COGNITIVE CONTROL OF EMOTIONS IN CHALLENGING CONTEXTS, 2nd Edition

EDITED BY: Nils Kohn, Carmen Morawetz, Jiajin Yuan, Mathias Weymar and Florin Dolcos

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COGNITIVE CONTROL OF EMOTIONS IN CHALLENGING CONTEXTS,
2nd Edition

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EDITORIAL
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Editorial: Cognitive Control of Emotions in Challenging Contexts

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Editorial on the Research Topic

Cognitive Control of Emotions in Challenging Contexts

The ability to cognitively regulate our emotions has emerged as an important moderating factor to multiple forms of psychopathology and human behavior. For this reason, the field of emotion regulation has faced a growing interest and popularity within social, cognitive, and affective neuroscience over the past two decades. Moving from strictly localized "amygdala-centered" concepts and top-down prefrontal control systems to broader interactive network dynamics (Smith and Lane, 2015; Morawetz et al., 2020) has clearly increased our understanding of how emotions can be controlled using a variety of emotion regulation (ER) strategies and analytic approaches (Morawetz et al., 2017). However, so far, research has mainly focused on investigating particular strategies, rarely considering situational and dispositional factors (Doré et al., 2016). By addressing this issue, this Research Topic contributes to the field of situational and dispositional factors influencing ER.

Situational and dispositional factors have the potential to influence the way we perceive and regulate our emotions. Situational factors may include chronic or acute stress, fatigue, hunger, and other temporally dynamic motivational factors, as well as dispositional factors related to personality and temperamental traits, both vices and virtues. The distinction between dispositional and situational factors is, in part, arbitrary and can be subsumed under challenging (or facilitating) contexts that influence emotional regulation. An acute state of hunger or sleep deprivation may make a person less able or willing to engage in regulatory behavior, leading to a host of sub-optimal decision processes.

This Research Topic brings together papers focusing on the contextual factors that can roughly be described by more situational and dispositional aspects and by their interaction. The present collection of manuscripts contributes substantially to the field by bringing together empirical reports, using a broad range of methodological approaches, along with reviews and opinion pieces. Situational and dispositional emotion regulation is elucidated using various human psychophysiological (hemodynamics, electrophysiology), neurostimulation, and behavioral methods. The Research Topics starts out with a discussion of the situational factors on cognitive ER and moves to their influence on more automatic ER, to make the transition to dispositional factors by highlighting examples of efficient ER training. The Research Topic ends with discussion of physiological and clinical factors influencing ER and demonstrates the broad potential impact of ER trainings as well as the need for multi-disciplinary approaches due to complex interactions.

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SITUATIONAL INFLUENCES ON EXPLICIT AND IMPLICIT EMOTION REGULATION

This e-book starts off with a section on situational factors with a focus on ER strategies. Haspert et al. studied the influence of acceptance-based regulation of painful stimuli, and found that participants were able to regulate both subjective pain intensity and unpleasantness ratings in acceptance trials. Additionally, heart rate was reduced, which indicates the use of acceptance-based strategies as a potential way of coping with pain. In their meta-analysis, Zaehringer et al. summarize evidence regarding the impact of ER strategies on psychophysiological measures. They find little convergence and only small mean effect sizes of reappraisal and suppression on autonomic measures and medium effect sizes for electromyographic measures. The authors further demonstrate that this inconsistency and surprising lack of effect by standard ER strategies on physiology is brought about by heterogeneities in task design and small sample sizes. This calls for a better standardization of methods in a first step, to better understand the effect of ER strategies on physiology, later on.

The flip side of maladaptive ER strategies is explored by Whiteman and Mangels, who show that rumination (i.e., the tendency to brood over one's problems and feelings) not only has a detrimental effect on mood and mental health (Nolen-Hoeksema et al., 2008; Kohn et al., 2014) but also negatively influences performance on an attention task. Specifically, induction of rumination led to more attention for reminders of errors, compared to corrective information on how to avoid the error in the future. ER strategies have the potential to shift attentional focus away from aversive stimuli (Haspert et al.), but also away from supportive stimuli, highlighting the situational appropriateness of ER strategies (Whiteman and Mangels). The contribution by Zhao et al. moves the focus from internal, situational use of ER strategies to the internalized, but externally focused concept of placebo effects. Placebo effects have characteristic similarities to automatic ER (Braunstein et al., 2017), as it is a top-down regulatory process, but outside of conscious awareness, that instills the belief that a sham treatment (e.g., the placebo) is efficient (Wager and Atlas, 2015). The authors show that a placebo intervention could effectively reduce not only the perception of pain but also empathy for pain and related activity in the posterior insula, hence demonstrating that a placebo mindset has the potential to alter physiology of empathic pain.

Kuehne et al. show that neurostimulation of the dorsolateral prefrontal cortex leads to poorer performance on an automatic ER task—i.e., the face-word Stroop task. This might be related to the detrimental influence of conscious cognitive control stimulated by anodal stimulation during the automatic task, which interferes with efficient task performance (Kuehne et al.). These findings could be taken as an indication of the delicate relationship with cognitive control and the fragility of controlling faculties, which can be influence by many challenging contexts, such as stress (Kohn et al., 2017) of overnight fasting (Kohn et al., 2015). This fragility is also demonstrated by two more papers using a go-nogo task which show that caffeine boosts response related decisions in a sleep deprived state (Chen, Zhang et al.), and that fast paced music interferes with conflict monitoring (Xiao et al.). Emotion control, regardless of whether implicit or explicit ER, necessarily requires the intactness of important cognitive features (Braunstein et al., 2017). Thus, situational interference or facilitation of cognitive abilities will have downstream consequences for eventual attempts to regulate emotion.

GENERATION AND INFLUENCE OF DISPOSITIONAL FACTORS ON EMOTION REGULATION

Several contributions highlight that dispositional factors do not necessarily have to represent stable and fixed personality characteristics, but preferentially using ER strategies can be a dispositional factor (Garnefski and Kraaij, 2006) and use of ER strategies can be trained (e.g., Dolcos et al.). Dolcos et al. show that training ER strategies can have beneficial effects on cognitive functions. The study impressively demonstrates that ER training can improve resilience and well-being and is reflected in brain and behavior. Furthermore, this influence of training ER strategies on cognition highlights the intertwined nature of cognition and emotion, which influence each other dynamically (Dolcos et al., 2011, 2020; Dolcos and Denkova, 2014). Dolcos et al. also demonstrate that ER training leads to increased connectivity among cognitive and emotion control regions and across regions of self-referential and control networks. Doerfel et al. aimed to replicate studies on the link between habitual use of ER strategies and the amygdala, which underscores the notion that restriction to amygdala connectivity is too reductionistic and ER might rather involve multiple hierarchical networks (Smith and Lane, 2015; Morawetz et al., 2020). Findings by Chen, Yu et al. further indicate that reappraisal via implementation intention technique (Gollwitzer, 1999; Achtziger et al., 2008) might be more efficient in regulating emotions that conscious cognitive regulation, which underlines the huge potential of ER trainings. The review by Panasiti et al. describes how emotion processing and regulation are important factors in Psoriasis, a chronical dermatological condition, which highlights the important interaction of body and emotion and also points to the potentially broad impact of efficient ER trainings. Finally, Wiener et al. describe, for the case of essential hypertonia, how the thalamic pulvinar nucleus might be engaged in the dysregulation of interactions between emotion processing brain networks and attentional/cognitive brain networks, which gives rise to a vicious cycle of negative emotion-physiology interactions.

Moving to concepts closer to stable personality factors and their interaction with ER and the affective and cognitive substrates, Xia et al. demonstrate that individuals with elevated trait anxiety have response inhibition deficits in the go/NoGo task. Interestingly, the authors link the deficits to influences on premotor inhibition control and evaluation and monitoring. This ties into the multi-faceted, hierarchical nature of ER, which relies on multiple brain networks interactions (Smith and Lane, 2015; Morawetz et al., 2020; Dolcos et al.), such as motor and monitoring systems in this study. Demonstrating the interdependence and dynamic nature of dispositional factors in development, Tsai et al.

show that the development of anxiety is related to early life stress and mediated by cognitive control abilities in adolescence, with cognitive control having a buffering function for the effect of stress on anxiety. Wagels et al. demonstrate how endogenous testosterone levels influence processing, regulation and expression of angry emotions depending on MAOA polymorphism.

Lischke et al. investigated the interaction of several dispositional factors with biological sex, in essence highlighting the many aspects contributing to the influence of dispositions on ER. The authors found that interoceptive accuracy, as measured by a task in which subjects have to monitor their own heartbeat, was differentially related to habitual use of reappraisal or suppression depending on the biological sex. Specifically, men showed a positive association between reappraisal use and interoceptive success that was absent in women (Lischke et al.). Flores-Torres et al. demonstrate a sex-dependent influence of a humor based mood induction on cognitive performance in the Iowa Gambling task. These findings further emphasize the importance of considering biological sex as a factor in automatic and also cognitive emotion regulation (McRae et al., 2008; Zlomke and Hahn, 2010). Building on findings of the relation of narcissism and emotion regulation (Zhang et al., 2015), Loeffler et al. investigated how facets of narcissism, such as grandiose and vulnerable narcissism, differentially influence emotion regulation abilities, in which sex does not have an influence. They find initial evidence for an increased use of maladaptive ER strategies in vulnerable narcissism, but not grandiose narcissism, which further highlights the need to not only consider multiple networks in the brain, but also consider multiple factors and sub-factors in personality when integrating dispositional effects on ER. This fundamentally calls for a stronger multi-disciplinary collaboration and integration of specific experts in execution and planning of contextual ER studies.

CONCLUSIONS

In summary, this Research Topic explores situational and dispositional factors or contexts that influence ER differentially. Importantly, the contributions highlight the need for a multi-faceted conceptual approach that integrates concepts like stress, fasting, along with trait factors and influence of sex. Given the complex interactive and dynamic nature, we call for an increased multi-disciplinary collaboration of experts in the investigation of contextual ER. At the neural level, integration of multiple, interacting brain networks can be seen as mandatory for future research, which should also more strongly incorporate bi-directional influences of emotion-cognition and emotion-body interactions. These profound interactions lay the basis for the broad utility of effective ER trainings like implementing intentions or cognitive-emotional training.

AUTHOR CONTRIBUTIONS

NK drafted the manuscript. All authors edited, revised, agreed to the final version of the manuscript, and contributed to the conception and conduction of the Research Topic.

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BRIEF RESEARCH REPORT
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Acceptance-Based Emotion Regulation Reduces Subjective and Physiological Pain Responses

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Acceptance-based regulation of pain, which focuses on the allowing of pain and pain related thoughts and emotions, was found to modulate pain. However, results so far are inconsistent regarding different pain modalities and indices. Moreover, studies so far often lack a suitable control condition, focus on behavioral pain measures rather than physiological correlates, and often use between-subject designs, which potentially impede the evaluation of the effectiveness of the strategies. Therefore, we investigated whether acceptance-based strategies can reduce subjective and physiological markers of acute pain in comparison to a control condition in a within-subject design. To this end, participants (N = 30) completed 24 trials comprising 10 s of heat pain stimulation. Each trial started with a cue instructing participants to welcome and experience pain (acceptance trials) or to react to the pain as it is without employing any regulation strategies (control trials). In addition to pain intensity and unpleasantness ratings, heart rate (HR) and skin conductance (SC) were recorded. Results showed significantly decreased pain intensity and unpleasantness ratings for acceptance compared to control trials. Additionally, HR was significantly lower during acceptance compared to control trials, whereas SC revealed no significant differences. These results demonstrate the effectiveness of acceptance-based strategies in reducing subjective and physiological pain responses relative to a control condition, even after short training. Therefore, the systematic investigation of acceptance in different pain modalities in healthy and chronic pain patients is warranted.

Keywords: pain regulation, emotion regulation, acceptance, cognitive strategies, acute pain, acceptance-based strategy, psychological modulation of pain, pain ratings

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INTRODUCTION

Pain is an unpleasant sensory and emotional experience (Merskey and Bogduk, 2016), sometimes even referred to as an emotion that involves a physical sensation (Price, 1999; Wieser and Pauli, 2016). Thus, it is not surprising that emotion regulation (ER) strategies (Gross, 1998), which address the modification of affective experiences, are also capable of modulating the perception of pain

Abbreviations: ACT, Acceptance and Commitment Therapy; ECG, electrocardiograph; ER, emotion regulation; HR, heart rate; MCS, manipulation check survey; PT, pain threshold; SC, skin conductance; VAS, visual analog scale.

(Masedo and Esteve, 2007; Braams et al., 2012; Kohl et al., 2013; Hampton et al., 2015). Numerous studies on commonly used ER strategies such as reappraisal and distraction (Gross, 2002; John and Gross, 2004) already demonstrated effective reductions of negative emotions (McRae et al., 2010; Kanske et al., 2011; Webb et al., 2012; Schönfelder et al., 2014) and pain (Van Damme et al., 2008; Verhoeven et al., 2011; Lapate et al., 2012; Hampton et al., 2015). The ability to regulate emotions was shown to correlate with the successful regulation of heat pain stimuli (Lapate et al., 2012), suggesting a general regulation skill for both emotion and pain.

A special case of ER are *acceptance-based strategies*, which are defined as the embracing of emotions or situations without judging or avoiding them (Hayes et al., 1999; Hofmann and Asmundson, 2008; Braams et al., 2012). The concept of acceptance-based strategies derives from the Acceptance and Commitment Therapy (ACT), a "third wave" cognitive and behavioral treatment approach, which focuses on contextual and experiential changes (Hayes et al., 2006; Hayes and Hofmann, 2017). The general goal of ACT is to increase *psychological flexibility* – the ability to stay present in the moment and to change or persist value-based behavior (Hayes et al., 2006). *Acceptance* (Hayes et al., 1999; Hofmann et al., 2009; Braams et al., 2012; Kohl et al., 2013) involves the active and aware embrace of events and is one of six core ACT processes underlying psychological flexibility (Hayes et al., 2006). Two closely related ACT processes and widely used conceptualizations of acceptance-based strategies in emotion and pain regulation research are *mindfulness* ("being present" and "non-judgmental") (Braams et al., 2012; Kohl et al., 2013) and *cognitive defusion* ("decrease in believability of or attachment to an event") (Kohl et al., 2013).

Even though acceptance-based strategies do not aim at the reduction of emotions or pain, various studies showed that they can alter the pain experience and therefore can be considered a regulation strategy (Kohl et al., 2012). Furthermore, there is an ongoing debate (Hofmann and Asmundson, 2008; Liverant et al., 2008; Hofmann et al., 2009; Wolgast et al., 2011) about the classification of acceptance within *the process model of ER* by Gross (Gross, 1998), suggesting that acceptance includes both antecedent- and response-focused components (for additional information on the conceptualization of acceptance, see **Supplementary Material**).

Previous studies found that acceptance-based strategies modulate behavioral pain measures such as pain threshold (PT) and tolerance more profoundly than other ER strategies – designed along the *process model of ER* – such as suppression of pain-related responses (Masedo and Esteve, 2007; Braams et al., 2012), reappraisal of the pain stimulus (Kohl et al., 2013), and distraction from pain (McMullen et al., 2008; Jackson et al., 2012; Moore et al., 2015). Similarly, so called *control-based protocols*, which are conceptualized as the exact opposite of ACT (Keogh et al., 2005) by instructing participants to ignore the pain stimulation and stop thinking about it, were found to be less effective in pain tolerance tasks than acceptance-based protocols (Keogh et al., 2005). A meta-analysis by Kohl et al. (2012) suggests that acceptance-based strategies compared to other regulation strategies are especially successful in increasing pain tolerance, while findings involving subjective pain measures such as pain intensity are less clear: acceptance-based strategies led to either decreased pain intensity compared to suppression (Masedo and Esteve, 2007) and control-based protocols (Gutierrez et al., 2004; Keogh et al., 2005), showed no difference when compared to distraction (McMullen et al., 2008; Moore et al., 2015), reappraisal (Kohl et al., 2013), or control-based protocols (Hayes et al., 1999; Paez-Blarrina et al., 2008a,b), or were even less effective than distraction (Kohl et al., 2013).

Most importantly, previous studies often used pre-to-post measurements or control conditions containing either spontaneous coping (Masedo and Esteve, 2007; Evans et al., 2014; Forsyth and Hayes, 2014) or no instructions at all (McMullen et al., 2008; Paez-Blarrina et al., 2008a; Braams et al., 2012). This might have led to an unsystematic use of ill-defined strategies and thus compromised the results. Some studies (Gutierrez et al., 2004; Keogh et al., 2005; Paez-Blarrina et al., 2008a; Kohl et al., 2013) even used no control condition at all, which makes it difficult to determine the actual effectiveness of a regulation strategy. Therefore, we chose to develop and include a neutral control condition to ascertain the effectiveness of acceptance-based strategies.

Only one study so far (Braams et al., 2012) implemented physiological measures to capture the effectiveness of acceptance-based strategies in modulating autonomous pain responses but used a between-subject design. A within-subject design might be better suited to account for potential inter-individual variance regarding physiological responses and regulation skills, which we consequently applied in our study.

In the present study, we compared an acceptance-based strategy with a carefully introduced control condition, where participants should not use any strategies, in a within-subject design. We complemented subjective measures of pain (intensity, unpleasantness) with psychophysiological pain responses (heart rate, HR; skin conductance, SC) (Rhudy et al., 2009; Loggia et al., 2011).

Our main goal was to test the successful reduction of experimentally induced pain by acceptance-based regulation. Thus, we hypothesized the acceptance-based strategy to result in decreased pain ratings and pain-evoked HR and SC responses compared to the control condition.

METHODS

Participants

An optimal sample size of 27 participants was calculated *a priori* using G*Power (Faul et al., 2009) assuming a medium to large effect size of Cohen's d of 0.5 (Braams et al., 2012), alpha error of 0.05 (one-tailed paired *t*-test) and power of 0.8 (Kohl et al., 2013). Potential drop-out was considered and 31 (17 women) participants were recruited via an online platform by the University of Würzburg. They received either course credit or €10 for participation. Participants did not take any central nervous or pain medication and had no current or prior history of chronic pain (self-report). One participant indicated close to no pain sensation (pain intensity: $M = 0.67$, pain unpleasantness:

M = 0.33; VAS 0–100) throughout the entire experiment and was therefore excluded from the final analysis. Thus, 30 participants (16 women; age M = 25.37, SD = 3.58) remained in the statistical analysis. The experimental procedure was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the medical faculty of the University of Würzburg. All subjects gave written informed consent before participating.

Thermal Pain Stimulation

Pain stimuli were delivered via a thermal stimulator with an active thermode area of 25 × 50 mm (Somedic SenseLab AB, Sösdala, Sweden). The thermode was attached to the volar forearm of the non-dominant hand. We assessed the individual pain threshold (PT) using the method of adjustment (Horn-Hofmann and Lautenbacher, 2015) to take individual differences in pain sensitivity (Nielsen et al., 2009) into account. For that, we instructed participants to adjust the thermode's temperature – starting at 35°C – by pressing two different buttons (± 0.5°C/keystroke; maximum temperature 49°C) until they reached a level of thermal sensation that went from hot to just painful. This procedure was repeated three times and the average of all three temperatures was used as the final PT (M = 44.87°C, SD = 2.06). During practice trials and the main experiment, pain stimuli were calibrated to the individual PT plus 1°C (target temperature) to achieve a moderate but painful stimulation (Lautenbacher et al., 1995; Horn et al., 2012; Reicherts et al., 2016). Heat stimulation started at a baseline temperature of 10°C below PT and rose at a rate of 5°C/s. Thus, the thermode reached the target temperature after 2.2 s. The target temperature was presented for 10 s. Afterward, the thermode cooled down in 2.2 s to the baseline temperature. The pain stimulus duration of 10 s was chosen following similar experimental designs (Lapate et al., 2012; Prins et al., 2014; Hampton et al., 2015) and was supposed to give the participants sufficient time to engage in the strategy. To prevent habituation to the pain stimulus, the position of the thermode was changed after the PT procedure, after the practice trials and after each 6th trial of the main experiment (starting position was counterbalanced across participants).

Instructions

The acceptance-based strategy was conceptualized along three core ACT processes, namely acceptance, mindfulness and cognitive defusion. Participants were instructed that acceptance involves the allowing of any experiences (*acceptance*) (Hayes et al., 2006) without further evaluation (*mindfulness*) (Braams et al., 2012). When participants saw the word "ACCEPT" on the screen, they should let their feelings run their natural course, allow themselves to stay with their emotions (Hofmann et al., 2009) and might employ the "clouds in the sky"-metaphor (Kohl et al., 2013) as a method of detachment from pain (*defusion*) and to facilitate understanding of the strategy. In the control condition "PERCEIVE," participants were instructed to sense the pain as it is and not use any strategies. To underscore the distinction between conditions, instructions were briefly summarized: whenever the word "ACCEPT" appeared on the screen, participants should apply the acceptance-based strategy, while no strategy should be used when the word "PERCEIVE" appeared.

Measures

Pain Ratings

Participants were instructed about the distinction of pain intensity and pain unpleasantness using the radio metaphor by Price et al. (1983). During the experiment, participants rated the heat pain stimuli using a digitized visual analog scale (VAS) presented on the screen, ranging from 0 = no pain/not unpleasant at all to 100 = maximum pain/extremely unpleasant, respectively.

Heart Rate

To measure electrocardiography (ECG), three electrodes were attached on the torso of the participant (right collarbone, left lower costal arch, left lower side of the torso). The continuous raw ECG-signal was sampled with 250 Hz, using a V-Amp amplifier and Brain Vision Recorder, V-Amp Edition 1.10, recording software (both Brain Products Inc., Munich, Germany). The signal was filtered (High cut-off: 30 Hz, Notch filter: 50 Hz) (Boucsein, 2012), R-waves were automatically detected and manually checked, the inter-beat intervals were calculated and then converted into the continuous HR (Koers et al., 1999) by the Vision Analyzer software (BrainProducts, Munich, Germany). HR signal was baseline corrected relative to 1 s interval before visual cue onset.

The effectiveness of ER might underlie temporal characteristics such as different strategy onsets, but only few studies have considered temporal dynamics so far (Dan-Glauser and Gross, 2011, 2015; Pavlov et al., 2014; Koval et al., 2015). To capture these, 25 1-s time bins were calculated (Dan-Glauser and Gross, 2015; Koval et al., 2015) by averaging intervals of 1 s, starting at cue onset (second 0) and ending with the offset of the fixation cross (second 25). A broad time interval was analyzed to capture potentially delayed psychophysiological responding following heat pain administration (Loggia et al., 2011). One participant was excluded from psychophysiological analyses due to bad data quality.

Skin Conductance

SC was recorded using two 8 mm Ag/AgCl surface electrodes (electrode gel: 0.5% NaCl) attached to the thenar and hypothenar eminence of the participant's non-dominant hand. Similar to the ECG signal, the SC signal was sampled with 250 Hz, with constant application of 0.5 V. The signal was filtered (High cut-off: 1 Hz, Notch filter: 50 Hz) (Boucsein, 2012) and baseline corrected relative to 1 s interval before visual cue onset via Vision Analyzer software (BrainProducts, Munich, Germany). Again, 25 1-s bins were calculated to capture potential variations across trial duration, equally to the HR analysis. One participant was excluded from psychophysiological analyses due to bad data quality.

Questionnaires

Participants completed several questionnaires addressing habitually preferred ER styles [AAQ-II (Bond et al., 2011; Hoyer and Gloster, 2013), ASQ (Hofmann and Kashdan, 2010;

Graser et al., 2012), ERQ (Gross and John, 2003; Abler and Kessler, 2009)], negative affect [STAI (Laux et al., 1981; Spielberger et al., 1983)], attitudes toward pain [FPQ-III (McNeil and Rainwater, 1998; Baum et al., 2013), PCS (Sullivan et al., 1995; Meyer et al., 2008), PSQ (Ruscheweyh et al., 2009)], optimism [LOT-R (Scheier et al., 1994; Glaesmer et al., 2008)] and resilience [RS-11 (Wagnild and Young, 1993; Schumacher et al., 2005)], which are supposed to affect pain and emotion processing, respectively (Rhudy and Meagher, 2000; Rhudy et al., 2004; Forys and Dahlquist, 2007; Geers et al., 2010; Hanssen et al., 2013; Boselie et al., 2014; Hampton et al., 2015; Moore et al., 2015; Biggs et al., 2016; Wieser and Pauli, 2016; Goubert and Trompetter, 2017; Hemington et al., 2017; Hinkle and Quiton, 2019). Questionnaires on ER styles were filled out before the experiment. All remaining questionnaires were presented after the experiment. Mean questionnaire scores and standard deviations are shown in **Table 1**.

Regulation Ratings/Manipulation Check

After each acceptance trial, participants rated how well they were able to regulate pain by applying the strategy (VAS 0–100; 0 = not at all; 100 = very well). As participants should not regulate pain in the control condition, no regulation ratings were taken. After the experiment, participants filled out a manipulation check survey (MCS) asking on a 9-point rating scale how clear the instructions were (1 = unclear, 9 = clear), how easily they could be implemented (1 = not at all, 9 = very well) and whether participants tried to distract themselves from pain during the main experiment (1 = not at all, 9 = very much).

Procedure

Participants were informed about the details of the experiment and signed a written informed consent. They filled out questionnaires (STAI-S, ERQ, ASQ, and FAH-II) and answered a sociodemographic survey. As soon as they completed the questionnaires, the individual PT was assessed. Afterward, the electrodes for ECG and SC measures were attached. Participants received written standardized instructions on a screen describing the two experimental conditions ("ACCEPT" vs. "PERCEIVE") and practiced each of them twice. The experimenter made sure that participants fully understood the instructions before starting the main experiment. Participants were separated from the experimenter by a folding screen and interacted with the experimenter solely for the relocation of the thermode. Each trial started with a central fixation cross on a gray screen. After 5 s, either the word "ACCEPT" or "PERCEIVE" appeared in the middle of the screen (cue onset), indicating the two conditions, respectively. The cue remained on the screen for 20 s before disappearing (cue offset). Five seconds after cue onset, the pain stimulation started. After cue and pain offset, a fixation cross was presented for 5 s, followed by the pain intensity and unpleasantness ratings, and the regulation ratings (acceptance only). The subsequent interstimulus interval varied between 15 and 18 s (randomly). The experiment consisted of 24 randomized trials (12 per condition, no more than two trials of the same condition in a row). After the experiment, participants filled out the remaining questionnaires (FPQ-III, PSQ, PCS, STAI-T, LOT-R, RS-11) and the MCS. The experimental procedure was controlled using the software Presentation (Version 17.2, Neurobehavioral Systems Inc., Albany, CA, United States).

TABLE 1 | Mean questionnaire scores (M) and standard deviations (SD).

Questionnaire	Scale	*N*	*M*	*SD*
AAQ-II	Total	30	16.37	7.21
ASQ	Concealing/Suppression	30	2.95	0.61
ASQ	Adjusting/Reappraisal	30	3.12	0.66
ASQ	Tolerating/Accepting	30	3.76	0.47
ERQ	Cognitive reappraisal	30	4.59	0.88
ERQ	Expressive suppression	30	3.33	1.01
FPQ-III	Total	30	76.93	16.19
LOT-R	Pessimism	30	4.00	2.32
LOT-R	Optimism	30	8.97	2.57
PCS	Total	30	14.87	7.25
PSQ	Total	29	3.67	1.24
RS-11	Total	30	59.00	8.15
STAI	State	30	38.57	8.15
STAI	Trait	30	37.70	8.79

AAQ-II, Acceptance and Action Questionnaire II; ASQ, Affective Style Questionnaire; ERQ, Emotion Regulation Questionnaire; FPQ-III, Fear of Pain Questionnaire-III; PCS, Pain Catastrophizing Scale; PSQ, Pain Sensitivity Questionnaire; RS-11, Resilience Scale 11; STAI, State-Trait Anxiety Inventory; LOT-R, Life-Orientation-Test Revised.

Statistical Analysis

Pain ratings (intensity and unpleasantness) were analyzed separately with pairwise *t*-tests comparing the acceptance vs. control condition. Pain intensity and unpleasantness ratings were compared with each other using pairwise *t*-tests of z-standardized difference scores between control and acceptance condition. Cohen's d_{av} was used as a measure of effect size (Cohen, 1988) as recommended by Lakens (2013). For analysis of HR and SC, we used a repeated-measures ANOVA with the within-factor condition (acceptance vs. control) and the within-factor time (twenty-five 1-s bins) and reported partial eta-squared η_p^2. In case the assumption of sphericity was violated (Mauchly), the Greenhouse-Geisser correction was applied. *Post hoc* comparisons of different factor levels were realized using pairwise *t*-tests. Pearson correlations were conducted to explore the association of pain ratings during the acceptance-based strategy and questionnaire scores (ERQ, ASQ, AAQ-II, STAI, PCS, FPQ-III, PSQ, LOT-R, and RS-11). The regulation ratings were analyzed using a repeated-measures ANOVA with the within-factor trials (4 levels) by averaging three successive trials. Significance level was defined as $p < 0.05$.

RESULTS

Pain Ratings

Analysis of pain intensity revealed a significant effect of *condition*, $t(29) = 3.23$, $p = 0.003$, $d_{av} = 0.217$, indicating lower pain intensity ratings for the acceptance compared to the control

condition. Similarly, analysis of pain unpleasantness revealed a significant effect of *condition*, $t(29) = 5.26$, $p < 0.001$, $d_{av} = 0.484$, indicating reduced pain unpleasantness ratings for the acceptance vs. control condition. Mean pain intensity and unpleasantness ratings are shown in **Figure 1**. Analysis of standardized difference scores yielded a stronger regulatory effect of acceptance for unpleasantness than for intensity pain ratings, $t(29) = -3.09$, $p = 0.004$, $d_{av} = -0.486$.

Heart Rate

Analysis of HR revealed no significant main effect of *condition*, $F(1, 28) = 0.76$, $p = 0.390$, $\eta_p^2 = 0.027$, but a significant main effect of *time*, $F(3.96, 110.98) = 17.14$, $p < 0.001$, $\eta_p^2 = 0.380$ and a significant interaction of *condition* and *time*, $F(6.34, 177.56) = 2.46$, $p = 0.024$, $\eta_p^2 = 0.081$. *Post hoc* analyses revealed lower HR for the acceptance condition compared to the control condition [second 20, $t(28) = -2.10$, $p = 0.045$; second 21, $t(28) = -2.22$, $p = 0.035$; second 22, $t(28) = -2.00$, $p = 0.056$; second 23, $t(28) = -2.03$, $p = 0.052$; second 24, $t(28) = -2.12$, $p = 0.043$, 25; $t(28) = -1.73$, $p = 0.094$]. The mean time course for both conditions is shown in **Figure 2**.

Skin Conductance

Analysis of SC showed no significant main effect of *condition*, $F(1, 28) = 0.10$, $p = 0.920$, $\eta_p^2 < 0.01$. A significant main effect of *time* was found, $F(1.94, 54.35) = 4.01$, $p < 0.001$, $\eta_p^2 = 0.125$, indicating a SC reaction to the heat pain stimulus (see **Figure 3**). There was no significant interaction between *condition* and *time*, $F(2.97, 83.20) = 0.30$, $p = 0.846$, $\eta_p^2 = 0.01$.

Correlations of Pain Ratings and ER Style Questionnaires

Correlation analysis revealed no significant associations between pain ratings of the acceptance condition and ER style questionnaire scores (ERQ subscales reappraisal and suppression; ASQ subscales suppression, reappraisal and accepting; AAQ-II total score) nor the resilience scale RS-11 total score; all $ps > 0.063$. There were also no significant correlations between the acceptance ratings and the remaining questionnaire scores (STAI state & trait, PCS total, FPQ-III total, PSQ total, LOT-R optimism & pessimism; all $ps > 0.083$).

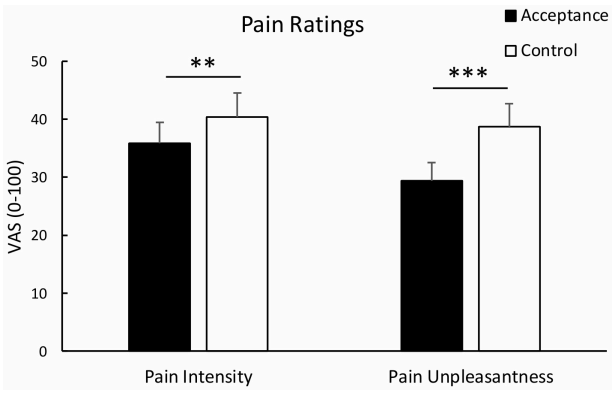

FIGURE 1 | Mean pain intensity and unpleasantness ratings with standard error bars for the acceptance and control condition. Both pain intensity and pain unpleasantness were significantly lower in the acceptance than the control condition. $^{**}p < 0.01$; $^{***}p < 0.001$.

Regulation Ratings/Manipulation Check

Analysis of regulation ratings did not show a significant change over *time*, $F(3, 87) = 2.48$, $p = 0.066$, $\eta_p^2 = 0.079$. However, there was a trend indicating better subjective regulatory performance toward the end of the experiment: Trials 1–3: $M = 60.04$, $SD = 19.72$; trials 4–6: $M = 58.53$, $SD = 19.40$; trials 7–9: $M = 61.34$, $SD = 16.45$; trials 10–12: $M = 64.67$, $SD = 17.79$.

In the MCS, participants rated the instructions of acceptance, $M = 7.80$, $SD = 1.10$, and the control condition, $M = 8.33$, $SD = 0.84$, as rather clear and easy to implement (acceptance: $M = 6.87$, $SD = 1.38$; control $M = 7.97$, $SD = 1.19$). Further, participants did not distract themselves from heat pain ($M = 3.43$, $SD = 2.11$).

