously report feeling the illusion as soon as they placed their arms into the apparatus but this spontaneous report was not systematically investigated. Future studies might address whether the illusion is spontaneously generated more easily in responders compared to non-responders. A more flexible sense of body part ownership may partially explain how responders relocate an observed injured body part of another to themselves, producing pain in the self.

Participants who reported sensitivity to pain when eating cold foods were significantly more likely to report pain sensation after observing others eat cold foods. This finding supports the idea that we feel the pain of others more if we have experienced the pain ourselves and implies a merging of self and other. Shared pain experience was also associated with increased state empathy but not trait empathy. While it is generally accepted that representations of self and other overlap during the experience of empathy, it is less clear how self/other merging occurs. We may feel what it is like for someone else to be in pain (*Like them*) or we may feel what it is like for us to be in pain (*Like us*) (Decety and Sommerville, 2003). *Like them* depends less on self representations of pain and more on "other" oriented empathic processes. *Like us* depends more on "self" oriented representations of pain and may plausibly be less dependent on "other" oriented empathic processes. Here participants with self experience of pain from cold food had increased pain experience when observing someone eat an ice-popsicle. Thus, our findings point more toward *Like us* mechanisms than toward *Like them*. *Like them* would have been expected to reveal no pain when observing someone biting an ice-popsicle but not feeling pain and equivalent pain when observing a facial expression of pain with and without the ice-popsicle.

Interestingly, participants who reported sensitivity to pain responded with increased pain intensity both to the pain with ice-popsicle picture and to the no pain with ice-popsicle picture. Previous research has used images depicting injuries that would hurt the observer if the same thing happened to them but are also clearly likely to hurt the person depicted (Morrison et al., 2004; Singer et al., 2004; Jackson et al., 2005; Osborn and Derbyshire, 2010). Here it is demonstrated that images depicting events that would only hurt the observer (if they have sensitive teeth) can cause pain in the observer. In this instance, respondents are not responding to the pain of the other but are responding to the fact that the action depicted, biting into an ice-popsicle, could cause them pain. At the same time, participants without tooth sensitivity, but with similar high levels of trait empathy to those with tooth sensitivity, did not respond with pain to the images depicting someone expressing pain while biting into an ice-popsicle. These findings provide a double dissociation away from an explanation of vicarious pain based on empathy with some participants responding despite the image not depicting pain, and thus reducing or eliminating a pain induced empathic response, and some participants not responding despite a pain induced empathic response to the pain images.

It is also interesting that there was more pain reported by the moderate sensitivity group to the pain without ice-popsicle image. This finding further suggests that the pain of the high sensitivity group is driven largely by the depiction of something that could hurt them rather than being a general response to an expression of pain. It remains uncertain, however, why the moderate pain group reported more pain than both the low and high sensitivity groups.

Including an additional control picture only depicting an ice-popsicle would have established if merely observing a salient affective stimulus causes pain in participants with sensitive teeth. Including this control image was rejected because an ice-popsicle alone was thought to be unlikely to generate pain. By itself, an ice-popsicle cannot induce pain, and so the participants would have no history of pain from ice-popsicles *per se*, only from biting into them. In addition, the possibility of causing a diminished response from showing many ice-popsicle pictures was also considered. Nevertheless, this lack of control limits the interpretation.

A number of additional limitations also mean that the results reported here should be treated with caution before replication. In particular, the critical interaction effect for experiment one only trended toward significance and many of our response measures relied on subjective assessment. Similarly for experiment two, there was insufficient statistical support for a significant three-way interaction that might indicate more specific influences of responder vs. non-responder during the rubber hand illusion. All studies were performed using convenience samples with numbers comparable to previous research. It is possible that the studies were simply underpowered to reveal smaller effects. All experiments involved a relatively limited demographic (mostly young females) that may introduce bias and difficulties in generalizing the findings. Experiment three, in particular, may involve demand characteristics driving pain report in those with sensitive teeth when viewing the ice-popsicle images. Future studies may benefit from including objective measures, such as GSR, alongside subjective report, to address at least some of these potential biases. We are currently investigating brain activation using fMRI with responders and non-responders to the ice popsicle.

CONCLUSIONS

The studies reported here demonstrate that responders more readily adopt the perspective of an other and more readily integrate a foreign body part into the self. The number of responders also increases when the observed pain is one that the participant is familiar with from their own history. Thus, experiencing pain when observing the pain of someone else may rely upon the integration of the other into a self orientated representation of injury or pain.

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Misophonia: physiological investigations and case descriptions

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Misophonia is a relatively unexplored chronic condition in which a person experiences autonomic arousal (analogous to an involuntary "fight-or-flight" response) to certain innocuous or repetitive sounds such as chewing, pen clicking, and lip smacking. Misophonics report anxiety, panic, and rage when exposed to trigger sounds, compromising their ability to complete everyday tasks and engage in healthy and normal social interactions. Across two experiments, we measured behavioral and physiological characteristics of the condition. Interviews (Experiment 1) with misophonics showed that the most problematic sounds are generally related to other people's behavior (pen clicking, chewing sounds). Misophonics are however not bothered when they produce these "trigger" sounds themselves, and some report mimicry as a coping strategy. Next, (Experiment 2) we tested the hypothesis that misophonics' subjective experiences evoke an anomalous physiological response to certain auditory stimuli. Misophonic individuals showed heightened ratings and skin conductance responses (SCRs) to auditory, but not visual stimuli, relative to a group of typically developed controls, supporting this general viewpoint and indicating that misophonia is a disorder that produces distinct autonomic effects not seen in typically developed individuals.

Keywords: misophonia, sound sensitivity, skin conductance response, auditory processing, aversive sounds, case reports, autonomic response

GENERAL INTRODUCTION

Misophonia, literally translated to "hatred of sound," is a chronic condition in which specific sounds provoke intense emotional experiences and autonomic arousal within an individual. Trigger stimuli include repetitive and social sounds typically produced by another individual, including chewing, pen clicking, tapping, and lip smacking. These experiences are not merely associative in nature, but drive the sufferer to avoid situations in which they may be produced, limiting one's ability to interact with others and often leading to severe problems in their social and professional lives. Also known as selective sound sensitivity syndrome, the term "misophonia" was first coined by Jastreboff (Jastreboff, 2000; Jastreboff and Jastreboff, 2001a,b, 2003) and little remains known about the condition. To our knowledge only two case studies (Hadjipavlou et al., 2008; Schwartz et al., 2011) and one clinical study (Schröder et al., 2013) have examined misophonia. In the latter study, psychiatrists presented questionnaires and administered interviews to 42 misophonics, an essential first step in showing that misophonia is a primary disorder with no obvious comorbidity with other known psychological or neurological conditions (Schröder et al., 2013).

The prevalence of misophonia is under active investigation but there exist several online support groups with thousands of members (Misophonia UK, Facebook and Yahoo). Sufferers of misophonia are fully aware of its presence and the abnormal responses they have to their trigger sounds. In addition, many sufferers have identified the condition in at least one close relative, suggesting a possible hereditary component. While effective treatments for misophonia remain elusive, individuals report utilizing coping mechanisms to minimize their exposure and response to triggering stimuli (discussed at length below). Further, misophonia appears to exhibit some general similarities to tinnitus. Jastreboff and Hazell (2004) propose that misophonia and tinnitus are both associated with hyperconnectivity between the auditory and limbic systems, suggesting that both conditions would evoke heightened reactions to their respective sounds. However, despite these general similarities, misophonia differs from tinnitus considerably, particularly in terms of how the condition is localized around certain human-produced sounds and situations as opposed to internally perceived, abstract sounds.

While the majority of typically developing individuals experience general and unelaborated emotional reactions to a range of sounds (Halpern et al., 1986), these widespread negative associations remain non-debilitating and at most an annoyance to the listener. One critical possibility is that the valenced associations present in typically developing individuals are matched to those with misophonia, with the latter merely experiencing a more extreme physiological response. Indeed, the sound of fingernails on a chalkboard is an emotionally evocative stimulus that elicits extreme discomfort in the typical population (Zald and Pardo, 2002; Kumar et al., 2012) and misophonic individuals often reference this stimulus in illustrating the extreme nature of their trigger sensations. In this study, we further elaborate on the symptoms and behaviors associated with misophonia as well as examine whether misophonics' physiological responses support their subjective reports of feeling autonomic arousal in response to certain sounds.

EXPERIMENT 1

INTRODUCTION

We first received information about misophonia in December of 2011 through members of an online misophonia support group. From initial descriptions, the condition appeared to have many intriguing qualities in addition to being quite unknown and unexplored. Misophonic individuals were invited to the lab for preliminary interviews with the hope of gaining a more concrete understanding of their experiences with the condition.

MATERIALS AND METHODS

Participants

Eleven individuals with misophonia from the San Diego and Los Angeles areas were recruited from the University of California, San Diego campus, through self-identified contact of our lab as well as through an online misophonia support group (4 males and 7 females, mean age = 35.82; range = 19–65).

Procedure

Thirty to sixty minute semi-structured interviews were conducted by members of our research group on the University of California, San Diego campus. As no set diagnostic criteria for misophonia exists for misophonia, eligibility for study inclusion was based on severity of symptoms paired with experiential descriptions reported by the subject. The five initial interviews were exploratory in nature and included a range of topics, including approximate age of onset, lists of sounds that elicit varying degrees of discomfort, whether or not certain individuals exacerbate the condition, coping mechanisms, common thoughts when experiencing symptoms, physical responses to the trigger sounds, effect of the condition on their daily lives, and other potentially comorbid medical conditions. From these interviews we were able to generate a core set of questions to create the general framework of the subsequent six interviews that were held.

RESULTS AND DISCUSSION

After conducting all 11 interviews, it was apparent that the experiences of the misophonics, though intrinsically variable between subjects, contained noticeable trends and similarities. The most salient categories of assessment and their traits are documented in **Table 1**. In addition, it should be noted that all diagnostic criteria listed by Schröder et al. (2013) were present in the reports of our misophonic subjects (see **Table 1**) even though these interviews were conducted prior to the publishing of that article.

The most important criterion in misophonia is that particular sounds will evoke a disproportional aversive reaction. Our subjects were recruited based on their reports of this characteristic. In accordance with previous reports, our misophonics reported that the worst trigger sounds are chewing, eating, and crunching sounds, followed by lip smacking, pen clicking, and

Table 1 | Summary of qualitative data gathered from interviews of the 11 misophonic subjects (4 males and 7 females, mean age = 35.82; range = 19–65) in Experiment 1, broken down into 18 of the most salient diagnostic categories.

Age of onset	8–10 years old (3)–27% As long as can remember (3)–27% Childhood (3)–27% 17 (1)–9% Early teenage years (1)–9%
Worst trigger sounds	Eating/chewing/crunching sounds (11) Lip smacking (2) Pen clicking (2) Clock ticking (2)
Other trigger sounds	Low frequency bass sounds (8) Pen clicking (4) Footsteps (3) Finger tapping (3) Whistling sounds (3) Typing (3) Lip smacking (2) Clock ticking (1) Plastic bags (1) Repetitive barking (1) Finger tapping (1) Sniffling (1)
Localized around certain individuals?	Yes (9)–82% No (2)–18%
Worsened over time?	Yes (5)–45% Stays the same (3)–27% No, gotten better (2)–18% N/A (1)–9%
Own trigger sounds ok?	Yes (10)–91% Avoids producing own trigger sounds (1)–9%
Repetitive sounds worse	Yes (9)–82% N/A (2)–18%
Runs in family?	Yes (6)–55% Not known (3)–27% N/A (2)–18%
Coping strategies	Avoiding or removing self from certain situations (7) (*D,E) Mimicry to "cancel out" sound or retaliate (6) Earplugs/headsets/music (6) Is conscientious about own sounds (5) Distract self (5) Ask others to stop (4) Positive internal dialog (1)
Effect of alcohol/caffeine	Alcohol lessens symptoms (7) Caffeine worsens symptoms (4) Symptoms not affected by caffeine (2) Does not use caffeine (2) Does not use alcohol (2) Symptoms not affected by alcohol (1) N/A (1)

(Continued)

Table 1 | Continued

Physical locations and descriptions of discomfort (*A)	Pressure in chest, arms, head, or whole body (5) Clenched/tightened/tense muscles (5) Increase in body temperature, blood pressure, or heart rate (2) Pained by trigger sounds (1) Hard to breathe (1) Sweaty palms (1)
Visual triggers	Jiggling/swinging legs (5)
Bothered by Ss sounds	Yes (6)–55% N/A (3)–27% No (2)–18%
Feelings and emotions associated with trigger sounds*	Sounds are invasive, intrusive, insulting, violating, offensive, disgusting, rude (9) (*A,D) Stress/anxiety (5) Anger or rage (4) (*D) Extreme annoyance/irritation (4) (*A,D) Panic (2) (*B) Impatience (1) Aggravation (1) (*D) Feeling trapped (1) (*B)
Other potentially comorbid medical conditions (*F)	Tinnitus (2) Obsessive-compulsive personality traits (2) Hyperacusis (1) Auditory processing disorder (1) ADD (1) PTSD (1) None (6)
Bothered by sounds produced by animals or children	Yes (1)–9% No (8)–73% N/A (2)–18%
Thoughts when experiencing trigger sounds	"I want to punch this person" "I hate this person" "Why won't they stop? I don't want to hurt their feelings by changing seats" (*C) "Why are they eating that way?" "Why are you doing that? It's rude" "Would you shut up?" "Stop it, I can't stand it" "Don't you know what you sound like?" "Why am I like this?" (*C) "Are they doing this on purpose?" "Why does he have to _____ so loudly?" "They should be more conscious of how they're affecting others" "I envy people who aren't bothered by sounds" (*C)
Effect on life	Realizes they are hyper focused on noises that should be in the background and are unable to ignore them (9) (*C,E) Cannot pay attention at a movie or in class when people are making trigger sounds (8) (*E) Tries not to be around people if they make trigger sounds (7) (*D,E) Can be triggered by sounds from television or videos (7) (*E) Triggers are worse when tired (7) Stays away from certain foods/avoids making certain sounds (3) (*D,E) Feels better when can locate source of sound (3) Thoughts of suicide (1)

The number of subjects reporting a criterion can be found in parentheses to the right of each description.
Criteria marked with an asterisk (*) designate diagnostic criteria (A–F) consistent with those proposed by Schröder et al. (2013).
Please see General Discussion for more details.

clock ticking (see **Table 1**). Other notable trigger sounds include low frequency bass sounds, footsteps, finger tapping, whistling sounds, and typing (see **Table 1**). Nine of our 11 misophonics reported that sounds repetitive in nature were particularly bad. In addition, six of our misophonics indicated that spoken "Ss" sounds were unpleasant, although not quite on the same level as trigger sounds.

In terms of aversive responses to these sounds, misophonics report a range of negative feelings, thoughts, as well as physical reactions. Some of the negative feelings experienced include intense anxiety, panic, anger, extreme irritation, and even rage (see **Table 1**). Additionally, in the context of our study, it is important to distinguish anxiety from fear. Specifically, while our subjects report feeling extreme stress and anxiety in response to trigger sounds, they did not report being afraid or fearful of them. Nine of our 11 misophonics reported trigger sounds as being invasive, intrusive, disgusting, or rude. They also reported feeling offended or violated by these sounds to the point where negative thoughts such as "I hate this person," "Stop it, I can't stand it," and "Don't you know what you sound like?" enter their minds. However, on top of the strong psychological effects, misophonics also report experiencing strong physical effects in response to trigger sounds. The most commonly reported physical effects were pressure in the chest, arms, head, or entire body as well as clenched, tightened, and tense muscles. Some misophonics reported an increase in blood pressure, heart rate or body temperature, sweaty palms, physical pain, and even difficulty breathing in response to trigger sounds (see **Table 1**). The aforementioned aversive responses evoked by trigger sounds are characteristic of a typical, autonomic nervous system response. In line with this, the worst situations for misophonics are often ones where they feel trapped and unable to escape, including long trips in cars or planes. Similarly, two misophonics report that trigger sounds at school or at home are worse than in places one can easily leave, such as a public place. However, despite extreme discomfort, misophonics generally do not physically act out on feelings of aggression. Some report instances of snapping at others while others internalize their frustration (see **Table 1**).

A final indication that misophonia produces physical and autonomic responses is the suggestion that pharmacological agents affect the condition. Four of our misophonics indicated that caffeine intensifies misophonic experiences while seven of misophonic individuals indicated that alcohol decreases symptomatology; these subjects describe that while under the influence of alcohol they can still hear the sound but their aversive response is not as strong.

In response to their aversive reactions to trigger sounds, misophonic individuals have developed a number of coping strategies including: avoiding or removing themselves from certain situations, mimicking trigger sounds, or the action producing it to "cancel out" or "retaliate," utilizing earplugs, headsets or listening to music, distracting oneself, reciting positive internal dialog to help calm themselves, asking others to stop making the sounds, as well as being conscientious about their own sounds (see **Table 1**).

The degree to which quality of life is affected varied between our misophonic participants. One subject reported that misophonia "…does not affect the quality of my life too much. But it seems ridiculous and I would like to get rid of it" while another subject reported that misophonia had in the past evoked thoughts of suicide. These reports indicate there might be different degrees of the misophonic condition, ranging from mildly hindering to severely debilitating.

Misophonic individuals most commonly describe onset of the condition in childhood. Two subjects reported that with age, they learned to better cope with their misophonia, five subjects reported that it worsened over time (due to increasing aversiveness as well as increasing number of triggering stimuli) and three recalled no change over time. It is not fully understood why differences in trigger accumulation and severity develop between misophonics but it appears that prolonged and repeated exposure to a sound may be a contributing factor. For example, one of our misophonic subjects related this to the "honeymoon" period in a new job or relationship, in which for a few years new sounds caused little irritation. However, over time the negative affect of these sounds intensified to become triggers as well.

Six of our misophonics reported that one or several close family members display misophonic-like symptoms and behaviors. Two subjects had no information on this topic and three reported that they do not believe that misophonia runs in their families. While these reports are only anecdotal, they suggest there may be a familial or genetic component to misophonia, calling for further investigation in future studies.

Interestingly, misophonic individuals further report that responses evoked by trigger sounds appear to be modulated by prior knowledge, context, and sound source, implying that the condition is not driven simply by the physical properties of sound alone. For example, nine of our misophonics indicated that their misophonia is isolated to or exacerbated by certain individuals, usually close friends, coworkers, or family members whom they are exposed to frequently (see **Table 1**). Another curious characteristic described by 10 of our misophonics is the fact that self-induced trigger sounds (trigger sounds produced by the misophonic individual themselves) will not evoke nearly as much of an aversive response as when produced by others. In fact, as mentioned earlier, mimicking trigger sounds is one of the coping strategies utilized by misophonics to "overwrite" the disturbing sound being produced by another individual. Several misophonics even report eating foods in synchrony with the other person. However, mimicking is also mentioned as a way to retaliate against the offending individual producing the sounds, thus acting as a way to cope with the anger evoked by the condition.

The interviews further revealed an interesting effect of the role of context on aversive responses. For instance, eight of our misophonics report eating and chewing sounds (severely offensive triggers associated with rudeness when produced by human adults) will not bother them nearly as much if produced by animals or babies (see **Table 1**). One individual described that, as these individuals have little control over their actions and "don't know any better," it helps in cancelling out strong aversive feelings. These results suggest that the aversive responses experienced by misophonics are explicitly tied to other individuals, implying an underlying social component to the condition. Accordingly, even though our subjects fit in with Schröder et al.'s (2013) diagnostic criterion of misophonics being aware of their condition, and recognizing their feelings as "excessive, unreasonable, or out of proportion," they will still comment on the inappropriateness of another person's behavior nonetheless.

Another recurring topic from the interviews is the role of attention in misophonia. Nine of our misophonics report being hyper-focused on sounds that normally exist as background noise. One misophonic subject described the inability to tune out background noises as being like an "involuntary cocktail party effect" while another mentioned that "noises are never in the background. People sounds crash right through jet engine sounds." Eight of our misophonics described being unable to pay attention to a movie or lecture when individuals around them produce trigger sounds, with partial remediation by distracting themselves and directing their attention elsewhere. In addition, it is possible that through understanding the role of attention in misophonia, potential treatments may be able to be developed.

In accordance with Schröder et al. (2013), our subjects reported a few symptoms shared with other diagnoses, however the complete symptomology of misophonia does not fit with any of the diagnostic categories in the diagnostic and statistical manual of mental disorders (DSM-IV). In their interviews, subjects described symptoms related to obsessive-compulsive disorder (OCD), attention deficit disorder (ADD), post-traumatic stress disorder (PTSD), auditory processing disorders as well as tinnitus and hyperacusis (see **Table 1**). However, these symptoms did not cover the full range of complaints, including the critical symptom of misophonia (a strong aversive response to particular sounds). Two of our misophonics reported being treated with medications, including antianxiety medications and antidepressants, that were intended to alleviate some of the effects of misophonia but as it stands, a treatment to fully address the root of the problem still remains elusive. Thus, our results are in line with the previous conclusion that misophonia is not part of another clinical, psychiatric, or psychological disorder (Schröder et al., 2013).

EXPERIMENT 2

INTRODUCTION

Qualitative assessments of misophonic subjects demonstrated the consistent association between specific sounds and intense emotional experiences. In order to confirm the presence of these emotional reactions and further examine their relationship to sound preferences present in the general population, we measured skin conductance response (SCR) while misophonic participants and typically developed individuals were exposed to aversive and non-aversive auditory, visual, and auditory-visual stimuli. SCR measures the electrical conductance of the skin and consequently the amount of sweat produced. Because sweat production is not under volitional control, SCR is widely accepted to indicate arousal of the sympathetic nervous system (Critcheley, 2002). For these reasons, we believe SCR to be an appropriate method of measuring autonomic arousal to various emotion-eliciting stimuli.

MATERIALS AND METHODS

Participants

Six misophonic subjects who also participated in Experiment 1 (2 males and 4 females; mean age = 22.8; range = 19–30) and five controls (mean age = 22; range = 19–29) matched on age and gender participated in the experiment; A sixth control was excluded due to an error during data collection. Controls were recruited from the student population at the University of California, San Diego. All participants reported normal hearing and vision, gave signed, informed consent prior to the experiment, and participated either for cash or in fulfillment of a course requirement. The study was reviewed and approved by the university's Human Research Protections Program. Total experiment time was less than 1 h.

Procedure and stimuli

Participants were seated 20 inches from an 18 inch monitor and provided Sennheiser® headsets. SCR recordings were acquired with BIOPAC System (MP100A-CE) and AcqKnowledge 4.1 recording software. A pair of Ag-AgCl electrodes was attached to the palmar surface of the middle and ring fingers of the participant's dominant hand. Prior to attachment, participants' hands were cleansed with an alcohol wipe and a skin conductance gel was applied to each electrode. SCR was recorded in micro Siemens at a rate of 30 samples/s. Participants were instructed to relax with their dominant hand placed palm up on their thigh and to minimize movement throughout the duration of the experiment. SCR was examined in subjects prior to experimental testing for typicality; absence of a normal response precluded a subjects' participation in the rest of the study.

Stimuli included 31 video clips either acquired from YouTube or recorded in the lab. Video content varied in order to cover a range of sounds and predicted emotional responses in misophonic subjects, selected based on interview data from Experiment 1. Example stimuli included birds singing, children laughing, whale song, nails on a chalkboard, lips smacking, gum chewing, etc. Each clip lasted for 15 s. Auditory and visual components of these videos were separated to generate auditory alone, visual alone, and auditory-visual conditions. Each auditory, visual, and auditory-visual stimulus was presented once for a total of 93 trials. Trial order was randomized into two orders and order was counterbalanced across participants. Critically, as each specific video was presented a total of three times (once in each auditory, visual, and auditory-visual condition), a consistent ordering of the presentation of each stimulus was maintained for each type: auditory alone, visual alone, followed by auditory-visual. Stimuli were presented with E-Prime® version 2.0.

On each trial, participants viewed a centrally presented fixation cross for a 5-s period, followed by either an auditory clip (A), visual movie (V), or auditory-visual movie (AV) for 15 s, concluded with an inter-trial interval of 10 s; during this 10-s interval subjects provided a verbal aversiveness rating on a scale of 0–4 based on how much discomfort they experienced in response to the preceding trial. Participants were informed that a rating of 0 would signify no discomfort at all and a rating of 4 would signify an extreme amount of discomfort, anxiety, or an urge to leave the room. Each aversiveness rating was recorded by the experimenter.

Data preprocessing

As our stimuli were presented in quick succession, a linear downward trend was observed throughout the recording session. To account for this artifact, separate linear regressions were fitted to the 5-s fixation period at the start of each trial through a line of best fit. Each observed value during the stimulus epoch was re-plotted as the residual of this line of best fit, normalizing for the pre-stimulus baseline period and removing artifact trends present throughout the epoch. A consistent pattern of results was additionally observed on non-detrended data.

Data analysis

SCR onset was time-locked to pre-stimulus fixation cross. Mean SCR was calculated from the 15-s stimulus epoch for each trial, following the fixation cross. Mean values exceeding three standard deviations from the mean SCR across all trials for each participant were deemed outliers and consequently removed from the dataset; an average of 1.9% of trials were removed per participant.

Statistical analyses

First, we conducted repeated measures ANOVAs across factors of Group (misophonics, controls), Measurement (SCR, aversiveness rating), and Condition (auditory, visual, auditory-visual) to observe overall effects. Follow-up ANOVAs, non-parametric independent samples tests and descriptive analyses were conducted to explore group differences. Follow-up correlations revealed further group differences as well as similarities. Greenhouse-Geisser corrections were used where appropriate, but we report the original degrees of freedom for clarity.

RESULTS

Overall group effects

As an overall examination of the data, we conducted a repeated measures ANOVA with factors Group (misophonics, controls), Measurement (SCR, subjective rating), and Condition (auditory, visual, auditory-visual). Results showed significant main effects of Group [$F_{(1,\ 9)} = 17.5, p < 0.005$], Condition [$F_{(2,\ 18)} =$

47.3, $p < 0.001$], and Measurement [$F_{(1,\ 9)} = 48.5$, $p < 0.001$], as well as significant interactions between Group × Condition [$F_{(2,\ 18)} = 18.8$, $p < 0.005$], Group × Measurement [$F_{(1,\ 9)} = 13.7$, $p < 0.01$], Measurement × Condition [$F_{(2,\ 18)} = 40.5$, $p < 0.001$], and Group × Measurement × Condition [$F_{(2,\ 18)} = 16.2$, $p < 0.005$].

However, as the primary goal of this study was to examine unisensory responses to stimuli in both groups, subsequent tests for group effects excluded multisensory (auditory-visual) trials and included only auditory and visual conditions. **Figure 1** shows misophonic and control subjects' average SCR data in auditory and visual conditions as a function of time. A repeated measures ANOVA with factors of Group (misophonics, controls), Measurement (SCR, subjective rating), and Condition (auditory, visual) similarly identified significant main effects of Group [$F_{(1,\ 9)} = 14.3$, $p < 0.005$], Condition [$F_{(1,\ 9)} = 47.5$, $p < 0.001$], and Measurement [$F_{(1,\ 9)} = 40.7$, $p < 0.001$], as well as significant interactions between Group × Condition [$F_{(1,\ 9)} = 17.5$, $p < 0.005$], Group × Measurement [$F_{(1,\ 9)} = 10.1$, $p < 0.05$], Measurement × Condition [$F_{(1,\ 9)} = 44.0$, $p < 0.001$], and Group × Measurement × Condition [$F_{(1,\ 9)} = 16.1$, $p < 0.005$]. This overall ANOVA validated the use of follow-up analyses to test specific hypotheses.

Group differences

We conducted additional follow-up repeated measure ANOVAs with factors of Group (misophonics, controls) and Condition (auditory, visual), first for subjective aversiveness ratings alone. Results showed main effects of Group [$F_{(1,\ 9)} = 12.4$, $p < 0.01$] and Condition [$F_{(1,\ 9)} = 46.5$, $p < 0.001$], and critically an interaction between the two [$F_{(1,\ 9)} = 17.1$, $p < 0.005$] supporting the differences between the groups (see **Figure 2A**). This difference between the groups was largely due to controls rarely rating stimuli as greater than 2 on the aversiveness scale (ranging from 0 to 4; see **Figures 3A,B**). Examining this model for SCR data yielded a similar pattern of results with main effects of Group [$F_{(1,\ 9)} = 6.77$, $p < 0.05$] and Condition [$F_{(1,\ 9)} = 11.9$, $p < 0.01$], and a marginally significant interaction between the two [$F_{(1,\ 9)} = 4.53$, $p = 0.06$] (see **Figure 2B**).

Given the small sample size of these groups, follow-up non-parametric independent-samples Mann-Whitney U-tests were used to compare groups across these critical conditions. Misophonics reported significantly higher ratings than control subjects in response to auditory stimuli, $U_{(9)} = 29.0$, $p < 0.01$, but not visual stimuli, $U_{(9)} = 23.5$, $p = 0.13$. The median rating of auditory trials was 1.82 ($SD = 1.38$) for misophonics and 0.42 ($SD = 0.77$) for controls while the median rating of visual trials was 0.29 ($SD = 0.98$) for misophonics and 0.19 ($SD = 0.55$) for controls. This pattern of results was consistent with SCR responses, with misophonics producing larger SCR responses than controls to auditory stimuli, $U_{(9)} = 28.0$, $p < 0.05$, but not visual stimuli, $U_{(9)} = 21.0$, $p = 0.33$. The median SCR of auditory trials was 0.15 micro Siemens ($SD = 0.40$) for misophonics and 0.03 micro Siemens ($SD = 0.11$) for controls while the median SCR of visual trials was 0.07 micro Siemens ($SD = 0.39$) for misophonics and 0.00 micro Siemens ($SD = 0.08$) for controls. The same pattern of results for these tests was observed with parametric independent samples t-tests.

In order to determine if higher SCR is directly correlated with higher aversiveness ratings, we examined individual subjects' aversiveness ratings relative to average SCR activity from all auditory, visual, and auditory-visual trials. Results identified a significant positive correlation between average aversiveness ratings and average SCR across all participants (see **Figure 4**), ($r_s = 0.700$, $N = 11$, $Z = 2.21$, $p < 0.05$), indicating that stimuli subjectively thought of as aversive generally evoked a proportional SCR.

Group similarities

As an examination of whether the stimuli that trigger aversive experiences in misophonic individuals are idiosyncratic to the condition or consistent to, though more extreme than,

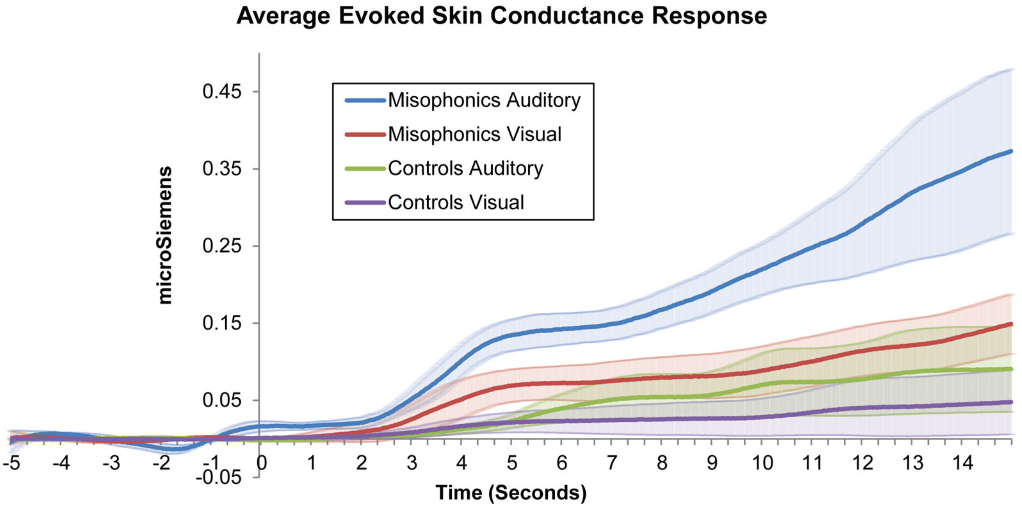

FIGURE 1 | Average misophonic and control participants' skin conductance response to auditory and visual stimuli as a function of time.