DISCUSSION

In the present study, we found that an acceptance-based pain regulation strategy led to a reduced perception of acute heat pain compared to a carefully instructed control condition as indicated by pain intensity and unpleasantness ratings. Also, HR was significantly lower during acceptance-based regulation of pain, while SC responses showed no significant difference between conditions. The present study demonstrates that acceptance-based strategies can modulate subjective and physiological correlates of pain in healthy controls even after brief practice.

Modulation of Pain Ratings by the Acceptance-Based Strategy

Acceptance compared to the control condition led to significantly reduced pain ratings, replicating previous findings (Gutierrez et al., 2004; Keogh et al., 2005; Masedo and Esteve, 2007; Paez-Blarrina et al., 2008a,b; Braams et al., 2012; Kohl et al., 2013). Especially pain unpleasantness was sensitive for the use of the acceptance-based strategy, as indicated by the significant difference across pain rating dimensions.

The pronounced modulation of the affective component of pain is in line with the theoretical foundation of acceptance-based strategies, which aim at changing the behavioral and emotional pain responses rather than its sensory experience (Hayes et al., 1999; Masedo and Esteve, 2007; Kohl et al., 2013). Nevertheless, we found that accepting the heat pain stimulation also decreased sensory aspects of pain. These results resemble the findings by Prins et al. (2014) who showed that a brief mindfulness induction (comprising acceptance-based strategies) led to stronger reductions of pain unpleasantness than pain intensity but only in high pain catastrophizers. The authors point out that the aim of mindfulness is not the reduction of symptoms but instead modifying the experience of the symptoms (Chiesa and Serretti, 2011; Prins et al., 2014), which is likely also the case in acceptance-based strategies.

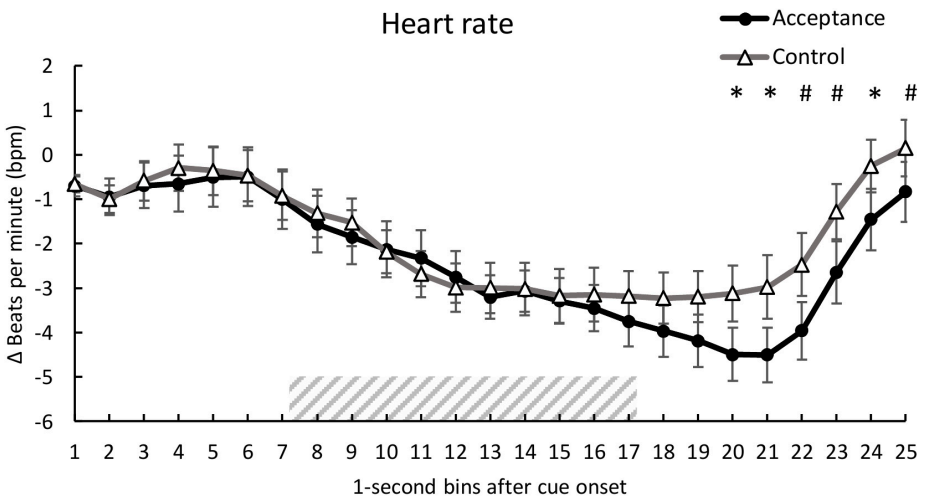

FIGURE 2 | Mean time course (1-s bins) of the heart rate (baseline-corrected 1 s before cue onset) with standard error bars for the acceptance and control trials. The dashed area represents the 10-s heat pain stimulus (7.2 s until 17.2 s after cue onset). There was a significantly lower HR for acceptance compared to the control trials during seconds 20, 21, and 24 of the trial. $^{*}p < 0.05$; $^{\#}p < 0.10$.

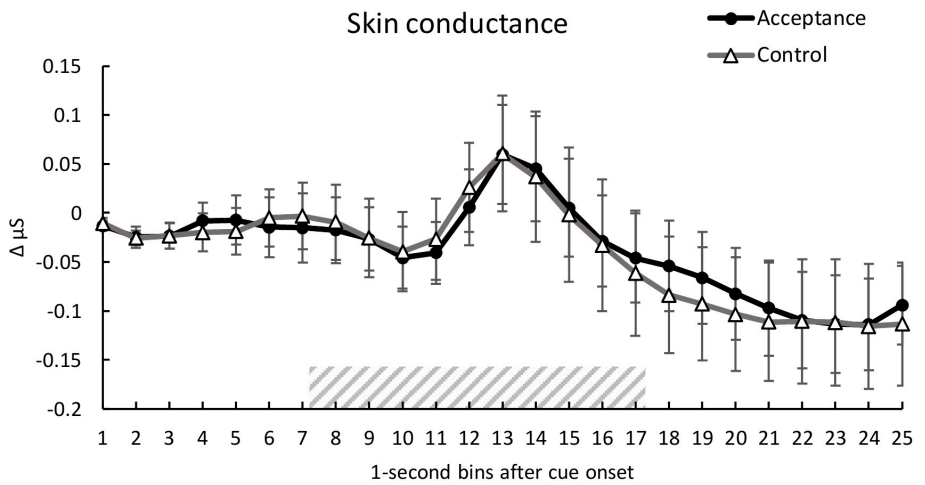

FIGURE 3 | Mean time course (1-s bins) of the skin conductance (baseline-corrected 1 s before cue onset) with standard error bars for the acceptance and control trials. The dashed area represents the 10-s heat pain stimulus (7.2 s until 17.2 s after cue onset). There were no significant differences between the two conditions over time.

Kohl et al. (2012) concluded in their meta-analysis that acceptance-based strategies probably are most effective at modulating behavioral pain measures whereas findings concerning pain ratings are rather inconsistent. This heterogeneity might be due to the combination of a pain tolerance task and the subsequent needless measure of pain ratings. One study (Kohl et al., 2013), for instance, found elevated pain tolerance markers *and* higher pain intensity ratings for a pain acceptance condition. Some previous studies instead demonstrated elevated pain tolerance while pain ratings remained unaffected (Hayes et al., 1999; Keogh et al., 2005) or even were reduced (Masedo and Esteve, 2007). Only one study (Braams et al., 2012) showed reduced pain ratings when investigating acceptance-based strategies by using brief pain stimuli instead of pain tolerance tasks. Future studies should incorporate both subjective pain processing and behavioral pain measures.

Effects of the Acceptance-Based Strategy on Physiological Pain Responses

In our study, we recorded HR and SC as psychophysiological pain responses (Loggia et al., 2011). Contrary to our hypothesis, analysis of SC did not show a significant difference between the acceptance and control condition. However, we found general SC responses following the pain stimulation around 6 s after pain onset, similar to previous studies (Breimhorst et al., 2011).

According to the meta-analysis by Kohl et al. (2012), findings regarding the influence of acceptance-based strategies on physiological correlates of emotion and pain are mixed. Several studies investigating acceptance-based strategies in the context of *emotion* regulation did not find any effects on HR (Eifert and Heffner, 2003; Dunn et al., 2009; Erisman and Roemer, 2010) or SC (Eifert and Heffner, 2003; Campbell-Sills et al., 2006; Erisman and Roemer, 2010). This indicates that accepting a negative affective state, which might also include pain, does not necessarily reduce physiological arousal (Kohl et al., 2012). Loggia et al. (2011) found that HR was a better predictor of pain ratings than SC, which might explain the different effects of the acceptance-based strategy on SC and HR in the present study.

We found the HR to be significantly lower in the acceptance compared to the control condition during cue offset, 3 s after the 10 s pain stimulation. This might indicate that acceptance-based strategies take some time to evolve their effect. Dan-Glauser and Gross (Dan-Glauser and Gross, 2015) did not find any differences between an acceptance-based and a control condition on negative emotions (8 s picture presentation) and concluded that acceptance-based strategies step in rather late in the emotion formation process (Gross, 1998). Similarly, our results might also reflect a later onset of acceptance-based strategy effects on pain. Alternatively, the more pronounced deceleration of the HR in the acceptance condition could reflect a faster recovery from pain. Temporal dynamics in subjective and physiological measures might become more evident in a longer tonic pain stimulation. Thus, different pain durations should be incorporated in future research. Furthermore, larger sample sizes might be helpful in investigating physiological responses, especially SC signals.

The questions remain, whether more training of acceptance-based strategies (Erisman and Roemer, 2010) and more detailed instructions (McMullen et al., 2008) might lead to even clearer subjective and physiological effects. Future research should systematically vary the amount of training prior to the experiment to detect critical aspects underlying the successful use of acceptance-based strategies.

Limitations and Outlook

The present results showed that the use of acceptance-based pain regulation was associated with reductions of subjective and physiological pain responses. The effect of acceptance on psychophysiological pain measures might be further explored using different pain stimulation intensities and modalities or endogenous pain inhibitory indices (Horn-Hofmann et al., 2018). Furthermore, it might be worthwhile comparing an acceptance-based strategy with other well-established regulation strategies such as reappraisal or distraction to identify shared and unique processes involved in the regulation of pain. Given potential gender differences in pain processing and coping (Fillingim et al., 2009), it would be interesting to address them in future pain regulation studies providing sufficiently large sample sizes.

We carefully instructed participants to follow all experimental instructions, and their compliance is supported by both our results and manipulation check. Nevertheless, we cannot completely rule out the use of acceptance during the control condition or alternative coping strategies (Cioffi and Holloway, 1993). In future studies, more detailed post experimental surveys and additional measures of experimental adherence should be employed to detect potential confounds.

An expectancy toward a certain outcome plays a crucial role in the effectiveness of mindfulness and acceptance-based strategies (Brown and Jones, 2010; Zeidan et al., 2012), hence eliminating its effect would be difficult let alone meaningless. However, it would be interesting for future research to capture participants' expectations regarding the effectiveness of pain regulation strategies systematically.

Although HR and SC serve as reliable psychophysiological indicators of pain responses (Rhudy et al., 2009; Loggia et al., 2011), they undoubtedly capture only a small portion of the processes involved in emotion and pain regulation (Kohl et al., 2012). HR variability, for instance, is a well-established measure of ER (Appelhans and Luecken, 2006) and might be a promising index for the regulation of pain unpleasantness (Appelhans and Luecken, 2008). However, analyzing HR variability would be at the expense of capturing temporal dynamics as its calculation requires prolonged intervals (Shaffer and Ginsberg, 2017).

In the present study, we did not continuously measure subjective pain to avoid distraction from the pain stimulation and to prevent disruption of strategy usage. Nevertheless, continuous ratings [e.g., with rating dials (Hutcherson et al., 2005)] in ER research reliably measured ongoing emotions without interfering with them or the strategy application (Hutcherson et al., 2005; Dan-Glauser and Gross, 2011). Incorporating continuous pain ratings might be a promising tool for future regulation research.

We did not find any associations between ER styles or other psychological factors such as anxiety or pain sensitivity and the effectiveness of the acceptance-based strategy in modulating pain. Yet, individual differences in preferred ER styles could still play a critical role in the effectiveness of pain regulation strategies. This might be especially relevant for research on chronic pain since the habitual use of maladaptive ER strategies, like experiential suppression, could represent a risk factor for pain chronification (Koechlin et al., 2018). Thus, studies using larger sample sizes are necessary to explore the role of psychological traits for pain regulation.

Future research should consider translating similar experimental designs – including carefully prepared control conditions – to chronic pain populations, providing a deeper understanding of the mechanisms involved in successful pain acceptance and advance the development of psychological interventions for chronic pain.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the

medical faculty of the University of Würzburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VH organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors wrote sections of the manuscript, contributed to conception and design of the study, manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.01514/full#supplementary-material

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Psychophysiological Effects of Downregulating Negative Emotions: Insights From a Meta-Analysis of Healthy Adults

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Assessing psychophysiological responses of emotion regulation is a cost-efficient way to quantify emotion regulation and to complement subjective report that may be biased. Previous studies have revealed inconsistent results complicating a sound interpretation of these findings. In the present study, we summarized the existing literature through a systematic search of articles. Meta-analyses were used to evaluate effect sizes of instructed downregulation strategies on common autonomic (electrodermal, respiratory, cardiovascular, and pupillometric) and electromyographic (corrugator activity, emotion-modulated startle) measures. Moderator analyses were conducted, with moderators including study design, emotion induction, control instruction and trial duration. We identified $k = 78$ studies each contributing multiple sub-samples and performed 23 meta-analyses for combinations of emotion regulation strategy and psychophysiological measure. Overall, results showed that effects of reappraisal and suppression on autonomic measures were highly inconsistent across studies with rather small mean effect sizes. Electromyography (startle and corrugator activity) showed medium effect sizes that were consistent across studies. Our findings highlight the diversity as well as the low level of standardization and comparability of research in this area. Significant moderation of effects by study design, trial duration, and control condition emphasizes the need for better standardization of methods. In addition, the small mean effect sizes resulting from our analyses on autonomic measures should be interpreted with caution. Findings corroborate the importance of multi-channel approaches.

Keywords: meta-analysis, emotion regulation, psychophysiology, reappraisal, suppression, autonomic nervous system, electromyography

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Emotion regulation is a vital part of our daily lives. It permits individuals to control the occurrence, intensity, type, and duration of emotions (Gross and Thompson, 2007). Strategies to regulate emotions not only alter the subjective experience of emotions (Gross, 1998a), but also map onto bodily responses such as changes in measures of the autonomic nervous system (Gross, 2002; Webb et al., 2012), emotion-expressive behavior (Dan-Glauser and Gross, 2011, 2015), somatic reflexes such as the emotion-modulated startle (Jackson et al., 2000), or neural

activation (Ochsner et al., 2004; Buhle et al., 2014). The habitual use of adaptive emotion regulation strategies is a hallmark of successful functioning and is associated with increased well-being, whereas difficulties with regulating emotions have been linked to many psychopathologies (Aldao et al., 2010; Joormann and Vanderlind, 2014; Schmahl et al., 2014). In light of the significance of emotion regulation, appropriate experimental paradigms are required that are suitable for research involving large sample sizes and patient populations.

In a typical emotion regulation study, emotions are experimentally induced using affective stimuli such as films (Gross and Levenson, 1995) or pictures (e.g., International affective picture system; Lang et al., 2009). Participants are instructed to regulate their emotional experience or to respond naturally without regulating their emotions (i.e., the control condition). By comparing the regulation with the control condition it is possible to determine the effect of regulation, which has been used as an indirect measure of emotion regulation effectiveness (Webb et al., 2012).

Assessing psychophysiological correlates has several important advantages. They move beyond on-line self-reports and retrospective assessments, as physiological responding is regarded as automatic, relatively unconscious, and fast (Bradley et al., 1993b; Öhman and Soares, 1994; Edelmann and Baker, 2002; Olsson and Phelps, 2004; Lapate et al., 2014). Research focusing on the direct effects of emotion regulation has found significant psychophysiological changes even when subjective experience remained unaffected (Gross and Levenson, 1993, 1997). Hence, psychophysiological measures can offer important insights into internal emotional experiences that are not available by assessing self-report. In addition, psychophysiological responses are easier to assess than neural physiological measures (e.g., functional magnetic resonance imaging) and are thus cost-efficient methods for quantifying differences in emotion regulation.

CONCEPTUAL FOUNDATIONS OF EMOTION REGULATION

There have been multiple attempts to classify emotion regulation strategies (Gross, 1998a,b; Larsen, 2000; Koole, 2009). One of the most influential models is the *process model of emotion regulation* (Gross, 1998a,b, 2015), which broadly categorizes strategies as either being antecedent-focused, i.e., strategies are implemented before the emotional response has fully unfolded, and as response-focused, i.e., strategies are implemented after the emotional response has already been generated. The process model distinguishes five major emotion regulation processes: situation selection (i.e., attempts to change a future emotional response), situation modification (i.e., changing the situation in order to modify its emotional effect), attentional deployment (i.e., distraction away from or concentration on an emotional stimulus to modify the emotion itself), cognitive change (i.e., reappraise a situation or to change the perspective so that the emotional experience is modulated), and response modulation (i.e., strategies to suppress expressive behavior, thoughts, or emotions). Situation selection, situation modification, attentional deployment, and cognitive change are regarded as antecedent-focused and response modulation is regarded as a response-focused process.

A majority of past emotion regulation studies have instructed participants to distract themselves from, reappraise or suppress[1] a target stimulus in order to downregulate emotions. These strategies correspond to attentional deployment, cognitive change, and response modulation, respectively, In addition, a considerable number of studies allowed participants to use a strategy of their own choice (Jackson et al., 2000; Dillon and LaBar, 2005; Piper and Curtin, 2006; Lissek et al., 2007; Driscoll et al., 2009; Lee et al., 2009; Golkar et al., 2014; Baur et al., 2015; Conzelmann et al., 2015; Grillon et al., 2015). The present meta-analysis thus focuses on these four major types of downregulation instructions, that is distraction, reappraisal, suppression, and downregulation instructions that allowed participants to choose their own strategy. Other strategies were out of the scope. For a comprehensive overview see **Table 1**.

PSYCHOPHYSIOLOGICAL RESPONSES OF EMOTIONS AND EMOTION REGULATION

There is great interest in understanding the relationship between emotions and psychophysiological responses including responses of the autonomic nervous system (i.e., cardiovascular, electrodermal, respiratory, pupillometric) and responses measured with the electromyogram (EMG) such as facial muscle activity (e.g., corrugator supercilii activity) and somatic reflexes (e.g., emotion-modulated startle). The interested reader is directed to detailed reviews by Cacioppo et al. (2000), Kreibig (2010), Siegel et al. (2018), and Stemmler (2004). See **Table 2** for an overview of relevant psychophysiological measures within the emotion regulation literature. Such relations have most commonly been studied in terms of two affective dimensions, that is valence (positive-negative) and arousal (high-low) (Lang, 1995; Bradley et al., 2001). Some measures such as heart rate, emotion-modulated startle, and facial activity are specific to the valence of the emotion (Bradley et al., 2001) and others such as skin conductance and pupil dilation are more specific to the arousal dimension (Greenwald et al., 1989; VanOyen Witvliet and Vrana, 1995; Bradley et al., 2001). Past research has also put a lot of effort into answering the question whether different emotion categories (e.g., disgust, sadness, fear) produce distinct physiological response patterns. In a recent meta-analysis the hypothesis could not be confirmed (Siegel et al., 2018). Rather, emotions seem to elicit an unspecific set of psychophysiological changes.

When it comes to the *regulation* of emotions, much evidence has accumulated suggesting that suppression is related to an

[1]Acceptance has become increasingly popular across the emotion regulation literature too, yet there has been a debate as to whether it belongs to antecedent (Webb et al., 2012) or response-focused processes (Hofmann and Asmundson, 2008) and as to whether it is a strategy or rather a function of different strategies. Given that very few studies on acceptance assessed psychophysiological responses, it is not included in the present review.

TABLE 1 | Emotion downregulation processes and their strategies considered in this meta-analysis.

Process	Strategy	Subtype	Example
EMOTION REGULATION INSTRUCTIONS			
Attentional deployment	Distraction	Active distraction	Participants are instructed to think about something positive or neutral that is unrelated to the target emotion/stimulus
Cognitive Change	Reappraisal	Reinterpret the emotional stimulus	Participants are instructed to reinterpret the emotional stimulus to decrease the target emotion
		Reappraise via perspective taking, i.e., distancing	participants are instructed to alter the impact of a stimulus by adopting a more objective perspective
		Reappraise Mixed	A mixture of reappraisal instructions
Response modulation	Suppression	Suppress the expression of emotion	Participants are instructed to hide the way they are feeling, e.g., not to smile
		Suppress the experience of an emotion	Participants are instructed to suppress their emotional experience
		Suppress thoughts of the emotion eliciting event	Participant are instructed to suppress thoughts about the emotion-eliciting event
		Suppression mixed	A mixture of suppression instructions
Downregulation unspecified	Own choice	Own choice	Participants are free to choose a strategy that works best for them. They are not allowed to create a different emotion or think of something unrelated to the stimulus
CONTROL INSTRUCTIONS			
		No instruction (C1)	No instructions are given
		Instructions not to regulate (C2)	Participants are told that they should not use a regulation strategy
		Instructions to maintain (C3)	Participants are instructed to maintain the target emotion
		Instructions to experience naturally (C4)	Participants are instructed to respond naturally without regulating it
		Control mixed (C5)	A mixture of control instructions

increase in sympathetic nervous system activity but no difference in self-report to negative stimuli (Gross and Levenson, 1993, 1997; Richards and Gross, 1999). The enhanced sympathetic activation following suppression has led researchers to conclude that suppression "exacts a palpable physiological cost" (Gross and Levenson, 1997, p. 101). In other words, because response-focused strategies involve an active modulation of expressive behavior, increased sympathetic activation might be the result of that effort (Butler et al., 2003). In contrast, past literature has proposed that reappraisal has little impact on sympathetic and cardiovascular measures (Gross, 1998a). A meta-analysis studying the overall physiological effect of different emotion regulation strategies confirmed this general pattern: cognitive change had a smaller effect on physiology than response modulation (Webb et al., 2012).

However, as noted earlier, there is a vast range of different psychophysiological outcome measures ranging from cardiovascular, electrodermal, respiratory, pupillometric, and electromyographic response systems and it has been shown that the nature of the relationship between cognitive emotion regulation and different psychophysiological responses can vary largely (Bernat et al., 2011). By simply combining all psychophysiological measures to a composite score is helpful in looking at the overall effectiveness of an emotion regulation strategy (as has been done in the meta-analysis by Webb et al., 2012), but it does not reveal which of the individual psychophysiological responses change or do not change with an emotion regulation strategy.

When looking at individual psychophysiological measures, findings are mixed with respect to the effects of emotion regulation on autonomic physiology. Reappraisal instructions focusing on decreasing negative emotions compared to a control condition have been shown to have no effect on (Gross, 1998a; Kalisch et al., 2005; Goldin et al., 2019), increase (Sheppes et al., 2009; Lohani and Isaacowitz, 2014), or decrease (Urry et al., 2009) skin conductance and to increase (Urry et al., 2006; van Reekum et al., 2007) or decrease (Bebko et al., 2011) pupil diameter. Contradictory patterns can also be found for suppression strategies. For example, individuals' heart rate was significantly increased (Hagemann et al., 2006; Ben-Naim et al., 2013), decreased (Gross and Levenson, 1993; Robinson and Demaree, 2009), or stayed the same (Gross, 1998a) when individuals suppressed negative emotions compared to a control condition. These inconsistencies may be due to the large heterogeneity between studies, which can substantially affect the magnitude of the physiological responses. The contradictory pattern of results across the literature does not allow a straightforward interpretation. The causes for these inconsistencies are, however, not well-understood, and this inevitably obscures the detection of common trends.

FACTORS RELATED TO THE IMPACT OF EMOTION REGULATION ON PSYCHOPHYSIOLOGY

Study Design

Studies using within-study designs found larger effects of emotion regulation on experiential, behavioral and physiological

TABLE 2 | Common psychophysiological measures of emotion regulation studies.

Body system	Measurement	Abbreviation	Measurement system (units)	Description
Cardiovascular	Cardiac output	CO	l/min	Blood volume pumped by the heart per minute.
	Diastolic blood pressure	**DBP**	**mmHg**	Lowest blood pressure of circulating blood on the walls of blood vessels in between two heartbeats, measured in millimeters of mercury.
	Ear pulse transit time	**EPTT**	**ms**	Time interval between the R-wave of the electrocardiogram to the pulse wave arrival at the ear.
	Finger pulse amplitude	**FPA**	**Arbitrary**	Amplitude of the pulse waveform measured in the finger. Indicator of dilation and constriction of the blood vessels.
	Finger pulse transit time	**FPTT**	**ms**	Time interval between the R-wave of the electrocardiogram to the pulse wave arrival at the finger.
	Heart rate/interbeat interval/heart period	**HR/HP**	**bpm/ms/ms**	Number of beats per unit of time/time between heart beats (inverse of heart rate).
	Heart rate variability	**HRV**	**Units vary by method**	Variation in heart rate. Refers specifically to the high-frequency HRV [also called respiratory sinus arrhythmia (RSA)].
	Low frequency HRV	LF	Units vary by method	Variation in heart rate. Refers specifically to the low-frequency HRV.
	Ratio of low- and high-frequency HRV	LF/HF	Units vary by method	Variation in heart rate. Refers specifically to the ratio between low- and high-frequency HRV.
	Mean arterial pressure	**MAP**	**mmHg**	Mean blood pressure of circulating blood on the walls of blood vessels in between two heartbeats, measured in millimeters of mercury.
	Pre-ejection period	PEP	ms	Period between the beginning of electrical stimulation of the heart to the opening of the aortic valve. Indicator of the cardiac contractile force (i.e., how hard the heart is beating).
	Stroke volume	SV	mL	Volume of blood pumped from the left ventricle per beat.
	Systolic blood pressure	**SBP**	**mmHg**	Maximum blood pressure of circulating blood on the walls of blood vessels in between two heartbeats, measured in millimeters of mercury.
	Total peripheral resistance	TPR	Unity vary by method	Overall resistance that must be overcome to push blood through the whole circulatory system (i.e., all major arterial trees).
Electrodermal	**Skin, conductance response**	**SCR**	**MicroSiemens**	Peak amplitude, magnitude or local maximum of the skin conductance response. Includes non-specific skin conductance responses during longer periods of time if reported as amplitude.
	Skin conductance level	**SCL**	**MicroSiemens**	Mean change of skin conductance over a specific period of time. Operationalized as simple average, change from baseline, area under the curve or integrated signal.
	Number of skin conductance responses	nSCR	n	Number of skin responses per unit of time (e.g. per minute).
Respiratory	Inspiration/expiration time	IT/ET	sec	Average inhalation/exhalation time per respiratory cycle.
	Respiration amplitude	**RA**	**mL**	Difference in volts between the point of maximum inspiration and the point of maximum expiration.
	Respiration rate	RR	c/min	Number of breaths per minute.
	Tidal volume	TV	mL	Air volume that moves into or out of the lungs while breathing quietly.
Pupillometric	**Pupil dilation**	**PD**	**mm**	Average diameter of pupil in millimeter during a specific period of time.
Electromyographic	**Emotion-modulated startle**	**Startle**	**MicroVolt**	Amplitude of the startle eyeblink response (orbicularis oculi) in response to affective stimuli.
	Corrugator supercilii activity	**cEMG**	**MicroVolt**	Muscular activity of the corrugator supercilii responsible for furrowing of the brow.
	Zygomaticus major activity	zEMG	MicroVolt	Muscular activity of the zygomaticus major responsible for smiling.
Other	**Finger temperature**	**FT**	**F/C°**	Temperature of the finger, in Fahrenheidt (F) or Celcius (C°).

The measures in bold were included in our meta-analysis; for the other measures the number of studies was insufficient (k < 5 studies per cell). Because heart rate (HR) and interbeat interval (IBI) are inversely related, we switched the direction of the effect sizes when IBI was extracted (instead of HR). Descriptions derived and adapted from Berntson et al. (2016), Blumenthal et al. (2005), Cacioppo et al. (2000), Dawson et al. (2016), and Siegel et al. (2018).

outcomes than did studies employing between-study designs (cf. Webb et al., 2012). Employing within-study designs reduces sampling error thereby increasing power. On the other hand, within-study designs may also increase task difficulty because participants are required to engage in more than just one emotion regulation strategy. In event-related designs typical for within-subject studies, participants may even shift continuously between different strategies.

Emotion Induction

Emotion regulation studies have used a variety of different emotional stimuli, including pictures (e.g., the International Affective Picture System; IAPS: Lang et al., 2009), film clips (Gross and Levenson, 1995), stressful tasks (e.g., the Trier Social Stress Test; Kirschbaum et al., 1993), dyadic interactions (Levenson and Gottman, 1983), or threat of shock paradigms (Delgado et al., 2008). Each type of stimulus provides a reliable method to generate emotions. However, a key dimension on which induction methods differ is whether they require participants to sit passively in front of a monitor or whether they employ a stressful task or conversation with a (romantic) partner. Somatic activity has a significant influence on autonomic response measures, especially on heart rate (Obrist, 1981). In addition, stressful tasks such as giving a speech alter the sympathetic nervous system to a stronger degree than picture viewing (Fechir et al., 2008). When it comes to potential differences between films and pictures, findings are mixed. Studies on emotion processing have been shown that e.g., heart rate returns to baseline if the picture remains still, but further slows down if the picture involves motion (Detenber et al., 1998; Simons et al., 1999). However, a recent study on emotion regulation reported that films and pictures did not differently affect the emotion regulation process on a physiological level, although films elicited a stronger absolute skin conductance response than pictures (Morawetz et al., 2016a). We are not aware of any other study directly assessing the impact of the emotion induction method on psychophysiological effects in the context of emotion regulation and thus we will address this question in the present analysis[2].

Control Instruction

Effects of emotion regulation strategies on psychophysiological measures can be determined by contrasting the emotion regulation instruction against different control instructions. For example, participants can be instructed to "maintain" the emotion they feel (Jackson et al., 2000), to "view" the emotional stimulus (Gross and Levenson, 1993), or to "respond naturally" (Shiota and Levenson, 2009). Previous literature has shown that differences in neural activation depend on the control condition instruction (Schaefer et al., 2002), with higher amygdala activation reported for "maintain" than for "view" instructions. The terminology used as control instructions (e.g., maintain vs. view) has not been systematically explored in psychophysiological studies of emotion regulation yet. However, it could have important influences on physiological processes as shown by an fMRI study (Diers et al., 2014). Similarly, Webb et al. (2012) found that the control condition moderated the physiological effects of emotion regulation (Webb et al., 2012).

[2]It should be noted that there might be more aspects of visual stimuli that could possibly influence effect sizes. For example, within the field of visual perception, studies show that faces are not as evocative as scenes (Alpers et al., 2011; Wangelin et al., 2012). A fine-grained moderator analysis of different aspects of picture and film stimuli however was not possible due to the small number of studies available and because most studies included in the present analysis used a blend of negative scenes and faces as stimuli.

Trial Duration

Another important aspect of the study design which varies largely across studies is the trial duration of the regulation period. According to the implementation and maintenance model (Kalisch, 2009; Paret et al., 2011), reappraisal for example is divided into two phases: In the early phase, participants choose and implement a regulation strategy, whereas in the late phase they maintain the strategy in working memory and monitor its success. Hence, reappraisal might need several seconds until it effectively reduces negative emotions. Thus, the effect of reappraisal might become larger with increasing trial duration, which might also affect physiology.

AIM OF STUDY

The primary aim of the present study was to quantitatively summarize the relation between popular emotion downregulation instructions (distraction, reappraisal, suppression, own choice) and common psychophysiological measures (i.e., cardiovascular, electrodermal, respiratory, pupillometric, electromyographic) in healthy adults. In light of the contradictory pattern of psychophysiological effects in the emotion regulation literature we aimed to answer the following questions: (a) What are the effects of distraction, reappraisal, suppression, and downregulation where participants choose a strategy that works best for them on individual psychophysiological response measures? (b) How consistent are these effects across studies? and (c) What aspects of the study design moderate the effects? In light of the hypothesis that psychophysiological measures are somewhat sensitive to the valence of the induced emotion and because the majority of studies on emotion regulation and psychophysiology induced negative emotions, the present meta-analysis focuses on the downregulation of negative stimuli (for an overview of studies employing positive stimuli see **Table S1**).

We first systematically searched for emotion regulation studies that instructed participants to use emotion regulation strategies and that assessed psychophysiological measures of our interest as dependent variable. To advance current knowledge, we performed meta-analyses to separately quantify the effects for each of these measures during emotion regulation. In addition, we performed moderator analyses to explore the impact of study characteristics on the effect sizes. Moderators of interest were study design, trial duration, control instruction, and emotion induction method. It is important to note that our ability to identify the effects of cognitive emotion regulation strategies on psychophysiological variables and potential moderators is limited by the published studies available for meta-analysis.

METHODS

Selection of Studies

Studies were identified through a systematic literature search of articles using the PubMed, Web of Science, and PsychINFO databases. The search strategy was developed to maximize the sensitivity of article identification by combining individual words and medical subject headings (MeSH)[1]. We searched for

the keywords *emotion regulation or emotional regulation* cross referenced with *psychophysiology* [MeSH], *psychophysiologic**, *autonomic, parasympathetic, sympathetic, respiration* [MeSH], *cardiovascular, electrocardiography* [MeSH], *respiratory sinus arrhythmia* [MeSH], *blood pressure* [MeSH], *heart rate* [MeSH], *startle, startle reflex* [MeSH], *electromyography* [MeSH], *pupil diameter, pupil dilation, electrodermal or skin conductance,* and *galvanic skin response* [MeSH] cross referenced with *stimulus, stimuli, film*, picture*, image*, script*, anxiety, fear*, threat**, and *video**. Additionally, reference lists from identified studies that met the inclusion criteria (see the next section for criteria) as well as relevant articles in the authors' library were reviewed for titles that might have been previously missed. Subsequently, studies identified in this manner ($n = 13$) were collected for inclusion.

The search process described above yielded a total of 1,353 potentially relevant articles on July 18, 2019 (after duplicates were removed)[3]. The first author and another independent reviewer (Stephanie Mall, research assistant) systematically examined titles and relevant abstracts using the Covidence website (www.covidence.org) to determine whether an article would be subsequently reviewed in full-text format. The following criteria were applied: The study presented original empirical results, was published in a peer-reviewed journal, was written in English or German, included adult healthy participants, and an explicit emotion regulation paradigm was assessed where participants are explicitly told to use emotion regulation strategies to modulate an emotion. We discarded studies that did not assess a psychophysiological measure of interest (e.g., EEG studies) at this point. Based on these criteria, the same two reviewers independently reviewed 157 studies in full-text format.