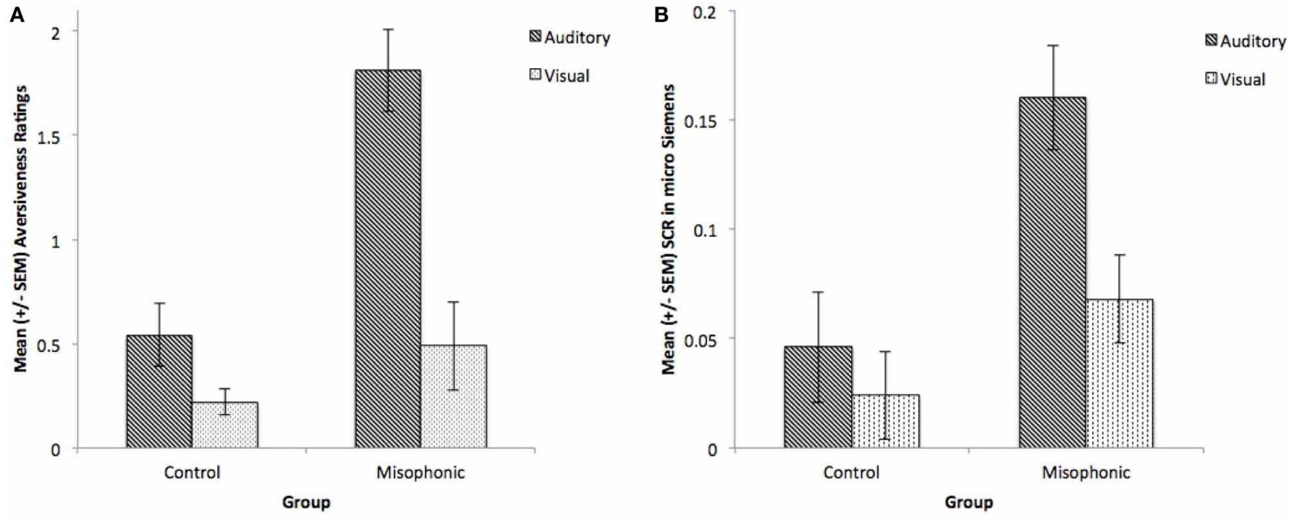

FIGURE 2 | Group means of controls and misophonics, per presentation condition (auditory and visual) for (A) subjective reports and (B) SCR.

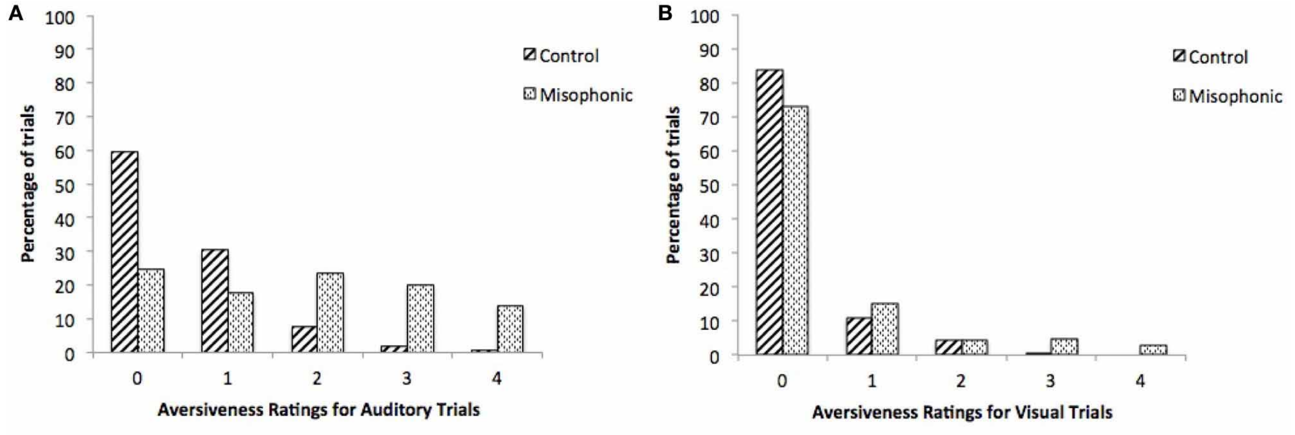

FIGURE 3 | Percentage of trials per index on the 5-point aversiveness scale, for controls and misophonics, during (A) auditory and (B) visual conditions.

preferences present in the general population, we examined the consistency of ratings across the groups. Findings indicated a significant positive correlation between misophonic and control aversiveness ratings across all three types of stimuli, ($r_s = 0.605$, $N = 93$, $Z = 5.80$, $p < 0.001$); this correlation is additionally present when examining the correlation between the groups for only auditory trials, ($r_s = 0.413$, $N = 31$, $Z = 2.26$, $p < 0.05$; see **Figure 5**) suggesting that misophonics and controls find similar stimuli to be aversive and non-aversive.

DISCUSSION

Experiment 2 provides, to the best of our knowledge, the first experimental investigation on misophonia, serving to validate the severity of this chronic condition beyond anecdotal description. Misophonic subjects rated auditory stimuli as more aversive than the same visual stimuli, and this pattern was consistent with SCR measurements. Furthermore, SCR and subjective ratings to auditory stimuli were greater in misophonic individuals than controls, supporting the specificity of aversive reactions in misophonia. Nevertheless, misophonic subjects demonstrated increased ratings and SCR regardless of stimulus type, as revealed by observed main effects of group, possibly denoting generalized anxiety to the stimuli used in the present study.

The significant positive correlation between average aversiveness ratings and mean SCR across all participants importantly confirms the validity of each subject's ratings during the task. Therefore, participant's physiological responses to stimuli were consistent with their subjective ratings. However, as shown in **Figure 4**, this positive correlation seems most likely driven by group differences between misophonics, (represented in green) and controls (represented in blue).

The significant positive correlation between misophonic aversiveness ratings and control aversiveness ratings reflects a general agreement of the relative valence of the inducing stimuli across the groups. In other words, misophonics and controls find similar stimuli to be aversive and non-aversive on a subjective level, suggesting that misophonics may experience an extreme form of the discomfort most individuals experience to normally aversive or irritating stimuli. This raises the important possibility that there is nothing intrinsically different about misophonic individuals from those in the general population and misophonic individuals are merely at the tail end of the distribution.

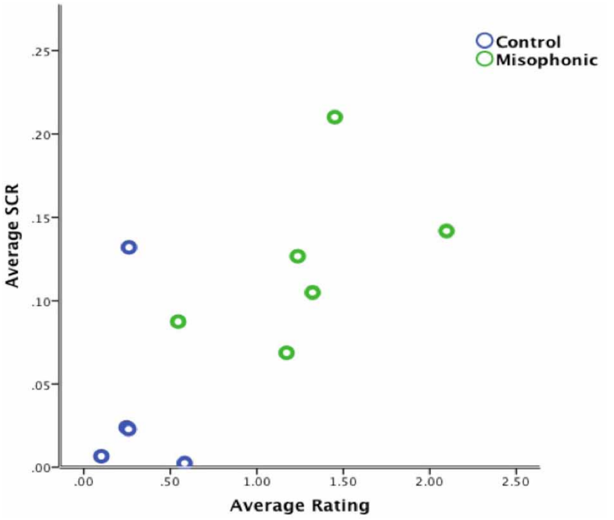

FIGURE 4 | Correlation of average aversiveness ratings and average SCR (in micro Siemens) for all trials across all subjects.

GENERAL DISCUSSION

In a preliminary examination of individuals with misophonia, we report qualitative and physiological investigations of the condition and its relationship to responses in the typical population. Experiment 1, which is comprised of qualitative assessments on eleven misophonic subjects, examined the qualities associated with misophonia in order to help develop reliable diagnostic criteria and understand the complex social factors involved. Results were consistent with early reports of the phenomenon, such as the critical characteristic of misophonia being a disproportionately aversive reaction is in response to common sounds in everyday life. Additionally, a visceral autonomic response is physically felt in misophonics in response to trigger sounds. In Experiment 2, physiological measurements were acquired on six misophonic individuals using SCR to provide an objective corroboration of misophonics' reports that specific sounds evoke intense emotional reactions. Results showed an increased autonomic response to trigger sounds, but not visual stimuli, in misophonics as compared with non-misophonic controls.

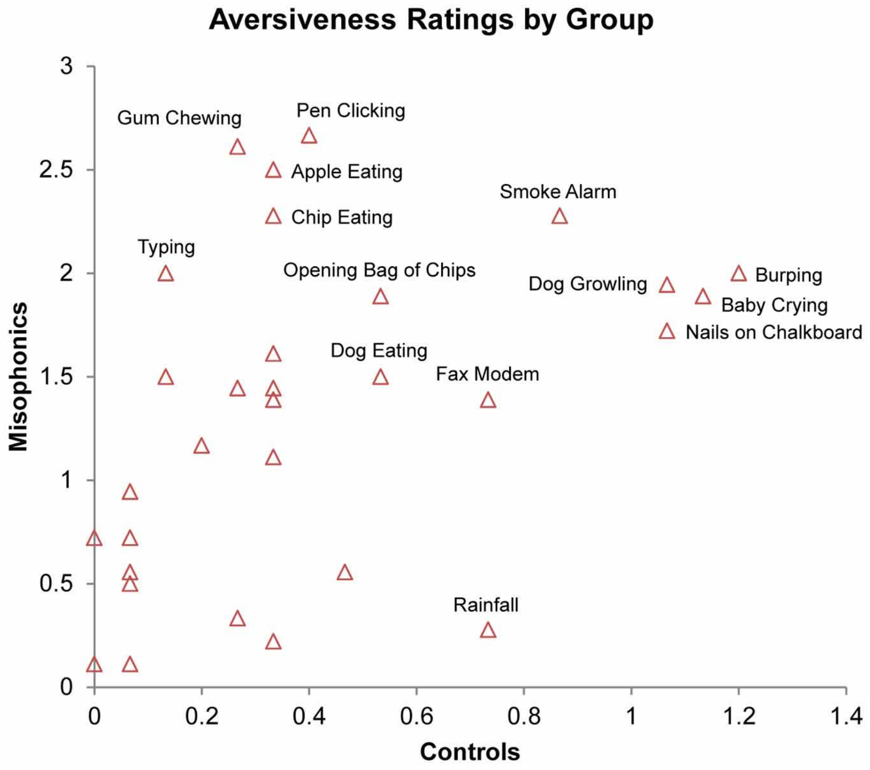

FIGURE 5 | Correlation of average aversiveness ratings of stimuli (x- and y-axis) across conditions in misophonics and controls. Select stimuli identified by proximal text.

Administering semi-structured interviews proved to be an effective way of determining the most critical symptoms, triggers and experiences associated with misophonia as well as the degree to which these varied across subjects. In addition to reporting psychological symptoms, all of our misophonics reported physical symptoms synonymous with autonomic arousal in response to trigger sounds. Furthermore, our qualitative results are in line with all of the diagnostic criteria proposed by Schröder et al. (2013) which, shortly summarized are: (A) aversive and angry feelings evoked by particular sounds, (B) rare potentially aggressive outbursts, (C) recognition by the misophonic individual that his/her behavior is excessive, (D) avoidance behavior, (E) distress and interference in daily life, and lastly, (F) the lack of another condition to account for all symptoms. Additionally, our principal finding that misophonic individuals experience physical, autonomic arousal that is measurable by SCR, provides empirical validation for some of the aforementioned critical criteria proposed by Schröder et al. (2013), particularly criterion A. Through conducting interviews, we also identified other interesting aspects of misophonia that were not previously apparent. In particular, subjects reported that misophonia can be modulated by social expectations as well as situational context, indicating that the condition may be more complicated than merely an aversive response to the purely physical properties of sounds. Additionally, the finding that misophonic individuals report involuntary, physiological distress in response to a very specific subset of social sounds supplements research on complex mind-body interactions, with high-level knowledge demonstrating prolonged and specific physiological reactions (e.g., as in placebos; Margo, 1999). However, at this time, these speculations remain based on anecdotes and need to be properly tested in the future before firm conclusions can be drawn.

To date, no research has examined the neurological origin of misophonia, and preliminary investigations suggest it is not due to any primary neurological or psychological disorder or trauma (Schröder et al., 2013). Nevertheless, misophonia displays similarities to a genetic condition known as synesthesia. In synesthesia, as in misophonia, particular sensory stimuli evoke particular and consistent, additional sensations and associations. Well-known forms of synesthesia include letters evoking a particular color, or sounds/music evoking colors (Cytowic, 1989; Baron-Cohen et al., 1996; Simner et al., 2006) but there are in fact many different subtypes of synesthesia, with a variety of "inducers" (e.g., music, taste, words, sequences) evoking certain "concurrents" (e.g., color, shapes, taste). While most synesthesia research has examined the perceptual sensations related to synesthesia, the condition seems to have an affective component as well. First, synesthetic congruency (e.g., when a grapheme-color synesthete sees a letter in the "correct" color) is related to positive affect (e.g., Callejas et al., 2007). Furthermore, both inducers (Ward, 2004; Ramachandran et al., 2012) and concurrents (Simner and Holenstein, 2007) can be of emotional rather than perceptual nature. Interestingly, the latter indicates that for certain subtypes of synesthesia, similar to misophonia, inducers evoke a particular feeling or emotion rather than a pure perceptual sensation. This has been studied in tactile-emotion synesthesia (e.g., feeling sandpaper evokes a feeling of jealousy; Ramachandran and Brang, 2008). Synesthetic associations, like misophonic experiences, are automatic (in the sense that they do not take effort or conscious deliberation), are consistent within an individual and persist throughout life, and seem to run in families (Asher et al., 2009; Tomson et al., 2011; for a review see Brang and Ramachandran, 2011). Given these similarities, neuroimaging findings in synesthetes may provide us with hypotheses on the neural basis of misophonia. First, associated sensations in synesthesia are found to be associated with co-activation in relevant (associated) brain areas (Nunn et al., 2002; Hubbard et al., 2005; Rouw et al., 2011). Furthermore, previous studies support a direct linking of relevant sensory regions in synesthesia (Hubbard and Ramachandran, 2001), mediated by an actual increase of anatomical connectivity (Rouw and Scholte, 2007; Zamm et al., 2013). Similarly, altered connections from a lesioned thalamus to the cerebral cortex (Ro et al., 2007; Beauchamp and Ro, 2008) led to a type of acquired synesthesia in which auditory stimuli produced tactile percepts. Differing in the level of specificity and complexity of evoked responses observed in synesthetes, individuals with misophonia display basic and non-elaborated responses to triggering stimuli, varying largely in the intensity of the response. Nevertheless, the underlying neurological cause of this condition may be similar to that of synesthesia in terms of enhanced connectivity between relevant brain regions. In short, a pathological distortion of connections between the auditory cortex and limbic structures could cause a form of sound-emotion synesthesia.

This study also provides the critical finding of a relationship between aversive stimuli in misophonia and mildly aversive stimuli in the general population. That is, in Experiment 2 we observed a significant correlation between aversive ratings across the groups, suggesting that misophonia may be based on mechanisms fundamentally present in the general population, but simply exaggerated in misophonia. Critically, as observed in the interviews in Experiment 1, many of the common aversive stimuli in misophonia are also deemed as socially inappropriate in western society (e.g., lip smacking, repetitive tapping, etc.). While speculative at present, this consistent pattern raises the possibility that the aversive nature of these stimuli to all individuals may be based on the same driving factors (though notably more mild) as in misophonia, leading to the development of these cultural norms.

The present paradigm was designed to include a range of aversive stimuli for misophonic individuals based on our preliminary interviews in Experiment 1. Accordingly, misophonic individuals reported a large number of the stimuli as aversive: mean 24.2% and median 24.7% stimuli with a rating of 3 or 4. In contrast, control participants reported very few stimuli as very aversive: mean 2.4% and median 0.0% stimuli with a rating of 3 or 4 (**Figures 3A,B**). Potential future studies are suggested to examine if this same pattern of group differences is consistent with stimuli that evoke a broader range of aversive responses in typically developed individuals.

As the current study is exploratory in nature and included a small sample of participants, there are several limitations to acknowledge. One limitation is that the presentation of stimuli in a controlled laboratory setting lacked the ecological validity of how these stimuli occur in the real world. As such, several misophonics reported that because they knew each clip would end in a matter of seconds, their physiological reactions were tempered, consistent with self-reports in Experiment 1 showing that contextual information about these cues mediated subjects' responses. We predict naturalistic observational studies of physiological reactions in misophonic individuals will show a similar but more extreme pattern of results to those observed here. A second limitation is that while SCR is a good measure of autonomic arousal in response to emotion-eliciting stimuli, it does not indicate what specific emotion is being experienced at the time. Instead it only indicates a very general, physiological arousal that can be interpreted in many ways. For example, SCR would not be able to differentiate anxiety and aggression. However, information as to what exactly a subject was feeling during each stimulus can potentially be inferred by obtained self-reports after each trial. A third limitation is the fact that no rigorous diagnostic tests or screenings were utilized during interviews to completely exclude the possibility that subjects' symptoms were being driven by another underlying condition. Also, interviews were conducted by members of our research group and not by psychiatrists. Potentially comorbid conditions were therefore determined from the self-reports of subjects (some of whom had previous, official diagnoses), and the discretion of the researchers. However, because these interviews were not conducted with the intent of being clinical or diagnostic in nature, but rather to gain more insight into the phenomenological experiences of individuals who identify with having misophonia, we believe these findings are still of considerable value to the research community and misophonic individuals alike. A fourth limitation of the study is the small sample size. As research on misophonia is limited to the last few years and little remains known about the condition, obtaining a large sample size for this study was not feasible. Nevertheless, while these results should be validated on a larger group of subjects, we believe they reflect properties of the condition generalizable to the misophonia community in general.