Inclusion/Exclusion Criteria

The 157 studies were examined to determine if they met the following inclusion criteria of our analysis: The study (1) included a control condition in which participants were confronted with emotional contents but did not regulate emotions (see **Table 1** for definitions of possible control instructions), (2) sampled a psychophysiological measure throughout the regulation phases, (3) did not assess an experimental intervention before the emotion regulation task that may influence the performance of emotion regulation, (4) provided sufficient information to compute the effect size, (5) induced negative emotions, (6) instructed participants to use one or more of the strategies provided in **Table 1**. If studies met inclusion criteria (1) to (6) but did not provide adequate information for effect size computation, we asked the authors for the needed information via e-mail.

Finally, a total of $n = 78$ studies fulfilled all inclusion criteria. Of those, $n = 68$ entered our quantitative synthesis (for an overview see **Table 3**). The remaining 10 studies (Delgado et al., 2008; Driscoll et al., 2009; Jamieson et al., 2012, 2013; Peters et al., 2014; Baur et al., 2015; Reinecke et al., 2015; Peters and Jamieson, 2016; Zaehringer et al., 2018; Kotwas et al., 2019) were not considered, as a meta-analysis on the respective combination of emotion regulation strategy and psychophysiological measure was not possible because the number of studies was too small. See **Figure 1** for a PRISMA flowchart depiction of the screening and selection of studies.

Data Extraction

The first author coded the sample sizes, group means, standard deviations, t and p-values for tests on group effects and participants' mean age of the eligible studies. Another person independently coded 50% of the included studies to evaluate reliability. Correlation analysis confirmed high interrater-reliability (mean $r = 0.95$, range $= 0.66$–1.0). In addition, inconsistencies between raters were identified and subsequently corrected. Additionally, the psychophysiological measure, and the specific emotion regulation strategy (distraction, reappraisal, suppression, own choice) were coded. When comparing emotion regulation studies, a major problem arises from inconsistencies in the way emotion regulation instructions are labeled. For example, studies that labeled a condition as "suppression" either instructed participants to use reappraisal (Eippert et al., 2007; Bernat et al., 2011) or to suppress thoughts or facial expressions (Gross and Levenson, 1993; Ohira et al., 2006). To prevent confusion, we specifically evaluated the particular emotion regulation instructions as reported in the articles and coded them according to the taxonomy adapted from Webb et al. (2012). See **Table 1** for definitions and examples. For this meta-analysis, we also subdivided the control strategies into five types (classifications can be derived from **Table 1**; adapted from Webb et al., 2012): no instruction at all (i.e., "view"), instruction "not to regulate in a certain manner," instructions to "respond naturally," instructions to "maintain" the target emotion or a combination of the above instructions. Furthermore, the researcher(s) also coded whether a study used a between-subject design with two independent groups for the control and the experimental group or a within-subject design with a single group undergoing both regulation and control conditions. In addition the nature of emotion induction if applicable [images, film, music, dyadic interaction, past experience or negative self-belief, threat of shock (ToS), stress task, anger task] was also coded. Finally, we coded the trial duration (i.e., the length of the regulation period of a trial, in seconds). We defined the length of a regulation period as the length of one regulation attempt. In event-related designs a regulation attempt thus corresponds to one trial (i.e., after instruction until picture offset), whereas in studies presenting films or stress tasks, a regulation attempt corresponds to the whole film viewing period or task period (i.e., after instruction until end of film/task).

Regarding electrodermal activity, there was great variability in the quantification of skin conductance across studies. We developed a taxonomy by which we divided electrodermal activity measures in skin conductance level, skin conductance response and number of skin conductance responses (see **Table 2**). A detailed description of the taxonomy and a table summarizing all included studies on electrodermal responses

[3]The search process was updated two times in total. The first search yielded a total of 848 potentially relevant articles on January 22, 2016 (after duplicates were removed). A second search 1 year later (on February 8, 2017) yielded an additional 210 potentially relevant articles (after duplicates were removed). A third search 2 years later (on July 18, 2019) yielded an additional 295 potentially relevant articles (after duplicates were removed).

TABLE 3 | Characteristics and effect sizes for studies included in the meta–analyses.

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Ajaya et al. (2016)	Reappraisal	HRV	Anger	B	120	Anger task	C1	66	60.61	20.62	40	−0.10
Aldao and Mennin (2012)	Reappraisal	HRV	Disgust, fear, sadness	B	62	F	C1	58	56.90	29.57	38	0.75
Azbel-Jackson et al. (2015), study 1	Suppression	HR	Negative	B	7	I	C2	60	70.00	21.50	60	−0.22
Azbel-Jackson et al. (2015), study 1	Suppression	SCL	Negative	B	7	I	C2	60	70.00	21.50	60	−0.04
Azbel-Jackson et al. (2015), study 2	Suppression	HR	Negative	B	7	I	C2	80	85.00	22.20	40	0.40
Azbel-Jackson et al. (2015), study 2	Suppression	SCL	Negative	B	7	I	C2	80	85.00	22.20	40	0.73
Bebko et al. (2011)	Reappraisal	PD	Negative	W	10	I	C4	84	47.62	19.67	40	−0.09
Ben-Naim et al. (2013)	Reappraisal	FPA	Negative	B	900	Dyadic	C1	254	50.00	24.00	86	−1.52
Ben-Naim et al. (2013)	Reappraisal	FPTT	Negative	B	900	Dyadic	C1	254	50.00	24.00	86	−0.18
Ben-Naim et al. (2013)	Reappraisal	HR	Negative	B	900	Dyadic	C1	254	50.00	24.00	86	0.33
Ben-Naim et al. (2013)	Reappraisal	SCL	Negative	B	900	Dyadic	C1	254	50.00	24.00	86	0.16
Ben-Naim et al. (2013)	Reappraisal	SCR	Negative	B	900	Dyadic	C1	254	50.00	24.00	86	−0.39
Ben-Naim et al. (2013)	Suppression	EPPT	Negative	B	900	Dyadic	C1	254	50.00	24.00	85	0.09
Ben-Naim et al. (2013)	Suppression	FPA	Negative	B	900	Dyadic	C1	254	50.00	24.00	85	−0.66
Ben-Naim et al. (2013)	Suppression	FPTT	Negative	B	900	Dyadic	C1	254	50.00	24.00	85	−0.32
Ben-Naim et al. (2013)	Suppression	HR	Negative	B	900	Dyadic	C1	254	50.00	24.00	85	0.35
Ben-Naim et al. (2013)	Suppression	SCL	Negative	B	900	Dyadic	C1	254	50.00	24.00	85	0.04
Braams et al. (2012)	Suppression	HR	Fear	B	16.5	ToS	C1	123	46.34	21.70	62	−0.04
Bulut et al. (2018), study 1	Reappraisal	HRV	Negative	B	300	I	C4	28	67.86	23.67	28	0.47
Butler et al. (2003), study 1	Suppression	MAP	Negative	B		Dyadic	C1	72	100.00	20.30	60	−0.09
Butler et al. (2006)	Reappraisal	HR	Negative	B	590.8	Dyadic	C1	190	100.00	20.00	62	−0.24
Butler et al. (2006)	Reappraisal	HRV	Negative	B	590.8	Dyadic	C1	190	100.00	20.00	62	0.51
Butler et al. (2006)	Reappraisal	RA	Negative	B	590.8	Dyadic	C1	190	100.00	20.00	62	0.12
Butler et al. (2006)	Suppression	HR	Negative	B	570.6	Dyadic	C1	190	100.00	20.00	69	0.10
Butler et al. (2006)	Suppression	HRV	Negative	B	570.6	Dyadic	C1	190	100.00	20.00	69	0.39
Butler et al. (2006)	Suppression	RA	Negative	B	570.6	Dyadic	C1	190	100.00	20.00	69	−0.76
Butler et al. (2014)	Reappraisal	SCL	Negative	B	590.8	Dyadic	C1	190	14.74	20.10	61	−0.28
Butler et al. (2014)	Suppression	SCL	Negative	B	570.6	Dyadic	C1	190	14.74	20.10	68	−0.26
Chu et al. (2019)	Reappraisal	HR	Anger	B	10	Anger task	C1	68	54.41	40.00	68	−0.14
Colby et al. (1977)	Suppression	SCL	Fear	W	6	ToS	C4	10	0.00		10	−0.11
Conzelmann et al. (2015)	Own choice	Startle	Negative	W	8	I	C3	31	48.39	22.00	31	−0.60
Dan-Glauser and Gross (2011)	Suppression	FT	Negative	W	8	I	C4	37	100.00	20.20	37	−0.16
Dan-Glauser and Gross (2011)	Suppression	HR	Negative	W	8	I	C4	37	100.00	20.20	37	−0.57
Dan-Glauser and Gross (2011)	Suppression	MAP	Negative	W	8	I	C4	37	100.00	20.20	37	−0.07
Dan-Glauser and Gross (2011)	Suppression	RA	Negative	W	8	I	C4	37	100.00	20.20	37	−0.82

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TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Dan-Glauser and Gross (2015)	Suppression	FPA	Negative	W	8	I	C4	37	100.00	20.20	37	0.42
Dan-Glauser and Gross (2015)	Suppression	FPTT	Negative	W	8	I	C4	37	100.00	20.20	37	−0.13
Dan-Glauser and Gross (2015)	Suppression	FT	Negative	W	8	I	C4	37	100.00	20.20	37	−0.16
Dan-Glauser and Gross (2015)	Suppression	HR	Negative	W	8	I	C4	37	100.00	20.20	37	−0.71
Dan-Glauser and Gross (2015)	Suppression	MAP	Negative	W	8	I	C4	37	100.00	20.20	37	−0.50
Dan-Glauser and Gross (2015)	Suppression	RA	Negative	W	8	I	C4	37	100.00	20.20	37	−0.45
Demaree et al. (2006)	Suppression	HR	Disgust	B	120	F	C4	69	52.17	19.32	35	0.09
Demaree et al. (2006)	Suppression	HRV	Disgust	B	120	F	C4	69	52.17	19.32	35	0.21
Demaree et al. (2006)	Suppression	RA	Disgust	B	120	F	C4	69	52.17	19.32	35	0.43
Demaree et al. (2006)	Suppression	SCL	Disgust	B	120	F	C4	69	52.17	19.32	35	0.12
Denson et al. (2014), study 1	Reappraisal	HR	Fear	B	600	Stress	C1	90	52.22	20.54	90	−0.09
Denson et al. (2014), study 1	Reappraisal	HR	Fear	B	300	Stress	C1	90	52.22	20.54	86	−0.07
Denson et al. (2011)	Reappraisal	HRV	Anger	B	180	F	C1	131	100.00	20.23	86	0.37
Denson et al. (2011)	Suppression	HR	Anger	B	180	F	C1	131	100.00	20.23	89	0.25
Denson et al. (2011)	Suppression	HRV	Anger	B	180	F	C1	131	100.00	20.23	89	0.17
Deveney and Pizzagalli (2008)	Reappraisal	cEMG	Negative	W	5	I	C3	32	78.13	23.97	26	−0.09
Di Simplicio et al. (2012), sample 1	Reappraisal	HR	Negative	W	4	I	C4	30	53.33	28.59	20	0.00
Di Simplicio et al. (2012), sample 1	Reappraisal	HRV	Negative	W	4	I	C4	30	53.33	28.59	20	0.05
Di Simplicio et al. (2012), sample 2	Reappraisal	HR	Negative	W	4	I	C4	30	53.33	28.59	10	0.09
Di Simplicio et al. (2012), sample 2	Reappraisal	HRV	Negative	W	4	I	C4	30	53.33	28.59	10	−0.15
Dillon and LaBar (2005), sample 1	Own choice	Startle	Negative	W	12	I	C3	48	77.08	22.00	12	−0.09
Dillon and LaBar (2005), sample 2	Own choice	Startle	Negative	W	12	I	C3	48	77.08	22.00	12	−0.75
Efinger et al. (2019)	Reappraisal	HR	Negative	W	8	I	C4	77	100.00	20.70	77	−0.27
Efinger et al. (2019)	Reappraisal	RA	Negative	W	8	I	C4	77	100.00	20.70	77	0.06
Efinger et al. (2019)	Reappraisal	SCL	Negative	W	8	I	C4	77	100.00	20.70	77	−0.19
Efinger et al. (2019)	Distraction	SCL	Negative	W	8	I	C4	77	100.00	20.70	77	−0.27
Fitzpatrick and Kuo (2016)	Distraction	SCL	Negative	W	10	I		30	66.67	30.07	30	0.00
Fuentes-Sánchez et al. (2019)	Reappraisal	SCR	Negative	W	8	I	C4	122	59.02	25.10	106	−0.01
Goldin et al. (2019)	Reappraisal	HR	Negative	W	12	Self-belief	C4	35	57.14	32.20	35	−0.03
Goldin et al. (2019)	Reappraisal	SCL	Negative	W	12	Self-belief	C4	35	57.14	32.20	35	−0.01
Golkar et al. (2014)	Own choice	Startle	Negative	W	5	I	C2	61	54.10	30.90	61	−0.47
Gomez et al. (2015)	Reappraisal	SCR	Disgust	B	10	I	C1	81	64.20	28.15	40	−0.11
Gross and Levenson (1993), study 1	Suppression	EPPT	Disgust	B	64	F	C1	43	0.00	19.30	43	0.07
Gross and Levenson (1993), study 1	Suppression	FPA	Disgust	B	64	F	C1	43	0.00	19.30	43	−0.38
Gross and Levenson (1993), study 1	Suppression	FPTT	Disgust	B	64	F	C1	43	0.00	19.30	43	−0.24
Gross and Levenson (1993), study 1	Suppression	FT	Disgust	B	64	F	C1	43	0.00	19.30	43	−0.30

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TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Gross and Levenson (1993), study 1	Suppression	HR	Disgust	B	64	F	C1	43	0.00	19.30	43	−0.53
Gross and Levenson (1993), study 1	Suppression	RA	Disgust	B	64	F	C1	43	0.00	19.30	43	−0.18
Gross and Levenson (1993), study 1	Suppression	SCL	Disgust	B	64	F	C1	43	0.00	19.30	43	0.24
Gross and Levenson (1993), study 2	Suppression	EPPT	Disgust	B	64	F	C1	42	100.00	19.20	42	−0.55
Gross and Levenson (1993), study 2	Suppression	FPA	Disgust	B	64	F	C1	42	100.00	19.20	42	−0.81
Gross and Levenson (1993), study 2	Suppression	FPTT	Disgust	B	64	F	C1	42	100.00	19.20	42	0.21
Gross and Levenson (1993), study 2	Suppression	FT	Disgust	B	64	F	C1	42	100.00	19.20	42	−0.96
Gross and Levenson (1993), study 2	Suppression	HR	Disgust	B	64	F	C1	42	100.00	19.20	42	−0.21
Gross and Levenson (1993), study 2	Suppression	RA	Disgust	B	64	F	C1	42	100.00	19.20	42	0.11
Gross and Levenson (1993), study 2	Suppression	SCL	Disgust	B	64	F	C1	42	100.00	19.20	42	0.46
Gross and Levenson (1997)	Suppression	SCL	Sadness	B	210	F	C1	180	100.00		180	0.29
Gross (1998a)	Reappraisal	FPA	Disgust	B	64	F	C1	120	50.00	21.00	80	0.12
Gross (1998a)	Reappraisal	FT	Disgust	B	64	F	C1	120	50.00	21.00	80	−0.33
Gross (1998a)	Reappraisal	HR	Disgust	B	64	F	C1	120	50.00	21.00	80	−0.09
Gross (1998a)	Reappraisal	SCL	Disgust	B	64	F	C1	120	50.00	21.00	80	−0.19
Gross (1998a)	Suppression	FPA	Disgust	B	64	F	C1	120	50.00	21.00	80	−0.60
Gross (1998a)	Suppression	FT	Disgust	B	64	F	C1	120	50.00	21.00	80	−1.04
Gross (1998a)	Suppression	HR	Disgust	B	64	F	C1	120	50.00	21.00	80	0.02
Gross (1998a)	Suppression	SCL	Disgust	B	64	F	C1	120	50.00	21.00	80	0.41
Hagemann et al. (2006)	Suppression	EPPT	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	−0.38
Hagemann et al. (2006)	Suppression	FPA	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	−0.25
Hagemann et al. (2006)	Suppression	FPTT	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	−0.39
Hagemann et al. (2006)	Suppression	FT	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	−0.55
Hagemann et al. (2006)	Suppression	HR	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	0.73
Hagemann et al. (2006)	Suppression	HRV	Negative	B	20	ToS, I	C1	252	51.98	20.50	168	−0.34
Hagemann et al. (2006)	Suppression	SCL	Negative	B	5	ToS, I	C1	252	51.98	20.50	168	0.49
Hallam et al. (2015)	Reappraisal	SCL	Negative	W	10	I	C4	40	50.00	20.00	26	0.00
Hallam et al. (2015)	Suppression	SCL	Negative	W	10	I	C4	40	50.00	20.00	26	−0.01
Jackson et al. (2000)	Own choice	Startle	Negative	W	14	I	C3	48	68.75	20.50	44	−1.04
Kim and Hamann (2012)	Reappraisal	cEMG	Negative	W	24	I	C4	36	50.00	20.19	33	−0.30
Kim and Hamann (2012)	Reappraisal	SCR	Negative	W	24	I	C4	36	50.00	20.19	32	0.11
Kinner et al. (2017)	Reappraisal	PD	Negative	W	5	I	C4	30	100.00	24.40	28	0.26
Kinner et al. (2017)	Reappraisal	SCR	Negative	W	5	I	C4	30	100.00	24.40	25	0.00
Kunzmann et al. (2005)	Suppression	HR	Disgust	W	117	F	C1	95	49.47	46.00	47	−0.26
Kunzmann et al. (2005)	Suppression	SCL	Disgust	W	117	F	C1	95	49.47	46.00	47	0.15
Leiberg et al. (2012)	Reappraisal	SCR	Negative	W	6	I	C4	24	100.00	24.10	24	0.17

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TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Lohani and Isaacowitz (2014), sample 1	Reappraisal	cEMG	Sadness	W	300	F	C1	48	79.17	71.42	42	−0.17
Lohani and Isaacowitz (2014), sample 1	Reappraisal	SCL	Sadness	W	300	F	C1	42	73.81	18.50	40	0.56
Lohani and Isaacowitz (2014), sample 1	Suppression	SCL	Sadness	W	300	F	C1	42	73.81	18.50	40	0.52
Lohani and Isaacowitz (2014), sample 2	Reappraisal	cEMG	Sadness	W	300	F	C1	42	73.81	18.50	40	−0.30
Lohani and Isaacowitz (2014), sample 2	Reappraisal	SCL	Sadness	W	300	F	C1	48	79.17	71.42	44	0.09
Lohani and Isaacowitz (2014), sample 2	Suppression	SCL	Sadness	W	300	F	C1	48	79.17	71.42	44	0.13
Lohani and Isaacowitz (2014), sample 1	Distraction	SCL	Sadness	W	300	F	C1	42	73.81	18.50	40	0.48
Lohani and Isaacowitz (2014), sample 2	Distraction	SCL	Sadness	W	300	F	C1	48	79.17	71.42	44	0.24
Low et al. (2008)	Reappraisal	HR	Negative	B	600	Stress	C3	81	58.02	20.60	56	0.29
Martins et al. (2018)	Reappraisal	PD	Negative	W	7	I	C4	48	68.75	69.10	48	0.06
Martins et al. (2018)	Reappraisal	PD	Negative	W	7	I	C4	48	60.42	21.06	48	0.06
Morawetz et al. (2016a)	Reappraisal	SCR	Negative	W	8	I, F	C4	59	33.90	32.47	47	0.08
Morawetz et al. (2016b)	Reappraisal	SCR	Negative	W	8	I	C4	23	52.17	25.70	16	−0.19
Morawetz et al. (2017)	Reappraisal	SCR	Negative	W	8	F	C4	23	65.22	22.95	22	−0.03
Ohira et al. (2006)	Suppression	HR	Negative	W	60	I	C4	10	100.00	24.22	9	0.04
Opitz et al. (2014), sample 1	Reappraisal	cEMG	Sadness	W	8	I	C4	30	53.33	61.90	29	−0.43
Opitz et al. (2014), sample 1	Reappraisal	HR	Sadness	W	8	I	C4	30	63.33	19.45	28	−0.02
Opitz et al. (2014), sample 1	Reappraisal	SCL	Sadness	W	8	I	C4	30	63.33	19.45	27	−0.02
Opitz et al. (2014), sample 2	Reappraisal	cEMG	Sadness	W	8	I	C4	30	63.33	19.45	28	−1.07
Opitz et al. (2014), sample 2	Reappraisal	HR	Sadness	W	8	I	C4	30	53.33	61.90	29	−0.14
Opitz et al. (2014), sample 2	Reappraisal	SCL	Sadness	W	8	I	C4	30	53.33	61.90	29	−0.27
Ortner (2015)	Reappraisal	SCR	Negative	B	8	I	C1	120	75.83		76	0.01
Plieger et al. (2017)	Reappraisal	SCL	Negative	W	4.5	I	C1	91	82.42	24.53	91	−0.28
Richards and Gross (1999), study2	Suppression	DBP	Negative	B	84	I	C1	85	100.00	18.80	74	0.36
Richards and Gross (1999), study2	Suppression	FT	Negative	B	84	I	C1	85	100.00	18.80	74	−0.37
Richards and Gross (1999), study2	Suppression	HR	Negative	B	84	I	C1	85	100.00	18.80	74	−0.11
Richards and Gross (1999), study2	Suppression	SBP	Negative	B	84	I	C1	85	100.00	18.80	74	0.27
Richards and Gross (1999), study2	Suppression	SCL	Negative	B	84	I	C1	85	100.00	18.80	74	−0.14
Roberts et al. (2008), sample 1	Suppression	DBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.91
Roberts et al. (2008), sample 1	Suppression	HR	Disgust	B	62	F	C1	40	60.00	20.80	40	−0.23
Roberts et al. (2008), sample 1	Suppression	SBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.60
Roberts et al. (2008), sample 1	Suppression	SCL	Negative	B	62	F	C1	40	60.00	20.80	40	0.00
Roberts et al. (2008), sample 2	Suppression	DBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.84
Roberts et al. (2008), sample 2	Suppression	HR	Disgust	B	62	F	C1	40	60.00	20.80	40	0.08
Roberts et al. (2008), sample 2	Suppression	SBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.66
Roberts et al. (2008), sample 2	Suppression	SCL	Negative	B	62	F	C1	40	60.00	20.80	40	0.35
Roberts et al. (2008), sample 3	Suppression	DBP	Disgust	B	62	F	C1	40	60.00	20.80	40	−0.31

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TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Roberts et al. (2008), sample 3	Suppression	HR	Disgust	B	62	F	C1	40	60.00	20.80	40	−0.61
Roberts et al. (2008), sample 3	Suppression	SBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.01
Roberts et al. (2008), sample 3	Suppression	SCL	Negative	B	62	F	C1	40	60.00	20.80	40	0.62
Roberts et al. (2008), sample 4	Suppression	DBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.12
Roberts et al. (2008), sample 4	Suppression	HR	Disgust	B	62	F	C1	40	60.00	20.80	40	0.26
Roberts et al. (2008), sample 4	Suppression	SBP	Disgust	B	62	F	C1	40	60.00	20.80	40	0.11
Roberts et al. (2008), sample 4	Suppression	SCL	Negative	B	62	F	C1	40	60.00	20.80	40	0.30
Robinson and Demaree (2009)	Suppression	HR	Sadness	W	120	F	C4	102	50.98	19.75	102	−0.23
Robinson and Demaree (2009)	Suppression	HRV	Sadness	W	120	F	C4	102	50.98	19.75	102	0.41
Robinson and Demaree (2009)	Suppression	SCL	Sadness	W	120	F	C4	102	50.98	19.75	102	0.26
Rohrmann et al. (2009), sample 1	Reappraisal	HR	Disgust	B	60	F	C1	120	0.00	25.47	36	0.22
Rohrmann et al. (2009), sample 2	Reappraisal	HR	Disgust	B	60	F	C1	120	0.00	25.47	36	−0.34
Rohrmann et al. (2009), sample 1	Suppression	HR	Disgust	B	60	F	C1	120	0.00	25.47	36	0.47
Rohrmann et al. (2009), sample 2	Suppression	HR	Disgust	B	60	F	C1	120	0.00	25.47	36	−0.66
Rohrmann et al. (2009), sample 1	Reappraisal	SCL	Disgust	B	60	F	C1	120	0.00	25.47	36	0.35
Rohrmann et al. (2009), sample 2	Reappraisal	SCL	Disgust	B	60	F	C1	120	0.00	25.47	36	−0.57
Rohrmann et al. (2009), sample 1	Suppression	SCL	Disgust	B	60	F	C1	120	0.00	25.47	36	0.85
Rohrmann et al. (2009), sample 2	Suppression	SCL	Disgust	B	60	F	C1	120	0.00	25.47	36	−0.23
Roth et al. (2014), study2	Suppression	SCL	Fear	B	197	F	C1	116	60.34	24.90	65	−0.04
Roth et al. (2014), study2	Distraction	SCL	Fear	B	197	F	C1	116	60.34	24.90	67	−0.77
Sheppes et al. (2009)	Reappraisal	FT	Sadness	B	190	F	C5	45	100.00	22.90	29	0.22
Sheppes et al. (2009)	Reappraisal	SCL	Sadness	B	190	F	C5	45	100.00	22.90	29	1.13
Sheppes et al. (2009)	Distraction	SCL	Sadness	B	190	F	C5	45	100.00	22.90	29	0.23
Shermohammed et al. (2017)	Reappraisal	HR	Negative	W	8	I	C1	25	48.00	20.89	19	0.65
Shermohammed et al. (2017)	Reappraisal	SCR	Negative	W	8	I	C1	25	48.00	20.89	17	0.12
Shiota and Levenson (2009, 2012), sample 1	Suppression	DBP	Disgust	W	180	F	C4	76	50.00	25.50	73	−0.66
Shiota and Levenson (2009, 2012), sample 1	Suppression	EPPT	Disgust	W	180	F	C4	76	50.00	25.50	74	0.33
Shiota and Levenson (2009, 2012), sample 1	Suppression	FPA	Disgust	W	180	F	C4	76	50.00	25.50	75	0.49
Shiota and Levenson (2009, 2012), sample 1	Suppression	FPTT	Disgust	W	180	F	C4	76	50.00	25.50	75	−0.12
Shiota and Levenson (2009, 2012), sample 1	Suppression	FT	Disgust	W	180	F	C4	76	50.00	25.50	76	−0.24
Shiota and Levenson (2009, 2012), sample 1	Suppression	HR	Disgust	W	180	F	C4	76	50.00	25.50	75	−0.40
Shiota and Levenson (2009, 2012), sample 1	Suppression	MAP	Disgust	W	180	F	C4	76	50.00	25.50	73	−0.66
Shiota and Levenson (2009, 2012), sample 1	Suppression	RA	Disgust	W	180	F	C4	76	50.00	25.50	72	−0.29
Shiota and Levenson (2009, 2012), sample 1	Suppression	SBP	Disgust	W	180	F	C4	76	50.00	25.50	73	−0.69
Shiota and Levenson (2009, 2012), sample 1	Suppression	SCL	Disgust	W	180	F	C4	76	50.00	25.50	73	−0.42
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	22	50.00	25.50	23	0.37
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	22	50.00	25.50	23	0.47

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TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	FT	Disgust, sadness	W	180	F	C4	22	50.00	25.50	23	0.36
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	HR	Disgust, sadness	W	180	F	C4	22	50.00	25.50	23	−0.29
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	RA	Disgust, sadness	W	180	F	C4	22	50.00	25.50	22	−0.34
Shiota and Levenson (2009, 2012), sample 2	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	22	50.00	25.50	23	−0.27
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	26	50.00	25.30	25	0.14
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	26	50.00	25.30	25	0.02
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	FT	Disgust, sadness	W	180	F	C4	26	50.00	25.30	26	0.12
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	HR	Disgust, sadness	W	180	F	C4	26	50.00	25.30	25	−0.11
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	RA	Disgust, sadness	W	180	F	C4	26	50.00	25.30	24	−0.10
Shiota and Levenson (2009, 2012), sample 3	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	26	50.00	25.30	24	0.10
Shiota and Levenson (2009, 2012), sample 4	Suppression	DBP	Disgust	W	180	F	C4	72	50.00	44.70	64	−0.27
Shiota and Levenson (2009, 2012), sample 4	Suppression	EPPT	Disgust	W	180	F	C4	72	50.00	44.70	71	−0.06
Shiota and Levenson (2009, 2012), sample 4	Suppression	FPA	Disgust	W	180	F	C4	72	50.00	44.70	71	0.27
Shiota and Levenson (2009, 2012), sample 4	Suppression	FPTT	Disgust	W	180	F	C4	72	50.00	44.70	72	0.11
Shiota and Levenson (2009, 2012), sample 4	Suppression	FT	Disgust	W	180	F	C4	72	50.00	44.70	72	−0.03
Shiota and Levenson (2009, 2012), sample 4	Suppression	HR	Disgust	W	180	F	C4	72	50.00	44.70	72	−0.30
Shiota and Levenson (2009, 2012), sample 4	Suppression	MAP	Disgust	W	180	F	C4	72	50.00	44.70	64	−0.28
Shiota and Levenson (2009, 2012), sample 4	Suppression	RA	Disgust	W	180	F	C4	72	50.00	44.70	66	−0.07
Shiota and Levenson (2009, 2012), sample 4	Suppression	SBP	Disgust	W	180	F	C4	72	50.00	44.70	64	−0.32
Shiota and Levenson (2009, 2012), sample 4	Suppression	SCL	Disgust	W	180	F	C4	72	50.00	44.70	69	−0.39
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	22	50.00	44.70	23	0.23
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	22	50.00	44.70	24	−0.28
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	FT	Disgust, sadness	W	180	F	C4	22	50.00	44.70	24	0.00
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	HR	Disgust, sadness	W	180	F	C4	22	50.00	44.70	24	−0.31
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	RA	Disgust, sadness	W	180	F	C4	22	50.00	44.70	23	−0.18
Shiota and Levenson (2009, 2012), sample 5	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	22	50.00	44.70	22	−0.10
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	26	50.00	43.20	26	0.17
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	26	50.00	43.20	26	0.21
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	FT	Disgust, sadness	W	180	F	C4	26	50.00	43.20	26	0.23
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	HR	Disgust, sadness	W	180	F	C4	26	50.00	43.20	26	−0.06
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	RA	Disgust, sadness	W	180	F	C4	26	50.00	43.20	24	−0.10
Shiota and Levenson (2009, 2012), sample 6	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	26	50.00	43.20	25	−0.09
Shiota and Levenson (2009, 2012), sample 7	Suppression	DBP	Disgust	W	180	F	C4	72	50.00	64.80	69	−0.30
Shiota and Levenson (2009, 2012), sample 7	Suppression	EPPT	Disgust	W	180	F	C4	72	50.00	64.80	68	−0.01
Shiota and Levenson (2009, 2012), sample 7	Suppression	FPA	Disgust	W	180	F	C4	72	50.00	64.80	65	0.23
Shiota and Levenson (2009, 2012), sample 7	Suppression	FPTT	Disgust	W	180	F	C4	72	50.00	64.80	65	0.16
Shiota and Levenson (2009, 2012), sample 7	Suppression	FT	Disgust	W	180	F	C4	72	50.00	64.80	72	0.11

(Continued)

TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Shiota and Levenson (2009, 2012), sample 7	Suppression	HR	Disgust	W	180	F	C4	72	50.00	64.80	69	−0.12
Shiota and Levenson (2009, 2012), sample 7	Suppression	MAP	Disgust	W	180	F	C4	72	50.00	64.80	69	−0.30
Shiota and Levenson (2009, 2012), sample 7	Suppression	RA	Disgust	W	180	F	C4	72	50.00	64.80	66	−0.26
Shiota and Levenson (2009, 2012), sample 7	Suppression	SBP	Disgust	W	180	F	C4	72	50.00	64.80	69	−0.27
Shiota and Levenson (2009, 2012), sample 7	Suppression	SCL	Disgust	W	180	F	C4	72	50.00	64.80	69	−0.46
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	24	50.00	64.80	23	−0.08
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	24	50.00	64.80	23	0.03
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	FT	Disgust, sadness	W	180	F	C4	24	50.00	64.80	24	0.10
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	HR	Disgust, sadness	W	180	F	C4	24	50.00	64.80	23	−0.19
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	RA	Disgust, sadness	W	180	F	C4	24	50.00	64.80	20	−0.19
Shiota and Levenson (2009, 2012), sample 8	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	24	50.00	64.80	23	−0.11
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	FPA	Disgust, sadness	W	180	F	C4	24	50.00	64.50	22	0.40
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	FPTT	Disgust, sadness	W	180	F	C4	24	50.00	64.50	22	−0.12
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	FT	Disgust, sadness	W	180	F	C4	24	50.00	64.50	23	0.58
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	HR	Disgust, sadness	W	180	F	C4	24	50.00	64.50	22	−0.10
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	RA	Disgust, sadness	W	180	F	C4	24	50.00	64.50	22	−0.26
Shiota and Levenson (2009, 2012), sample 9	Reappraisal	SCL	Disgust, sadness	W	180	F	C4	24	50.00	64.50	22	−0.64
Soto et al. (2016)	Suppression	HR	Disgust	W	58	F	C1	59	54.24	19.51	48	−0.19
Soto et al. (2016)	Suppression	SCL	Disgust	W	58	F	C1	59	54.24	19.51	47	−0.15
Stiller et al. (2019)	Reappraisal	HR	Negative	B	165	F	C2	61	73.77	24.30	41	0.15
Stiller et al. (2019)	Reappraisal	SCL	Negative	B	165	F	C2	61	73.77	24.30	41	0.49
Stiller et al. (2019)	Suppression	HR	Negative	B	165	F	C2	61	73.77	24.30	40	0.58
Stiller et al. (2019)	Suppression	SCL	Negative	B	165	F	C2	61	73.77	24.30	40	0.35
Strauss et al. (2016)	Reappraisal	PD	Negative	W	5	I	C4	25	64.00	19.80	25	0.14
Svaldi et al. (2010)	Reappraisal	FPTT	Sadness	W	125	F	C1	25	100.00	38.30	21	−0.11
Svaldi et al. (2010)	reappraisal	HR	Sadness	W	125	F	C1	25	100.00	38.30	25	−0.32
Svaldi et al. (2010)	reappraisal	HRV	Sadness	W	125	F	C1	25	100.00	38.30	21	−0.67
Svaldi et al. (2010)	reappraisal	SCL	Sadness	W	125	F	C1	25	100.00	38.30	23	0.10
Svaldi et al. (2010)	Suppression	FPTT	Sadness	W	211	F	C1	25	100.00	38.30	21	−0.68
Svaldi et al. (2010)	Suppression	HR	Sadness	W	211	F	C1	25	100.00	38.30	25	−0.16
Svaldi et al. (2010)	Suppression	HRV	Sadness	W	211	F	C1	25	100.00	38.30	21	−0.18
Svaldi et al. (2010)	Suppression	SCL	Sadness	W	211	F	C1	25	100.00	38.30	23	0.50
Urry et al. (2006)	Reappraisal	PD	Negative	W	5	I	C3	17	52.94	62.90	14	0.43
Urry et al. (2009)	Reappraisal	PD	Negative	W	8	I	C3	26	57.69	64.80	26	0.46
Urry et al. (2009)	Reappraisal	SCL	Negative	W	8	I	C3	26	57.69	64.80	26	−0.42
Urry (2009)	Reappraisal	cEMG	Negative	W	8	I	C2	41	63.41	20.00	40	0.03
Urry (2009)	Reappraisal	HR	Negative	W	8	I	C2	41	63.41	20.00	40	−0.14

(Continued)

TABLE 3 | Continued

Study name	Strategy	Measure	Emotion	Design	Trial duration (s)	Nature of emotion induction	Control instruction	N total	Percent of women	Age (mean)	N analyzed	Effect size
Ury (2009)	Reappraisal	SCR	Negative	W	8	I	C2	41	63.41	20.00	39	0.18
Ury (2010)	Reappraisal	cEMG	Negative	W	4	I	C4	54	48.15	18.80	54	−0.32
Ury (2010)	Reappraisal	HR	Negative	W	4	I	C4	54	48.15	18.80	53	0.03
Ury (2010)	Reappraisal	SCL	Negative	W	4	I	C4	54	48.15	18.80	52	0.03
Uy et al. (2013)	Suppression	HRV	Disgust	W	133	F	C1	7	57.14	29.80	7	0.45
van Reekum et al. (2007)	Reappraisal	PD	Negative	W	8	I	C4	29	62.07	63.00	21	0.53
Williams et al. (2009), study 1	Reappraisal	HR	Fear	B	180	Stress	C1	39	64.10	20.60	26	−0.15
Williams et al. (2009), study 2	Reappraisal	HR	Fear	B	180	Stress	C1	47	65.96	21.30	30	0.05
Wolgast et al. (2011)	Reappraisal	cEMG	Disgust, fear, Sadness	B	153	F	C1	94	51.06	27.40	62	−0.79
Wolgast et al. (2011)	Reappraisal	SCL	Disgust, fear, Sadness	B	153	F	C1	94	51.06	27.40	62	−0.87
Wu et al. (2016), study 2	Reappraisal	SCL	Sadness	B	180	F	C1	42	100.00	22.31	42	−0.18
Yuan et al. (2014)	Suppression	SCL	Anger	B	1800	Anger task	C1	64	0.00	29.52	43	−0.72

cEMG, corrugator electromyography; DBP, diastolic blood pressure; EPTT, ear pulse transit time; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; HRV, heart rate variability; MAP, mean arterial pressure; PD, pupil dilation; RA, respiration amplitude; SBP, systolic blood pressure; SCL, skin conductance level; SCR, skin conductance response; B, between–subject design study; W, within–subject design study; F, film; I, images; C1, no instruction given ("view"); C2, instruction not to regulate; C3, instruction to maintain target emotion; C4, instruction to respond naturally; C5, a combination of C1–C4; Ntotal, number of participants in the study; Nanalyzed, number of participants in the subsample.

with information about the categorization can be found in the supplement (p. 2 and **Table S2**).

Statistical Analysis

Cohen's *d* was used as the effect size measure in the meta-analyses. For between-subject studies, effect sizes were calculated from the means and standard deviations of the control and experimental (regulation) groups. For within-subject studies, we used the means and standard deviations of the control and experimental (regulation) conditions. If these values were not available, effect sizes were calculated using *t*-values. Furthermore, the variances of the effect sizes were determined. In within-subject designs, the variance of the effect size estimate depends on the correlation between the paired measurements. If the correlation was not available from the original data, the median correlation from the other studies entering the meta-analysis was used. Effect sizes were interpreted based on Cohen's guidelines (Cohen, 1988). Therefore, effects at the 0.2, 0.5, and 0.8 levels were considered as small, medium, and large, respectively.

Since the experimental conditions of the studies differ in many ways, it is unlikely that the studies share a common effect size. Fixed-effect models are therefore implausible. Following recommendations of Borenstein et al. (2010) we conducted random effects meta-analyses. We calculated average effect sizes and 95% confidence intervals (CI). Heterogeneity of effect sizes was assessed with the I^2-statistic which represents the proportion of total variation in the estimated effect sizes that is due to heterogeneity between studies (Higgins and Thompson, 2002). The analyses were performed separated by psychophysiological measure and emotion regulation strategy. Meta-analyses were only conducted when five or more independent samples were available[4].

For each significant meta-analysis we constructed a funnel plot with the effect sizes on the horizontal axis and their standard errors on the vertical axis. Egger's tests (Egger et al., 1997) were applied to evaluate asymmetry in funnel plots which may be caused by publication bias.

Several studies included two or three assessments within a given measure (e.g., skin conductance level during the regulation of sad and disgusting stimuli) so that there was more than one effect size reported for a specific sample. In these cases, we used the mean of the multiple effect sizes. To calculate the variance of this mean effect size, we assumed that the correlation between the effect sizes was 0.5. If studies reported sufficient results from multiple independent samples (e.g., men and women, prone to disgust vs. not prone to disgust), each of them entered the analysis. Effect sizes for interbeat interval and heart rate were included in the same analyses. To align to polarity of the effect sizes, the parameter for interbeat interval was multiplied by minus one. Thus, a negative size of interbeat interval corresponds to decreased heart rate.

As physiological measures have been shown to discriminate between negative and positive emotional states (Levenson et al., 1990; Bradley and Lang, 2000; Kreibig, 2010), we aimed for

[4]Some studies included several independent samples. The minimum number of independent studies required to conduct a meta-analysis was accepted as three.

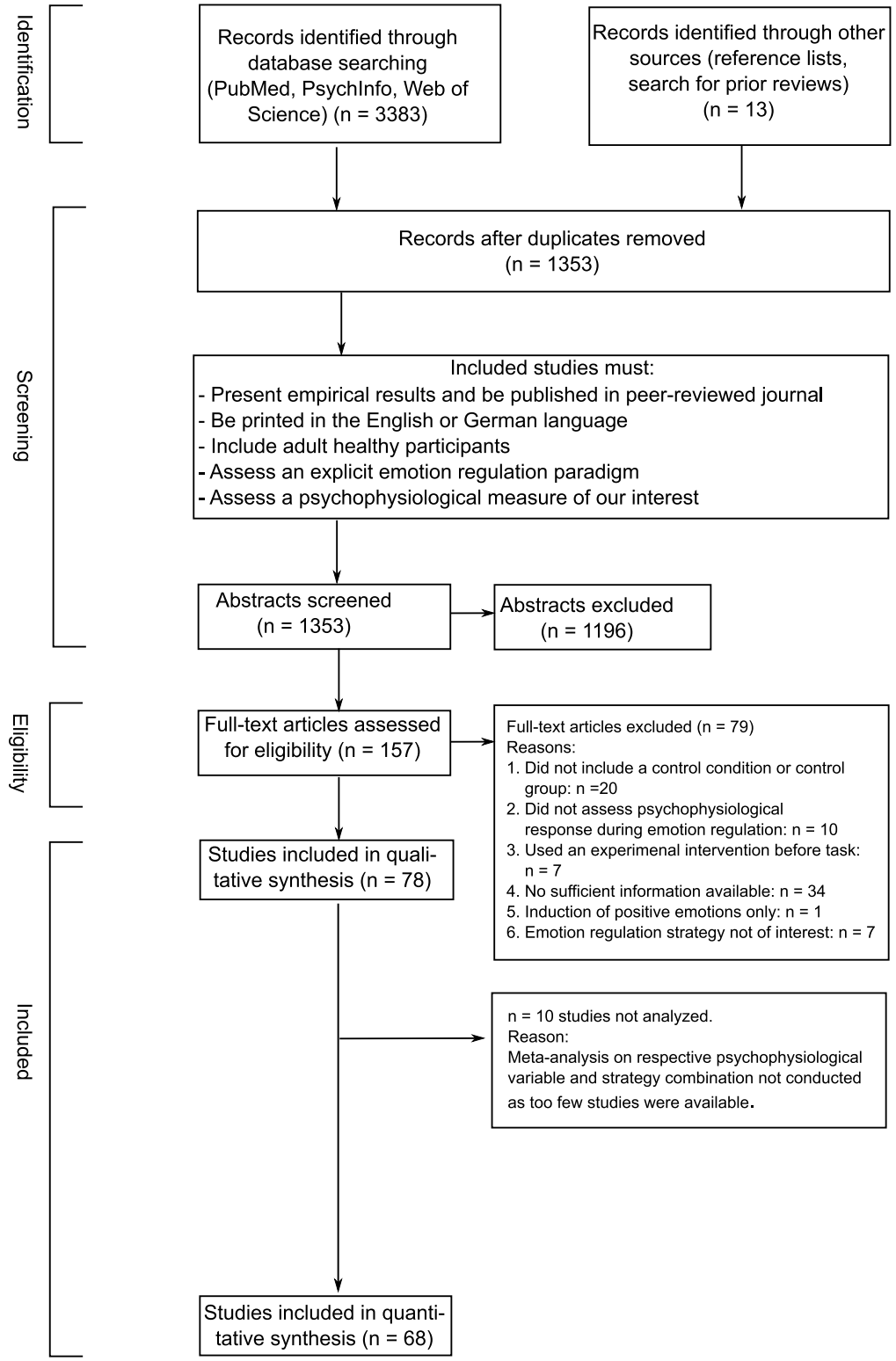

FIGURE 1 | PRISMA flowchart of the literature search process.

distinguishing between positive and negative target emotions in our analyses. Only 13 studies in total (Gross and Levenson, 1997; Demaree et al., 2004; Ohira et al., 2006; Giuliani et al., 2008; Driscoll et al., 2009; Dan-Glauser and Gross, 2011, 2015; Gruber et al., 2014; Baur et al., 2015; Conzelmann et al., 2015; Gomez et al., 2015; Wu et al., 2016; Kotwas et al., 2019) induced positive emotions. Combinations of psychophysiological measure and emotion regulation strategy resulted in a maximum of three studies. Therefore, meta-analyses on the regulation of positive emotions were not computed in the present study. See an overview of studies using positive emotions in the **Table S1**.

We conducted moderator analyses to test whether features of the experimental context influenced the effect sizes. We used four moderator variables in our analyses: study design (within-subject vs. between-subject), nature of control condition (instruction to respond naturally vs. no instruction), nature of emotion induction (films vs. pictures), and trial duration (i.e., length of a regulation trial, in seconds), as far as there were enough studies for statistical comparison. To evaluate the effects of moderators we used meta-regression analyses and present the regression coefficients.

Statistical analyses were conducted with the metaphor package from R (version 3.2) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined at the 5% level.

Heterogeneity

We investigated whether the variance between the observed effect sizes was larger than what would be expected on the basis of sampling variance alone (Hedges, 1982; Rosenthal and Rubin, 1982). If the effect sizes are heterogeneous it means that the mean effect size does not represent individual effect sizes for studies within the population in that moderators of the effect sizes may be present (e.g., nature of emotion induction). In an analysis with a small number of effect sizes, especially if they are based on small sample size studies, the *Q*-statistic may be non-significant even when there is considerable variability among the effect sizes. Therefore, we computed the percent of variability in effect sizes due to heterogeneity using the I^2 statistic (Higgins and Thompson, 2002). *I* represents the amount of variability in effect sizes that is accounted for by heterogeneity as a proportion of the total variability. According to Higgins and Thompson's (2002) general guidelines, mild heterogeneity would be suggested by an $I^2 = 30\%$ of the variability in effect sizes, moderate heterogeneity by an I^2 between 30 and 50%, and notable heterogeneity when I^2 is $> 50\%$ of the variability.

Moderator Analyses

We conducted moderator analyses to test whether features of the experimental context influenced the observed effect sizes. We used four moderator variables in our analyses: study design (within-subject vs. between-subject), nature of control condition (instruction to respond naturally vs. no instruction)[5], nature of emotion induction (films vs. pictures)[6], trial duration (i.e., length of a regulation trial, in seconds), as far as there were sufficient cases for statistical comparison. We used meta-regression (Thompson and Sharp, 1999) to evaluate moderators. The advantage of meta-regression is that continuous moderators (e.g., trial duration) can be evaluated alongside categorical moderators (e.g., within- vs. between-participants designs). For the meta- regressions, β is the beta weight or coefficient assigned to the predictor; *t* (and the associated *p*-value) tests whether the beta weight is significantly different from zero.

RESULTS

Descriptive Analyses

Across the 78 studies that were initially considered in our qualitative analysis, heart rate (HR) and skin conductance level (SCL) was measured most frequently, with three times as many effect sizes as for any other measure (see **Figure 2** for an overview). Thus, emotion regulation strategies and psychophysiological measures were not evenly represented in the published literature. Certain combinations of emotion regulation strategy and psychophysiological measures occurred frequently in published experiments (e.g., reappraisal and measuring heart rate) whereas other combinations were rare or non-existent (e.g., suppression while measuring stroke volume).

Sixty-nine individual studies entered our quantitative analyses (for a flowchart of the selection and screening process see **Figure 1**). Study characteristics of these studies are presented in **Table 3**. There are $n = 4{,}474$ *unique* individuals across all of the 68 included studies (meaning that this is the total *n* across all studies) with many individuals contributing data to more than one effect size for a total of $n = 13{,}380$ data points across all meta-analytic comparisons. Because not all studies reported demographic statistics, reported information about age and sex is only an estimated number.

Meta-Analyses

As the 68 studies contributed data to multiple effect sizes, we computed 267 individual effect sizes (see **Table 3**) that entered 24 different meta-analyses (see **Table 4** and **Figure 3**). Overall, computed individual mean effect sizes for each combination of regulation strategy with measure did not exceed $d = 0.62$ (own choice effect on startle; see **Table 4**). **Figure 3** also highlights that some meta-analyses revealed large confidence intervals and non-significant effect sizes, suggesting that these effects are rather inconsistent (e.g., suppression effect on skin conductance response, ear pulse transit time, diastolic blood pressure and finger pulse amplitude, reappraisal effect on finger pulse amplitude, heart rate variability, and distraction effect on skin conductance level). Largest effect sizes were obtained for electromyographic responses (startle and corrugator activity), followed by suppression effects on some cardiovascular measures (i.e., finger temperature and mean arterial pressure). For many

[5]We were unable to test other types of control instructions as there were too few studies available.

[6]We were unable to test other types of emotion inductions (i.e., music, dyadic interaction, past experience or personally relevant thought, threat of shock, stressor task, anger task) as there were too few studies available.

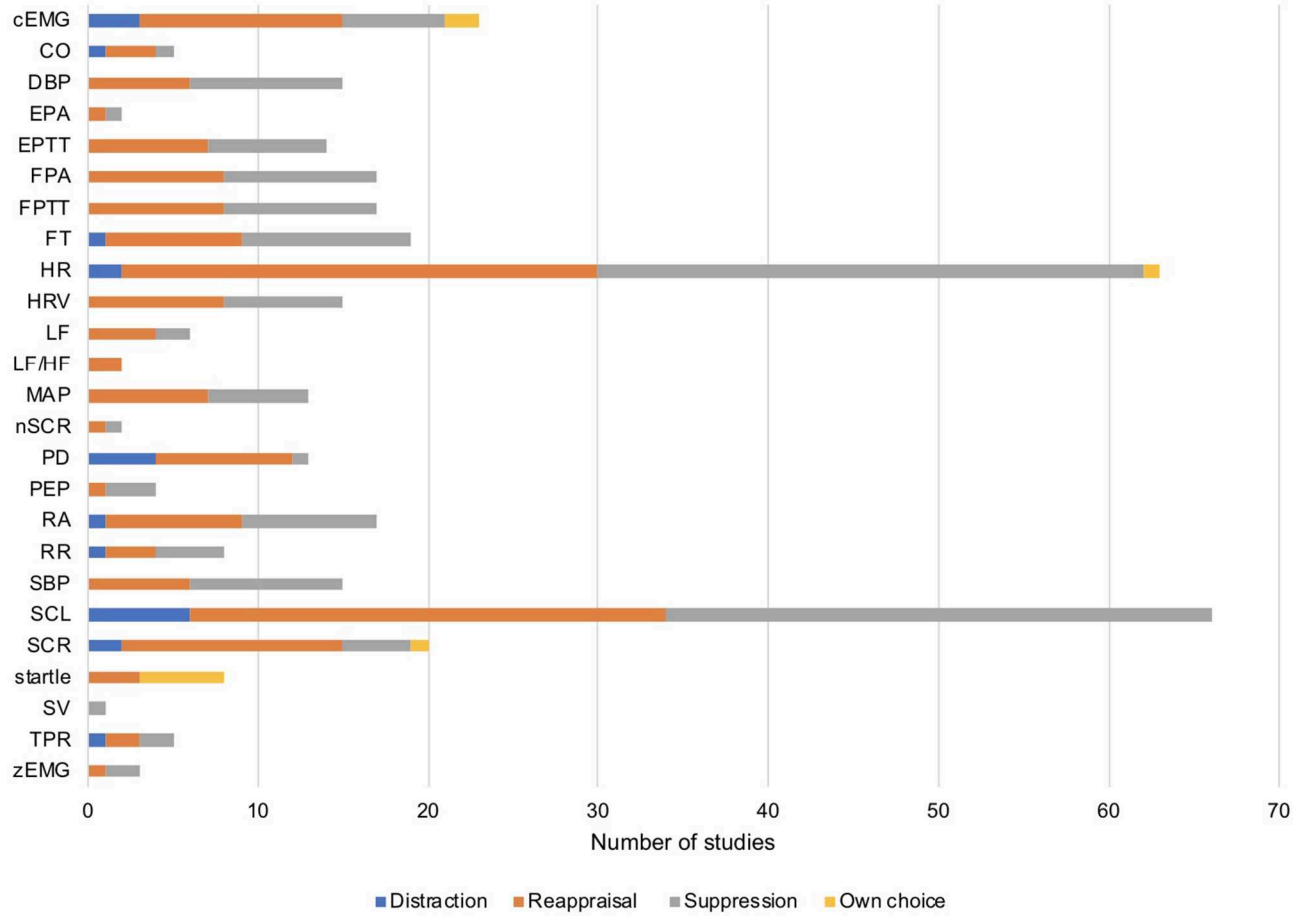

FIGURE 2 | Number of available effect sizes for each measure as a function of emotion regulation strategy (distraction, reappraisal, suppression, own choice). Note that the statistic refers to the k = 78 studies initially identified in our qualitative analysis. cEMG, corrugator activity; CO, cardiac output; DBP, diastolic blood pressure; EPA, ear pulse amplitude; EPTT, ear pulse transit time; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; HRV, heart rate variability; LF, low frequency HRV; LF/HF, ratio between low and high frequency HRV; MAP, mean arterial pressure; nSCR, number of skin conductance responses; PD, pupil dilation; PEP, pre-ejection period; RA, respiration amplitude; RR, respiration rate; SBP, systolic blood pressure; SCL, skin conductance level; SCR, skin conductance response; SV, stroke volume; TPR, total peripheral resistance; zEMG, zygomatic activity.

computed mean effect sizes confidence intervals around the mean effect were large (see **Figure 3**), indicating that the accuracy of our analysis to predict the true effect was rather low. Moreover, heterogeneity differed largely across meta-analyses (see **Table 4**). For individual forest plots of each meta-analysis see **Figures S1–S23**.

Cardiovascular Responses

Reappraisal significantly decreased heart rate (d = −0.09, CI = [−0.17, −0.01], $p = 0.03$, k = 28, $I^2 = 21.90$), yet the effect size was very small and direction of effects across individual studies were inconsistent (see **Figure S6**). Reappraisal had no significant effect on all other tested cardiovascular measures (i.e., finger pulse amplitude, finger pulse transit time, finger temperature, and heart rate variability) with mean effect sizes ranging between −0.02 and 0.16 (see **Table 4**).

Suppression significantly decreased finger temperature (d = −0.33, CI = [−0.59, −0.07], $p = 0.02$, k = 10, $I^2 = 70.03$; see **Figure S16**), and mean arterial pressure (d = −0.34, CI = [−0.55, −0.12], $p = 0.01$, k = 6, $I^2 = 16.45$; see **Figure S19**), with small to medium effect sizes and mild to notable heterogeneity. Suppression did not significantly change diastolic blood pressure, ear pulse transit time, heart rate, heart rate variability, systolic blood pressure, and skin conductance response (see **Table 4** for details and statistics).

Electromyographic Responses

When considering studies that instructed participants to choose a strategy that worked best for them only, downregulation of negative emotions had a significant negative effect on the emotion-modulated startle (d = −0.62, CI = [−1.02, −0.22], $p = 0.01$, k = 5, $I^2 = 47.35$)[7] with a large effect size and

[7]Instructions to downregulate negative emotions (own choice and reappraisal instructions combined) had a significant negative effect on the emotion-modulated startle too (d = −0.44, CI = [−0.75, −0.14], $p = 0.01$, k = 8, $I^2 = 74.76$).

TABLE 4 | Mean computed effect sizes for each emotion regulation strategy and psychophysiological measure.

Strategy	Response system	Measure	k	Effect size	SE	CI lower	CI upper	I^2	*p*	Direction of effect
Distraction	Electrodermal									
		SCL	6	−0.004	0.175	−0.454	0.447	95.53	0.984	–
Reappraisal	Cardiovascular									
		FPA	8	−0.015	0.215	−0.524	0.495	88.90	0.948	–
		FPTT	8	−0.021	0.074	−0.195	0.153	24.73	0.785	–
		FT	8	0.159	0.091	−0.056	0.373	21.99	0.124	–
		HR	28	−0.092	0.039	−0.171	−0.012	21.91	0.026*	REG < CTL
		HRV	8	0.106	0.164	−0.282	0.494	87.62	0.537	–
	Electrodermal									
		SCL	26	−0.065	0.069	−0.206	0.077	71.11	0.355	–
		SCR	12	−0.041	0.031	−0.028	0.109	33.01	0.218	–
	Pupillometric									
		PD	8	0.136	0.071	−0.033	0.305	69.82	0.098	–
	Respiratory									
		RA	8	−0.097	0.051	−0.218	0.024	00.00	0.101	–
	Electromyographic									
		cEMG	9	−0.321	0.098	−0.546	−0.096	42.84	0.011*	REG < CTL
Suppression	Cardiovascular									
		DBP	8	0.039	0.199	−0.431	0.510	83.99	0.849	–
		EPPT	7	−0.048	0.107	−0.309	0.213	54.77	0.670	–
		FPA	9	−0.108	0.165	−0.488	0.272	84.160	0.530	–
		FPTT	9	−0.174	0.100	−0.404	0.057	70.10	0.121	–
		FT	10	−0.327	0.115	−0.586	−0.067	70.03	0.019*	REG < CTL
		HR	29	−0.093	0.067	−0.231	0.045	78.28	0.177	–
		HRV	7	0.126	0.122	−0.174	0.425	78.76	0.344	–
		MAP	6	−0.338	0.084	−0.554	−0.123	16.45	0.010**	REG < CTL
		RA	9	−0.285	0.118	−0.558	−0.012	61.21	0.042*	REG < CTL
		SBP	8	−0.018	0.164	−0.407	0.371	78.32	0.917	–
	Electrodermal									
		SCL	31	0.106	0.064	−0.025	0.236	77.57	0.108	–
Own choice	Electromyographic									
		Startle	5	−0.621	0.145	−1.021	−0.219	47.35	0.013**	REG < CTL

*k, number of studies; SE, standard error; CI, confidence interval; cEMG, corrugator electromyography; DBP, diastolic blood pressure; EPTT, ear pulse transit time; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; HRV, heart rate variability; MAP, mean arterial pressure; PD, pupil dilation; RA, respiration amplitude; SBP, systolic blood pressure; SCL, skin conductance level; SCR, skin conductance response. I^2, percent of variability in effect sizes that is due to heterogeneity between studies. *$p \leq 0.05$, **$p \leq 0.01$.*

moderate heterogeneity (see **Table 4** and **Figure S23** for details). This means that the instruction to decrease negative emotions reduced, on average, the startle response compared to the control instruction. Moreover, reappraisal significantly decreased corrugator activity (d = −0.32, CI = [−0.55, −0.10], $p = 0.01$, k = 9, $I^2 = 42.84$) with medium effect size and moderate heterogeneity (see **Table 4** and **Figure S2** for details). However, number of studies on the startle (k = 5) and corrugator activity (k = 9) was small and thus should be interpreted with caution.

Electrodermal Responses

No significant effect was obtained for distraction on skin conductance level compared to the control condition (d = −0.004, CI = [0.98, 0.45], $p = 0.45$, k = 6, $I^2 = 95.35$; see **Figure S1**). Similarly, reappraisal had no significant effect on skin conductance level (d = −0.07, CI = [−0.21, 0.08], $p = 0.35$, k = 26, $I^2 = 71.11$; see **Figure S10**) and skin conductance response (d = 0.04, CI = [−0.03, 0.11], $p = 0.11$, k = 12, $I^2 = 33.01$; see **Figure S11**), compared to the control condition.

In addition, suppression did not significantly change the skin conductance level (d = 0.11, CI = [−0.03, 0.24], $p = 0.11$, k = 31, $I^2 = 77.57$; see **Table 4** and **Figure S22**).

Respiratory Responses

Suppression significantly decreased respiration amplitude (d = −0.29, CI [−0.56, −0.01], $p = 0.04$, k = 9, $I^2 = 61.21$; see

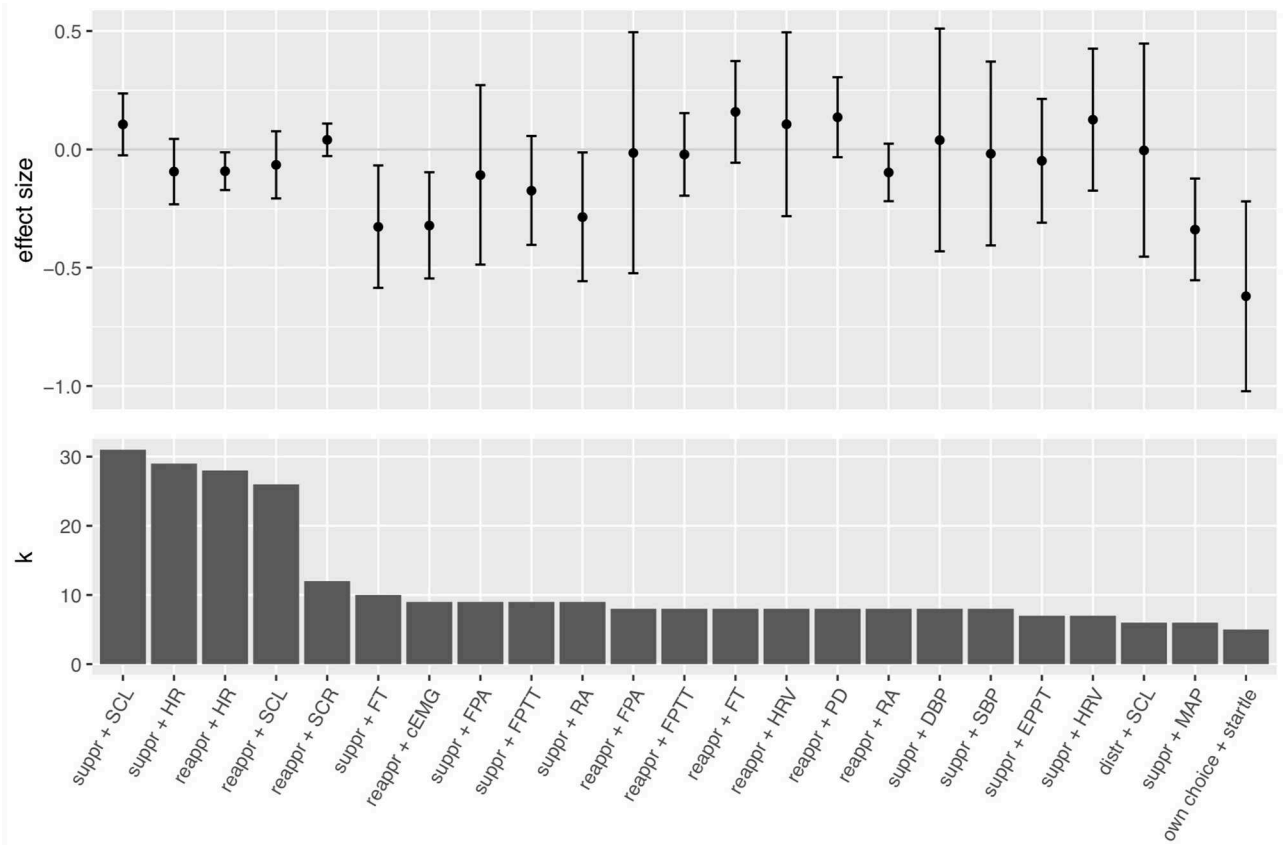

FIGURE 3 | Mean effect sizes and confidence intervals for each conducted meta-analysis (upper panel) sorted by number of samples k of the meta-analysis, respectively (lower panel). Suppr, suppression; reappr, reappraisal; distr, distraction; HR, heart rate; SCL, skin conductance level; SCR, skin conductance response; FT, finger temperature; cEMG, corrugator activity; FPA, finger pulse amplitude; FPTT, finger pulse transit time; RA, respiration amplitude; HRV, heart rate variability; PD, pupil dilation; DBP, diastolic blood pressure; SBP, systolic blood pressure; EPTT, ear pulse transit time; MAP, mean arterial pressure.

Figure S20). Sample size was small (k = 9) and thus should be interpreted with caution.

Pupillometric Responses

On average, reappraisal did not significantly change pupil dilation in response to negative stimuli compared to a control condition (see **Table 4** and **Figure S8** for details). Descriptively, this result might have been driven by one study (Bebko et al., 2011) which found a decrease in pupil size during reappraisal, whereas other studies (van Reekum et al., 2007; Urry et al., 2009; Strauss et al., 2016) found an increase in pupil size during reappraisal. Overall sample size (k = 8) was small and thus should be interpreted with caution.

Evaluation of Publication Bias

For each significant meta-analysis we constructed a funnel plot with the effect sizes on the horizontal axis and their standard errors on the vertical axis. Egger's tests (Egger et al., 1997) were applied to evaluate asymmetry in funnel plots which may be caused by publication bias. Egger's test revealed that there was significant asymmetry only for the effect of reappraisal on heart rate ($p = 0.008$). Individual funnel plots are presented in the supplement (**Figure S24**).

Moderator Analyses

We report moderator analyses only for reappraisal and suppression. For distraction and own choice the number of studies was too small or the distributions of the moderators were inadequate.

Study Design

Study design (within-subject vs. between-subject) significantly moderated effect sizes of suppression on finger temperature ($\beta = 0.54$, $p \leq 0.01$), finger pulse amplitude ($\beta = 0.78$, $p \leq 0.001$), and heart rate ($\beta = -0.38$, $p \leq 0.01$). See **Table 5** for details. The effect of suppression on finger temperature were significant for between-subject design studies ($d = -0.62$, $p \leq 0.001$, $k = 5$), whereas the effect on heart rate became significant for within-subject designs ($d = -0.29$, $p \leq 0.001$, $k = 10$).

Nature of Control Instruction

Effect sizes of suppression on finger temperature ($\beta = 0.54$, $p \leq 0.01$), finger pulse transit time ($\beta = 0.42$, $p < 0.05$),

and finger pulse amplitude ($\beta = 0.78$, $p < 0.001$) were significantly moderated by the control instruction (instruction to respond naturally vs. no instruction) (see **Table 6**). The effect of suppression on heart rate ($\beta = -0.29$, $p < 0.05$) and skin conductance level ($\beta = -0.35$, $p \leq 0.01$) was also moderated by the control instruction (instruction to respond naturally vs. no instruction). When studies with no instruction were considered only, suppression significantly increased skin conductance level ($d = 0.19$, $p \leq 0.01$, $k = 21$), decreased finger temperature ($d = -0.62$, $p \leq 0.001$, $k = 5$), and finger pulse transit time ($d = -0.40$, $p \leq 0.01$, $k = 5$). Conversely, when studies with instruction to respond naturally were considered only, suppression significantly decreased heart rate ($d = -0.32$, $p \leq 0.01$, $k = 8$).