While these data serve to support the veracity of the subjective reports in misophonia as an intrusive and labile condition, numerous additional avenues remain for future research. Critically, as this condition appears to be chronic, the nature of how subjects' triggers evolve over time should be investigated. How does context contribute to and modulate misophonia and can contextual information or expectation effects bias subjects' responses to aversive stimuli? Critically, what are the mechanisms (genetic, neurological, and/or psychological) that underlie the condition? While speculative at present, one potential neural mechanism for misophonia may lie in aberrant anatomical or functional connections between auditory and limbic regions, akin to the finding of increased structural connectivity in synesthesia. Regardless of the mechanisms that underlie misophonia, the present research supports its validity as an intrusive condition and highlights the need for additional research into contributing factors and potential treatments.

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GENERAL COMMENTARY
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Contagious scratching: shared feelings but not shared body locations

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A commentary on

The neural basis of contagious itch and why some people are more prone to it
by Holle, H., Warne, K., Seth, A. K., Critchley, H. D., and Ward, J. (2012). Proc. Natl. Acad. Sci. U.S.A. 109, 19816–19821.

Listening to a lecture on "itching—what's behind it?" can induce observable scratching behavior and self-reported itchiness in the audience (Niemeier and Gieler, 2000). In another study, Papoiu et al. (2011) showed 5 min movies of scratching or rest (either with or without an itch-inducing histamine injection) and noted that watching scratching can increase self-reported itchiness and scratching although the effects tended to be small in participants without a pre-existing dermatological condition.

Previous speculations concerning the neural basis of socially contagious itching have centered on the action-based mirror system (e.g., Ikoma et al., 2006). Recently, Holle et al. (2012) attempted to explore this using fMRI. The stimuli consisted of brief (20 s) movies depicting scratching to the arm or upper chest, and the control movies consisted of tapping the same body part (i.e., the control stimuli involve both a motor act and self-directed touch but imply quite different bodily states). The movies were cropped at the neck to avoid facial expression. The movies depicting scratching were effective inducers of self-reported itch. Participants tested outside the scanner were videotaped and the scratch movies tended to induce scratching behavior (participants in the scanner were instructed not to scratch). The movies depicting scratching (minus tapping) activated many of the regions associated with physically induced itch (via histamine administration) including the premotor cortex, inferior frontal lobe, anterior insula, and primary somatosensory cortex. Thus, contagious scratching is by no means limited to motor-related regions of the brain.

In this commentary, we carry out an additional analysis of the gestures of the videotaped participants in Holle et al. (2012) to examine which aspects of the scratching gesture were reproduced. Two independent raters were asked to determine: (A) whether the participants scratched themselves vs. performed some other body-directed action (e.g., touching); (B) to note the bodily location acted upon; and (C) the hand used. The second rater was blind as to the nature of the visual stimulus presented to the participants and a third rater (again blind) was used to adjudicate between disagreements. **Figure 1A** shows that when participants observed a movie depicting scratching they were more likely to scratch themselves ($\chi^2 = 3.81$, $P < 0.05$). That is, both the quality of itchiness (self-reported) and the action of scratching (as observed) is vicariously shared—as already noted by Holle et al. (2012). However, our new analysis shows that other features of the event are *not* vicariously shared. **Figure 1B**) shows the hand used to perform the scratching action in relation to the hand observed to perform the action[1]. It can be seen that participants use their left and right hands equally often to scratch themselves and this is independent of the hand used in the visual stimulus ($\chi^2 = 0.14$). Similarly, we coded the part of the body that was scratched. Although the visual stimuli depicted scratching only to the arms and chest (and with cropping at the neck), the vast majority of the participants' own scratches were directed toward their face and hair (see **Figure 1C**). That is, the bodily location of itching/scratching is not vicariously shared but, instead, gravitates toward the head.

A tendency to scratch body parts distant to that observed was also reported by Papoiu et al. (2011). In that study the participant had been injected with histamine (or saline) in one arm and this would be expected to induce localized itching. In everyday contexts, self-touch (including scratching) is common during social encounters and may be amplified by anxiety (Ekman and Friesen, 1969) or cognitive effort (Barroso et al., 1980) with the hands and face being the most common targets (Goldberg and Rosenthal, 1986). Whatever the reason for the head being the bodily target, our data suggests the driving mechanism behind contagious scratching is related to the processing of affective or sensory quality rather than sharing of bodily locations/effectors. The fact that the anterior insula (involved in affect and interoception) was the only part of the brain to show a sustained response across the duration of the movies depicting itch is consistent with this. Furthermore, non-human primates, who are also susceptible to contagious itch (Nakayama, 2004), show the same pattern of scratching body parts different to the ones observed (Feneran et al., 2013) However, the vicarious perception of itch appears to differ from comparable findings of vicarious experiences of pain (Osborn and Derbyshire, 2010) or touch (Banissy et al., 2009) in response to seeing pain and touch. In both of these

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[1] Only the actions coded as scratching are displayed, although the pattern is essentially the same when non-scratch actions are analysed.

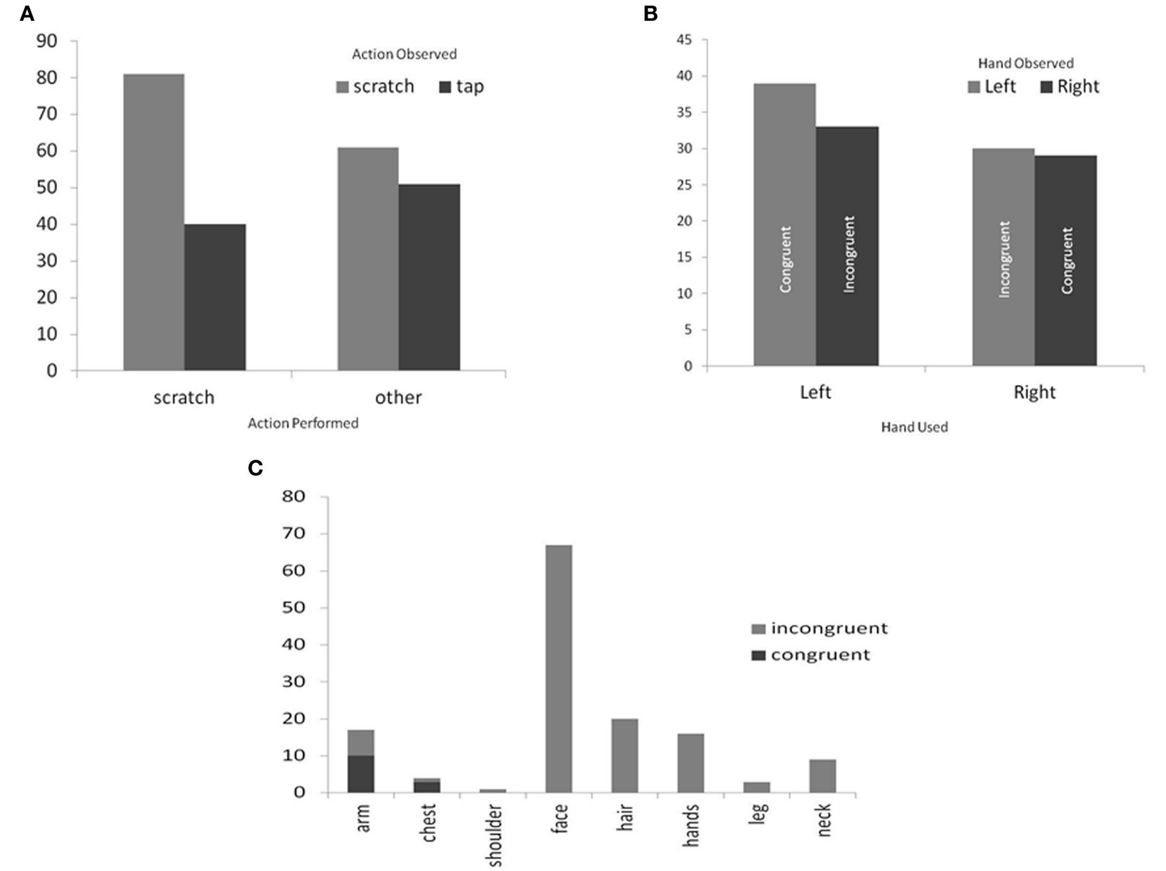

FIGURE 1 | Frequency counts for (A) different actions performed in relation to the current action observed (B) the hand used to perform scratching in relation to the hand observed and (C) the part of the body that was scratched (note: participants only ever saw the arm and torso scratched).

cases, there is a direct correspondence between the body observed and the location of vicarious experience (i.e., seeing touch to the arm is felt on the arm), at least in normal-bodied individuals (i.e., non-amputees).

It would be interesting to know whether the bodily target differs between socially induced itch (i.e., vicarious perception) vs. conceptually induced itch (e.g., images of fleas). A more recent behavioral study by Lloyd et al. (2013) used static images of itch-related stimuli (e.g., fleas) and actions (i.e., scratching) and found that these induce both itchiness and scratching relative to neutral control stimuli. Images of bugs on the skin tended to be more potent inducers than images of scratching actions themselves. Again, this is consistent with the idea that contagious itchiness may be more driven by vicarious perception of the feeling state (itchiness/unpleasantness) rather than contagion of the motor act or bodily target.

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Interpersonal motor resonance in autism spectrum disorder: evidence against a global "mirror system" deficit

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The mirror neuron hypothesis of autism is highly controversial, in part because there are conflicting reports as to whether putative indices of mirror system activity are actually deficient in autism spectrum disorder (ASD). Recent evidence suggests that a typical putative mirror system response may be seen in people with an ASD when there is a degree of social relevance to the visual stimuli used to elicit that response. Individuals with ASD ($n = 32$) and matched neurotypical controls ($n = 32$) completed a transcranial magnetic stimulation (TMS) experiment in which the left primary motor cortex (M1) was stimulated during the observation of static hands, individual (i.e., one person) hand actions, and interactive (i.e., two person) hand actions. Motor-evoked potentials (MEP) were recorded from the contralateral first dorsal interosseous, and used to generate an index of interpersonal motor resonance (IMR; a putative measure of mirror system activity) during action observation. There was no difference between ASD and NT groups in the level of IMR during the observation of these actions. These findings provide evidence against a global mirror system deficit in ASD, and this evidence appears to extend beyond stimuli that have social relevance. Attentional and visual processing influences may be important for understanding the apparent role of IMR in the pathophysiology of ASD.

Keywords: mirror neurons, interaction, transcranial magnetic stimulation, primary motor cortex, electromyography

INTRODUCTION

The "mirror neuron hypothesis" is perhaps the most controversial recent theoretical account of autism spectrum disorder (ASD). Briefly, mirror neurons, which are cortical cells that fire during the performance and observation of behavior (Rizzolatti and Sinigaglia, 2010), were first identified in macaques (Di Pellegrino et al., 1992), and an analogous fronto-parietal "mirror system" has since been established in humans via a range of non-invasive neuroimaging and neurophysiological techniques (Rizzolatti and Sinigaglia, 2010). Beyond motor behavior, mirror systems have also been identified with respect to overlapping brain regions involved in the experience and observation of emotion, sensation, and pain (Keysers and Gazzola, 2009; Fitzgibbon et al., 2012). As mirror systems appear to simulate other's brain activity, they have been linked to a range of higher-order social cognitive processes, several of which are impaired in ASD. Accordingly, it has been suggested that dysfunction within mirror system circuitry, or of mirror neurons themselves, might contribute to ASD (Iacoboni and Dapretto, 2006; Oberman and Ramachandran, 2007; Rizzolatti and Fabbri-Destro, 2010). There are, however, arguments against such impairment (Gallese et al., 2011; Hamilton, 2013), and debate as to whether mirror systems are actually deficient in ASD.

Supporting evidence for mirror system dysfunction in ASD comes from a range of neurophysiological (Oberman et al., 2005; Bernier et al., 2007), neuroimaging (Dapretto et al., 2006; Hadjikhani et al., 2006, 2007), and brain stimulation studies (Theoret et al., 2005; Enticott et al., 2012c). These studies generally utilize an index of interpersonal motor resonance (IMR), which broadly refers to the activation of an individual's motor (or sensorimotor) system during the observation of another person's motor behavior (Uithol et al., 2011). Accordingly, IMR is typically considered a putative measure of mirror system activity. There seems to be little doubt that there are instances in which IMR is reduced in ASD, although increasingly there are studies that report no such deficit (Oberman et al., 2008; Raymaekers et al., 2009; Dinstein et al., 2010; Fan et al., 2010; Bastiaansen et al., 2011; Marsh and Hamilton, 2011). Among those studies that do report a deficit, perhaps most controversial is what these findings actually mean for our understanding of ASD; for example, whether they reflect an underlying neuropathophysiology that contributes to the clinical presentation, or are simply a neurobiological consequence of a lifetime of aberrant social engagement.

Given the proposed link between mirror systems and interpersonal understanding, there has been some interest in IMR during the observation of interactive or social behavior. For instance, there is evidence that IMR is enhanced during the observation of interactive behavior (Iacoboni et al., 2004; Oberman et al., 2007), particularly when there is a negative affective component (Enticott et al., 2011). Increased IMR is also seen during the observation of joint and complimentary actions

(Newman-Norlund et al., 2007; Sebanz et al., 2007; Newman-Norlund et al., 2008). This is clearly of relevance to our understanding of ASD, which is characterized by difficulties in understanding other people and their interactions (Rapin, 1997). A study of 13 boys with ASD (and matched controls) showed that typical sensorimotor resonance [indexed via electroencephalogram (EEG) mu suppression] was evoked in ASD, but only when the intransitive hand gesture was performed by a familiar individual (e.g., parent) (Oberman et al., 2008). Although several factors may have underpinned this particular finding (e.g., familiarity, emotional relevance), this led the authors to speculate that the mirror system in ASD may be sensitive to the "social relevance" of the stimuli.

The current study used transcranial magnetic stimulation (TMS) to investigate IMR, a putative measure of mirror system activity, during the observation of individual and interactive hand movements among individuals with ASD. In line with the suggestion that social relevance may promote a typical mirror system response in ASD, it was hypothesized that IMR would be reduced in ASD for individual but not interactive conditions.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 32 individuals with ASD [i.e., diagnosed with either autism (high-functioning) or Asperger's disorder] and 32 neurotypical (NT) controls (see **Table 1** for participant demographics). All clinical participants had been diagnosed by an experienced clinician (psychologist, psychiatrist, or paediatrician) according to DSM-IV criteria (American Psychiatric Association, 1994). The diagnosis was confirmed via diagnostic report or through communication with the diagnosing clinician. Eleven of the clinical participants were medicated (6 selective serotonin reuptake inhibitor, 2 selective serotonin reuptake inhibitor /atypical antipsychotic, 2 selective serotonin reuptake inhibitor/atypical antipsychotic/benzodiazepine, 1 tetracyclic antidepressant, 1 atypical antipsychotic, 1 serotonin-norepinephrine reuptake inhibitor). Control participants all reported no history of neurological or psychiatric illness (including substance abuse). All participants met safety criteria for TMS and provided written informed consent. Ethical approval was granted by the human research ethics committees of Alfred Health, Monash University, and Southern Health.

Table 1 | Participant demographics.

	ASD	Controls
n	32	32
Mean age in years (SD)	24.75 (8.11)	25.53 (6.36)
Gender (M:F)	24:8	23:9
Mean years of formal education (SD)†	14.67 (4.03)	17.48 (3.44)
Handedness (EHI) (R:L:A)	24:4:4	29:3:0
Mean KBIT-2 VIQ (SD)*	99.88 (17.72)	108.29 (13.54)
Mean KBIT-2 PIQ (SD)	107.78 (20.02)	112.52 (13.72)
Mean KBIT-2 FSIQ (SD)	104.63 (20.06)	112.13 (13.93)
Mean AQ (SD)#	30.97 (8.84)	13.29 (5.72)
Mean RAADS (SD)#	103.84 (39.29)	33.52 (22.86)
Mean DBC Total (SD)*	60.19 (21.64)	1.00 (–)
Mean DBC Autism Screen (SD)*	20.71 (7.16)	1.00 (–)

**p* < 0.05, †*p* < 0.01, #*p* < 0.001.

EHI, Edinburgh handedness inventory (Oldfield, 1971); KBIT-2, Kaufman brief intelligence test, second edition; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FSIQ, full-scale intelligence quotient; AQ, autism spectrum quotient (Baron-Cohen et al., 2001); RAADS, Ritvo autism-aspergers diagnostic scale (Ritvo et al., 2008); DBC, Developmental Behaviour Checklist (Einfeld and Tonge, 2002).