Emotion Induction

Moderator analyses of effect sizes were conducted for film vs. picture only, as too few studies employing other emotion induction methods for each strategy and psychophysiological measure combination were available to interpret moderator analyses in a meaningful way. Emotion induction (films vs. pictures) did not significantly moderate the effect sizes of reappraisal and suppression on skin conductance level and heart rate (see **Table 7**).

Trial Duration

Trial duration significantly moderated the effect of reappraisal on skin conductance response ($\beta = -0.03$, $p = 0.05$, $k = 12$) and the effect of suppression on skin conductance level ($\beta = -0.03$, $p < 0.05$, $k = 31$), diastolic ($\beta = -0.41$, $p < 0.05$, $k = 8$) and systolic blood pressure ($\beta = -0.39$, $p < 0.01$, $k = 8$) in that the effect became more negative with longer trial durations (see **Table 8**). The moderating effect of trial duration on suppression and skin conductance level was mainly driven by one study (Yuan et al., 2014).

TABLE 5 | Moderator analyses on study design (within-subject design vs. between-subject design).

Strategy	Measure	k	k (within)	k (between)	N total	β	SE	*p*
Reappraisal	SCL	26	17	9	1,082	−0.001	0.161	0.997
Reappraisal	HR	28	16	12	1,176	−0.131	0.085	0.134
Suppression	SCL	31	11	20	1,805	−0.176	0.126	0.174
Suppression	FT	10	5	5	701	0.543	0.138	0.004**
Suppression	FPTT	9	5	4	608	0.080	0.219	0.725
Suppression	FPA	9	4	5	666	0.775	0.115	0.000**
Suppression	RA	9	5	4	467	−0.188	0.263	0.497
Suppression	HR	29	10	19	1,640	−0.379	0.113	0.002**

*k, number of studies; SE, standard error; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; RA, respiration amplitude; SCL, skin conductance level; β regression coefficient (within vs. between). **p ≤ 0.01.*

TABLE 6 | Moderator analyses on nature of control instruction (instruction to respond naturally vs. no instruction).

Strategy	Measure	k	k C4	k C1	N total	β	SE	*P*
Reappraisal	SCL	23	12	11	986	−0.063	0.127	0.625
	SCR	11	7	4	491	0.087	0.113	0.460
	HR	25	13	12	1,039	−0.033	0.083	0.696
Suppression	SCL	28	7	21	1,665	−0.347	0.130	0.012*
	FT	10	5	5	701	0.543	0.138	0.004*
	FPTT	9	4	5	608	0.422	0.156	0.030*
	FPA	9	4	5	666	0.775	0.115	0.000**
	HR	26	8	18	1,500	−0.293	0.130	0.034*

*k, number of studies; SE, standard error; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; SCL, skin conductance level; SCR, skin conductance response; C4, instruction to respond naturally; C1, no instruction; β regression coefficient (respond naturally vs. no instruction). *p ≤ 0.05, **p ≤ 0.01.*

TABLE 7 | Moderator analyses on emotion induction (films vs. pictures).

Strategy	Measure	k	k films	k pictures	N total	β	SE	*p*
Reappraisal	SCL	23	16	7	900	0.126	0.167	0.458
Reappraisal	HR	20	12	8	723	−0.150	0.086	0.101
Suppression	SCL	26	22	4	1,431	0.049	0.187	0.795
Suppression	HR	25	19	6	1,256	0.145	0.144	0.324

k, number of studies; SE, standard error; HR, heart rate; SCL, skin conductance level; β, regression coefficient (films vs. pictures).

TABLE 8 | Moderator analyses on trial duration.

Strategy	Measure	k	N total	β	SE	*p*
Distraction	SCL	6	287	0.084	0.081	0.354
Reappraisal	HR	28	1176	0.015	0.012	0.209
	HRV	8	305	0.071	0.053	0.232
	PD	8	250	−2.492	1.996	0.258
	SCL	26	1,082	0.021	0.021	0.324
	SCR	12	530	−0.028	0.013	0.053*
	cEMG	9	354	0.000	0.051	0.997
Suppression	DBP	8	440	−0.408	0.141	0.028*
	EPPT	7	551	0.022	0.024	0.403
	FPA	9	666	−0.030	0.039	0.464
	FPTT	9	608	−0.011	0.026	0.677
	FT	10	701	0.130	0.086	0.172
	HR	29	1640	0.028	0.022	0.214
	HRV	7	491	0.044	0.047	0.392
	RA	9	467	−0.032	0.048	0.526
	SBP	8	440	−0.387	0.094	0.006**
	SCL	31	1,805	−0.026	0.012	0.039*

*k, number of studies; SE, standard error; cEMG, corrugator electromyography; DBP, diastolic blood pressure; EPTT, ear pulse transit time; FPA, finger pulse amplitude; FPTT, finger pulse transit time; FT, finger temperature; HR, heart rate; HRV, heart rate variability; MAP, mean arterial pressure; PD, pupil dilation; RA, respiration amplitude; SBP, systolic blood pressure; SCL, skin conductance level; SCR, skin conductance response; β regression coefficient (refers to 1 min change in trial duration). *p ≤ 0.05, **p ≤ 0.01.*

DISCUSSION

Over the past two decades, emotion regulation has become a vibrant research field. Our literature search corroborates this trend. It revealed an increase of almost 60% of potentially relevant publications for our meta-analysis within the recent 3 years. The vast growth of literature illustrates a vigorous interest in understanding the psychophysiological mechanisms of emotion regulation.

Previous studies on the psychophysiological responses to emotion regulation revealed inconsistent results. Moreover, distraction and reappraisal strategies appeared to have no or little effect on psychophysiology (Webb et al., 2012), and suppression significantly increased sympathetic arousal (Gross and Levenson, 1993; Gross, 1998a). This meta-analysis provides the first attempt to elucidate common trends with means of a quantitative summary of the effects of common emotion regulation strategies on different cardiovascular, electrodermal, respiratory, pupillometric, and electromyographic measures. We performed a structured literature review and conducted a meta-analysis for each combination of psychophysiological measure and emotion regulation strategy whenever there were enough studies available. In brief, we found that suppression significantly decreased mean arterial pressure, finger temperature, and respiration amplitude, whereas reappraisal led to decreased heart rate and decreased corrugator activity (see **Table 4** and **Figure 3** for an overview of effects). When participants were free to choose between emotion regulation strategies, a significant inhibition of the emotion-modulated startle (sometimes referred to as fear-potentiated startle) response could be observed. Due to the limited number of studies on distraction, we were not able to conduct meta-analyses on psychophysiological responses except for skin conductance level, and this meta-analysis revealed no significant effect. Publication bias appeared to have an overall minor effect.

As **Figure 3** illustrates, aggregated effect sizes from the tested autonomic responses were small in general. We did not compute an overall effect size across all psychophysiological measures. Yet aggregated effect sizes for each psychophysiological measure correspond with the results reported by Webb et al.'s meta-analysis (Webb et al., 2012). They had reported an overall small negative effect of response modulation (e.g., suppression strategies) on psychophysiology ($d = 0.19$, [CI = 0.14, 0.01]). Attentional deployment (e.g., distraction strategies) had no significant effect on physiological measures ($d = 0.00$, CI = [0.14, 0.15]), and so did cognitive change (e.g., reappraisal) ($d = 0.05$, [CI = 0.07 to 0.16]) (Webb et al., 2012). We conclude that effects of emotion regulation on autonomic measures—if at all present—seem to be rather small and raise the question whether emotion regulation success can be reliably quantified with autonomic measures. It should however be noted that the psychophysiological measures entering our analysis were limited. **Figure 2** illustrates that there were a number of measures not included as too few studies were available. For example, measures of cardiac function that can be derived via impedance cardiography have received scant attention in the previous literature but provide promising results: Studies have shown that emotion regulation changed total peripheral resistance with medium to large effect sizes (Jamieson et al., 2012, 2013; Peters et al., 2014; Peters and Jamieson, 2016).

Activation of the sympathetic nervous system causes an increase in skin conductivity, pupil dilation, heart rate, pre-ejection period, blood pressure, peripheral vasoconstriction, and increased respiration amplitude and respiration rate. Successful emotion regulation should be accompanied by a reduction of sympathetic activity (McRae and Shiota, 2017). Our study reveals that the effects are not quite that straightforward. Suppression lowered finger temperature (indicative of increased sympathetic activity), yet also decreased mean arterial pressure and respiration amplitude (indicative of lower sympathetic activity). Similarly, reappraisal decreased heart rate (indicative of lower sympathetic activity) but did not change any of the other tested autonomic measures. McRae and Shiota (2017) point out that psychophysiological effects often diverge in patterns that correspond to different psychological states (Kreibig, 2010; Shiota et al., 2011), which can result in misinterpretations about the association between psychophysiological responses and the underlying psychological processes (Cacioppo and Tassinary, 1990; Cacioppo et al., 2007). Psychophysiological responses are usually influenced by various factors, such as stress, workload, or tiredness, and thus may distort the effects of emotion regulation. Decreased pupil size during reappraisal was observed in one study and has been interpreted to be the result of decreased emotional arousal (Bebko et al., 2011). Alternatively, studies have interpreted larger pupil size during reappraisal as an indicator of higher cognitive effort (Urry et al., 2006; van Reekum et al., 2007). They infer that pupil size may increase during successful emotion regulation as an indicator of increased cognitive processing. The ambiguity of such effects implies that we need a better understanding of cognitive and emotional processes causing autonomic change, and how these changes relate to emotion regulation success.

Another problem is the inconsistency of direction of effect sizes. Different directions of effect sizes rendered the meta-analyses insignificant and infer that there are important factors not yet understood. For example, the meta-analysis of pupil dilation during reappraisal (see **Figure S8**) revealed that one study (Bebko et al., 2011), which received a strong weight in the analysis, found a significant decrease in pupil diameter during reappraisal, while other studies found an increase in pupil diameter (e.g., van Reekum et al., 2007; Urry et al., 2009; Strauss et al., 2016). Similarly, our meta-analysis on heart rate during suppression (see **Figure S17**) revealed that studies found mean heart rate acceleration in response to suppression (e.g., Hagemann et al., 2006; Stiller et al., 2019), whereas other studies found a heart rate deceleration (Kunzmann et al., 2005; Dan-Glauser and Gross, 2011, 2015). Therefore, the second aim of the present work was to explore the impact of methodological differences using several moderators (trial duration, nature of emotion induction, nature of control instruction, study design).

Effects of suppression on heart rate, finger temperature and finger pulse amplitude were significantly moderated by study design (within vs. between-subject). Between-subject design studies showed a significant decrease in finger temperature and

finger pulse amplitude during suppression whereas studies with a within-subject design revealed no significant effect. Conversely, within-subject design studies showed a significant decrease in heart rate whereas studies with a between-subject design revealed no significant effect. The moderating effect of study design on heart rate might also reflect that between-subject design studies in this particular meta-analysis assessed extremely diverse emotion induction methods. For example, two studies (Butler et al., 2006; Ben-Naim et al., 2013) assessed emotion regulation in dyadic interactions. Hagemann et al. (2006) used startle tones in combination with pictures. Rohrmann et al. (2009), Gross (1998a), Denson et al. (2011) used film stimuli. Within-subject design studies considered in this meta-analysis used films and pictures only. Therefore, the nature of emotion induction may account for some variance in the effect sizes obtained across studies using between-subject designs. When data from more studies will be available in the future, it might be possible to confirm this assumption.

Effects of reappraisal and suppression on several electrodermal and cardiovascular measures (i.e., skin conductance level, finger temperature, finger pulse transit time, finger pulse amplitude, and heart rate) were significantly moderated by the nature of control instructions. Except for finger pulse amplitude, the effects became significant when no instruction (i.e., "view" instruction) was given but did not become significant when the instruction to respond naturally was given. This does not correspond with findings by Webb et al. (2012) who found that emotion regulation strategies in general had smaller effects on experiential, behavioral and physiological measures combined when the control condition required participants to "view" or "not to regulate" and larger effects when the control condition required participants to respond naturally. In contrast to our study, they did not determine the moderating effect of control instruction on physiological effects of emotion regulation but considered the overall effect of psychophysiological, behavioral and experiential measures. Control conditions requiring participants to simply view a negative stimulus might correspond to a physiological baseline condition. However, when receiving the instruction to respond naturally, participants might unconsciously pay more attention to their emotional response, which may be particularly sensitive to psychophysiological responses.

Trial duration significantly moderated effect sizes of suppression on skin conductance level, diastolic and systolic blood pressure, and of reappraisal on skin conductance response in that the effects became more negative with increasing trial length. Studies on electrodermal responses may be difficult to compare within the conducted meta-analyses because trial durations varies largely across studies. This might be especially problematic for skin conductance level, as longer time windows carry the risk that non-specific skin conductance responses occur. If these phasic responses are not separated from the tonic parts, they might influence the absolute skin conductance level (Boucsein et al., 2012). Hence, skin conductance level assessed over several seconds in an event-related design might be different than skin conductance level assessed over several minutes in a block-design. We accounted for this variability in parts by conducting a moderator analysis with trial duration as the moderator. We observed effects in both positive and negative direction. Studies with very short trial duration tend to report an increase in skin conductance, whereas studies with longer or extremely long trial durations tend to report a decrease in skin conductance. However, we acknowledge that our analysis did not allow to differentiate for example between studies that assessed skin conductance averages but eliminated the tonic parts (Hallam et al., 2015; Plieger et al., 2017) and studies that assessed skin conductance level without separating the phasic from the tonic responses. We encourage future researcher to use similar research methodology and terminology as suggested by the committee report on publication recommendations (Boucsein et al., 2012) to make studies more comparable in the future. In total, the varying effects of skin conductance across studies may be in part due to the high variability in assessment and quantification.

Compared to the tested *autonomic* responses (i.e., cardiovascular, electrodermal, pupillometric and respiratory responses), our present analysis revealed that effects of measures assessed with *electromyography* were medium and consistent across individual studies (see **Figures S2**, **S23**). Regarding the emotion-modulated startle, we found a significant decrease through emotion downregulation with a mean effect size of $d = -0.62$. Corrugator activity significantly decreased with reappraisal of negative emotions with a medium effect size of $d = -0.32$. As both analyses included a rather small number of studies resulting in large confidence intervals, they should be treated with caution (see **Figure 3**). Nevertheless, the results on electromyography showed more consistent results compared to the autonomic measures assessed in the present review and this encourages possible reasons that might have accounted for this consistency.

Studies have shown that both the emotion-modulated startle and corrugator activity are specific to valence: The startle is inhibited in response to pleasant but potentiated in response to unpleasant stimuli with stronger responses for high- than for low-arousing stimuli (Vrana et al., 1988; Bradley et al., 1993a; Hamm et al., 1997; Schupp et al., 1997; Hawk and Cook, 2000). Corrugator supercilii is generally considered to correspond to changes in valence, too (Tassinary et al., 2007). The valence-specificity might facilitate to measure the correspondence to changes in valence and hence allows to track the regulation effect more closely, compared with autonomic measures that rather reflect changes in arousal. However, there are also studies showing that in the context of emotion regulation, the startle response is more sensitive to changes in arousal (Dillon and LaBar, 2005; Zaehringer et al., 2018).

Animal studies have shown that the amygdala, a key structure in emotion processing, directly modulates the auditory startle reflex via modulation of midbrain neurons (Rosen and Davis, 1988; Davis, 1992), which has been recently complemented by fMRI work in human subjects (Kuhn et al., 2019). Researcher have argued that the emotional modulation as indexed by the startle reflex may serve as a direct indicator of amygdala activation independent of task demands (Grillon and Baas, 2003). Similarly, the amygdala projects to the facial motor

nucleus thereby coupling emotional facial expressions to the motive circuit (Davis, 2000). The amygdala is a robust neural target of emotion regulation (Buhle et al., 2014) and altered amygdala activation with emotion regulation thus likely mediates the modulatory effect on the startle response and corrugator activity. Taken together, the specificity to the valence dimension and the direct modulation via the brain's motivational system may contribute to the findings of emotion regulation effects on emotion modulated startle and corrugator activity.

With regard to the emotion-modulated startle, it is also possible that the emotion regulation instruction might have influenced the obtained effect sizes. Participants in these studies were free to choose an emotion regulation strategy that worked best for them. By allowing participants to choose from different strategies, they might be more successful in regulating their emotions, which could result in larger effects. Moreover, the startle response unfolds within milliseconds, whereas autonomic responses such as pupil dilation, electrodermal responses, and heart rate variability rather unfold over several seconds, or even minutes. Therefore, the startle response may be easier to measure because it is clearly time-locked to the startle probe and all changes can be measured in studies with shorter observation times during the trials, whereas a skin conductance response with a slower response latency to peak may carry over effects to the next trial. In addition, emotion-modulated startle studies largely converge on the measurement and quantification of the startle response, whose setup is known to be relatively simple. In our meta-analysis on the emotion-modulated startle, all studies rectified and integrated the raw EMG signal with a time constant of 20 ms, calculated the startle amplitude by subtracting a 20 or 50 ms pre-startle baseline from the peak 20–120 or 20–150 ms after startle probe onset and finally t- or z-transformed the mean amplitudes (Jackson et al., 2000; Dillon and LaBar, 2005; Golkar et al., 2014; Conzelmann et al., 2015).

In contrast, we observed tremendous variation in the quantification of the autonomic indices. For example, studies on skin conductance level during reappraisal assessed baseline activity during a neutral condition that included the presentation of neutral stimuli (Wolgast et al., 2011; Lohani and Isaacowitz, 2014), right before stimulus onset (e.g., Shiota and Levenson, 2009), right before instruction (Opitz et al., 2014), after instruction (Urry et al., 2009), or reported no baseline assessment (Goldin et al., 2019). These studies then either subtracted mean activity of the respective baseline from mean activity during the regulation period (e.g., Shiota and Levenson, 2009; Opitz et al., 2014), calculated raw means (Goldin et al., 2019), or area under the curve (Urry et al., 2009). It should be noted that these observations remain solely on a descriptive level. We did not conduct a moderator analysis to account for this variation since too few studies were available. Future studies would be helpful to corroborate our considerations.

The meta-analyses we presented in this article suggest that electromyographic measures such as the emotion-modulated startle might be robust options to assess emotion regulation effects, whereas autonomic measures might be context dependent and thus should be selected carefully. Autonomic measures are still important and interesting for emotion regulation research as they allow to track the extended reaction of the body to an emotional event or a series of events, whereas the emotion-modulated startle is being assessed at one given time and thus does not allow to track the time-course of the regulation period.

Limitations and Future Research

While the present study represents the first meta-analysis of specific psychophysiological effects during distraction, reappraisal, suppression, and instructions to choose a downregulation strategy, it is not without limitations. First of all, we emphasize that the number of available studies was small with the exception of heart rate and skin conductance level. In particular, most of the significant meta-analyses in the present study included few studies and these studies often stemmed from an even smaller number of labs (e.g., mean arterial pressure, finger temperature; see **Figure 3**). Thus, we need more research to test whether the effects would become insignificant with increasing number of independent studies. Similarly, absence of significance in meta-analyses with small number of samples should not be taken as evidence that there is no effect at all. Thus, studies that assess less common psychophysiological measures and emotion regulation instructions are urgently needed to increase knowledge about psychophysiological responses during emotion regulation.

Furthermore, no meta-analysis is free of a potential publication bias. The bias refers to the phenomenon that significant findings get published earlier and are more likely than non-significant findings. Statistical analyses indicated that there might be some publication bias, but this seemed not to appreciably impact the results. In addition, psychophysiological measures are usually not the primary outcome of emotion regulation studies, and many published studies have reported negative findings. Thus, we consider the publication bias to be relatively small in this review.

We also highlight the substantial variability in the research methodology used across the emotion regulation studies included in our meta-analysis. We explored the impact of methodological differences using several moderators (trial duration, nature of emotion induction, nature of control instruction, study design) and showed that central design aspects are explaining some differences in the overserved autonomic effect sizes. This raises the question to which degree the studies included in the present review are actually comparable.

Sample size was very small and conducting the meta-analyses and moderator analyses required a large number of separate analyses. In light of this, significant results presented here should be treated with caution as multiple comparisons might have increased the chances of false discovery. More research is needed to confirm our results. We also acknowledge that we assessed a limited sample of potential moderators. As mentioned above, there was tremendous variation in the quantification of the autonomic indices, which we were not able to account for as there were too few studies available to conduct meaningful moderator analyses. Finally, we highlight that our meta-analysis was limited to the regulation of negative emotions only, mainly focusing on reappraisal and suppression.

In light of these limitations, we need particularly larger and more comparable studies with identical setup to control the moderator variables identified in this meta-analysis (in particular trial duration, comparable control conditions and the same study design). One important future direction for researchers in the area of psychophysiological response patterns to emotion regulation is to design large-scale, comprehensive studies that directly compare psychophysiological measures and emotion regulation strategies ideally using the same assessment and quantification of psychophysiological responses.

With psychophysiological recordings we cannot control which regulation strategies are really being applied by participants. The variability of autonomic responding across different emotion regulation contexts further complicates an accurate interpretation of effects and may be particularly problematic in studies focusing on just one psychophysiological outcome measure. Experiments using simultaneous recordings from multiple psychophysiological channels would be helpful to e.g., identify potential response patterns uniquely characterizing different emotion regulation strategies (e.g., pupil, heart rate, skin conductance, etc.). However, major progress is unlikely without coordinated effort across labs to systematically address these questions.

There is also a need for studies that carefully tease apart attention, arousal and other cognitive processes that may influence autonomic responses in order to gain a better understanding of the interpretation of autonomic responses during emotion regulation. Systematic variations in different experimental setups may help to dissociate the underlying cognitive and emotional processes that cause autonomic activity in order to draw clear inferences.

CONCLUSION

This meta-analysis represents the first attempt to determine the mean effects of different emotion regulation strategies on individual psychophysiological measures. Our results indicate that (a) effects of reappraisal decreased heart rate and corrugator activity, whereas suppression increased sympathetic arousal but decreased respiration amplitude and mean arterial pressure, (b) effects of autonomic measures, even if significant, were small and heterogeneous across studies, while electromyographic measures showed medium effect sizes and (c) the study design, control instruction and trial duration moderated some but not all effect sizes. As available studies were few, our findings remain preliminary. In order to use meta-analyses to compare effects of psychophysiological responses in different regulation contexts, more comparable methodological set-ups should be used in the empirical study of emotion regulation. The induction of specific types of emotions and the assessment of less common psychophysiological measures and regulation strategies will allow future meta-analyses to fully discover the potential influences on psychophysiological response during emotion regulation.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

JZ, CP, CS, and GE were involved in the conception of the work. JZ planned and conducted the literature search, coded the data and together with CJ-S designed and carried out the data analysis. JZ drafted the manuscript. CP, CJ-S, CS, and GE revised it critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.00470/full#supplementary-material

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State and Trait Rumination Effects on Overt Attention to Reminders of Errors in a Challenging General Knowledge Retrieval Task

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Rumination is a recurrent and repetitive manner of thinking that can be triggered by blockage of personally relevant goals, creating a temporary state of abstract and evaluative self-focus. Particularly when focused on passive "brooding" over one's problems and feelings, however, rumination can increase negative affect, interfere with problem-solving, and, through a negative feedback cycle, become a chronic trait-like style of responding to personal challenges, particularly in women. Given the pervasiveness of rumination and its potential impact on cognitive processes and emotional states, the present study asks how it impacts attention to feedback that either reminds individuals of goal-state discrepancies (reminders of errors) or could help to remediate them (corrective information). Using eye-tracking, we examined both state and trait rumination effects on overt measures of attention [first fixation duration (FFD) and total fixation duration (TFD)] during simultaneous presentation of these two types of feedback following failed attempts to answer challenging verbal general knowledge questions (average accuracy ∼30%). After a pre-induction baseline, we induced either a state of rumination using a series of writing exercises centered on the description of an unresolved academic concern or a state of distraction by centering writing on the description of a neutral school day. Within our women-only sample, the Rumination condition, which writing analysis showed was dominated by moody brooding, resulted in some evidence for increased initial dwell time (FFD) on reminders of incorrect answers, while the Distraction condition, which did not elicit any rumination during writing, resulted in increased FFD on the correct answer. Trait brooding augmented the expression of the more negative, moody brooding content in the writing samples of both Induction conditions, but only influenced TFD measures of gaze duration and only during the pre-induction baseline, suggesting that once the inductions activated rumination or distraction states, these suppressed the trait effects in this sample. These results provide some support for attentional-bias models of rumination (attentional scope model, impaired disengagement hypothesis) and have implications for how even temporary states of rumination or distraction might impact processing of academic feedback under conditions of challenge and failure.

Keywords: eye-tracking, gaze, brooding, reflection, feedback, fixation, RRS

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INTRODUCTION

Rumination is a recurrent and repetitive manner of thinking that can be triggered by blockage of personally relevant goals, creating a temporary state of abstract and evaluative self-focus that can eventually lead to a more chronic, trait-like style of ruminative responding to personal challenges (Watkins and Nolen-Hoeksema, 2014). Prominent models of rumination [Martin and Tesser's (1996) Control Theory; Nolen-Hoeksema's (1987) Response Styles Theory] describe both temporary (state) and chronic (trait) rumination as being maladaptive for both affect and goal-directed behavior (for a review, see Nolen-Hoeksema et al., 2008). This is particularly the case for the Ruminative Brooding (RB) subtype, which produces a sustained, but unproductive focus of attention on negative outcomes and their associated feelings. In contrast, the Reflective Pondering subtype is proposed to be more adaptive in nature because it taps the tendency to deliberately "reflect" on concrete means for problem solving (Treynor et al., 2003).

To date, few studies have examined the effects of either ruminative subtype within an academically relevant context (e.g., Lyubomirsky et al., 2003; Ciarocco et al., 2010). This is surprising given that students may face various types of cognitive and affective challenges during difficult performance assessments. For example, rumination is purported to underlie the detrimental social-cognitive phenomenon of stereotype threat (Beilock et al., 2007). The present study aims to address this gap in knowledge, specifically by examining how inducing a state of brooding-focused rumination in students influences selective attention to negative feedback during a challenging general-knowledge retrieval task (e.g., "What is the capital of Canada?"; Butterfield and Mangels, 2003; Whiteman and Mangels, 2016; Mangels et al., 2018). Here, we enlisted eye-tracking gaze metrics to examine how reminding individuals of past unattained academic goals through a narrative expression exercise (rumination induction) influenced selective attention to reminders of retrieval errors during the task. Specifically, we used fixation dwell time to evaluate selective attention when the correct answer was presented simultaneously and thus in *competition* with reminders of one's recent mistake.

In their habit-goal framework of rumination, Watkins and Nolen-Hoeksema (2014) argue that it is not only internal events (e.g., negative affect experienced during bouts of dysphoria or depression) that can trigger rumination but also external events that are construed as impediments to goal attainment (e.g., negative environments, locations, and/or behaviors of others). Similarly, social-cognitive theories of rumination argue that bringing one's immediate and personal goal-state discrepancies into awareness can cause momentary ruminative thoughts to come online and attention to be deployed toward related, self-relevant content, even among otherwise mentally healthy individuals (Martin and Tesser, 1996; Moberly and Watkins, 2008). Thus, if someone is already in a state of rumination, primed by reminders of past goal-state discrepancies, then receiving repeated negative feedback regarding task performance could be just the type of external event that might trigger maladaptive attentional patterns associated with greater internal and external attention to the error itself, rather than on remediating the error by focusing on corrective information (see also Nolen-Hoeksema and Morrow, 1991; Siegle et al., 2002; Moberly and Watkins, 2010).

Using Narrative Expression to Induce Rumination

Roberts et al. (2013) found that instructions for research participants to dwell on an ongoing, real-world concern of theirs resulted in more ruminative thoughts about their concern during an unrelated go/no-go task than those who were instructed to focus on a resolved goal. As in Roberts et al. (2013), the current study asks students to initially identify their unresolved academic concerns but, unlike that study, then prompts them to descriptively write about (i.e., externally narrate) their concerns, thus adapting methodology used in expressive writing paradigms (e.g., Pennebaker, 1997; McAdams and McLean, 2013). The use of expressive writing provides a means for explicitly measuring whether participants are actively processing the state induction prompts and, furthermore, to quantify thoughts according to whether they are more brooding-like or more reflective in nature (Marin and Rotondo, 2017). In keeping with typical expressive writing methods, we pit expressive narration against a non-expressive condition in which individuals offer neutral narrations about how they spend a typical day in their schedule (e.g., Gortner et al., 2006; Sloan et al., 2008). Neutrally writing about a mundane daily routine creates an ideal comparison condition because it, similarly, focuses attention on an autobiographical episode in the academic domain, while at the same time keeping focus away from specific academic concerns.

Narrative expression can provide direct insight into participants' thoughts and feelings, but not without the caveat that formulating and transmitting a coherent narrative to others may influence the framing of the situation itself. Past studies using expressive writing have yielded mixed outcomes for well-being and problem-solving in intervention-based studies (for a review, see Frattaroli, 2006). On the one hand, expressive writing can be a helpful, adaptive process and, by promoting self-affirmation through positive self-reflection (SR) and constructive meaning-making (e.g., Banks and Salmon, 2013; Cohen and Sherman, 2014), can offer writers an opportunity to confront, organize, and insightfully restructure their ongoing problems and issues (Lyubomirsky et al., 2006). Indeed, in some studies that use this kind of prompting, expressive writing has been shown to actually *reduce* rumination (Gortner et al., 2006; Sloan et al., 2008) and improve performance on exams (Ramirez and Beilock, 2011).

On the other hand, expressive writing can also be maladaptive, particularly when it is characterized more by unconstructive reasoning processes (Banks and Salmon, 2013), which instead focus writers' attention on negative abstractions of the causes and undesirable consequences of their problems and prime more critical views of the self and fixed views of the situation (Lilgendahl et al., 2013). Not surprisingly, this latter style of expressive writing would seem to exemplify what it means to brood. Importantly, Marin and Rotondo (2017) have shown that

the extent to which one's expressive writing typifies brooding-like rumination rather than SR is linked with lower self-acceptance and more negative views of the self. Thus, it is conceivable that being prompted to write in such a way about an ongoing and unresolved academic (vs. being prompted to write about a typical day in one's schedule) could bring about a brooding-like ruminative state that keeps attention negatively focused on the self and signals of one's failures.

Measuring the Effect of Rumination on Selective Attention to Negative Feedback

Past research has shown that trait Rumination is associated to a narrowed attentional focus onto negative, self-relevant information (Donaldson et al., 2007; Altamirano et al., 2010), as well as difficulty inhibiting and disengaging from negative information (Vanderhasselt et al., 2011), possibly because of repeated introspection on the perceived self-relevance of this material (Berman et al., 2010). With focus directed inwardly on negative self-referential thoughts, ruminators are less likely to retrieve potentially useful information during problem solving (Bernblum and Mor, 2010), or to process new, surrounding information (Levens et al., 2009). To explain these and other similar findings, various theories of attentional bias have been proposed, including the attentional scope model (Whitmer and Gotlib, 2013) and impaired disengagement hypothesis (Koster et al., 2011). In particular, the latter hypothesis suggests that negatively brooding over goal-state discrepancies impairs the ability to disengage attention from such troubles, at the expense of deploying attention elsewhere.

One way to explicitly measure how attention might be biased toward information that is perceived to be negative and/or self-relevant is through eye-tracking measures. Eye-tracking provides a direct and continuous measure of overt attention to visual stimuli by measuring exactly where individuals are looking (i.e., fixating their gaze) and for how long. Although this method can be particularly useful for informing questions regarding attention selection across multiple stimuli (see Armstrong and Olatunji, 2012), to date, only a few gaze fixation studies have been conducted for expressly studying the attentional mechanisms of rumination, and these have focused exclusively on trait rather than state forms of rumination (Duque et al., 2014; Owens and Gibb, 2017).

These findings implicate trait rumination in creating a maladaptive attentional bias toward negative stimuli, one that may serve to reinforce a ruminative, depressive mood. For example, Duque et al. (2014) found that higher trait rumination predicted a greater negative attentional bias in a free viewing study (i.e., more time spent processing sad and angry faces, but not neutral or happy faces), as measured by "total fixation duration" metric [i.e., TFD; the summed amount of time spent fixating an area of interest (AOI) while it is presented on-screen], even after controlling for depression. Similarly, Owens and Gibb (2017) found that greater *brooding-like* ruminative tendencies within a mentally healthy adult sample predicted increased dwell time on sad vs. happy faces. Interestingly, a recent eye-tracking study found that individuals who exhibited stable trait Brooding both at the time of study and over the course of the following year not only were slower to disengage attentional focus away from negative information but also were slower to engage attention with more positive stimuli (Allard and Yaroslavsky, 2019).

Given that habitual, trait-like forms of rumination may arise from repeated experience of more temporary states of rumination (Watkins and Nolen-Hoeksema, 2014), we might expect to observe similar patterns of attentional bias when individuals are temporarily induced to experience a ruminative state. To test this in the context of our academically relevant task, we presented trial-level feedback following attempts to answer general knowledge questions (e.g., What is the capital of Canada?) that consisted of an initial, centrally presented small circle colored to indicate response accuracy (red for incorrect, green for correct), followed by "competitive" answer feedback. Critically, if the participant's answer was wrong, this competitive feedback would show the incorrect answer (e.g., Toronto) in red simultaneously with the correct answer (e.g., Ottawa) presented in gray, separated into the upper and lower halves of the screen such that they could not be fixated simultaneously (if the participant was correct, both halves would show the correct answer, with one in green, the other in gray).

During this competitive feedback, we predicted that following errors, participants induced into a state of rumination would demonstrate increased dwell time on reminders of their incorrect answer, compared to individuals induced to distract themselves away from academic concerns. Furthermore, attention to the reminder of the incorrect answer, which is informationally redundant with the initially presented accuracy feedback (i.e., red circle), could come at the cost of decreased dwell time to the simultaneously presented, but more informative correct answer. With regard to measuring dwell time, we used both TFD and first fixation duration (FFD). Although TFD is the more commonly used method in eye-tracking studies of rumination with faces (e.g., Owens and Gibb, 2017), given that the competitive answer feedback involved verbal stimuli, FFD may be better at isolating the participants' initial lexical/semantic processing of the answers (Rayner and Duffy, 1986). In contrast, TFDs would inform the extent to which the participant fixed on the answers well after the meaning of those words had been acquired and potentially after exploring other parts of the display as well.

Study Summary

In summary, the present study examined whether being induced to ruminate vs. distract impacts overt attention to competitive answer feedback in challenging general knowledge task, as measured by TFD and FFD. Using a novel induction task that was based on narrative expression, we hypothesized that participants who had been induced to think about an unresolved academic concern (i.e., Rumination condition) would be biased to dwell longer on potentially "rumination-congruent" reminders of the incorrect responses than individuals whose narratives had been directed to focus on a neutral, average day (i.e., Distraction condition). Additionally, greater attention to the incorrect answer might come at the cost of attention to the correct answer, despite the latter's greater information value.

We note that even though our primary interest was in whether students without clinical depression might show evidence of negatively biased attention when reminded of unmet academic goals, many previous rumination induction studies find the most adverse effects for individuals who are concurrently in a depressive mood state (for a review, see Nolen-Hoeksema et al., 2008). Thus, we assessed trait rumination and depression in order to examine whether these individual difference factors interacted with our state-level manipulations of attention. Past studies have also suggested that gender may play a role in defining the effects of rumination, in that women more than men tend to ruminate over their affective state in the face of negative outcomes and difficult life events (Nolen-Hoeksema and Jackson, 2001; Mezulis et al., 2002; Johnson and Whisman, 2013). Although past studies of rumination induction have not reported effects of gender (e.g., Lyubomirsky and Nolen-Hoeksema, 1995; Lyubomirsky et al., 1998; Lyubomirsky et al., 2003), the particular general knowledge task used in this study often demonstrates stronger effects in women with regard to both manipulations of context and individual difference variables compared to men (see Whiteman and Mangels, 2016; Mangels et al., 2018; Abraham et al., 2019). Therefore, we felt that restricting our sample to women would provide the most robust test of our hypotheses, even if it would limit the generalizability of the results.

MATERIALS AND METHODS

Participants

Fifty-nine women were recruited from the Baruch College undergraduate population via the institution's research participation subject pool. They ranged in age from 18.0 to 34.2 years (M = 20.50, SEM = 0.40), self-reported being native English speakers or fluent by age 6, had normal or corrected-to-normal hearing and vision, and had no history of eye disorders (e.g., detached or torn retina, macular degeneration, glaucoma, color blindness). To limit our sample to students without clinically significant depression, while still including a representative range of participants, an additional inclusion criterion was that they scored 19 or lower on the Beck Depression Inventory II (BDI-II; Beck et al., 1996). As compensation for their participation, subjects received either research credit as part of a course requirement (69.5%), monetary compensation at a rate of $10/h (8.5%), or some combination of both credit and money (22.0%).

Four participants were excluded from both the behavioral and eye-tracking analyses (three Distraction conditions and one Rumination condition) because they did not have enough semantic error trials for analysis. In particular, two participants self-terminated before Block 2, one participant performed 1.5 times the upper interquartile range of scores in the first two blocks, and one participant was an outlier with regard to orthographic errors (26%, as confirmed by a boxplot outlier analysis)[1]. Additionally, four more subjects (two from each Induction condition) did not have a minimum number of usable eye-tracking trials (minimum = 3; Chua et al., 2012) in one or more conditions after pre-processing to remove trials with excessive signal loss or initial central fixation failure (see section "Eye Tracking" for details), necessitating their removal from the eye-tracking analyses, although they were retained for behavioral analysis. Exclusion of these subjects resulted in 55 subjects for behavioral analysis and 51 subjects for the eye-tracking analysis.

Table 1 shows the distribution of these participants across Induction conditions, as well as their group characteristics. For both analysis groups, there were no condition differences in BDI-II scores, or in trait levels of rumination as measured by either the overall Ruminative Responses Scale (RRS; Nolen-Hoeksema and Morrow, 1991) or the Brooding and Reflection subscales[2] (all ps > 0.26). However, the two groups did differ marginally in their age [behavioral sample: $t(53) = 1.93$, $p = 0.06$; eye-tracking sample: $t(49) = 1.78$, $p = 0.08$] and in years of education [behavioral sample: $t(53) = 2.38$, $p = 0.02$; eye-tracking sample: $t(49) = 1.83$, $p = 0.07$]. However, both differences were small in actual magnitude, amounting to less than 1.5 years of age and one semester of education.

Materials

General Knowledge Stimuli

Stimuli consisted of 138 items from a larger, previously normed pool of 406 general knowledge question and answer stimuli[3]. These were divided into two bins of 69 items for use in each block of the general knowledge task. Bin order was counterbalanced across blocks within each Induction condition. Using information from the normed database, questions for

[1]Orthographic errors (i.e., misspelled but otherwise semantically accurate responses that overlapped orthographically with the correct answer to a degree of 75–99%) were excluded because they would likely lead to different patterns of eye movements (e.g., comparing letter for letter) than semantic errors. After excluding the participant outlier, the rate of orthographic errors in the remaining sample was very low (Rumination: M = 0.06, SEM = 0.006; Distraction: M = 0.06, SEM = 0.006), and this proportion did not differ as a function of Induction condition and/or Block (all ps > 0.11).

[2]The preferred shortened form of the RRS was used, which has the Depression subscale removed (Treynor et al., 2003).

[3]www.mangelslab.org/bknorms

TABLE 1 | Sample characteristics with mean scores of pre-test self-report questionnaires and demographics.

	Behavioral sample		Eye-tracking sample	
Variable	**Rumination**	**Distraction**	**Rumination**	**Distraction**
n	28	27	26	25
Age	21.33 (0.72)	19.77 (0.34)	21.36 (0.78)	19.81 (0.36)
Years of education	13.94 (0.22)	13.22 (0.20)	13.86 (0.23)	13.28 (0.21)
BDI-II	6.64 (0.90)	8.33 (1.18)	6.69 (0.95)	7.84 (1.20)
RRS Total	39.57 (2.00)	42.78 (2.06)	40.07 (2.12)	42.60 (2.23)
Brooding	9.71 (0.71)	10.67 (0.67)	9.88 (0.75)	10.52 (0.71)
Reflection	9.46 (0.69)	9.22 (0.59)	9.54 (0.74)	9.24 (0.63)

Standard errors of the mean appear in parentheses in this and all other tables.

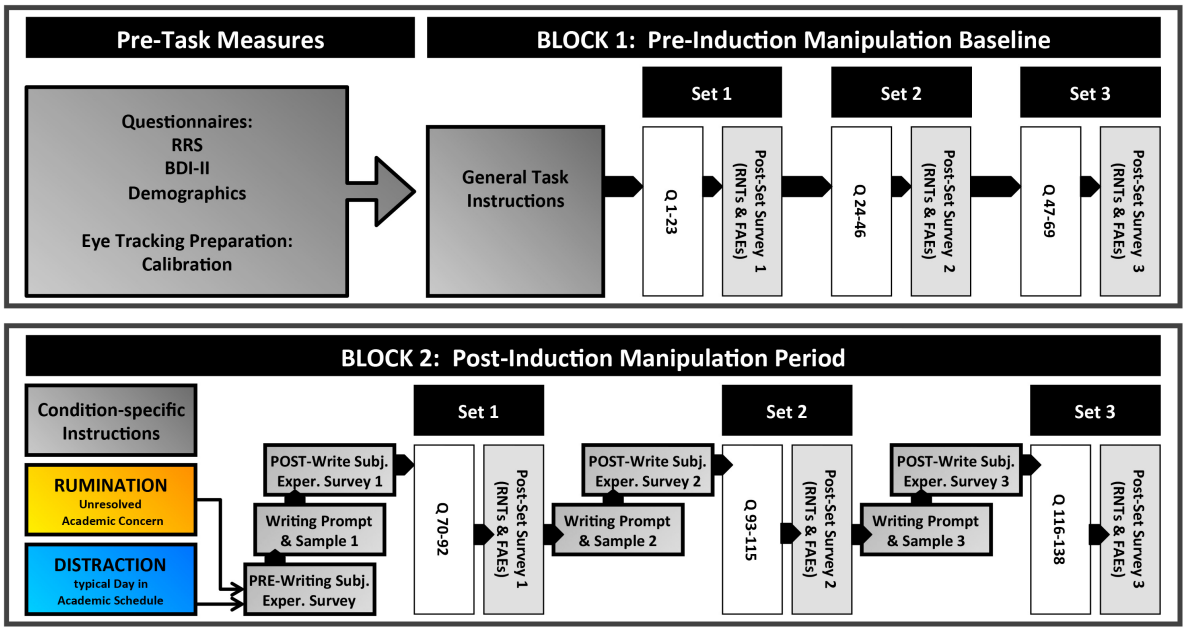

FIGURE 1 | Overview of study procedures. Please refer to section "Overview" for detailed explanation.

each bin/block were matched for average difficulty (i.e., target accuracy of 0.35). The length for all correct answer words was pre-set to range from four to nine letters (Bin 1: M = 6.36, SD = 1.16; Bin 2: M = 6.44, SD = 1.31), which typifies the word length shown elsewhere to only require a single fixation for effective lexical processing (Rayner, 1979, 1984). We also ensured that all correct answer word stimuli had been rated previously as being familiar to 95% of the Baruch College undergraduate population, thus reducing the likelihood that large variations in semantic word fluency would influence gaze fixation behavior (Gernsbacher, 1984; Rayner and Duffy, 1986; Shatzman and McQueen, 2006).

Software and Hardware

The general knowledge task was delivered using Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA) and programmed to sync up and interface with Tobii Studio Software (Version 2.3.1; Tobii Technology, Inc., Falls Church VA) in a dual-computer setup. In the testing booth, the general knowledge stimuli were presented on a 23″ widescreen LCD monitor (1920 × 1080 screen resolution; 60 Hz refresh rate) that was part of a Tobii TX300 integrated eye tracker system, which recorded gaze data at a sampling rate of 300 Hz. Data were pre-processed using Tobii Studio software and then exported and processed further in Matlab (Mathworks, Natick, MA, United States) using an in-house script.

Design and Procedure

Overview

The complete study procedure, from initial pre-task measures through the final task block, are illustrated in **Figure 1**.

Following informed consent, subjects first filled out the pre-task questionnaires, including the RRS, the BDI-II, and a set of demographic questions. They were then escorted to a well-lit room where they were seated comfortably, without a chin rest or head constraints, approximately 60 cm in front of the integrated Tobii computer monitor/eye tracker system. A nine-point calibration procedure was carried out to establish eye position.

Prior to Block 1, all subjects were presented with general task instructions detailing the basic structure of a general knowledge trial. Block 1, which served as the pre-induction manipulation baseline, was subdivided into three 23-question sets (for individual question trial structure, see section "Trial Sequence"). Each question set was followed by a short survey of the subjects' subjective experiences during the preceding set (see section "Post-set Surveys"), including the extent to which they experienced recurrent negative thoughts (RNTs) and had negative feelings after errors (FAEs).

After completing Block 1, subjects began Block 2, which was defined as the post-induction manipulation period. This block began with *Condition-Specific Instructions* (see section "Condition-Specific Instructions") regarding a writing-based task where participants were prompted to retrieve from autobiographical memory either an ongoing and unresolved negative academic situation from their life (Rumination condition) or a situation from a non-emotional, typical academic day (Distraction condition). After identifying an appropriate situation, they completed a *pre-writing* survey that queried the degree of concerned thinking they had recently experienced about their situation of focus. Then, they engaged in writing short narrative responses (3–5 min) to a specific prompt (see section "Induction-Related Writing Prompts"). This was followed by

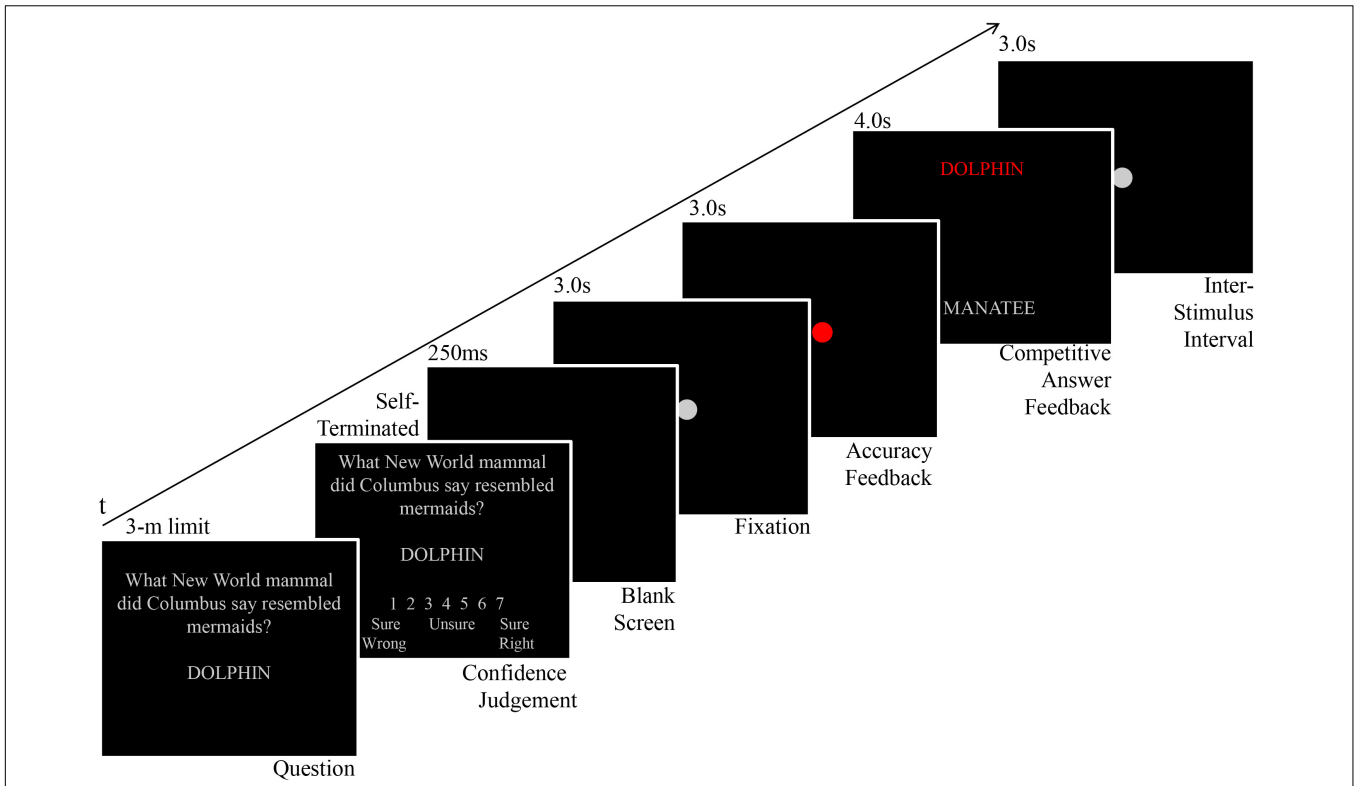

FIGURE 2 | Trial structure. Example shows a trial with an incorrect answer. If the subject's answer had been correct (i.e., Manatee), a green circle and green correct answer would have been shown, along with the correct answer in gray.

a rating of their *post-writing* subjective experiences about the writing task itself. They then engaged in answering a set of 23 general knowledge questions. As in Block 1, each question set was followed by the post-set survey of subjective experiences. This sequence, from the writing sample to the post-set surveys, was repeated for two more sets for a total of three sets (69 questions) in Block 2.

Trial Sequence

As shown in **Figure 2**, for each individual trial, questions were presented in gray font on a black background. Subjects had a 3-min time limit to submit their response, after which they rated their response confidence on a scale from 1 (sure wrong) to 4 (unsure) to 7 (sure right). They were then presented with a short blank screen for 250 ms, followed by a 3-s fixation period, consisting of a screen-centered gray circle that subtended 1° of visual angle (VA). Then, an initial indicator of participants' performance accuracy was presented for 3 s, also consisting of another centered circle, 1° VA in diameter, where the color red indicated an error response and the color green indicated a correct response.

Immediately after, the competitive answer feedback was shown. The correct answer was always presented in gray, but participants' responses were presented in green if correct and in red if incorrect. These two answers were presented in center-justified, vertical alignment, separated by approximately 19.1 cm and subtending at about 17° VA. Whether the gray, task-given correct answer appeared on the top of the screen or at bottom on any given trial was pseudorandomly counterbalanced for correct and incorrect trials separately, such that a given answer type did not consecutively appear in the same location for more than three trials.

Each word stimulus was 1.1 cm (∼1°VA) tall and could be as wide as 9.9 cm (i.e., nine letters long, or ∼9°VA), but as narrow as about 4.4 cm (i.e., four letters long, or 4°VA). This competitive answer feedback was presented for 4 s, a duration consistent with other eye-tracking studies using a competitive, free-viewing stimulus design (Kellough et al., 2008; Duque et al., 2014; Owens and Gibb, 2017). After offset of the competitive answer feedback, an inter-stimulus interval ensued, consisting of a 3-s presentation of a screen-centered gray circle, subtending 1°VA.

Post-set Surveys

After each 23-item set of general knowledge questions, we asked participants to rate the frequency of their RNTs and the relative pleasantness of their FAEs. Each post-set survey question was rated on a 1–9 Likert scale, with 1 reflecting the negative or low end of the subjective experience, 9 reflecting the positive or high end, and 5 indicating an experiential midpoint (i.e., neutrality).

Condition-Specific Instructions

Just prior to the onset of the induction manipulation in Block 2, the following general statement was presented to all participants:

"*Based on your responses so far, you encountered some difficulty answering the first block of questions. Although this difficulty is happening within the context of this research study, perhaps you have encountered difficulties in actual academic situations of your own life. During real-life academic difficulties, many students often report taking the time to. . ..*"

This final phrase was completed by condition-specific instructions to either "*think about their academic difficulties in real life*" and identify an ongoing and unresolved academic concern of theirs that had come about recently and was currently causing them distress (Rumination Condition) or to "*distract themselves from the general knowledge questions or any real-life academic difficulties*" by identifying a recent non-emotional day in their academic schedule for which they could remember with good accuracy the events that took place (Distraction Condition). To help participants with this process, they were supplied with two condition-specific, scenario-based examples of suitable situations of focus, described as being previously offered by actual participants (see *Supplemental: Condition-Specific Instructions* for the full set of condition-specific instructions and *Supplemental: Condition-Specific Examples* for the condition-specific scenario-based examples).

Once participants identified their situation of focus for the writing task, they briefly described it to the experimenter who ensured it was suitable for their condition. If it was not suitable, or they struggled to identify one at all, participants were redirected with a few verbal prompts until they were successful. Participants were then asked to complete a short, condition-specific four-question *pre-writing* survey that queried the degree of concerned thinking they had recently experienced about their situation of focus on a 9-point Likert scale with 1 indicating low levels of concern and 9 indicating extreme levels of concern (see *Supplemental: Pre-Writing Survey* for the full set of items).

Induction-Related Writing Prompts

After a suitable situation had been identified, but prior to starting each of three 23-item sets of questions in Block 2, participants were presented with condition-specific prompts on how to craft their writing samples.

For the Rumination condition, the writing prompts were based on three important assumptions of Martin and Tesser's (1996) Control Theory of rumination. First, given their claim that rumination is born out of goal-state discrepancies that are persistent and revolve around a common instrumental theme, the first prompt asked participants to factually describe with as little emotional expression as possible what their ongoing academic concern was and why it seemed to be persisting. Second, given that rumination over unresolved goals can be passive and automatic, the next prompt asked participants to describe the kinds of recurrent and repetitive thoughts that tended to easily come to mind about their ongoing academic concern. Third, given that rumination comes online when the rate of progress toward a goal is slower than what the individual wants it to be, the final prompt asked participants to describe the degree of investment of their time and energy that had been expended in vain in attempts to resolve their concern.

For the Distraction condition, the prompts were fashioned based on "fact control writing" often used in the expressive writing literature (e.g., Seeley et al., 2017), where participants write a factual account with little to no emotion of a recent day in their schedule. Thus, the first prompt asked participants to factually describe the events of a recent, non-emotional day from their academic schedule. The second prompt asked them to describe precisely *when* in the day (i.e., at what exact time) the events they had previously described occurred. Finally, the third prompt asked participants to describe precisely *where* they were (i.e., at what exact spot on or around campus) when the aforementioned events they had described occurred (see *Supplemental: Induction-Related Writing Prompts* for exact wording of prompts for both Rumination and Distraction conditions).

The prompts in each condition were always presented in the order mentioned above (i.e., no counterbalancing was used), given that this particular sequence was deemed ideal for creating a natural and continuous mental thread. To further facilitate continuity, participants' previous writing samples were shown to them prior to completion of the next one. When completing all writing prompts, participants were also asked to constrain their focus to *past-oriented* thinking about their situation. This was particularly important for the Rumination condition because, although ruminating about past negative events is commonly associated with concern for the future (Watkins et al., 2015), such future-oriented, recurrent, and repetitive negative thinking is more often described as being a form of "worry" than rumination (Martin and Tesser, 1996; Watkins, 2008).

After writing for each prompt, participants were asked to fill out a short *post-writing* survey that queried their subjective experiences while completing that particular writing sample. The five items for the survey were selected from the "experiential self-focus" rumination induction prompts originally developed by Nolen-Hoeksema and Morrow (1993) and adapted for use in survey form. Using a scale that ranged from 1 to 9, with 1 reflecting an extreme amount of a given negative self-focus characteristic (hopelessness, restlessness, sadness, agitation, and fatigue), 9 reflecting an extreme amount of the corresponding positive self-focus characteristic (e.g., hopefulness, calmness, happiness, relaxation, and energy), and 5 indicating a middle, neutral point.

Data Analysis

ANCOVAs

We conducted a series of customized analyses of covariance (ANCOVAs) that included the categorical factors of Induction condition, Set (except on measures of eye-tracking due to trial counts; see below), and Block (except on measures of the writing exercise, which only occurred in Block 2), alongside subjects' continuous BDI-II scores and RRS Brooding and Reflection scores as covariates (i.e., predictor variables). Although parameter estimates were rendered for all three covariates, including all interaction terms between each of the covariates and manipulated variables, the ANCOVAs did not include

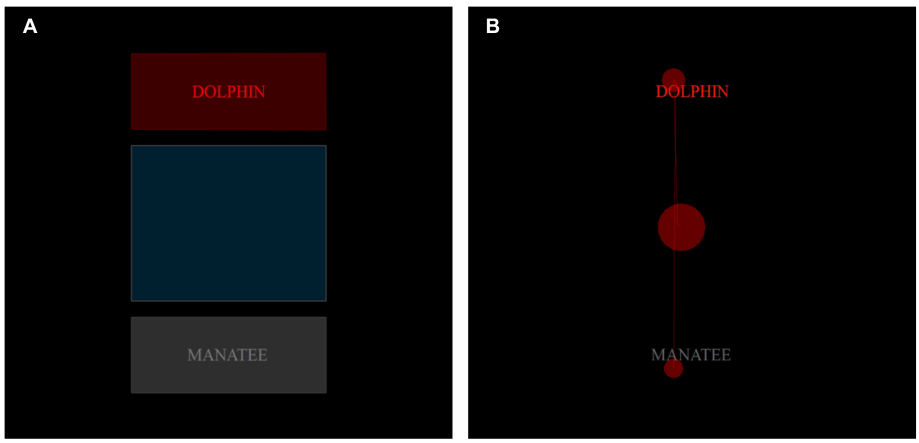

FIGURE 3 | Competitive answer feedback AOIs and sample eye-tracking data. **(A)** Areas of interest (AOIs) are superimposed over each feedback type (red = incorrect subject-given answer, gray = correct task-given answer, blue = initial central fixation area). **(B)** A short snippet (<1 s) of eye-tracking data from a single subject is superimposed to illustrate fixations (red circles, where diameter is a function of duration) and saccades (thin red lines). During the task, the participants were free to view the competitive answer feedback for a 4 s period.

interaction terms between Brooding, Reflection, and BDI-II themselves, given that these trait/mood covariates were included mainly to determine if state effects were present even when controlling for these effects and/or they moderated any observed state effects. Additionally, prior to entering eye-tracking and subjective experience metrics into these ANCOVAs, we partialed out any variance associated with differences in performance accuracy on the general knowledge task in order to control for differences in accuracy, given that basic differences in error frequency could influence our key eye-tracking metrics[4]. This was done to increase the likelihood that any observed differences in those variables were the result of the induction and not individual differences in general knowledge.

For all analyses, an alpha level of $p < 0.05$ was used as criterion for significance, but marginally significant findings ($0.05 \leq p < 0.10$) regarding experimental manipulations are also reported and explored because of *a priori* predictions with these factors. On the other hand, marginal effects involving trait and mood effects are only reported given that these analyses were highly exploratory. Effect sizes are specified in all cases using the partial eta squared statistic. Where necessary, Greenhouse–Geisser corrections were used for violations of sphericity, and where appropriate, linear trend analyses were conducted for the three-level within-subjects factors of "Set" or "Prompt" to especially explore how differences may have unfolded within the post-induction period of the task. Any *post hoc* explorations of significant main effects or interactions were carried out using the Holm–Bonferroni procedure for corrections for multiple comparisons (Holm, 1979).

Eye-Tracking

For each trial, a static, rectangular-shaped AOI with a width of 14.1 cm (12.5°VA) and a height of 5.6 cm (5°VA) was centered over each of the two pieces of word feedback for the full duration of their presence on-screen (i.e., 4 s, see **Figure 3** for a pictorial representation of the AOIs used in the current study). Since any one word stimulus itself was 1.1 cm (∼1°VA) tall, and could be as wide as 9.9 cm (i.e., nine letters long, or ∼9°VA), the overlay of the AOI centrally on top of the longest possible word stimuli (including participants' typed responses) permitted a buffer of additional screen space of 2.1 cm (i.e., ∼2°VA) from the outer borders of nine-letter word stimuli out to the edge of the AOI in any direction. These AOIs were used for the word stimuli for every trial, regardless of word length.

AOIs with these kinds of parameters have been used elsewhere in other studies investigating visual fixations of word stimuli (Dampuré et al., 2014). Although seemingly conservative, these AOI parameters were also chosen given that during normal reading, the information necessary for making accurate semantic assessments of fixated word stimuli is limited to foveal vision (Rayner, 1979), and central foveal vision can subtend up to 5°VA (Duchowski, 2007). Given that Hansen and Ji (2010) report the error rate for the accuracy of model-based gaze estimation systems like that of the Tobii TX300 to be between 1° and 2°VA, applying such conservative parameters for the two word feedback AOIs in our study likely helped account for any degree of this technical uncertainty.

Whether participants looked at the two pieces of word feedback on any given trial (and for how long) was defined by assessing the degree of gaze fixation (expressed in ms accrued) that occurred within each of the two AOIs. In accord with standard settings used on current Tobii eye trackers, fixations

[4]We also considered whether it was necessary to include age or education as a covariate in our analyses, due to some marginal differences in these participant characteristics between Rumination and Distraction groups. We found that age correlated with task accuracy in the total sample ($r = -0.29$, $p < 0.05$), but because we had already partialed out variance due to differences in task accuracy in the eye-tracking and post-task surveys, we did not feel that it was necessary to further partial out variance due to age.

were defined using the Velocity-Threshold Identification (I-VT) fixation classification algorithm, where a velocity threshold of any directional shift of the eye that was below 30 visual degrees per second across data points was used to operationalize a single fixation. To preserve the continuity of gaze data in momentary instances (i.e., <75 ms) of signal loss, a gap fill-in interpolation algorithm was applied, and any adjacent fixations found to be within 0.5° VA of one another were merged. Any defined fixation ultimately determined to be shorter than 60 ms in length was re-classified as saccade data.

Any trial was excluded from analysis if gaze fixation was not centered between the two feedback AOIs at the start of the trial in a region 11.75 cm (10.5° VA) in height and 14.1 cm (12.5° VA) in width (see **Figure 3**; left panel). We also excluded any trial from analysis where the summation of available fixation time for that trial was less than 2.67 ms (i.e., two thirds the duration of competitive feedback presentation), or if that time was more than 2 SD below the participant's mean summed-fixation time across all trials (e.g., Chua et al., 2012). After these exclusions, if we had retained set as a factor, there would have been 17 participants excluded, and therefore we opted to collapse over this factor to retain the maximal number of participants. Even after collapsing, four subjects did not have a minimum of trials in all critical conditions (as a function of answer type, answer location, and task block), necessitating their exclusion from all further analyses.

Our measures of interest were FFD, defined as the time spent looking at an answer AOI the first time it was fixated upon, and TFD, defined as the overall time in ms, summed across all fixations, spent looking at an answer AOI. FFD and TFD values were generated for each of the two AOIs in every single trial, after which single-subject averages of each gaze fixation metric were calculated for error trials as a function of answer type [subject-given incorrect answer (red) vs. task-given correct answer (gray)], task block (Block 1 or 2), and Induction condition (Rumination or Distraction).

Only those error trials that represented semantic errors were included for analysis, thereby excluding orthographic errors (see Footnote 1) and correct trials. There were two reasons why we did not include correct answers in our analyses. First, in order to make the answer feedback for correct and incorrect trials visually similar, feedback on a correct trial had to include the correct answer in both positions on the screen, with one in green and one in gray. As a result, there was no meaningful competition for attention between the two answers in terms of information, only in terms of color. Thus, any looking-time differences to one of these correct answers would be based purely on color and would not inform our primary research questions. Second, the experiment was purposefully designed to have more incorrect than correct trials so that participants would experience challenge and difficulty throughout the task. This gave us enough incorrect trials to withstand some trial loss due to signal drop out, but too few correct trials for analysis.

We also initially calculated FFD and TFD as a function of Answer location (i.e., whether the gray, task-given correct answer was presented at the top of the screen or at the bottom). However, prior to conducting the main eye-tracking analyses of interest, we determined that we could simplify our statistical model by collapsing across this factor because the number of useable trials at each location did not interact with condition and/or block (all $ps > 0.26$), and thus, any effect of location should influence the Rumination and Distraction conditions equally. Although there were no significant differences in the number of trials across conditions ($p > 0.91$), there were significantly more trials in both conditions that were retained in Block 1 (Rumination: $M = 31.5$, $SEM = 2.02$; Distraction: $M = 32.5$, $SEM = 2.06$) compared to Block 2 (Rumination: $M = 29.7$, $SEM = 1.89$; Distraction: $M = 28.1$, $SEM = 1.93$), $F(1, 49) = 7.43$, $p = 0.009$, $\eta_p = 0.132$.

RESULTS

Rumination and Distraction State Inductions

Pre-writing Survey

Following identification of their condition-specific situation, but before beginning their first writing sample, participants self-reported their degree of concern regarding the situation they would be writing about. In line with expectations, identifying an unresolved negative academic situation (Rumination condition) generated more concern than identifying a non-emotional day in one's academic schedule (Distraction condition), $F(1, 47) = 53.72$, $p < 0.001$, $\eta_p^2 = 0.53$ (see **Figure 4A**). Neither BDI-II nor RRS subscores were associated with the strength of these ratings, whether overall or via interaction with the Induction condition factor (all $ps > 0.38$).

Writing Content Analysis

Participants' three induction-related writing samples were rated sentence by sentence for RB and SR writing content types according to the coding system of Marin and Rotondo (2017). Briefly, RB was any negative statement that described an undesirable outcome/consequence, its cause, or any negative evaluation. SR was any positive or neutral statement that provided an evaluation/explanation about the self, others, or the self–other relationship. Also included were statements that provided constructive or insightful reasoning toward problem-solving or any adaptive action toward resolving one's concerns. Because one sentence could contain more than one phrase, each one capturing a *different idea*, it was possible that one sentence could be coded as containing both RB and SR content. However, in cases where it was deemed that the participant wrote both RB and SR content about the *same idea* in the same sentence, that sentence was coded as only containing either RB or SR content, based on whichever type was expressed as the concluding remark. Upon the completion of coding, within any single writing sample, the number of sentences containing RB and SR content were each then separately summed and divided by the total number of sentences written, thus rendering separate, but non-mutually exclusive proportions for each rumination content type in that writing sample. Additional details regarding this coding can be found in *Supplemental: Writing Content Analysis*.