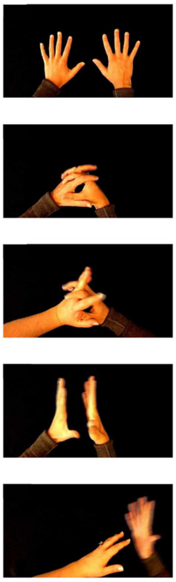
MATERIALS

Consistent with previous research (Gangitano et al., 2004; Fadiga et al., 2005; Theoret et al., 2005; Enticott et al., 2008a,b, 2012a,c), IMR was assessed by administering single pulse TMS to left primary motor cortex (M1), and recording responses in the right first dorsal interosseous via electromyography (EMG), during the observation of short videos featuring hand actions that involve the first dorsal interosseous. Stimuli were identical to those used in a previous study (Enticott et al., 2011), and involved five different videos of approximately 3–4 s duration (see **Figure 1** for screenshots and descriptions): one demonstrating static hands (i.e., control/baseline condition), two demonstrating an individual's hand movements (involving the left and right hands from what was clearly the same person), and two demonstrating interactive hand movements (involving a left hand and a right hand from what were clearly two different people). The individual and interactive videos involved one in which the movement type was "approach" (i.e., right hand approaching the left hand) and one in which the movement type was "removal" (i.e., right hand moving away from the left hand). Ratings confirming the interactive and emotional content within each video are presented elsewhere, but essentially the "interactive removal" clip was rated as more emotional and more negative than the other clips (Enticott et al., 2011). The videos were designed such that the motor properties were matched for the two "approach" videos and for the two "removal" videos, thus enabling a valid comparison with respect to our index of mirror neuron activity. EMG equivalence within the two "approach" videos and the two "removal" videos was confirmed via separate EMG recordings, with <0.05 mV root mean square difference in EMG activity in the right first dorsal interosseous between the matched videos.

Single pulse TMS was administered using a Magstim-200 stimulator (Magstim Company Ltd., UK). EMG signals were amplified using PowerLab/4SP (AD Instruments, Colorado Springs, CO), and sampled via a CED Micro 1401 mk II analogue-to-digital converting unit (Cambridge Electronic Design, Cambridge, UK).

PROCEDURE

Participants were seated 120 cm in front of a 22″ widescreen (16:9) LCD monitor on which the video stimuli were presented (visual angle of video stimuli: 17.99 × 14.25°, although as seen in **Figure 1** the hand actions comprised only a small proportion of the screen). Participants were not administered a formal test of visual acuity, but those that required eye glasses wore them throughout the procedure. Coil location for the stimulation of M1 was the scalp position that produced the largest amplitude



1. Static Hands (dorsal view)
Dorsal view of two still hands from the same person

2. Individual approach
Left and right hands from the same person clasp together

3. Interactive approach
Left and right hands from clearly different people clasp together

4. Individual removal
Left and right hands from the same person release a clasp

5. Interactive removal
Left hand moves from left of screen to touch another person's right hand, right hand moves away thereby avoiding touch from left hand

FIGURE 1 | Screenshots and descriptions of the five stimuli.

MEP in the contralateral first dorsal interosseous while at rest. Resting motor threshold was the lowest stimulation intensity that produced motor-evoked potentials of at least 50 μV on 3/5 consecutive trials. Participants watched the video presentation, which was comprised of each of the five videos presented ten times in a quasi-random sequence. There was a 2000 ms interval between each clip, during which a black screen was displayed. For the static clip, a single TMS pulse was administered to left M1 approximately 2 s into the video. For the approach clips, a single TMS pulse was administered to left M1 immediately before the hands made contact. For the removal clips, a single TMS pulse was administered to left M1 immediately after the right hand started to move away from the left hand. This was based on optimal index finger/thumb aperture for generating sufficient IMR (Gangitano et al., 2001), and each involved index finger flexion/extension. TMS pulses during the video presentation were delivered at 120% of the RMT. Pulses administered during the video presentation were approximately 5–6 s apart. Triggering of the TMS stimulator was achieved via a light-sensor device that was placed over the upper left corner of the screen; embedded within each video was a brief white light that was hidden beneath the sensor and would appear at the designated frame, thus triggering the TMS pulse and EMG recording. Before and after the video presentation, participants were administered ten TMS pulses while at rest (4 s inter-stimulus interval) to determine whether the procedure itself, which might be considered a form of low-frequency repetitive TMS that could affect corticospinal excitability (Fitzgerald et al., 2006), induced any changes in corticospinal excitability.

DATA ANALYSIS

Trials in which there was evidence of tonic muscle activity within 200 ms prior to TMS administration were not included in the analyses (<0.5% of all trials). Consistent with our previous research (Enticott et al., 2011, 2012a,b,c), raw median MEP values were converted to reflect a percentage change relative to the baseline "static hands" condition [i.e., MEP percentage change (MEP-PC)], with a greater score indicative of greater IMR. Data screening of MEP-PC revealed non-normality, and we performed a square root data transformation. As a square root transformation cannot be performed for negative values (and some MEP-PC values were negative), prior to the transformation we added a constant of 100 to each of the values to ensure that they were all positive. Two extreme outliers (±3 *SD* from mean) following the transformation (interactive approach; both control participants) were adjusted to 0.01 above the next most extreme value. Normality was reassessed following transformation and found to be within acceptable limits. Data were analysed via a 2 (group: ASD vs. controls) × 2 (interpersonal type: individual vs. interactive) × 2 (movement type: approach vs. removal) mixed-model analysis of variance (ANOVA). Independent samples and paired samples *t*-tests were used for all follow-up analyses. We also used *t*-tests to examine whether there were any between-group differences in corticospinal excitability (i.e., raw median MEP values) across the various condition, and to determine whether the procedure itself had any influence on corticospinal excitability (i.e., raw median MEP values before and after the video presentation).

RESULTS

Untransformed data are presented in **Figure 2**. For the overall mixed model analysis, there was no main effect of group, $F_{(1,\,62)} = 0.11$, $p = 0.915$, $\eta_p^2 < 0.001$, nor was there an interaction effect for movement type × group, $F_{(1,\,62)} = 0.70$, $p = 0.406$, $\eta_p^2 = 0.01$ interpersonal type × group, $F_{(1,\,62)} = 3.13$, $p = 0.082$, $\eta_p^2 = 0.05$, or interpersonal type × movement type × group, $F_{(1,\,62)} = 3.09$, $p = 0.084$, $\eta_p^2 = 0.05$. Thus, concerning our hypothesis, there was no evidence for an *overall* IMR deficit in

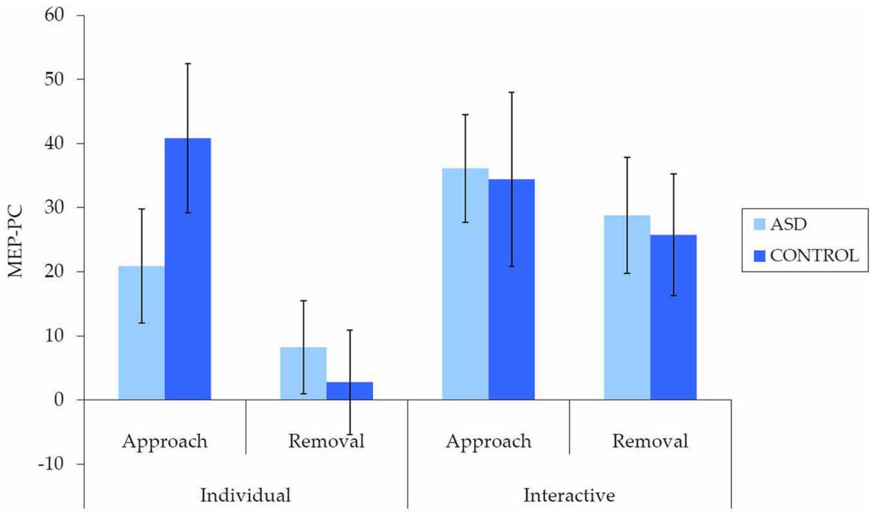


FIGURE 2 | Mean (±SE) (untransformed) MEP-PC by group for each condition; a greater score is indicative of enhanced IMR.

ASD for either the individual or interactive videos, nor was there evidence for any other reduction in IMR activity in ASD.

There were also a number of main and interaction effects that did not involve between-group effects. There was a main effect of interpersonal type, $F_{(1,\ 62)} = 8.66$, $p = 0.005$, $\eta_p^2 = 0.12$, with greater MEP-PC for interactive than individual movements, and a main effect of movement type, $F_{(1,\ 62)} = 8.64$, $p = 0.005$, $\eta_p^2 = 0.12$, with greater MEP-PC for approach than removal movement types. There was also an interaction effect between interpersonal type and movement type, $F_{(1,\ 62)} = 4.82$, $p = 0.032$, $\eta_p^2 = 0.07$. Subsequent analyses revealed greater MEP-PC for interactive removal than individual removal, $t_{(63)} = -3.38$, $p = 0.001$, $d = 0.47$, but no difference between individual approach and interactive approach, $t_{(63)} = -0.54$, $p = 0.957$, $d = 0.01$.

This pattern of results did not differ when including only right-handed participants: there was no main effect of group, $F_{(1,\ 51)} = 0.13$, $p = 0.723$, $\eta_p^2 = 0.002$, nor was there an interaction effect for movement type × group, $F_{(1,\ 51)} = 1.62$, $p = 0.209$, $\eta_p^2 = 0.03$, interpersonal type × group, $F_{(1,\ 51)} = 3.96$, $p = 0.052$, $\eta_p^2 = 0.07$, or interpersonal type × movement type × group, $F_{(1,\ 51)} = 3.52$, $p = 0.066$, $\eta_p^2 = 0.07$. This suggests that these findings are unlikely to have been affected by handedness, or between-group differences in handedness.

Examination of raw MEP values indicated that corticospinal excitability was comparable for the ASD and NT groups (**Figure 3**). Independent samples t-tests revealed no between-group differences in median MEP amplitude for any of the five conditions [static hands: $t_{(62)} = 0.27$, $p = 0.788$, $d = 0.07$; individual approach: $t_{(62)} = -0.77$, $p = 0.939$, $d = 0.02$; interactive approach: $t_{(62)} = 0.43$, $p = 0.667$, $d = 0.11$; individual removal: $t_{(62)} = 0.29$, $p = 0.769$, $d = 0.07$; interactive removal: $t_{(62)} = 0.32$, $p = 0.749$, $d = 0.08$].

There was also no evidence to suggest that the TMS procedure altered corticospinal excitability in either group. Independent samples t-tests revealed no between-group differences in corticospinal excitability either before, $t_{(62)} = 0.47$, $p = 0.640$, $d = 0.12$ (ASD: $M = 0.86$ mV, $SE = 0.11$; NT: $M = 0.79$ mV, $SE = 0.11$), or after the video presentation, $t_{(62)} = 0.58$, $p = 0.563$, $d = 0.15$ (ASD: $M = 0.85$ mV, $SE = 0.13$; NT: $M = 0.76$, $SE = 0.09$). Similarly, paired samples t-tests revealed no differences in corticospinal excitability before and after the video presentation for either the ASD, $t_{(31)} = 0.14$, $p = 0.889$, $d = 0.02$, or NT group, $t_{(31)} = 0.27$, $p = 0.792$, $d = 0.05$.

As there were some between-group differences on demographic/cognitive variables (education, VIQ), we also performed Pearson correlations between measures of IMR and education/IQ. As presented in **Table 2**, these correlations were all weak and non-significant, suggesting that IMR was unlikely to have been influenced by these between-group differences.

DISCUSSION

The current study utilized individual and interactive displays of hand movements to investigate IMR in ASD, which is broadly considered a means of testing the involvement of the "mirror system" in the neuropathophysiology of ASD. With respect to the observation of interactive hands, our hypothesis was supported: individuals with ASD did not show evidence of reduced IMR during the observation of interactive behavior. Contrary to our expectations, however, individuals with ASD did not exhibit evidence of reduced IMR compared to NT control participants during the observation of individual movements. Thus, in the current paradigm, there was no evidence for a reduction in IMR in ASD for either individual or interactive hand movements. Importantly, our analysis of raw MEP amplitudes confirmed that this was not attributable to baseline (or other) differences in the EMG response to TMS (i.e., corticospinal excitability), while the TMS procedure itself did not affect corticospinal excitability in either group. Additional findings that did not involve between-group effects were largely consistent with previous research (Enticott et al., 2011), and indicated greater IMR for interactive (relative

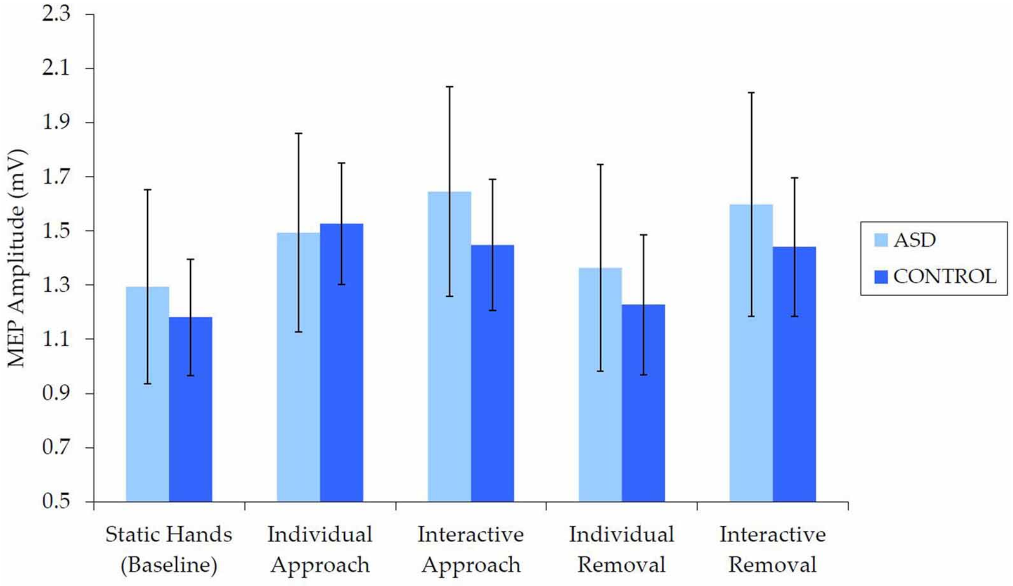


FIGURE 3 | Mean (±SE) raw (median) MEP by group for each condition, which demonstrates no differences in corticospinal excitability.

Table 2 | Correlations between IMR and education/IQ (p-value in parentheses).

	Individual approach	Interactive approach	Individual removal	Interactive removal
Education	0.111 (0.384)	−0.004 (0.976)	−0.038 (0.766)	0.056 (0.662)
VIQ	0.040 (0.754)	−0.033 (0.798)	−0.178 (0.163)	0.016 (0.898)
PIQ	0.011 (0.935)	−0.034 (0.790)	−0.152 (0.233)	0.034 (0.794)
FSIQ	0.035 (0.786)	−0.033 (0.798)	−0.174 (0.173)	0.033 (0.795)

to individual) and approach (relative to removal) videos, and an increase in activity for the interactive removal (relative to individual removal) video.

While there was no evidence to suggest a mirror system impairment in ASD, there were some interaction effects that approached significance; specifically, interpersonal type × group, and interpersonal type × movement type × group. These were each associated with a small to medium effect size, but raise the possibility of a type II error. Examination of mean data suggests the possibility of subtle differences in the pattern of responding for each group (e.g., enhanced interactive compared to individual in the ASD group). Taken together with other results, however, these again are not indicative of an "impairment" in ASD. Nevertheless, teasing out these subtle differences in mirror system activation will be an important consideration in future research.