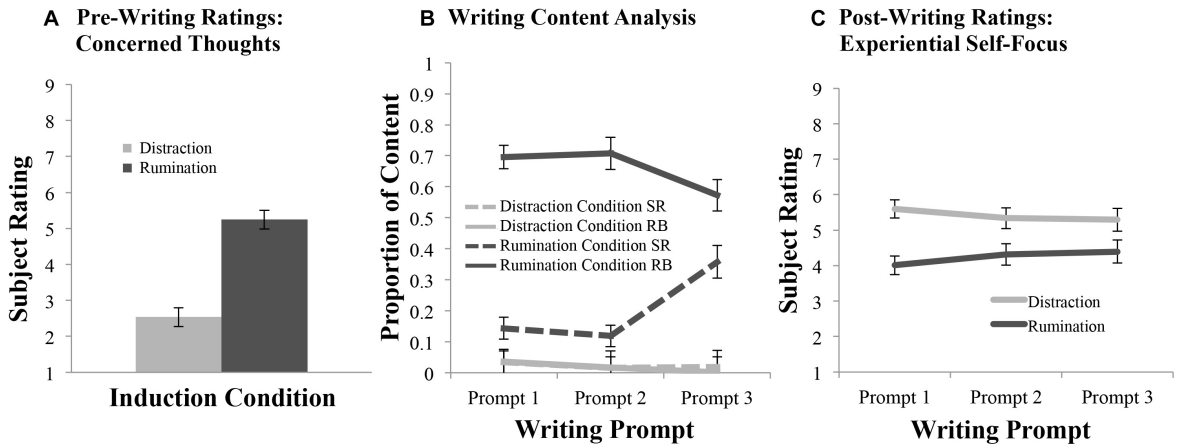

FIGURE 4 | Writing task ratings. **(A)** Subjects' average pre-writing ratings of the degree of concerned thinking (1 = low, 9 = high) regarding the situation of focus for the writing-based task. Ratings are plotted as a function of Induction condition (Distraction in light gray; Rumination in dark gray). **(B)** The proportion of ruminative writing content (*Y*-axis), whether in Ruminative Brooding (RB; solid lines) or Self-Reflection (SR; dotted lines) type, is plotted as a function of Induction condition (Distraction in light gray; Rumination in dark gray) across each of the three Writing prompts during the post-induction period. **(C)** Subjects' average post-writing ratings of the valence of experiential self-focus (1 = extreme negative amount, 9 = extreme positive amount) during the writing-based task, as a function of Induction condition and Writing prompt.

An ANCOVA that included the categorical factors of Induction condition, Rumination content type (RB vs. SR), and Writing prompt (three prompts) alongside the continuous trait covariates (see section "Data Analysis" above) demonstrated a significant three-way interaction involving all categorical factors, $F(2, 94) = 3.63$, $p = 0.032$, $\eta_p^2 = 0.07$, which subsumed several significant two-way interactions [Induction condition by Rumination content type: $F(2, 94) = 29.09$, $p < 0.001$, $\eta_p^2 = 0.38$; Induction condition by Writing prompt: $F(2, 94) = 3.18$, $p = 0.046$, $\eta_p^2 = 0.06$; Rumination content type by Writing prompt: $F(2, 94) = 4.53$, $p = 0.013$, $\eta_p^2 = 0.09$], as well as main effects of Induction condition, $F(1, 47) = 714.32$, $p < 0.001$, $\eta_p^2 = 0.94$, and Rumination content type, $F(1, 47) = 27.91$, $p < 0.001$, $\eta_p^2 = 0.37$. Below, we unpack the three-way interaction, whose results largely validate the effectiveness of the induction manipulation in expected ways.

First, as shown in **Figure 4B**, RB content was significantly greater for the Rumination condition compared to the Distraction condition following all three writing prompts (Prompt 1: $p < 0.001$; Prompt 2: $p < 0.001$; Prompt 3: $p < 0.001$). On the other hand, although SR content was low and did not differ between Rumination and Distraction conditions following the first two prompts (ps > 0.53), by the third prompt, participants in the Rumination condition included significantly more SR in their writing than those in the Distraction condition ($p = 0.001$). Indeed, following the third prompt, RB and SR rates were not statistically different within the Rumination condition after correcting for multiple comparisons ($p = 0.54$). This was *not* due to a substantial decrease in RB content here compared to the earlier two writing samples (all ps > 0.42 after correction), but rather to an increase in SR content (Prompt 1 vs. 3: $p = 0.003$; Prompt 2 vs. 3: $p < 0.001$).

Next, we evaluated the role that trait rumination and mood state may have played in the expression of ruminative content in the writing samples. The only significant finding associated with trait Brooding was a main effect of *increased* ruminative expression overall, regardless of Induction condition, Content type, or Writing prompt, $F(1, 47) = 9.65$, $p = 0.003$, $\eta_p^2 = 0.17$. However, for trait Reflection, a significant three-way interaction emerged that included Induction condition and Writing prompt, $F(2, 94) = 4.27$, $p = 0.017$, $\eta_p^2 = 0.08$. Specifically, trait Reflection was associated with a *significantly reduced* amount of ruminative expression (collapsed across ruminative Content type), but only in the Rumination condition, and only after the third prompt, $\beta = -0.58$, $t = 3.88$, $p < 0.001$, $\eta_p^2 = 0.24$. Although we found a marginally significant three-way interaction involving pre-task mood (i.e., BDI-II scores), Induction condition, and Writing prompt, $F(2, 94) = 2.55$, $p = 0.083$, $\eta_p^2 = 0.05$, that also subsumed a marginally significant two-way interaction involving BDI-II and Writing prompt, $F(2, 94) = 2.55$, $p = 0.083$, $\eta_p^2 = 0.05$, these will not be explored further (see section "ANCOVAs").

Post-writing Ratings

An ANCOVA demonstrated a significant two-way interaction effect between Induction condition and Writing prompt on post-writing experiential self-focus, $F(1.69, 79.32) = 7.79$, $\varepsilon = 0.84$, $p < 0.001$, $\eta_p^2 = 0.14$, which subsumed a significant main effect of Induction condition, $F(1, 47) = 8.47$, $p = 0.006$, $\eta_p^2 = 0.15$. *Post hoc* tests of the two-way interaction revealed that only after the first writing exercise did the Rumination group evidence significantly more negative self-focus than the Distraction group (see **Figure 4C**). However, there was an overall trend for self-focus to move toward neutrality in both groups, as was confirmed by exploration of a significant two-way linear trend effect involving Induction condition and Writing prompt, $F(1, 47) = 9.87$, $p = 0.003$, $\eta_p^2 = 0.17$. Whereas those induced to ruminate reported experiencing

self-focus that was initially "somewhat negative" but then trended upward toward being more neutral, those induced to distract initially reported self-focus that was "somewhat positive" but then trended downward toward neutrality. Thus, although those induced to ruminate experienced more negative self-focus than those induced to distract, this difference was only prominent earlier in the post-induction period.

Turning to the possible influence of pre-task levels of RRS and depression, we found a marginal three-way interaction involving Induction condition, Writing prompt, and Brooding, $F(1.69, 79.32) = 3.30$, $\varepsilon = 0.84$, $p = 0.073$, $\eta_p^2 = 0.07$, and a significant two-way interaction effect involving trait Reflection and Writing prompt, $F(1.57, 79.32) = 5.71$, $\varepsilon = 0.84$, $p = 0.019$, $\eta_p^2 = 0.11$. Exploration of this latter significant interaction yielded no significant parameter estimates (all ps > 0.14). No effects involving pre-task BDI-II levels were found (all ps > 0.55).

General Knowledge Task Performance

Task Accuracy

When we submitted task accuracy rates to our ANCOVA, no main effects or interactions of Induction condition, Block, or Set emerged (all ps > 0.18; see **Table 2**). Although we did find a significant three-way interaction involving Induction condition, Block, and trait Brooding, $F(1, 47) = 4.99$, $p = 0.030$, $\eta_p^2 = 0.10$, as well as Induction condition, Block, and BDI-II, $F(1, 47) = 4.12$, $p = 0.048$, $\eta_p^2 = 0.08$, none of the *post hoc* comparisons associated with these interactions survived Holm–Bonferroni corrections (all ps > 0.24).

Post-set Thoughts and Feelings

Table 2 also shows the mean ratings of RNTs and FAEs that participants reported experiencing during the general knowledge task.

Recurring negative thoughts

In general, all participants reported experiencing a fairly low frequency of RNTs (i.e., ratings of ∼3) across the general knowledge task. When submitting RNTs to our customized ANCOVA, we found a marginally significant two-way interaction involving Induction condition and Block, $F(1, 47) = 2.88$, $p = 0.096$, $\eta_p^2 = 0.06$, that subsumed a main effect of the Block factor, $F(1, 47) = 16.56$, $p < 0.001$, $\eta_p^2 = 0.26$. *Post hoc* testing of the two-way interaction revealed that in the Rumination condition only, participants indicated having *fewer* RNTs in Block 2 post-induction period than they did in the Block 1 pre-induction baseline ($p = 0.001$).

When considering RNT frequency in relation to pre-task individual differences measures, however, both the aforementioned two-way interaction and another two-way interaction involving Induction condition and trait Reflection, $F(1, 47) = 6.43$, $p = 0.015$, $\eta_p^2 = 0.12$, were qualified by a significant three-way interaction involving all three factors, $F(1, 47) = 4.39$, $p = 0.042$, $\eta_p^2 = 0.09$. *Post hoc* testing of the three-way interaction indicated a *positive* association between Reflection and RNTs in Block 1 only and for women the Rumination condition, $\beta = 0.54$, $t = 2.93$, $p = 0.005$, $\eta_p^2 = 0.17$. Trait Brooding, on the other hand, was found to only interact with Induction condition, $F(1, 47) = 11.44$, $p = 0.001$, $\eta_p^2 = 0.09$. Brooding predicted significantly more RNTs across the entire task for subjects, but only in the Distraction condition, $\beta = 0.58$, $t = 2.93$, $p = 0.007$, $\eta_p^2 = 0.15$. Moreover, Brooding unexpectedly predicted marginally *fewer* RNTs for those in the Rumination condition, $\beta = -0.37$, $t = 1.80$, $p = 0.084$, $\eta_p^2 = 0.06$.

Feelings after errors

Table 2 also shows that all participants generally reported feeling "somewhat unpleasant" (i.e., ratings of ∼4) after making an error during the general knowledge task. When submitting these subjective experience ratings to our customized ANCOVA, however, we found no effects of Induction condition. Rather, we found a significant main effect of Set, $F(2, 94) = 6.08$, $p = 0.003$, $\eta_p^2 = 0.11$, such that, compared to Set 1 ratings, all

TABLE 2 | Task accuracy and ratings of task-related recurring negative thoughts (RNTs) and feelings after errors (FAEs), as a function of Induction condition and Block and Set.

		Block 1 (pre-induction baseline)			Block 2 (post-induction period)		
Variable	**Condition**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Accuracy							
	Rumination	0.323 (0.022)	0.280 (0.028)	0.280 (0.024)	0.290 (0.023)	0.300 (0.021)	0.300 (0.024)
	Distraction	0.325 (0.023)	0.347 (0.029)	0.307 (0.024)	0.318 (0.023)	0.345 (0.022)	0.310 (0.024)
RNTs							
	Rumination	3.80 (0.36)	3.93 (0.36)	4.19 (0.37)	2.90 (0.35)	2.81 (0.38)	2.76 (0.37)
	Distraction	4.05 (0.37)	4.05 (0.36)	3.56 (0.38)	3.63 (0.36)	3.37 (0.38)	3.23 (0.37)
FAEs							
	Rumination	4.09 (0.24)	3.62 (0.26)	3.44 (0.28)	4.20 (0.23)	3.91 (0.27)	3.92 (0.23)
	Distraction	3.76 (0.25)	3.45 (0.27)	3.42 (0.29)	3.78 (0.24)	3.54 (0.27)	3.95 (0.23)

All means are adjusted for BDI-II, Brooding, and Reflection covariates; RNTs and FAEs are also adjusted for task accuracy. Recurring Negative Thoughts (RNTs) were rated on a scale of 1 (none at all) to 9 (an extreme amount), with 5 representing a moderate amount. Feelings After Errors (FAEs) were rated on a scale of 1 (extremely unpleasant) to 9 (extremely pleasant), with 5 representing neither pleasant nor unpleasant.

participants reported feeling more unpleasant after errors in Set 2 ($p < 0.005$) and Set 3 ($p < 0.05$), regardless of task block. There was also a marginal main effect of Block, $F(1, 47) = 2.96$, $p = 0.092$, $\eta_p^2 = 0.06$, which was led by participants reporting numerically more unpleasant feelings in Block 2 compared to Block 1, regardless of question set. With regard to the influence of trait and mood factors, we found only a significant main effect of trait Brooding, $F(1, 47) = 5.59$, $p = 0.022$, $\eta_p^2 = 0.11$, where those higher in this trait tendency had worse feelings about errors, regardless of condition or set. There was also a marginal main effect of BDI-II, $F(1, 47) = 3.20$, $p = 0.080$, $\eta_p^2 = 0.06$, but this will not be explored further.

Relationship between writing content and post-set thoughts and feelings

The rumination induction technique introduced in Block 2 was designed to activate brooding thoughts that would potentially carry over into participants' subjective experience during the general knowledge task itself. To test for such a relationship, we examined the extent to which the proportion of RB content in the Rumination condition writing samples[5] correlated with RNTs or FAEs, as a function of set. In support of the effectiveness of the induction, we observed a significant inverse relationship between proportion of RB content and FAEs during Set 2, $r(27) = -0.575$, $p < 0.001$, which is when negative FAEs peaked for all participants, regardless of condition. Thus, the degree to which participants were able to access and to express RB during the writing exercise was related to greater negative feelings about their mistakes, at least at a point in the task when those negative feelings were more likely to be salient for all participants. Interestingly, the proportion of self-reflective content (SR) in their writing was positively related to FAEs, $r(27) = 0.606 = p < 0.001$, consistent with a buffering effect of this more adaptive type of rumination on negative affect. These significant relationships between writing content and FAEs were maintained even when controlling for trait differences in Brooding and Reflection [correlation with RB: $r(24) = -0.567$, $p = 0.002$; correlation with SR: $r(24) = 0.615$, $p < 0.001$]. No significant relationships with FAEs were found during the other sets (all ps > 0.20) and no significant relationships were found for RNTs in any set (all ps > 0.13).

Eye-Tracking Metrics

Table 3 shows the average duration of first fixation and total fixation to both types of competitive answer feedback (i.e., task-given correct answer and subject-given answer) during error trials.

TABLE 3 | Average gaze fixation durations (in seconds) during error trials.

Variable	Answer type	Condition	Pre-induction baseline	Post-induction period
FFD				
	Correct answer			
		Rumination	0.310 (0.024)	0.301 (0.028)
		Distraction	0.265 (0.024)	0.356 (0.029)
	Incorrect answer			
		Rumination	0.185 (0.012)	0.207 (0.011)
		Distraction	0.201 (0.012)	0.199 (0.011)
TFD				
	Correct answer			
		Rumination	1.778 (0.073)	1.656 (0.082)
		Distraction	1.775 (0.075)	1.752 (0.084)
	Incorrect answer			
		Rumination	0.846 (0.051)	0.868 (0.052)
		Distraction	0.838 (0.053)	0.804 (0.053)

FFD, First Fixation Duration; TFD, Total Fixation Duration.

First Fixation Duration

An ANCOVA that included Induction condition, Block, and Answer type, along with the continuous RRS and mood variables, revealed a significant three-way interaction, involving all categorical factors, $F(1, 43) = 12.31$, $p = 0.001$, $\eta_p^2 = 0.22$. This higher-order interaction subsumed two marginally significant two-way interactions [Answer type by Block: $F(1, 43) = 3.15$, $p = 0.083$, $\eta_p^2 = 0.07$; Induction condition by Block: $F(1, 43) = 3.50$, $p = 0.068$, $\eta_p^2 = 0.08$], as well as significant main effects of Block, $F(1, 43) = 6.68$, $p = 0.013$, $\eta_p^2 = 0.13$, and Answer type, $F(1, 43) = 49.26$, $p < 0.001$, $\eta_p^2 = 0.53$. We also observed a marginally significant main effect of trait Brooding on FFDs in this analysis, $F(1, 43) = 3.83$, $p = 0.056$, $\eta_p^2 = 0.08$, that will not be explored further.

With regard to the main effect of Answer type, participants' FFDs on the correct answer word were longer ($M = 0.308$, $SEM = 0.017$) than they were on reminders about their incorrect response ($M = 0.198$, $SEM = 0.007$), a relatively large difference that can be seen in the top half of **Table 3**. Due to this large overall difference, we will unpack the significant three-way interaction using a simple effects approach after first splitting by Answer type and conducting separate two-way mixed-measures ANCOVAs on FFDs to the subject-entered incorrect answer and FFDs to the task-provided correct answer.

When assessing FFDs on the incorrect response only, we found only a marginally significant two-way interaction between Induction condition and Block, $F(1, 43) = 2.89$, $p = 0.096$, $\eta_p^2 = 0.06$. Consistent with predictions, exploration of this interaction indicated that within the Rumination condition, FFDs on reminders of recent performance failures were longer during the post-induction period (i.e., Block 2) than they were during the pre-induction baseline (i.e., Block 1), although this effect did not survive *post hoc* Holm–Bonferroni corrections for multiple comparisons (uncorrected $p < 0.05$). In contrast, this same block-based comparison within the Distraction condition did not approach significance, nor did either of the condition-based comparisons within each block (all ps > 0.33).

In contrast, when assessing FFDs on the correct answer, we found a significant Induction condition by Block interaction, $F(1, 43) = 8.30$, $p = 0.006$, $\eta_p^2 = 0.16$, which also subsumed

[5]Floor effects on the levels of RB and SR in the Distraction condition precluded a corresponding analysis for that induction condition.

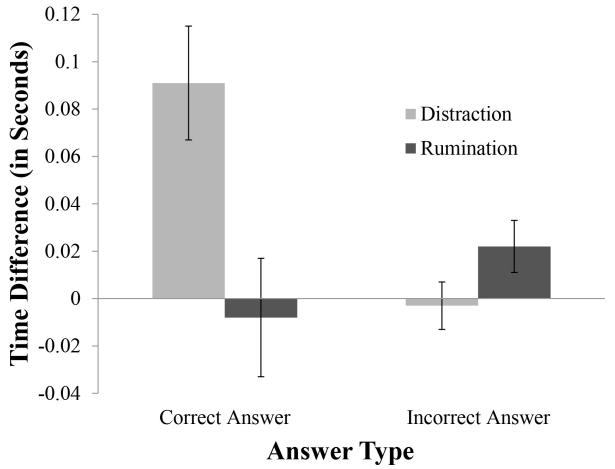

FIGURE 5 | Pre-to-post induction differences in First Fixation Duration (FFD). Changes in FFD between the pre-induction baseline (i.e., Block 1) and post-induction period (i.e., Block 2) are plotted as difference scores (i.e., Block 2 FFD - Block 1 FFD). Difference scores are plotted as a function of Induction condition (Distraction in light gray; Rumination in dark gray) and Answer type (i.e., correct gray answer and incorrect red answer).

a main effect of Block, $F(1, 43) = 5.74$, $p = 0.021$, $\eta_p^2 = 0.12$. Specifically, among those in the Distraction condition, FFDs on the correct answer were significantly longer during the post-induction period than they were during the pre-induction baseline ($p < 0.005$). This same block-based comparison within the Rumination condition was not significant, nor were any of the condition-based comparisons within each block (all ps > 0.18). **Figure 5** illustrates the contrasting pre-post induction differences of the Rumination and Distraction conditions on both the correct answer compared to the reminder of the incorrect answer.

Total Fixation Duration

For this gaze metric, we found only a significant main effect of Answer type, $F(1, 43) = 185.32$, $p < 0.001$, $\eta_p^2 = 0.81$, indicating that all participants' TFDs on the correct answer were much longer ($M = 1.740$, $SEM = 0.053$) than their TFDs on reminders about their incorrect response ($M = 0.839$, $SEM = 0.035$), and a significant main effect of Block, $F(1, 43) = 6.05$, $p = 0.018$, $\eta_p^2 = 0.12$, where TFDs observed in the post-induction period were *shorter* ($M = 1.270$, $SEM = 0.033$) than those seen in the pre-induction baseline ($M = 1.309$, $SEM = 0.029$). There were no overall differences or interactions involving the Induction condition factor (all ps > 0.15).

Interestingly, trait RRS predicted TFD, regardless of Induction condition. In particular, we observed a significant three-way interaction involving Answer Type, Block, and trait Brooding, $F(1, 43) = 7.89$, $p = 0.007$, $\eta_p^2 = 0.16$, which subsumed both a main effect of Brooding, $F(1, 43) = 6.08$, $p = 0.018$, $\eta_p^2 = 0.12$, and a two-way interaction involving Answer type and Brooding, $F(1, 43) = 5.92$, $p = 0.019$, $\eta_p^2 = 0.12$. Unpacking the three-way interaction, we found that within the pre-induction baseline only (i.e., Block 1), Brooding surprisingly predicted significantly longer TFDs on the *correct answer* feedback type, regardless of Induction condition, $\beta = 0.50$, $t = 3.40$, $p = 0.001$, $\eta_p^2 = 0.20$. No parameter estimates involving the relationship of Brooding with TFDs on reminders of participants' *incorrect responses* in either Block 1 or Block 2 were significant (all ps > 0.27).

We also observed a significant three-way interaction involving Answer type, Block, and trait Reflection, $F(1, 43) = 4.37$, $p = 0.43$, $\eta_p^2 = 0.09$. *Post hoc* examination of parameter estimates again revealed an effect involving only the correct answer feedback type, and only within the pre-induction baseline (i.e., Block 1). However, this particular trait style of ruminative responsiveness surprisingly predicted significantly *shorter* TFDs to this novel corrective information for all subjects, $\beta = -0.41$, $t = 2.89$, $p = 0.006$, $\eta_p^2 = 0.15$. No parameter estimates involving the relationship of Reflection with TFDs on reminders of participants' incorrect responses in either Block 1 or Block 2 were significant (all ps > 0.39). Finally, in contrast to the significant moderation of TFD effects by both trait RRS subtypes, pre-task BDI-II scores exhibited only a marginal interaction with Induction condition and Block, $F(1, 43) = 2.87$, $p = 0.097$, $\eta_p^2 = 0.06$, that will not be discussed further.

DISCUSSION

In the context of a challenging general knowledge retrieval task (see also Butterfield and Mangels, 2003; Whiteman and Mangels, 2016), the present study asked whether women induced into a state of rumination or distraction would allocate attention differently to reminders of their retrieval mistakes (i.e., incorrect answer) vs. new information (i.e., the correct answer), as measured by two metrics of gaze fixation duration – FFD and TFD. Both the rumination and distraction induction procedures involved completing handwritten narratives contextualized to be academically relevant. However, whereas the Distraction condition involved retrieval of the non-emotional details in the schedule of an average school day, the Rumination condition involved retrieval of details about an unresolved academic concern. On both our experimenter-quantified (i.e., writing content) and subjective self-report (i.e., post-writing experiential self-focus) measures, our findings support the conclusion that the women in this study carried out the writing exercises in induction-congruent ways, both replicating and extending previous studies (e.g., Roberts et al., 2013; Marin and Rotondo, 2017). Thus, we can be reasonably confident that our task-related findings can be interpreted from the assumption that participants had been successfully induced into states of either rumination or distraction.

Before discussing those task-related effects in detail, we first expand on the similarity between the pattern of RB and SR in our writing samples and those of Marin and Rotondo (2017), who examined ruminative content in 15 min writing samples taken once a day over 3 days. In Marin and Rotondo (2017), participants instructed to write about a recent, stressful experience maintained a relatively high degree of focus on the causes of that experience and related negative evaluations (i.e.,

RB) across the 3 days, with greater degrees of expression of this maladaptive form of rumination being associated with more negative self-focus and lower self-acceptance. However, by their third writing sample, participants also evidenced an increased degree of positive evaluation about their circumstances (i.e., SR). Both patterns are similar to that found in the present study and stand in contrast to studies where expressive writing has been found to be more beneficial for mood and behavior (e.g., Gortner et al., 2006; Sloan et al., 2008; Ramirez and Beilock, 2011). In particular, our prompts, which were aligned specifically with components of Martin and Tesser's (1996) socio-cognitive theory of rumination, appeared to keep women brooding over their unresolved issues as they sequentially described their concern, the thoughts associated with it, and the time and energy they had spent unsuccessfully trying to resolve it. Only after the third time they had written about their unresolved situation were the women able to introduce more active reflection on how to move beyond it.

Despite the apparent effectiveness of the induction procedure, we did not find robust evidence for our hypothesis that being induced to ruminate versus distract increased attention to reminders about one's errors. Although there was some evidence from planned comparisons that women in the Rumination condition increased their FFDs to the incorrect answer after the induction, this effect was not strong enough to survive correction for multiple comparisons. No other gaze duration effects specific to state Rumination were found. Thus, these findings provide weaker support than expected for both the impaired disengagement (Koster et al., 2011) and attentional scope theories of rumination (Whitmer and Gotlib, 2013). However, this may be related in part to the type of information presented. Past studies have primarily utilized passive viewing of negative faces or self-relevant words [e.g., passive viewing of emotional faces with no explicit task-based instruction (Duque and Vázquez, 2015; Owens and Gibb, 2017) and passive viewing of emotional or self-focused words in a simple target discrimination task (Grol et al., 2015; Southworth et al., 2017)].

Although we presented the incorrect answer in red, a color that some studies have shown to be implicitly arousing and negative (Elliot et al., 2007, 2009), the words themselves were not intrinsically negative. Instead, it was the internal construal of the meaning of this feedback in reference to achievement-related goals that might generate ruminative thoughts, something that may not be captured by gaze fixation. Gaze fixation metrics can only speak to where and how long the eyes dwell on the screen, but do not necessarily speak to what individuals are focusing on internally. Although models of eye movements and attention are often based on the principle that where one is looking is what one is thinking about (e.g., Just and Carpenter, 1976), at any given moment, the object(s) of internal and external focus can be different (Hunt and Kingstone, 2003), such as has been shown in the eye-tracking patterns of individuals who are mind wandering (Reichle et al., 2010).

Additionally, in our general knowledge task, participants had a choice between processing feedback information they already knew (i.e., that they had made a mistake) or updating their already existing knowledge by attending to the correct answer. The difference in information value between these two stimuli may have been sufficient to reduce the strength of any attentional biases toward their reminder of their error. Indeed, FFDs to reminders of recent performance failures were two-thirds the duration they spent fixating the novel corrective information, which is not surprising given the sensitivity of eye-tracking measures to word frequency and other lexical/semantic features (e.g., Reichle et al., 2003; Staub et al., 2010). Future studies where the competitive answer feedback represents the first time that participants learn of their response's accuracy (i.e., eliminating the initial red or green circle indicating accuracy) may increase the sensitivity of our general knowledge task to such attentional-bias predictions by making sure the participant's incorrect answer and the task-provided correct answer both provide new, although qualitatively different, information.

The effect of state rumination on FFDs to reminders of the participants' errors may also have been stronger if we had been able to separately analyze FFDs associated with each set of questions in the post-induction period, rather than having to collapse across the three sets to achieve sufficient trial counts. Indeed, our measures of subjective experiences suggest that the rumination induction may have had a stronger influence on the first two sets compared to the third. Specifically, after the first writing exercise, we observed the largest differential between the Rumination and Distraction conditions on post-writing negative experiential self-focus. Although on that particular measure there was a regression toward neutral ratings for both Induction conditions after the second and third writing exercises, in the second set, a stronger relationship between the ruminative writing content and subjective task experiences emerged. Specifically, in this set, the participants in the Rumination condition who included more RB content in their writing sample also reported greater negative feelings about their task-related errors (FAEs). Interestingly, it was during this set of trials that FAEs appeared to be heightened for all participants, regardless of Induction condition (or block), suggesting that carryover from the writing exercise was greatest at a point in the task when the negative impact of repeated failure became the most salient. However, even though FAEs in the third and final set remained more negative overall, relative to the first set, the writing samples in the Rumination condition at this point in the post-induction period changed to include more of a putatively "adaptive" form of rumination—SR. Given evidence that SR in the writing exercise could reduce the sting of negative feedback (i.e., positive correlation with FAEs in Set 2), it is possible that by the third set, any selective attentional bias toward the reminder of the incorrect response in the Rumination condition, similarly, may have been mitigated by these adaptive influences.

Alternatively, the effects of rumination on feedback may simply be better explained by the inability to disengage from internally focused attention to the goal-based appraisal of the negative feedback rather than by overt attention to the external feedback itself. For example, in an event-related potential (ERP) study of trait rumination that used a similar general knowledge retrieval paradigm as in the current study (Whiteman and Mangels, 2016), we found that women higher in trait Brooding demonstrated evidence of more sustained attention

to negative feedback, particularly as the task progressed and errors accumulated, as indexed by the magnitude and duration of a late positive potential (LPP) waveform over posterior scalp regions. Notably, the LPP is a putative ERP index of motivated attention to a visually evocative stimulus (Schupp et al., 2004; Foti and Hajcak, 2008) but can continue to be modulated by internal representations of emotional stimuli sustained even after stimulus offset (Hajcak and Olvet, 2008).

Additionally, one future way to evaluate this hypothesis using eye-tracking methodology would be to examine pupil dilation to the initial, centrally presented negative feedback (i.e., the red circle). Pupil dilation can provide an index of noradrenergically mediated arousal and internal processing effort (e.g., Eckstein et al., 2017), and previous studies have found increases in the extent and duration of pupil dilation to emotionally relevant information in relation to rumination (e.g., Siegle et al., 2003; Duque et al., 2014). For the present study, however, our interest was not in arousal, but in whether the induction of rumination would bias attention toward reminders of the mistake, rather than toward new information through which participants could correct their errors. For this question, we felt that gaze duration was a more appropriate measure. Additionally, when setting up our experiment, we found that the bright lighting conditions necessary to optimize gaze tracking made it difficult to optimally record pupillometry, which required dimmer lighting to allow for an appropriate range of pupillary responses. Given our primary interest was in selective attention to competitive feedback, we optimized our lighting for gaze tracking, precluding analysis of pupil activity.

Although our measures of gaze dwell time did not yield strong evidence for increased overt attention to reminders of errors in the Rumination condition, the Distraction condition reliably led to an increased FFD to the *correct* answer feedback type compared to the pre-induction baseline (i.e., Block 1). One interpretation of this finding is that writing about a neutral school day distracted the women away from any academic concerns existing either inside or outside of the task, leaving greater resources to attend to new information following errors. This increase in FFD on the correct answer could also reflect a general increase in intrinsic curiosity about this information, motivated by an interest in integrating this information into their existing knowledge base (cf. Kang et al., 2009). Thus, from a mechanistic perspective, distraction may therefore serve as an adaptive emotion regulation strategy (e.g., McRae et al., 2010), helping to down-regulate negative affect and redirect attention onto actions or objects of thought that are external to the self.

In comparison, the lack of similar findings in the Rumination condition could be another symptom of a less adaptive attentional focus. Indeed, some related work that used gaze fixation to index motivation toward attainment of a personally relevant goal found that individuals looked less at a goal-related stimulus if they believed the goal reflected by that stimulus was unattainable (Light and Isaacowitz, 2006). By this view, the instruction to ruminate about an unresolved academic concern may have primed women in our study to believe that an effort to resolve their poor performance was fruitless, and thus, any sustained overt attention to the correct answer would not be useful in this regard. Although a reliable decrease in FFD to the correct answer during the post-induction period would have given stronger evidence for this interpretation, we can at least conclude that the Rumination condition did not increase overt attention to the correct answer in the manner observed in the Distraction condition.

Finally, turning to our exploration of whether pre-task levels of trait Brooding and/or Reflection might influence subjective and objective measures within the task, we found a number of interesting findings. First and not unexpectedly, during the writing exercises, women who already had a trait tendency toward Brooding were more likely to describe their situation with phrases labeled as RB, regardless of whether they were writing about an unresolved academic issue or a neutral day. These findings are similar to those of Roberts et al. (2013), who also found that trait Brooding predicted significantly more reports of ruminative thoughts in their state Rumination condition. In contrast, a trait tendency to reflect seemed to buffer against the particular high levels of brooding content found in the Rumination condition, at least by the third time participants engaged in writing about their situation, which is when SR content increased for all women in the Rumination condition. Thus, when engaged in retrieval of autobiographical episodes, trait Brooding and Reflection tendencies appeared to either augment or buffer the expression of the more negative, moody brooding content in their writing samples, respectively.

Second, to the extent that trait RRS significantly affected gaze duration, it did so only for TFDs, and only in the pre-induction baseline, before any of the state effects described above unfolded. However, somewhat counterintuitively, Brooding predicted *increased* TFDs to corrective feedback, whereas Reflection predicted *decreased* TFDs to this information in that initial block. Unlike FFDs, however, which support initial lexical and semantic processing of the answers (Reichle et al., 2003; Staub et al., 2010), interpretation of TFDs in this task are less straightforward. There are multiple reasons why women might return to the correct answer component of the competitive feedback after fixations elsewhere. For example, the longer TFDs associated with greater trait Brooding might represent multiple short gaze fixations as they go back and forth from other areas of the screen, periodically reminding themselves of the correct answer, or a more sustained return to the correct answer as internal thoughts wander to task-relevant thoughts (i.e., "Why didn't I put *that* answer?") or even task-irrelevant thoughts (e.g., Reichle et al., 2010).

In contrast, consistent with the general association of trait Reflection with the desire to "take space" from one's issues in order to proactively self-reflect (Treynor et al., 2003), the shorter TFDs associated with this particular RRS subcomponent could represent looking elsewhere on-screen (i.e., blank space, center of the screen in active preparation of the next question) once the correct answer had been initially processed. Unfortunately, the self-reports of RNTs do not provide much insight here, as they yielded state and trait rumination effects that were complex and difficult to interpret, possibly because RNTs had very low frequencies regardless of either condition or block. Whatever the reason for the opposing effects of trait Brooding and Reflection, however, the lack of interaction between trait RRS and state

condition during the post-induction period suggests that, at least in this sample, effortful attempts to complete the written Rumination and Distraction narratives may have temporarily dominated the influence of trait tendencies on overt measures of attention in this task.