These findings add to the controversy surrounding the role of mirror systems in ASD (Gallese et al., 2011; Hamilton, 2013) by further demonstrating that there are stimuli that evoke typical IMR in this population. Nevertheless, they are by no means entirely inconsistent with the literature, as there are a number of studies that report no mirror system impairments in ASD. For instance, Oberman et al. (2008) found that children with ASD showed appropriate sensorimotor resonance when observing grasping actions of a familiar person, while both Fan et al. (2010) and Raymaekers et al. (2009) found no evidence of reduced sensorimotor resonance among 20 children with ASD who observed hand movements. Several fMRI studies have also reported no abnormalities in the BOLD response in presumed mirror system regions among adults with ASD, with stimuli including transitive hand actions (Marsh and Hamilton, 2011) ($n = 18$ ASD), still images of hand gestures (Dinstein et al., 2010) ($n = 13$ ASD), and facial expressions (Bastiaansen et al., 2011) ($n = 21$ ASD). Studies that have and have not found these impairments in ASD seem to be comparable with respect to sample size, clinical characteristics, neuroscience techniques, and broad types of visual stimuli; thus, the heterogeneity of ASD might appear to be the most likely candidate to explain these inconsistent findings. The current results, however, cannot be attributed to such heterogeneity, as most of the participants in this study also completed a previous study in which IMR impairments in ASD were revealed during the observation of single hand transitive action (Enticott et al., 2012c). Interestingly, Theoret et al. (2005) found a deficit in IMR among individuals with ASD only when viewing a hand from an egocentric position, and it was suggested that this may reflect deficits in the representation of self. While the hands in the current study were positioned in this way, the use of multiple hands (including presentations involving hands from multiple people) may have reduced or eliminated any self-referential aspect to the stimuli.

These findings clearly argue against a global mirror system deficit in ASD, and thus these findings place substantive limitations on the "mirror neuron hypothesis of autism." In the context of the previous literature, this study does not necessarily argue against any mirror system dysfunction in ASD. It does, however, suggest that there are situations in which IMR during action observation, a putative index of a mirror system response, is typical in ASD. It is now critical to establish the conditions under which IMR impairments are evident in ASD, and how this might relate to (or perhaps stem from) the behavioral phenotype of ASD.

There are other possible explanations regarding evidence for IMR deficits in ASD, and some of these would indeed argue against any level of mirror system dysfunction in ASD. For instance, it might be suggested that any observed deficits in IMR are not due to dysfunctional mirror system activity, but rather result from impairments in biological motion processing and attention in ASD that prevent subsequent mirror system activity. Concerning the former, there is evidence to suggest that individuals with ASD show atypical perception of biological motion, both at a behavioral level (e.g., reduced visual preference for biological motion; Klin et al., 2009; Annaz et al., 2012) and at a brain level (i.e., abnormal pattern of brain activation during biological motion perception; Kaiser and Pelphrey, 2012). Thus, it is conceivable that any deficit in IMR may actually result from earlier abnormalities in visual perception. This would not, however, provide an explanation for the current findings, where IMR during the observation of biological motion appeared largely typical, and certainly not significantly reduced.

The issue of attentional processing is difficult to disentangle from the perception of biological motion, but might provide a better alternative explanation for the current findings in the context of past literature. Clinically, individuals with ASD are generally thought to have a preference for objects over people (Rapin, 1997). Thus, when there is an object present (as in our previous study that showed IMR impairment; Enticott et al., 2012c), individuals with ASD may devote more attentional resources to the object and less to the human action (thus preventing IMR). This, however, fails to account for those studies demonstrating impairment in ASD when viewing intransitive actions (i.e., when there is no object present; e.g., Oberman et al., 2005; Theoret et al., 2005). Alternatively, and consistent with the weak central coherence account of ASD (which emphasizes enhanced local processing at the expense of global processing; Happe, 2005), they may attend to a specific feature of the object or the hand (e.g., the space between the fingers) rather than the active muscle region. In the current study, there were no objects present, perhaps encouraging individuals with ASD to entirely attend to the biological motion aspects (thereby promoting IMR). It may also be the case that the stimuli used in this study held greater interest or relevance for ASD participants than in other studies, meaning that they were more likely to sufficiently attend to the presentation (resulting in an IMR response that did not differ from controls). In some respects this is a motivational account, whereby participants with ASD need to be motivated to devote adequate attentional resources to the motion aspect of the stimuli. In any case, it would again argue against a specific mirror system deficit in ASD.

The issues of attention and processing of biological motion seem to be critical to truly understanding whether mirror systems play a role in the pathophysiology of ASD. At a minimum, future studies could integrate eye tracking techniques into existing neuroimaging or electrophysiological paradigms, or provide visual cues for ensuring that a particular aspect of biological motion is attended to. This issue is not specific to studies devoted to mirror circuitry, but would presumably apply to a range of neurobehavioral testing paradigms used commonly in ASD (e.g., tests of executive function or theory of mind). It is important to note that even if findings are modulated by these visual and attentional factors, it still does not necessarily argue against the mirror neuron hypothesis of autism, but would suggest an earlier and more general mechanism that leads to underactivity of the mirror system in ASD.

Limitations to this study include measurement of only the left cerebral hemisphere, a failure to probe individual participants about their interpretation of the stimuli, and the inclusion of medicated participants (although no between-group differences in corticospinal excitability were evident, medication effects cannot be ruled out). As noted, future research in this area should look to integrate neuroscience techniques (e.g., fMRI, TMS, EEG) with eye-tracking technology; this will go some way toward testing whether aberrant IMR is related to differences in visual attention (e.g., focusing on an object at the expense of a moving hand). A failure to detect group differences might also be due to the large variability of responses within each group, particularly for the *individual approach* condition. It is also important to note that the stimuli used here are very different to those used in classic "mirror neuron" studies among primates (which typically involve meaning, object-oriented actions). Thus, one might argue that the failure to find a difference is due to a failure to elicit mirror neuron activity in either group. While we cannot know whether true "mirror neurons" were indeed elicited by our stimuli, this is the case in all such non-invasive human research, and we have been careful to instead refer to IMR and mirror systems (i.e., increased motor cortical activity during the observation of motor behavior). It remains that both groups did demonstrate such increases in motor cortical activity. Nevertheless, the issue of whether these non-invasive paradigms are actually indexing (at least in part) true mirror neurons remains an important but elusive problem for this field of research.

In any event, these findings suggest that ASD is not characterized by a global deficit in mirror system activity, as there are conditions that produce largely appropriate levels of IMR in ASD. It remains to be determined why individuals with ASD do sometimes show reduced activity IMR during action observation, and whether this truly underpins the social and communicative deficits that characterize these conditions.

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Can studies of pain help to bridge the gap between sensory and social impairments in autism?

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In May of 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM) will release its 5th edition. In this edition, the DSM-IV-TR categories of autistic disorder, Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder (not otherwise specified) will be combined into a single "autism spectrum disorder" (ASD) category. ASD will be diagnosed according to two symptom domains: "social communication impairment" and "restricted interests/repetitive behaviors." The latter domain includes an additional feature that involves "hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment" (Huerta et al., 2012). The relationship between the symptom domains that comprise ASD is not well-understood, and it has been suggested that these domains are largely independent (Dworzynski et al., 2009). Unusual sensory processing in ASD may, however, be associated with a disruption in higher-level social processes (Leekam et al., 2007), and therefore the social and sensory features of ASD may be inherently linked. In this general commentary, we propose that pain, as both a sensory and social experience, provides a potential paradigm with which to explore the relationship between sensory abnormalities and social impairments in ASD.

Physical pain is defined as the sensory and emotional experience associated with actual or potential tissue damage (IASP, 1994). Initial research suggests that individuals with ASD may have an insensitivity to physical pain (e.g., Nader et al., 2004). Although more research is needed to better characterize the experience of pain in individuals with ASD, such sensory abnormalities may be related to deficits in higher-order perceptual processes (Leekam et al., 2007). In particular, individuals with ASD may also demonstrate difficulty in the ability to vicariously experience the pain of others, a process that has been argued as integral to social perception (Keysers et al., 2010).

Indeed, several investigations have demonstrated that the processing of pain within a social context may be unusual in individuals with ASD. For instance, research suggests that when healthy controls observe another person experience physical pain (i.e., *empathy for physical pain*), similar (although not identical) neural networks are activated as if experiencing actual physical pain (Lamm et al., 2011). Among both control and ASD groups, however, this response is inversely correlated with alexithymia (a common feature of ASD; Bird et al., 2010). Furthermore, using transcranial magnetic stimulation, observing images of another person experience physical pain reveals no motor inhibition in individuals with ASD compared to controls (Minio-Paluello et al., 2009). In healthy subjects, an inhibited motor response is typically found (Avenanti et al., 2005).

Although not a sensory experience like physical pain, "social pain," the experience of actual or potential damage to one's feeling of social connection or value, has also been shown to share overlapping neural networks with physical pain (Eisenberger, 2012). It has been hypothesized, that these shared neural mechanisms indicate that social pain is processed in the same way as physical pain. Moreover, it is suggested that this physiological overlap came about as an evolutionary adaptive process, whereby social pain mechanisms developed upon already existing processes for physical pain (MacDonald and Leary, 2005). In doing so, social pain is felt to encourage the development and maintenance of social bonds (Eisenberger, 2012). Thus, abnormalities within the physical pain network may impact upon the experience of social pain in ASD.

As expected, abnormalities in the neural experience of social pain have also been reported in individuals with ASD. For instance, two neuroimaging studies of social exclusion have found reduced activation within social pain brain regions identified in neurotypicals. Intriguingly, however, individuals with ASD reported levels of distress to the stimuli similar to that of controls (Bolling et al., 2011; Masten et al., 2011a). This suggests that people with ASD may not be impaired in their ability to recognize social pain, but that social pain may be processed differently. This is supported by a behavioral study of social pain in ASD; while there was no between group difference in the identification of social pain, people with ASD did not experience a subsequent reduction in mood that was found among controls (Sebastian et al., 2009).

Like empathy for physical pain, some brain regions active during the experience of social pain are also active when witnessing social pain in another (i.e., *empathy for social pain*) (e.g., Kross et al., 2011; Masten et al., 2011b). In a recent behavioral study exploring empathy for social pain in individuals with ASD, a similar empathy for social pain response to controls was observed when viewing *accidental* norm violations. In contrast, empathy for social pain was significantly reduced in ASD compared to controls when the norm violations were intentional (Paulus et al., 2013). This lack of behavioral resonance with another's social pain reflects the findings of reduced empathy for pain brain activity in individuals with ASD and its related features (Minio-Paluello et al., 2009; Bird et al., 2010), yet only in the condition requiring reflection on another person's mental state (i.e., identifying the intentionality of the behavior). Future imaging investigations should explore whether empathy for social pain recruits differential neural networks to controls, as is seen in social pain.

Taken together, these studies indicate that both physical and social pain are processed atypically in individuals with ASD. As these types of pain share overlapping neural substrates, sensory abnormalities in processing physical pain may, on some level, be associated with impaired social processing in ASD. Pain may therefore serve as a useful model in an attempt to bridge the gap between sensory abnormalities and impaired social function in ASD. This might contribute toward a more unified model of ASD. This is not only of potential importance in better understanding and managing ASD, but to psychiatric illnesses more generally where social impairments are becoming increasingly recognized (Cacioppo et al., 2007).

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Vicarious motor activation during action perception: beyond correlational evidence

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Neurophysiological and imaging studies have shown that seeing the actions of other individuals brings about the vicarious activation of motor regions involved in performing the same actions. While this suggests a simulative mechanism mediating the perception of others' actions, one cannot use such evidence to make inferences about the functional significance of vicarious activations. Indeed, a central aim in social neuroscience is to comprehend how vicarious activations allow the understanding of other people's behavior, and this requires to use stimulation or lesion methods to establish causal links from brain activity to cognitive functions. In the present work, we review studies investigating the effects of transient manipulations of brain activity or stable lesions in the motor system on individuals' ability to perceive and understand the actions of others. We conclude there is now compelling evidence that neural activity in the motor system is critical for such cognitive ability. More research using causal methods, however, is needed in order to disclose the limits and the conditions under which vicarious activations are required to perceive and understand actions of others as well as their emotions and somatic feelings.

Keywords: action perception, action simulation, mirror neurons, brain lesion, transcranial magnetic stimulation (TMS)

VICARIOUS MOTOR ACTIVATIONS DURING ACTION PERCEPTION

There is now extensive neurophysiological evidence that monkeys—and possibly humans—are equipped with a particular class of neurons active during action execution and action perception (Cattaneo and Rizzolatti, 2009; Mukamel et al., 2010). These so called "mirror neurons" are thought to implement a mechanism matching perceived actions to one's own motor representation of similar actions (di Pellegrino et al., 1992; Gallese et al., 1996; Fogassi et al., 2005). By showing that action perception modulates activity within the motor system, the discovery of mirror neurons has provided direct neurophysiological evidence in favor of the older notion that action perception is inherently linked to action execution (Lotze, 1852; James, 1890; Prinz, 1997). This idea was further supported in humans by functional magnetic resonance imaging (fMRI) (Etzel et al., 2008; Gazzola and Keysers, 2009; Kilner et al., 2009; Oosterhof et al., 2010), electroencephalography (EEG) (Cochin et al., 1999; Lepage and Théoret, 2006; Arnstein et al., 2011), and magnetoencephalography (MEG) (Nishitani and Hari, 2002; Nishitani et al., 2004) evidence that the action observation network (AON), i.e., the neural network activated by seeing others' actions, largely overlaps with the brain network involved in action execution. This has supported the notion that perceiving and understanding others' actions may be based on their vicarious representations within the observer's motor system.

One of the most convincing evidence that action observation vicariously activates motor circuits involved in performing the observed action in humans comes from single-pulse transcranial magnetic stimulation (TMS) studies. This neurophysiological method implies that single magnetic pulses are administered over the participants' primary motor cortex to record motor-evoked potentials from the targeted muscles and assess the excitability of their corticospinal representation under different experimental conditions. Many studies have shown that observing others' actions increases the excitability of the observers' corticospinal motor system (Fadiga et al., 1995; Catmur et al., 2007; Enticott et al., 2010, 2011; Senot et al., 2011). This "motor resonance" appears to be present for both transitive and intransitive movements (Fadiga et al., 2005; Romani et al., 2005; Borgomaneri et al., 2012) and is specific for the muscles involved in the observed action (Urgesi et al., 2006a; Alaerts et al., 2009; Candidi et al., 2010). Moreover, motor resonance is largely automatic and occurs early in time (Lepage et al., 2010; Barchiesi and Cattaneo, 2012). Furthermore, motor resonance is temporally coupled with the observed action when this is dynamically displayed (Gangitano et al., 2004) and seems to encode specific motor features such as the direction (Stefan et al., 2005; Barchiesi and Cattaneo, 2012) and the apparent effort of the action (Alaerts et al., 2010a,b; Tidoni et al., 2013). These findings demonstrate that action observation induces a dynamic simulation of the observed movement in the onlooker's motor system. Studies using cyclic movements

(Borroni et al., 2005) or static images of actions (Urgesi et al., 2006b, 2010; Avenanti et al., 2013), however, also indicate that action simulation may be biased toward the future phases of the observed movements, suggesting the motor system is involved in the predictive coding of observed actions as also highlighted by intracortical recordings in monkeys' premotor cortex (Umiltà et al., 2001).

Interestingly, motor resonance appears to be sensitive to higher order aspects of others' actions, such as the goal or the intention of the actor (Cattaneo et al., 2009; Tidoni et al., 2013), suggesting that motor cortex activity is influenced by processing occurring in higher-order regions within the AON. In keeping, there is now direct evidence that resonance in the motor cortex reflects computations carried out in the inferior frontal cortex (IFC, including the ventral premotor cortex and the posterior part of the inferior frontal gyrus) and the inferior parietal lobule (IPL). This is demonstrated by perturb-and-measure studies (Paus, 2005; Avenanti et al., 2007) in which off-line suppression of neural activity in IFC disrupts the motor facilitation induced by action observation (Avenanti et al., 2007, 2013; Enticott et al., 2012) and dual coil studies in which stimulation of IFC and IPL modulates motor cortex reactivity to observed actions (Koch et al., 2010; Catmur et al., 2011).

BRAIN STIMULATION AND LESION METHODS TO HIGHLIGHT CAUSAL LINK BETWEEN AON AND ACTION PERCEPTION

While neurophysiological and brain imaging techniques have been essential in highlighting that action simulation is automatically triggered by action observation, it should be noted that these approaches only provide correlational evidence and cannot establish whether neural activity in motor regions is necessary for action perception. Behavioral studies have shown that action execution affects the perception of others' actions, suggesting a close link between motor and perceptual processing in social interactions (Kilner et al., 2003; Hamilton et al., 2004; Schütz-Bosbach and Prinz, 2007a,b; D'Ausilio et al., 2010; Sacheli et al., 2012, 2013). Motor experts present superior perceptual abilities in the prediction of others' actions (Abernethy et al., 2008; Aglioti et al., 2008) and short-term action execution training improves perception of full (Hecht et al., 2001; Urgesi et al., 2012) and point-light (Casile and Giese, 2006) displays of the same action even if no visual feedback is provided during the execution phase. On the other hand, non-use of specific body parts, following massive deafferentation of lower limbs in spinal cord injury patients, leads to impaired recognition of their movements depicted in static images (Pernigo et al., 2012) and point-light (Arrighi et al., 2011) displays.

While behavioral studies have shown an influence of action execution on action perception these approaches do not tell "where" in the brain these two functions interact. Thus, to test the causal role of specific visuo-motor nodes of the AON in action perception is fundamental to recur to causal methods, i.e., investigating the effect of brain damage or non-invasive brain stimulation of parieto-frontal AON regions on the ability to perceive and recognize others' actions (Avenanti and Urgesi, 2011).

Mounting evidence suggests that IFC and IPL are critical for action perception. In two studies participants were presented with videos of an actor lifting and placing a box that could be of different weights and were asked to estimate the weight of the box (Pobric and Hamilton, 2006) or to recognize whether the actor was trying to provide deceiving information about the weight of the box (Tidoni et al., 2013). It was found that online repetitive TMS over IFC but not over occipital cortex or temporo-parietal junction worsened participants' performance in such tasks that required to monitor spatio-temporal features of seen actions (e.g., arm acceleration). Notably, no change in performance was found in "temporal" control tasks requiring to estimate how long the actor's hand was visible (Pobric and Hamilton, 2006) or in a "spatial" control task requiring to monitor the hand path during lifting and placing (Tidoni et al., 2013). Taken together these studies suggest that IFC is actively involved in processing seen kinematics and in particular in integrating their spatial and temporal features, which may be important to predict others' actions (see also Stadler et al., 2012; Avenanti et al., 2013; Costantini et al., 2013).

The integration of spatio-temporal features is critical for biological-motion perception in order to blend the coherent motion pattern of a series of point-lights into a unitary perception of a moving individual. While voxel-based morphometry (Gilaie-Dotan et al., 2013) and fMRI studies (Saygin et al., 2004) suggest a relation between IFC and biological motion perception, causal methods have recently demonstrated that off-line TMS suppression of IFC activity (van Kemenade et al., 2012) or vascular lesion to IFC (Saygin, 2007) impairs the ability to detect biological motion from point light displays.

Another group of studies has suggested a role of IFC in processing configurational aspects of observed actions (e.g., limb displacement, postures). In such studies participants were presented with static images showing hand grips (Jacquet and Avenanti, 2013), upper or lower limb actions (Urgesi et al., 2007b) or whole body movements (Urgesi et al., 2007a). In all the studies it was found that stimulation of IFC but not of control regions impaired the ability to visually discriminate between pictures depicting two slightly different actions. Notably, brain damage patients with lesions occurring in IFC but not in posterior regions were also impaired in similar tasks (Moro et al., 2008). Interestingly, these impairments in processing configurational aspects of others' actions appear specific for biologically movements because IFC stimulation does not impair visual discrimination of images implying biomechanically impossible body movements (Candidi et al., 2008).

While brain stimulation studies suggest a role of the AON, and of IFC in particular (**Figure 1**), in processing specific spatio-temporal and configurational features of seen actions, neuropsychological evaluation of brain damage patients shows that lesions in IFC and premotor cortices may lead to more global deficits in action perception and understanding. Lesion in IFC and premotor cortices reduces the ability to: (i) associate pictures of pantomimes (e.g., licking) to the corresponding appropriate object (ice cream) (Saygin et al., 2004); (ii) judge whether a transitive action or an intransitive gesture is correctly performed (Pazzaglia et al., 2008a); (iii) associate the sounds evoking human actions

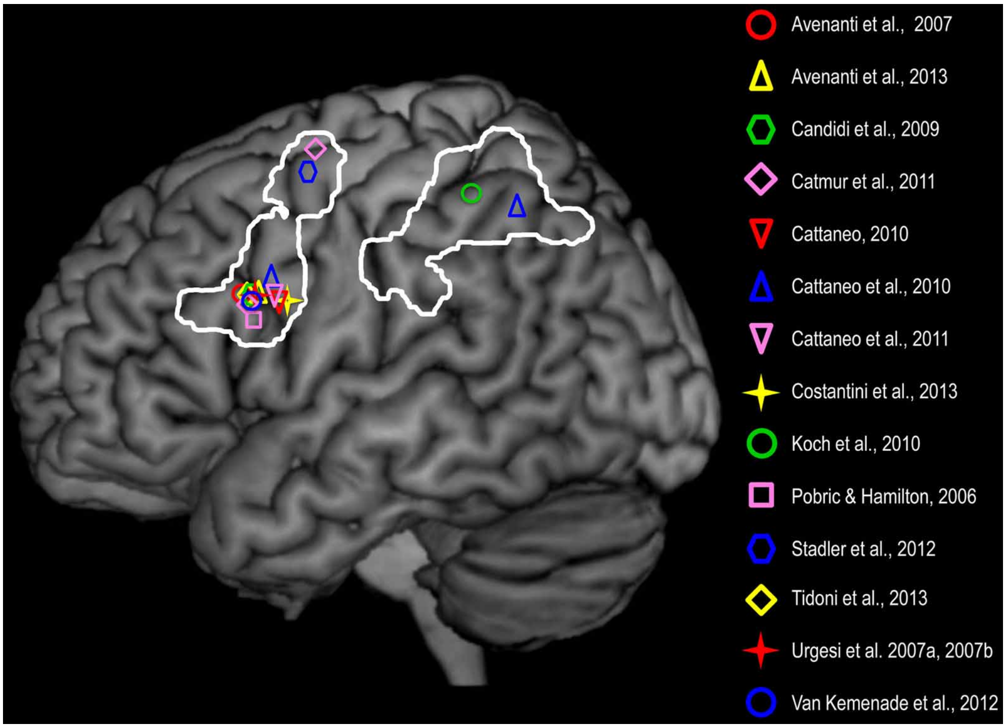

FIGURE 1 | Frontal and parietal brain sites whose non-invasive stimulation affected: (i) motor resonance, as shown by perturb-and-measure (Avenanti et al., 2007, 2013) and dual coil TMS (Koch et al., 2010; Catmur et al., 2011); (ii) proactive gaze shift during observation of actions toward objects, as shown by virtual lesion (Costantini et al., 2013); and (iii) visual action perception as shown by virtual lesion (Pobric and Hamilton, 2006; Urgesi et al., 2007a,b; Candidi et al., 2008; van Kemenade et al., 2012; Tidoni et al., 2013) and state-dependent TMS (Cattaneo, 2010; Cattaneo et al., 2010, 2011). In the study of Catmur et al. (2011) IFC and dorsal premotor cortices were stimulated in the right hemisphere but are represented on a left hemisphere. The white lines define frontal (IFC and dorsal premotor) and parietal (IPL and somatosensory) nodes of the AON and are based on a meta-analysis of 139 functional imaging studies investigating action perception (Caspers et al., 2010).

with pictures representing the same actions (Pazzaglia et al., 2008b); (iv) or re-order pictures of human actions compared to physical events (Fazio et al., 2009). On the other hand, lesion of the IPL impairs the recognition of transitive gestures (Buxbaum et al., 2005; Weiss et al., 2008; Kalénine et al., 2010) and of biological motion (Battelli et al., 2003). Moreover, Tranel et al. (2003) showed that patients with lesions in both IFC and IPL were impaired in tasks involving recognition of action from static pictures. Interestingly, there is a specific relation between the motor deficits shown by brain lesion patients and their impairment in action recognition (Eskenazi et al., 2009; Serino et al., 2010). For instance, patients with fronto-parietal lesions who were impaired in performing limb (limb apraxia) or mouth gestures (buccofacial apraxia) were also impaired in the audio-visual matching of hand and mouth actions, respectively (Pazzaglia et al., 2008b). Although the clinical pattern of apraxic patients is complex and cannot be reduced to the dysfunction of the AON visuo-motor nodes, the effector-specific correspondence between their motor and perceptual deficits further hints at the strict link between action execution and perception. In sum, there is now strong evidence that the activation of parieto-frontal nodes of the AON is not merely associated to action observation, but it appears to be critical to perceive and understand the actions of others.

STATE-DEPENDENT BRAIN STIMULATION IN ACTION PERCEPTION

One important limitation of causal approaches is that brain damage or non-invasive brain stimulation have remote effects. Although TMS is more focal than other non-invasive brain stimulation methods (i.e., transcranial direct current stimulation), and provides extremely high time-resolution, it modulates activity not only in the neurons under the coil but also in interconnected regions (Ruff et al., 2009; Siebner et al., 2009; Avenanti et al., 2012a,b; Arfeller et al., 2013). Thus, impairment of action perception due to vascular or "virtual," TMS-induced lesions over specific motor regions may be at least partially due to the disconnection of a larger circuit (i.e., the AON) or the spread of the TMS-induced excitation along its connections (Valero-Cabré et al., 2005, 2007). The simultaneous combination of TMS with functional imaging promises to be of especially great value to tease apart the functional relevance of TMS-induced local and remote neural effects.

Moreover, one should notice that classical virtual lesions approaches do not elucidate how distinct neural populations within the stimulated area interact to give rise to perception and behavior (Silvanto et al., 2008; Avenanti and Urgesi, 2011; Silvanto and Pascual-Leone, 2012). Recently, the TMS-adaptation and TMS-priming paradigms have been developed to tackle such limitation. The paradigms are based on the well-established notion of state-dependency, i.e., that TMS effects depend on the initial state of the stimulated neurons (Lang et al., 2004; Siebner et al., 2004, 2009; Bestmann et al., 2010). In such paradigms the functional state of the neurons is manipulated by means of perceptual (or motor) adaptation or priming. Although the underlying neurophysiological mechanisms are not well understood (Ruzzoli et al., 2011; Schwarzkopf et al., 2011; Perini et al., 2012), the phenomenology of TMS-adaptation and TMS-priming is very robust and consists in a TMS reduction or reverse of the behavioral effects classically induced by perceptual adaptation or priming. These effects unambiguously indicate the presence of neurons encoding for the adapted/primed feature in the stimulated area and their relevance for perceptual processing.

To date, state-dependent TMS has been used to explore perceptual encoding of goal and grip configurations in frontal, parietal, and visual nodes of the AON. For example, in a TMS-priming study of Cattaneo (2010) participants were presented with target pictures showing a hand grasping an object and were asked to judge whether the movement was fast or slow. Observed grasp types varied from precision (index finger and thumb involved only) to whole-hand grasp. Target pictures were preceded by similar prime pictures. Without TMS and with sham stimulation, a clear priming effect was observed as a shortening of reaction times and as a bias toward the priming grasp type in the classification responses. The perceptual advantage of priming was reversed by TMS over IFC, suggesting that distinct populations in such regions are tuned to different observed grasp types and are critical for perception. In a recent TMS-adaptation study, Cattaneo et al. (2010) used perceptual adaptation to goal-directed actions and showed that IFC and IPL contain distinct populations encoding the goal of observed action (i.e., grasping or pulling) independently from the effector (i.e., hand or foot) used to perform such actions. To test whether the same motor neurons involved in performing an action are critical for visual perception of the same action, Cattaneo et al. (2011) used cross-modal motor-to-visual TMS-adaptation. They asked participants to repeatedly perform an action (pushing or pulling) and then to categorize static images showing an actor's hand displacing a ball as pushing or pulling actions. Repeated motor performance induced a visual aftereffect when categorizing action stimuli, with a bias toward pulling after execution of pushing and a bias toward pushing after execution of pulling. Thus, the aftereffect following motor adaptation was a bias toward the action opposite to the one that had been trained, suggesting a motor-to-visual adaptation of the same visuo-motor neurons involved in action execution and observation. Notably, TMS over IFC but not over control regions disrupted such visuo-motor aftereffects. Thus, cross-modal TMS-adaptation provides complimentary evidence to fMRI adaptation studies investigating the attenuation of hemodynamic responses in AON regions after repeated execution and observation of actions. These studies reported action-specific cross-modal adaptation in fronto-parietal AON areas (Chong et al., 2008; Kilner et al., 2009; Lingnau et al., 2009), suggesting the same neural populations are activated in response to specific actions that are either observed or executed. Using the TMS-adaptation paradigm allowed documenting that the same populations of neurons involved in action execution are also critical for action perception.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, the studies reviewed here provide striking evidence that action perception not only correlates with motor activations in the observer's brain, but also requires these activations for allowing dynamic representations of others' actions. Successful social interactions, however, require motor, sensorial, cognitive, and emotional representations of the behavior of conspecifics. There is now substantial evidence that perceiving the emotions (Carr et al., 2003; Gallese et al., 2004; Dapretto et al., 2006; Bastiaansen et al., 2009) as well as the bodily sensations of others such as touch (Keysers et al., 2004; Blakemore et al., 2005; Bufalari et al., 2007; Ebisch et al., 2008; Schaefer et al., 2009; Gazzola et al., 2012) or pain (Singer et al., 2004, 2006; Avenanti et al., 2005, 2009a; Valeriani et al., 2008; Lamm et al., 2011; Voisin et al., 2011) vicariously activates those brain regions involved in the first hand experience of such emotions and bodily sensations. Although it is held that the mechanism underlying perception of others' sensory or emotional feelings is similar to that underlying action perception (Gallese et al., 2004; Keysers et al., 2010; Gallese and Sinigaglia, 2011), fewer studies have addressed the issue of causality in the former relative to the latter case. However, some of these studies have been important in clarifying that, for example, somatosensory cortices are not only active but are also critical for recognition of others' emotional expressions (Adolphs et al., 2000; Pitcher et al., 2008; Banissy et al., 2010) and others' tactile experiences (Bolognini et al., 2011, 2012, 2013; Rossetti et al., 2012). Further studies, however, are needed to corroborate the causal link between vicarious activations and the understanding of others' sensorial and emotional states.

One critical question for future research concerns the degree to which vicarious activations interact with other mechanism to give rise to perception and understanding of others' actions and feelings. Mirroring and simulating others' actions and feelings may be just one strategy amongst many to gain knowledge of others' mental states. There may be inter-individual differences in the extent to which this strategy is deployed as well as some modulatory effect of social context and previous experience. Vicarious somatomotor activations are often correlated with interindividual differences in personality (Gazzola et al., 2006; Avenanti et al., 2009b; Minio-Paluello et al., 2009; Schaefer et al., 2012) and are influenced by previous experience with the same situation (Calvo-Merino et al., 2006; Cross et al., 2006; Cheng et al., 2007; Fourkas et al., 2008; Abreu et al., 2012; Candidi et al., 2012; Tomeo et al., 2012), and social group belonging (Xu et al., 2009; Avenanti et al., 2010; Hein et al., 2010; Azevedo et al., 2012). They are modulated also by a number of other factors ranging from body ownership (Schütz-Bosbach et al., 2006, 2009) to social tasks and contexts (Kokal et al., 2009; Donne et al., 2011; Sartori et al., 2011). It is thus fundamental to understand the functional significance of such differential activations and causal methods may provide direct information about how and when simulation plays a critical role in our understanding of others' mind.

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The influence of group membership on the neural correlates involved in empathy

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Empathy involves affective, cognitive, and emotion regulative components. The affective component relies on the sharing of emotional states with others and is discussed here in relation to the human Mirror System. On the other hand, the cognitive component is related to understanding the mental states of others and draws upon literature surrounding Theory of Mind (ToM). The final component, emotion regulation, depends on executive function and is responsible for managing the degree to which explicit empathic responses are made. This mini-review provides information on how each of the three components is individually affected by group membership and how this leads to in-group bias.

Keywords: group membership, social categorization, social neuroscience, empathy, vicarious responses

In their Perception-Action Model of empathy, Preston and de Waal (2002) state that "the attended perception of the object's state automatically activates the subject's representations of the state, situation, and object, and that activation of these representations automatically primes or generates the associated autonomic and somatic responses, unless inhibited." Their view of empathy included various phenomena such as emotional contagion, cognitive empathy, guilt, and helping which according to their model all relied on the perception-action mechanism. While typically empathy has been investigated using behavioral paradigms, more recently it is becoming tangible to investigate the neural architecture that underlies this process (Preston and de Waal, 2002; Boston, 2007; Singer and Lamm, 2009; Decety, 2011; Shamay-Tsoory, 2011; Bernhardt and Singer, 2012). Decety (2011) recently proposed a three component basis for empathic experiences, highlighting affective, cognitive, and emotion regulative components. These components are deemed necessary for experiencing empathy where the affective component is identified as a bottom-up, or automatic, process and the cognitive and emotion regulative components are identified as top-down modulators. That is, sharing the pain of others occurs automatically but behavioral responses are differentiated by cognitive factors (for example, perspective taking) and emotion regulative factors (for example, motivation). Social neuroscience has also begun investigating the modulating factors that interfere with empathic responses such as inter-individual differences (Singer et al., 2004; Hein and Singer, 2008), closeness (Beeney et al., 2011), and groups (Ito and Bartholow, 2009; Chiao and Mathur, 2010). Group membership describes a group of people sharing similar and recognizable characteristics where an individual can categorize others as belonging to that particular social group (Abrams, 2012). The focus of the present review is to identify how group membership affects each of the three components of empathy and to illustrate how this accumulates to a biased view of how we see the world.

AFFECTIVE EMPATHY: THE ABILITY TO SHARE THE AFFECTIVE STATES OF OTHERS

The main problem in understanding empathy from a neuroscience perspective is explaining how we can overcome the physical distance between our brain and that of others. How can we make sure we experience the same emotions as others and how can we understand the emotions of others by just observing their behaviors? Simulation theory suggests that we understand other people's actions and emotions by mirroring their actions and feelings onto our own mind state (Preston and de Waal, 2002; Rizzolatti and Fabbri-Destro, 2008; Keysers and Gazzola, 2009; Rizzolatti and Sinigaglia, 2010). According to the classical view, perception-action coupling of motor actions is supported by mirror neurons located in areas such as the inferior parietal lobule (IPL) and posterior inferior frontal gyrus (Iacoboni et al., 1999; Rizzolatti et al., 2001), however, fMRI studies have shown that additional regions such as superior temporal sulcus (STS), dorsal and ventral premotor cortex and superior parietal lobule are also involved in perception-action coupling of motor actions (Molenberghs et al., 2009, 2010; Caspers et al., 2010).

The human mirror system does not passively respond to the observation of actions but is influenced by the mindset of the observer (Molenberghs et al., 2012c). Crucially for this review, previous studies have shown that group membership can modulate perception-action coupling. For example, a recent fMRI study (Molenberghs et al., 2012b) investigated the effect group membership has on our ability to accurately represent action perception. Participants were randomly divided into red or blue teams and they were told they had to compete against a member of the other team by pressing a button response as quickly as possible. In a subsequent experiment, participants were shown video clips of either in-group or out-group members making button-press responses as quickly as possible in a similar competitive situation, where their job was to identify which team member pressed the button fastest. On average both groups in the video clips pressed the buttons equally fast but behavioral analysis showed that participants responded that their team members pressed the button faster. Additional fMRI analyses showed differential neural activation when presented with actions of in-group members compared with out-group members. That is, for those participants who showed an in-group bias behaviorally (those participants that said their team members were faster), greater activity in the IPL was shown when observing in-group members perform the action compared with members from the out-group (Molenberghs et al., 2012b). The IPL plays an important role in perception action coupling and its modulation by group membership suggests we simulate the actions of in-group members more easily. This is in line with a recent EEG study by Gutsell and Inzlicht (2010), who found larger EEG mu suppression (which has previously been associated with mirror neuron activity) when observing actions of in-group members compared to actions of out-group members. Interestingly, this effect increased with the amount of prejudice toward the out-group (Gutsell and Inzlicht, 2010). This reduced perception-action coupling for out-group members also extends to feelings of empathy. For example in a TMS study, Avenanti and colleagues (2010) found a reduction in motor-evoked potential (MEP) amplitude in the hand of participants (induced by TMS to the contralateral motor cortex) when watching an in-group member being painfully stimulated (compared to touch) but no such effect was found when watching out-group members in pain. This suggests that participants simulated the pain of the in-group member but not the pain of the out-group member.

Though predominantly focused on action-perception, vicarious experiences through mirroring have also been shown to extend to emotion and sensory domains as well (Carr et al., 2003; Keysers et al., 2004, 2010; Keysers and Fadiga, 2008; Keysers and Gazzola, 2009). Observing another person's emotional or sensory state elicits activity in a homologous area in the observer, supporting the notion that we vicariously experience the emotional and sensory states of others and represent these states onto our own emotional and sensory repertoires (Keysers and Gazzola, 2009). Indeed a recent meta-analysis including 125 fMRI studies on the mirror system found that perception-action coupling of emotional expressions through vicarious experience is not limited to the aforementioned mirror areas but also involves brain areas involved in, for example, experiencing pain such as the insula and cingulate cortex (Molenberghs et al., 2009). The role of the mirror system in action understanding and affective empathy is controversial (Saxe, 2005, 2006; Hickok, 2009; Decety, 2010) but our view here is that vicarious responses are at least partially involved in affective empathy through mirroring processes, though we acknowledge that they are only part of the story. For example Decety (2011) views affective empathy more broadly as just mirroring and his model of affective empathy also includes affective arousal which he identifies as "the automatic discrimination of a stimulus as appetitive or aversive, hostile or hospitable, pleasant or unpleasant, threatening or nurturing."

Neuropsychological evidence suggests that greater vicarious empathic responses are elicited from own-ethnicity members compared with other-ethnicity members (Avenanti et al., 2006, 2010; Ito and Bartholow, 2009; Xu et al., 2009; Chiao and Mathur, 2010; Azevedo et al., 2012; Gutsell and Inzlicht, 2012; Sessa et al., 2013). For example, a recent fMRI study showed that when observing a member of the same ethnicity experiencing painful stimulation, greater activity in the dorsal anterior cingulate cortex (dACC) and anterior insula (AI) were found compared with when a member from a different ethnicity was experiencing pain (Xu et al., 2009). Race, however, is not the only factor to influence empathic responses to in-groups and out-groups. Group membership has also been found to moderate activation of the AI in response to observing painful situations. Hein and Colleagues (2010) showed in their fMRI study that greater activation in the left AI was found when in-group members (those from the same sporting team) received pain compared with out-group members (those from another sporting team). This activity was also found to correlate positively with the willingness to share the pain with an in-group member compared with an out-group member. When and out-group member received pain, rather than an increase in AI activity, more activity occurred in the right ventral striatum [an area typically associated with pleasure and schadenfreude (Singer et al., 2006; Takahashi et al., 2009)], and this activity was negatively correlated with the willingness to share the pain of the out-group member (Hein et al., 2010). In a similar fMRI study, Cikara and colleagues (2011) monitored neural activity when participants watched video clips of two sporting teams (participant favorite vs. other) compete against each other. They found that when the participants' team won, increased activity in the ventral striatum was observed. More importantly, though, when the participants' team lost, greater activity in the AI and dACC were shown suggesting that participants were empathizing with the pain that the players of their favored team felt. However, sharing the emotions with others alone cannot explain the rich experience of empathy. Empathy also involves a cognitive and emotional regulative component.

COGNITIVE EMPATHY OR THE ABILITY TO REASON ABOUT OTHERS' MENTAL STATES

Vicariously sharing other people's emotions helps us partially understand how other people are feeling, but to completely understand the beliefs, desires and intentions of others, one must also reason about the mental state of others. This cognitive aspect of empathy is typically associated with regions associated with mental state reasoning or so called Theory of Mind (ToM) and often involves regions such as the medial Prefrontal Cortex (mPFC), Temporoparietal Junction (TPJ), and adjacent posterior Superior Temporal Sulcus (pSTS) (Amodio and Frith, 2006; Saxe, 2006; Decety and Lamm, 2007; Frith, 2007; Keysers and Gazzola, 2007; Uddin et al., 2007; Shamay-Tsoory et al., 2009; Van Overwalle and Baetens, 2009; Cheon et al., 2010; Shamay-Tsoory, 2011).

Cognitive empathy can also be modulated by group membership. Adams et al. (2009) used an fMRI modified version of the "Reading the Mind in the Eyes Test" (Baron-Cohen et al., 2001) in which participants are presented with pictures of just the eyes of people and participants then have to judge what the person in the picture is thinking or feeling. Adams et al. (2009) used pictures of Asian and Caucasian people and then let native Japanese and white Americans judge the mental state of those people. They found a behavioral intra-cultural advantage for understanding the mental state of in-group members compared to out-group members and showed that this in-group bias was associated with increased activity in the posterior STS. In line with Adams et al. (2009), research surrounding ToM has consistently shown the importance of the STS in understanding the mental states of others (Fletcher et al., 1995; Allison et al., 2000; Gallagher and Frith, 2003; Amodio and Frith, 2006). Similarly, Cheon et al. (2011) found that Korean participants showed more empathy for in-group members experiencing emotional pain than out-group members and that this was related to increased activity in the TPJ. Similar studies have also illustrated the importance of the mPFC in in-group bias. For example, Mathur and colleagues (2010) found increased activation in the mPFC when watching in-group members experience emotional pain compared to out-group members and this increase predicted greater empathy and altruistic motivation for one's in-group. Another fMRI study found mPFC activation when participants watched pictures of social groups but not for extreme low-status groups (Harris and Fiske, 2006).

The mPFC also has an important role in social categorization, with increased activation in this region previously associated with in-group concepts compared to out-group concepts in both existing (Morrison et al., 2012) and newly created groups (Molenberghs and Morrison, 2012). Volz and colleagues (2009) also found that during an fMRI modified version of the minimal group paradigm (Tajfel et al., 1971) high in-group favoritism was associated with increased activation in the mPFC. Taken together, the aforementioned findings suggest that increased activation in cognitive empathy regions are associated with increased understanding of the mental state of in-group compared to out-group members (Adams et al., 2009; Mathur et al., 2010; Cheon et al., 2011), in-group minus out-group social categorization (Volz et al., 2009; Molenberghs and Morrison, 2012; Morrison et al., 2012) and in-group favoritism (Volz et al., 2009), suggesting further the modulating role of group membership on empathic experiences.

EMOTIONAL SELF-REGULATION OR THE CONTROL OF EXPLICIT EMOTIONS

To reiterate, affective empathy is partially supported by simulating the emotional states of others whereas cognitive empathy relies partially on understanding another's mental state through cognitive reasoning. Given this capacity to experience the affective and mental states of others, it seems necessary that an additional network be set to moderate the degree to which we experience these effects or explicitly express these states. Without an emotion regulative network, shared emotional states may inhibit our ability to perform tasks that require emotional distance (e.g., a surgeon operating on a child or a defense lawyer supporting a psychopath) or it may interfere with our ability to hide automatic biases (e.g., a parent being derogative to a teacher of a different racial background). Essentially, there needs to be a neural function that inhibits or facilitates empathic responses more explicitly to allow for appropriate functioning in day-to-day life (Decety, 2011). Areas involved with emotion regulation such as the rostral anterior cingulate cortex (rACC), dorsolateral (dlPFC) and ventromedial (vmPFC) prefrontal cortex have previously been shown to modulate the effects of empathy (Amodio et al., 2006, 2008; Cheng et al., 2007; Beer et al., 2008; Ito and Bartholow, 2009; Decety et al., 2010; Decety, 2011).

For example, Cheng and colleagues (2007) investigated the neural processes underlying expert and naïve populations' reactions to a person experiencing painful (penetrated with acupuncture needles) and non-painful (Q-tip) stimulation. Evidence from their fMRI investigation revealed increased activity for the pain matrix network (dACC, insula, somatosensory cortex) in naïve participants. On the other hand, the experts (physicians with acupuncture experience) provided no activity in these areas, instead neural activity was recorded in vmPFC which is involved in emotion regulation (Decety, 2011) and TPJ which has previously been implicated in self-other differentiation and ToM (Decety and Lamm, 2007). These results suggest that the acupuncturists could influence their vicarious pain experience by down-regulating these responses through emotional regulation and increased self-other differentiation. Using a similar paradigm, Decety et al. (2010) used EEG to identify the time course of empathic responses and the regulation thereof. The authors identified that for naïve participants, early (N110) and late (P3) activity showed differential responses for painful and non-painful stimuli but when the experienced physicians viewed this stimulus set, there were no differences in early or late processes which suggests that emotion regulation can impede on early processing of painful stimulus presentation (Decety et al., 2010).

Relevant to emotion regulation is the ability to inhibit explicit emotional reactions. It is important to regulate explicit emotional expressions to maintain egalitarian status within society. An example of this was shown in an fMRI study by Richeson and colleagues (2003) who argued that people (especially those with high racial bias) during interracial contact must inhibit racial attitudes and this would result in depletion of executive functions (i.e., response inhibition) which in turn would lead to impaired performance on a subsequent task that requires these functions. They tested this hypothesis by measuring White participants internal beliefs toward racial groups (Blacks and Whites) using an Implicit Association Test (IAT). Additionally, they asked participants to comment on a few questions with a Black Experimenter (mixed-race interaction) and then participants completed a Stroop task to measure executive functioning (task inhibition). Results showed that those who scored higher on the IAT for racial bias, also showed more interference effects on the subsequent Stroop task. When followed up with an fMRI task where participants were presented with Black and White faces, they found increased activation in the ACC and the dlPFC when Black faces were presented, suggesting greater response inhibition during these trials. A significant positive relationship was also found between the increase in ACC and dlPFC activation and the IAT and Stroop task, where this increase in the right dlPFC mediated the effect between IAT and Stroop interference. Collating this evidence, it suggests that people who show higher interracial bias try to inhibit automatic stereotypes, ultimately leading to a reduction in cognitive resources.

Another nice example of emotion regulation was shown in an fMRI study by Cunningham and colleagues (2004). They showed White participants pictures of Black (out-group) and White (in-group) faces either very briefly (30 ms) or for a longer duration (525 ms). The authors predicted that when these pictures would be presented very briefly, participants would not have enough time to regulate their emotions (i.e., negative responses to the Black faces). The fMRI results showed there was increased activation in the amygdala for Black faces compared to White faces when the stimuli were presented very briefly but no such effect was found when the stimuli were presented for longer. Instead they found increased activation in the dlPFC and ACC in the long stimulus presentation condition. When correlating the scores of an IAT regarding race bias with that of neural activity, a positive relationship was shown between behavioral data and fMRI activity in the amygdala for Black and White faces. Similarly, Black-White differences in amygdala activity between the short and long image presentations were predicted by frontal activation. Taking these findings together, it suggests that an automatic race bias against Black faces in White participants is moderated using reflective cognitive processes that only take effect after a period of time. Given that it is not socially acceptable to show explicit in-group bias, the authors interpreted this effect as increased emotion regulation of an automatic bias.

However, social categorization can also override automatic biases. For example, Van Bavel et al. (2008) investigated whether arbitrary and temporary novel group membership could override the effects of predominant group memberships within society (i.e., race as described in their study). Therefore, they randomly assigned participants to a mixed-race team. Pairing behavioral paradigms with functional MRI, the authors measured activity in the fusiform face area (FFA), which has previously been shown to be modulated by face perception and visual expertise (Gauthier et al., 1999, 2000; Golby et al., 2001; Van Bavel et al., 2011), when participants were presented with pictures of faces of in-group and out-group members. The results revealed greater activity in bilateral FFA for in-group faces compared to out-group faces. Interestingly this effect was specific to in-group vs. out-group and was not modulated by race (see also Van Bavel and Cunningham, 2009 and Van Bavel et al., 2011 for similar results). This provides evidence that categorizing people from a different race into an in-group can inhibit automatic racial biases.

CONCLUSION

The current review aimed to highlight how group membership modulates the affective, cognitive, and regulative components of empathy. We have shown that in-group bias is not only a result of increased vicarious simulation of the actions (Gutsell and Inzlicht, 2010; Molenberghs et al., 2012b) and feelings (Xu et al., 2009) of in-group compared to out-group members but also follows from increased activation in ToM regions (Adams et al., 2009; Mathur et al., 2010; Cheon et al., 2011) when trying to understand the mental state of in-group vs. out-group members. These group biases can be influenced by emotional regulation (Ito and Bartholow, 2009) depending on expertise (Cheng et al., 2007; Decety et al., 2010) and context (Richeson and Shelton, 2003; Cunningham et al., 2004) so that we respond in a socially acceptable way to our environment. Lastly, it seems that arbitrary re-categorization can override automatic biases such as race (Van Bavel et al., 2008). Seeing as group membership modulates responses at each component of empathy, future investigations should identify methods of reversing these biases at each of the three distinguishable levels.

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