CONCLUSION

Throughout college, many students will experience some type of impediment to attaining their academic goals, making them vulnerable to recurrent and self-focused thoughts as they try to minimize and resolve goal-state discrepancies. Theorists in both cognitive and clinical domains have identified a tendency to habitually ruminate in response to personal challenges and negative mood states as being integral to the development of depression, especially for women (e.g., Nolen-Hoeksema, 1987; Nolen-Hoeksema and Morrow, 1991; Watkins and Teasdale, 2001). Here, we demonstrated that even the simple process of being reminded of and writing about one of these unresolved academic situations was sufficient to at least temporarily increase otherwise mentally healthy women's negative self-focus (e.g., greater endorsement of hopelessness), compared to writing about a neutral school day. Furthermore, although the ability of the induction to elicit RB writing content was related to trait rumination, the state induction itself appeared sufficient to override any influence of these trait tendencies on behavior, and least in this female sample that was not clinically depressed.

In our academically relevant general knowledge retrieval task, we found some evidence (from planned comparisons) for consequences of the Rumination condition in the form of increased initial dwell time (FFD) on reminders of their past mistakes, coupled with even stronger evidence for the benefits of the Distraction condition for increasing initial dwell time on potentially corrective information (see also **Figure 5**). Taken together, these findings provide not only some support for predictions from attentional theories of rumination predicting an exaggerated focus on negative, self-relevant information (Koster et al., 2011; Whitmer and Gotlib, 2013) but also the view that distraction can be a beneficial method of emotion regulation in the face of failure (cf. Nolen-Hoeksema et al., 2008; McRae et al., 2010). Even though both differences amounted to fractions of a second in gaze duration, these differences could still have implications for downstream learning, given that ERP studies using a variant of this general knowledge task have shown neural differences predicting successful encoding of correct answers starting as early as 300 ms after word onset (i.e., Butterfield and Mangels, 2003).

Despite intriguing results from this first-known study testing the influence of state rumination on the differential allocation of overt attention to feedback following failures, we have already described a number of ways in which future studies could improve study sensitivity. The functional relationship between differences in dwell time and error correction in this task is also important to establish. In at least one intentional encoding experiment, longer dwell time (as indexed by both FFD and TFD metrics) predicted greater subsequent recognition of verbal stimuli (Pazzaglia et al., 2014). Taken together with our current results, it would suggest that rumination could lead to better memory for one's own mistakes whereas distraction would lead to better correction of those mistakes. We also acknowledge that our current findings are limited to a female sample, leaving open the question of how men would respond to our writing-based induction. Addressing these open issues would be valuable given the implications for developing interventions for students who, when facing significant academic difficulties, may experience states of rumination that interfere with optimal attention to learning resources needed to reach their academic goals.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the CUNY IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RW and JM conceived the research problem, method, and design, interpreted the data, and wrote the manuscript. RW ran the participants and analyzed the data. This research was conducted in partial fulfillment of the Ph.D. dissertation of RW. Both authors contributed to the article and approved the submitted version.

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Placebo Effect on Modulating Empathic Pain: Reduced Activation in Posterior Insula

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Little evidence exists to confirm whether the sensory-related neural activity that occurs when observing others in pain is highly responsive to empathy for pain. From a perspective of intervention, the present study employed placebo manipulation with a transferable paradigm to explore whether the sensory regional activation that occurs when viewing pictures of others in pain could be modulated by the placebo effect. We first performed a screening behavioral experiment for selecting placebo responders and then entered them into a functional magnetic resonance (fMRI) experiment in which they were exposed to the same conditions as before. Participants were informed that it was equally possible to be assigned to the treatment group (placebo manipulation) or the no-treatment group (control); they all, in fact, received treatment and placebo effect would be detected by comparing placebo conditions and no-placebo control condition. Each participant experienced a phase of reinforcing placebo belief with pain in self and a phase of testing transferable placebo effect on empathy for pain. As a result, we found significant activation in sensory areas, including the posterior insula (PI) and the postcentral gyrus, and in the middle cingulate cortex while participants observed pictures of others in pain. More importantly, for the first time, we observed relieved activation in the PI modulated by the placebo effect only associated with pain pictures but not with no-pain pictures. This suggests that sensory activity in the PI might be involved in the processing for empathic pain. This new approach sheds light on research and applications in clinical settings.

Keywords: empathy for pain, picture-based paradigm, posterior insula, sensory area, placebo effect

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INTRODUCTION

Individual experience tells us that, when seeing others in pain, we seem to not only understand their situations but also share their feelings of pain to some extent. The pain developed from observing actual or threatened tissue damage in another person is called empathy for pain (Zaki et al., 2016). It is believed that empathy for pain has a certain relationship with the direct experience of pain: evidence has shown that direct pain and empathic pain interact with each

other (Vachon-Presseau et al., 2011; Reicherts et al., 2013; Hurter et al., 2014), and some overlapping brain regions have been confirmed (Singer et al., 2004; Gu et al., 2010; Osborn and Derbyshire, 2010; Valentini, 2010). These findings suggest that shared psychological representations may be involved in both direct pain and empathic pain. However, empathic pain may be a double-edged sword. In the case of perceiving others' suffering, the psychoneural resonance in pain-processing areas between other and self may trigger empathic concern, but the same signals may also constitute a threat to the individual that can lead to personal distress. This distress can be costly, both physiologically and cognitively, and can eventually conflict with the observer's capacity to be of assistance to the other, therefore should be alleviated (Decety, 2011).

In line with previous studies, the experience of direct pain: (a) can be coded for pain localization, quality, and intensity, processed by both the primary and secondary somatosensory cortices (S1, S2) and by the posterior insula (PI); and (b) can be coded for both the unpleasant or distressing experience of pain and the drive to terminate such an experience, processed by the midcingulate cortex (MCC), anterior insula (AI) and the amygdala (Price et al., 1987; Treede et al., 1999; Neugebauer et al., 2004; Bernhardt and Singer, 2012; Eisenberger, 2015). Considerable studies have reported the MCC and AI, which are considered to represent similar affective characteristics to direct pain, to be activated during empathy for pain (Singer et al., 2004; Gu et al., 2010; Valentini, 2010). Although areas involved in the sensory discriminative dimension of pain (S1, S2 and the PI; Decety, 2011) were detected as well when observing others in pain (Avenanti et al., 2005; Bufalari et al., 2007; Moriguchi et al., 2007; Danziger et al., 2009; Osborn and Derbyshire, 2010), some researchers considered that they might just be a non-specific activation, based on both the perception of touch and of body parts movement (Keysers et al., 2010; Bernhardt and Singer, 2012). Thus, further experimental evidence is needed to clarify whether the activities in sensory areas are highly responsive to the perception of pain in others. which should be obtained in a stricter control experimental setting. Most previous studies have only observed the changes in brain activation in the above-mentioned areas of empathy for pain by comparing painful and non-painful conditions. Few studies observed them from the perspective of the modulation of empathic pain. With the paradigm of modulation, brain activation of empathy for pain could be observed both by comparing the control and modulation conditions for the painful condition and by comparing painful and non-painful conditions. These brain changes could be more definitively explained by the differences of empathic pain experiences in multiple conditions.

In the present study, we aimed to use placebo manipulation to modulate empathic pain, considering its advantages in several aspects. First, the placebo effect works by manipulating expectations towards a specific target. Wager et al. (2004) found that analgesic placebo manipulation could lower the activation in sensory areas only when intense shocks were delivered, whereas no changes occurred with mild shocks. Similarly, other investigators revealed that anxiolytic placebo manipulation reduced activation in regions related to emotion processing when participants observed unpleasant pictures instead of neutral pictures (Zhang et al., 2011), suggesting that the placebo effect might only work when the target was relevant for survival and human wellbeing (Wager and Atlas, 2015). Furthermore, placebo manipulation was designed to show altered brain activation between the original level and modulated level (e.g., high vs. low) of empathy for pain without changing the content of existing stimuli. In this case, there were neural components highly responsive to empathic pain and fewer unexpected neural components compared with observed altered brain activation between two different stimuli contents (e.g., pain vs. no pain). In contrast, if reduced activation in one region is observed when comparing pain with neutral pictures, one cannot judge whether the activation is closely related to pain content, or to other irrelevant components, as the contents in the two situations varied. Finally, compared with other techniques, for example, cognitive reappraisal, placebo manipulation seems to recruit fewer cognitive components applied for modulation. A previous study indicated that the placebo effect was as equally effective in reducing negative arousal as cognitive reappraisal when participants were instructed to use the two strategies to observe unpleasant pictures, without necessarily mobilizing large amounts of dorsal lateral prefrontal cortex (DLPFC) activation, which is specifically engaged in the process of cognitive appraisal (Zhang et al., 2013). These findings support the idea that placebo manipulation is a suitable tool to be applied in our study for modulating brain activation related to empathic pain.

In terms of experimental paradigms to research empathic pain, Lamm et al. (2011) have classified previous experiments on empathy for pain into picture-based paradigms (showing pictures of body parts receiving pain) and cue-based paradigms (employing abstract visual symbols to signal pain in others). The meta-analysis from the same study demonstrated that generally, the picture-based design induced much greater activation in somatosensory regions when compared to the cue-based design. Based on the cue-based paradigm, Rütgen et al. (2015) utilized placebo analgesia manipulation and tested whether seeing others in pain was also influenced by relieving pain in self. They observed decreased activation in the anterior midcingulate cortex (aMCC) as well as the AI in both the pain in self and in other conditions in the placebo group. However, they did not show whether somatosensory regional activation also reduced others' pain by the placebo analgesia effect. We argue that the failure to observe decreased somatosensory activity could be largely attributed to the application of the cue-based paradigm. For example, one research studied how cumulative experiences of social discrimination impact brain response during empathic responding, they found lack of significant dACC and aINS activation and considered this case might be explained by the nature of the task which is more dependent on cognitive perspective taking or on affective sharing (Fourie et al., 2019).

To overcome these problems, first, in order to elicit reliable activation of sensory areas we applied the picture-based paradigm in this study. To get a robust placebo effect on empathy for pain, we referred to the indirect placebo effect paradigm proposed by Zhang et al. (2011), in which the placebo belief

was configured in direct pain first and then transferred its effect to negative emotion. The results demonstrated significantly increased activation with placebo treatment in the subgenual anterior cingulate cortex (sgACC)/orbital frontal cortex (OFC), a region which has been shown to engage in placebo anticipation (Wager et al., 2004), and decreased activation in the amygdala, insula, and dACC when viewing unpleasant pictures (Zhang et al., 2013). Based on this idea, we developed our experiment by first forming the placebo belief in direct pain and then transferring this effect to empathy for pain. Several additional strategies were also employed in the placebo effect design, including a cover story of a "random-controlled" assignment to improve the reliability of the experiment, a within-group design to minimize the influence of individual differences, a two-round training to reinforce placebo belief, and a former behavioral experiment to screen out placebo responders for the functional magnetic resonance (fMRI) experiment. Three questions are addressed in this article: (1) whether significant activation in sensory areas (e.g., S1, S2 and the PI) could be observed in the network of empathy for pain? (2) If the answer is yes, whether the induced sensory regional activation when seeing others in pain could be alleviated by the placebo effect? And (3) whether sgACC and adjacent OFC activations would take part in placebo modulation?

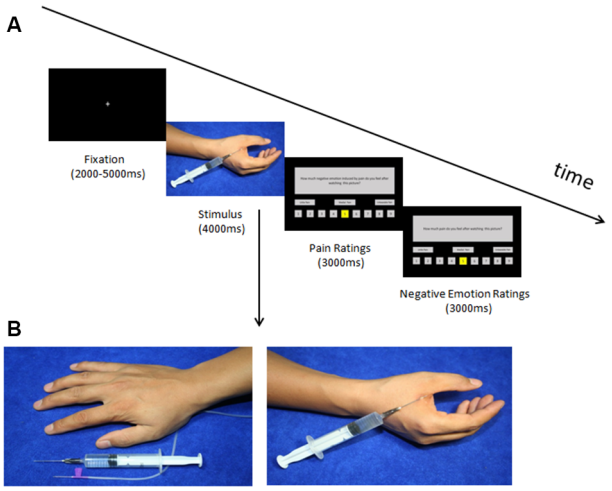

FIGURE 1 | (A) Timeline of the trials in the test phase and **(B)** two sample pictures. **(A)** Trial structure of the test phase. A fixation point appeared followed by the picture; after the picture disappeared the participants rated the pain intensity and negative emotion induced by watching the picture (within 3 s each). **(B)** In the no-pain condition, two needles (injection and intravenous) were placed next to the hands, whereas, in the pain condition, a needle was inserted into the hands.

MATERIALS AND METHODS

Participants

The sample size was calculated by simulation based on R (R Development Core Team, 2011). RStudio[1] was used to run the custom R script to perform the analysis. In order to estimate the effect size, we referred to a previous study in our lab that had a similar design (Zhang et al., 2011). Since the value of Cohen's *d* in that study is quite large (bigger than 1.5), we set Cohen's *d* value as 0.8, which is still large but more reasonable. The within-subject correlation was set as 0.7, according to results of the same study. Based on the estimated parameters above, we generated 3,000 bootstrap samples and the result showed that to reach 80% power we needed at least a sample size of 17.

First, we conducted a behavioral experiment to select the placebo responders as the final individuals participating in the fMRI experiment. Evidence from previous research indicates that the placebo effect is relatively reproducible when the contexts remain consistent (Whalley et al., 2008; Morton et al., 2009). Forty-eight participants (female = 33, mean age = 23.10 years, standard deviation = 2.34) were enrolled and informed that there was a chance they would enter a subsequent fMRI experiment 1 month later. Ultimately, 24 participants were identified for the fMRI experiment (female = 18, mean age = 22.88 years, *SD* = 1.96). This study was approved by the ethics committee of the Chinese Academy of Science; prior written informed consent was obtained from all participants. None of the participants had a history of neurological, psychiatric, or major medical disorders.

[1]https://www.rstudio.com/

Materials

All pain stimuli used in both the behavioral and fMRI experiments were delivered by a CO_2 laser stimulator (Precise Laser-DM 300, China) with a 2.5 mm spot diameter and a 100 ms pulse duration. Stimulation was applied to the dorsum of the right hand within a 3 cm × 3 cm square, with each stimulus applied to a different spot to avoid habituation. The distance from the laser probe to the skin surface was 9 cm. Participants were exposed to individually calibrated high or low painful stimulation, in which the output energy was kept between 200 and 350 mJ to prevent skin damage. The average intensity for high and low painful stimuli was respectively 317.27 ± 23.05 mJ and 223.71 ± 17.84 mJ.

Before the behavioral experiment, we conducted a picture validation. Twenty-five participants were recruited to rate 72 digital colored photographs taken by our lab members, in which someone's body parts were shown either in painful or non-painful situations. In the pain pictures, one or two needles were injected into a person's hand or foot (e.g., in the dorsum or palm of the hand); whereas in the control pictures, the needle was placed next to the hand or foot, without penetrating the skin (see **Figure 1**). All the participants were instructed to rate the degree of pain elicited in each picture on a scale from 0 to 100 (0 = non-painful, 100 = unbearably painful).

Thirty-six pictures were selected for the behavioral experiment, consisting of 18 pain pictures which got top pain scores (mean = 59.26, *SD* = 5.04) aimed to induce participants' empathy for pain and 18 no-pain pictures which got bottom pain scores (mean = 12.64, *SD* = 1.91) were used as a baseline. In addition, 96 pictures which were adapted from the 36 pictures in the behavioral experiment by reversal and repetition were applied in the fMRI study, including 36 original pictures and

36 reversed ones by them, six repeated pictures with topmost scores of pain pictures and six reversed ones by them, and six repeated pictures with bottommost scores of no-pain pictures and six reversed ones by them. The newly formed pictures contained 48 pain pictures (mean = 59.60, *SD* = 4.75) and 48 no-pain pictures (mean = 12.39, *SD* = 1.81).

Procedures

The procedure of the behavioral experiment, which focused on selecting placebo responders, was quite similar to the fMRI experiment. Prior to the behavioral experiment, all 48 participants were informed that they would participate in a double-blind clinical study, aiming at examining whether a new type of magnetic equipment could alleviate pain directed to the self and others. The working principle of the equipment was explained to be in accordance with the acupuncture theory of traditional Chinese medicine, that is, when the magnetic equipment worked on distinct acupoints, corresponding treatment effects would exert and act on the targeted body parts or mental problems. The working state (on and off) of the equipment was described to be controlled by an internal program compiled in advance. As a result, it was hard for participants to infer the working state of the equipment externally. The so-called treatment equipment was, in fact, a sham, and no effect was delivered at all. The experiment consisted of three main phases: a "calibration procedure" with pain stimuli, a "conditioning phase" to build up the placebo belief, and a "test phase" to measure the placebo effect on alleviating empathy for pain.

In the calibration phase, we tested the pain threshold individually to determine the personalized stimulus intensity. Participants were asked to rate those stimuli in an ascending as well as in a descending order, according to a 9-point scale ranging from 1 = "perceptible, but non-painful sensation" to 9 = "unbearable pain" and 5 = "moderate pain." Finally, three stimuli consistently rated as 6–8 (painful, but bearable) and three stimuli consistently rated as 1–3 (perceptible, but non-painful sensation) were selected respectively as pain and no-pain stimuli.

The conditioning manipulation phase was conducted with "random-controlled" instructions. All participants were informed that they would be randomly allocated to either the treatment group or the control group. However, in truth, all participants were assigned to the treatment group and experienced treatment (placebo manipulation). Hence, all the participants completed the placebo and no-placebo control conditions in a within-group design and the placebo effect would be detected by comparing placebo condition and no-placebo control condition. That is, in this study, each participant would experience placebo condition and no-placebo control condition in sequence. Placebo condition was the "treatment" situation in which magnetic equipment (i.e., the placebo adopted in this study) was "on" and no-placebo control condition was the "no treatment" situation in which magnetic equipment was "off." Here, we adopted an innovative approach including two steps to help each participant build up a reliable placebo belief in the treatment. First, all participants were informed they would be given a "real" treatment experience of direct pain. An electrode of the magnetic equipment was linked to their Hegu acupoints (i.e., on the dorsum of their hands) which acupoint represents an analgesic effect, according to traditional Chinese medicine. Participants were then informed they would receive two blocks of stimuli (five stimuli for each block) that they rated as painful in the calibration phase. Since the treatment equipment worked only during one of the blocks, participants felt pain alleviation under the treatment condition, whereas they experienced increased pain under the no-treatment condition. By comparing the different experiences on receiving treatment or not, participants would learn by themselves how it felt when there was an analgesic treatment. The actual manipulation of this step was that in one block while the equipment was "on" we delivered stimuli individually rated as no pain, whereas in the other block while the equipment was "off" we delivered stimuli rated as pain, for each subject. This step ensured that participants could learn the kind of analgesic experience during placebo treatment. The purpose of the second step was to help participants believe that they were allocated to the treatment group, by training. Participants were informed that they would receive another 10 blocks of pain stimuli (five stimuli of each) and were asked to judge which group (treatment or no treatment) they belonged to. Participants were instructed to make judgments by their own unique experiences on receiving treatment or no. The actual manipulation in this step was that for each participant we delivered five blocks of no-pain stimuli (placebo manipulation, abbreviated P) and five blocks of pain stimuli (no placebo control, abbreviated C), the 10 blocks were presented either in the order P-C-P-C-P-C-P-C-P-C or C-P-C-P-C-P-C-P-C-P. One order was applied to half participants and the other order was applied to the other half participants in a counterbalanced way. Following the learning of the analgesic experience induced by treatment in the first step, and the adequate repetitive learning of 10 blocks in the second step, as we expected, all participants judged they were in the treatment group and had experienced a real analgesic treatment.

Compared to most placebo effect studies, in which participants were directly notified that they would receive the treatment, the special "random-controlled" verbal instructions employed in our study have at least two advantages: to begin with, as the participants primarily believed to be taking part in a randomized-controlled study, their placebo belief was built based on the repetitive learning about their experience of "treatment" rather than the direct notification from the investigator. In this way, they would naturally believe that they were receiving analgesic treatment and were less likely to suspect the validity of the treatment. In addition, since participants were not directly informed whether they would receive the treatment or not, our design, to some extent, could avoid some ethical issues induced by open verbal deception existing in placebo clinical research.

In the test phase, we aimed at examining whether the placebo belief built in the direct pain condition could transfer to situations when seeing others in pain. Beforehand, we

moved the electrode from the Hegu acupoint to the Quchi acupoint. Participants were told that the treatment on this acupoint could relieve their feelings of pain and reduce negative emotions arising when seeing others in pain. Thirty-six pictures of pain and non-pain were divided into six blocks, each block consisted of three pain and three no-pain pictures. The average ratings of pain intensity between each block were already controlled to be statistically equal. The order of the experimental conditions for each individual was the same as in the second step of the conditioning phase. After each picture was presented, participants were required to rate for pain intensity (1–9, 1–no pain, 9–unbearable pain) and negative emotion (1–9, 1–no negative emotion, 9–unbearable negative emotion) induced by seeing others in that situation. At the end of the behavioral experiment, we interviewed each of the participants and asked whether they considered the treatment effective. Finally, 24 placebo responders were selected in terms of their performance in the behavioral experiment and were recalled for the fMRI Experiment 1 month later. The procedure of the fMRI experiment was relatively identical to the behavioral experiment, except for the fact that the test phase of empathy for pain was conducted in the scanner. In addition, in the test phase, the number of pictures was increased to 96 and split into eight blocks, each containing six pain and six no-pain pictures. The pictures are visually presented to the participants by using an MRI-compatible projection system. One trial of the fMRI experiment is shown in **Figure 1**.

Image Acquisition

Data were collected on a GE 3.0T Trio MRI scanner at the Chinese Academy of Sciences, Institute of Psychology. High-resolution T1-weighted structural images were acquired with a 3D gradient–echo pulse sequence (TR = 6.9 ms, TE = 3 ms, FA = 8°, FOV = 256 mm × 256 mm, matrix size = 256 × 256, slice thickness = 1 mm, Voxel size = 1.0 mm × 1.0 mm × 1.0 mm), Functional images were acquired using a T2*-weighted echoplanar imaging (EPI) sequence with 37 transverse slices covering the whole brain (TR = 2,000 ms, TE = 30 ms, FA = 90°, FOV = 220 mm × 220 mm, matrix size = 64 × 64, slice thickness = 3.5 mm, interslice gap = 0.5 mm, Voxel size = 3.0 mm × 3.0 mm × 4.0 mm).

fMRI Data Processing and Analyses

All pre-processing and statistical analysis of the images was performed using Statistical Parametric Mapping (SPM8[2]). In the pre-processing, the first five functional EPI volumes were discarded to allow for the T1 equilibration. Subsequently, the remaining data were slice time corrected. Head motion correction was applied and individual structural images (T1-weighted MPRAGE) were co-registered to the mean functional image using a rigid-body transformation. Functional images were normalized into a standard anatomical space (3 × 3 × 3 mm isotropic vexes) based on the Montreal Neurological Institute (MNI) template. The resulting fMRI data were then spatially smoothed with an 8 mm FWHM Gaussian isotropic kernel. The imaging data of one participant, who met the exclusion criteria of 2.0 mm and 2.0° in maximum head motion, was deleted.

In the first-level analysis, to assess the neural activity corresponding to the processing of pain and no pain pictures under placebo and no-placebo control conditions, four separate regressors (PP, watching pain pictures in the placebo condition; PN, watching no pain pictures in the placebo condition; CP, watching pain pictures in the no-placebo control condition; CN, watching no pain pictures in the no-placebo control condition) were created for model specification. These regressors were time-locked to the onset of picture presentation and then convolved with a canonical hemodynamic function. Residual effects of head motion were corrected by including the six estimated motion parameters of each participant, which worked as regressors of no interest in the design matrix. A high-pass filter with a cut off frequency of 1/128 Hz was used to adjust for low-frequency components, and serial correlations were accounted for with an autoregressive AR (1) model.

In the second-level analysis, the relevant parameter contrasts generated on an individual level were submitted to a group analysis by using a random effect model. A 2 × 2 full factorial analysis of variance (ANOVA) was conducted with data from 23 participants (1 participant was excluded as a result of reaching the criteria of 2.0 mm and 2.0° max head motion, the behavioral data were deleted as well). A repeated-measures ANOVA, with two within-participants factors: CONDITION (placebo vs. no-placebo control) and PICTURE (painful vs. non-painful,) were applied to assess main effects and interactions. For specific regions of interest (ROIs) of insula, postcentral and orbital gyri, we applied a small-volume correction (SVC) on these ROIs with an anatomical mask according to the AAL template (Tzourio-Mazoyer et al., 2002) provided by WFU PickAtlas software (Version 3.0[3]). For the whole-brain analyses, results with a threshold set at $p < 0.001$ (voxel level, uncorrected), and two or more contiguous voxels were reported. For the SVC analyses, the threshold was set at $p < 0.001$ (voxel level, uncorrected, two or more contiguous voxels). All fMRI results were not corrected by FDR and FWE.

Behavioral Measures Analyses

Participants' ratings on both pain intensity and negative emotion of empathy for pain induced by watching the pictures were analyzed using SPSS 18.0 (IBM software). In the behavioral experiment, paired sample *t*-tests were performed to selected placebo responders. To explore whether the placebo effect on the selected placebo responders was reproducible and consistent, we used two linear regression analyses to detect whether the ratings of placebo responders from the prior behavioral experiment could predict those of the latter fMRI experiment. In the fMRI experiment, two repeated measure ANOVAs were conducted to detect if the placebo effect worked when watching the pictures with two within-subject factors, namely CONDITION (placebo vs. no-placebo control) and PICTURE (pain vs. no pain).

[2]http://www.fil.ion.ucl.ac.uk/spm

[3]https://www.nitrc.org/projects/wfu_pickatlas/

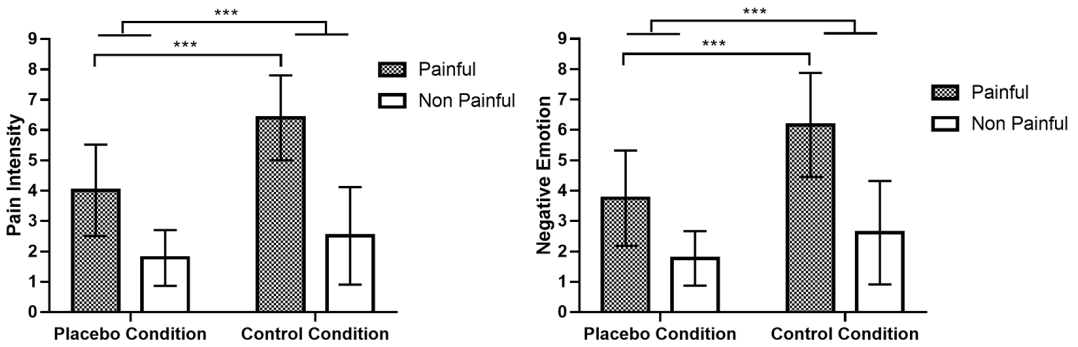

FIGURE 2 | Ratings of pain intensity and negative emotion induced by pain and no pain pictures. Comparing placebo and no-placebo control conditions, pain pictures induced higher ratings of pain intensity and negative emotion in the no-placebo control condition compared with the placebo condition ($p < 0.001$), and the difference between pain and no pain pictures was also much higher in the no-placebo control condition than in the placebo condition ($p < 0.001$). ***$p < 0.001$.

Subsequently, a simple effect test was performed to explain the interaction effects.

RESULTS

Behavioral Results

In the behavioral experiment for selecting placebo responders, 24 participants showed a significant placebo effect, in which they reported much higher ratings both on feelings of pain intensity (PI) and on negative emotion induced by seeing others in pain (NE) in the no-placebo control condition than in the placebo condition, $t_{(23)} = 5.072$, $p < 0.001$, Cohen's $d = 1.035$, 95% confidence interval (CI) for Cohen's $d = (0.529, 1.527)$, and $t_{(23)} = 6.664$, $p < 0.001$, Cohen's $d = 1.360$, 95% CI for Cohen's $d = (0.793, 1.912)$, respectively. Of these, no one reported the treatment as ineffective. Regression analyses found that, for the selected placebo responders, ratings of PI under the placebo condition (pain vs. no pain) from the behavioral experiment could significantly predict the PI ratings in the fMRI experiment ($F_{(1,22)} = 19.210$, $\beta = 0.691$, $p < 0.001$, adjusted $R^2 = 0.453$), as well as the rating of NE under the placebo condition (pain vs. no pain) in the behavioral experiment. The predictability was also significant ($F_{(1,22)} = 12.951$, $\beta = 0.618$, $p = 0.002$, adjusted $R^2 = 0.352$).

In the test phase of the fMRI experiment, there was a significant main effect of CONDITION on ratings of PI, $F_{(1,22)} = 43.606$, $p < 0.001$, $\eta^2 = 0.665$, 90% CI for $\eta^2 = (0.428–0.766)$, as well as on ratings of NE, $F_{(1,22)} = 41.191$, $p < 0.001$, $\eta^2 = 0.652$, 90% CI for $\eta^2 = (0.410–0.757)$. Similarly, the main effect of PICTURE was significant on ratings of PI, $F_{(1,22)} = 125.508$, $p < 0.001$, $\eta^2 = 0.851$, 90% CI for $\eta^2 = (0.723–0.896)$, and on ratings of NE ($F_{(1,22)} = 95.596$, $p < 0.001$, $\eta^2 = 0.813$, 90% CI for $\eta^2 = (0.658–0.869)$. The interaction effect between CONDITION and PICTURE was significant both for ratings of PI, $F_{(1,22)} = 29.856$, $p < 0.001$, $\eta^2 = 0.576$, 90% CI for $\eta^2 = (0.311–0.703)$, and for ratings of NE, $F_{(1,22)} = 29.944$, $p < 0.001$, $\eta^2 = 0.576$, 90% CI for $\eta^2 = (0.312–0.704)$. Simple effect analyses revealed that for both PI and NE ratings, the difference between pain and no pain pictures in the no-placebo control condition was significantly smaller than that in the placebo condition, $t_{(22)} = 5.457$, $p < 0.001$, Cohen's $d = 1.138$, 95% CI for Cohen's $d = (0.602, 1.658)$, and $t_{(22)} = 5.478$, $p < 0.001$, Cohen's $d = 1.141$, 95% CI for Cohen's $d = (0.606, 1.664)$, respectively. The results are illustrated in **Figure 2**.

fMRI Results

Brain Network When Seeing Others in Pain

To identify the neural network of empathic pain in this experiment, we contrasted the pain pictures with the no pain pictures in the no-placebo control condition (CP-CN). Significant brain activity was detected in the postcentral gyrus, PI and MCC (see **Figure 3** and **Table 1**).

Brain Regions Showing Attenuated Activity in Empathy for Pain by the Placebo Effect

To investigate whether the brain network of empathy for pain could be relieved by the placebo effect, we calculated the interaction between CONDITION and PICTURE [(CP-PP) − (CN-PN)]. Significant activation was observed in the postcentral gyrus, the PI, and the superior temporal gyrus (see **Figure 3** and **Table 1**). In addition, we conducted a contrast test to explore whether the placebo effect also worked on no pain pictures (CN-PN) and no significant activation was found.

Activity in the Modulation Network of the Placebo Effect

To determine whether the modulation network of the placebo effect was activated, we tested the main effect of the placebo effect [(PP+PN) − (CP+CN)]. Our results showed significant activity in the OFC; see **Figure 4** and **Table 1**.

Correlation Analysis

It was found that there was a significant positive correlation between changes in PI activation and changes in pain evaluation between pain and no-pain condition under the placebo modulation, brain activity was predicted by pain intensity ratings, $\beta = 0.357$, $p = 0.016$; no significant correlation in other contrasts was found.

TABLE 1 | Activated regions in the contrast of (CP-CN), (CP-CN) − (PP-PN) and (PP+PN) − (CP+CN).

Brain regions	BA	KE	T	p(unc.)	MNI		
					x	*y*	*z*
CP-CN							
Right inferior parietal lobule	40	11	4.36	0.001	69	−33	27
Left Postcentral Gyrus	5	9	3.73	0.001	−36	−45	63
Left Postcentral Gyrus			3.34	0.001	−24	−45	69
Left Superior Temporal Gyrus	38	4	3.63	0.001	−45	18	−33
Left Insula	13	8	3.41	0.001	−36	−12	9
Left Middle Cingulate Gyrus	24/31	2	3.40	0.001	−15	−12	48
Left Inferior Parietal Lobule	40	4	3.32	0.001	−63	−36	24
*Left Postcentral Gyrus (cluster level, p = 0.092)		6	3.73	0.001	−36	−45	63
*Left Insula (cluster level, p = 0.049)		8	3.41	0.001	−36	−12	9
(CP-CN) − (PP-PN)							
Right Superior Temporal Gyrus	22	12	3.96	0.001	66	−48	18
Left Superior Temporal Gyrus	41	8	3.54	0.001	−39	−39	9
Left Superior Temporal Gyrus		2	3.52	0.001	−45	18	−33
Left Insula		3	3.35	0.001	−39	−15	9
*Left Insula (cluster level, p = 0.081)		2	3.35	0.001	−39	−15	9
(PP+PN) − (CP+CN)							
Left Inferior Frontal Gyrus_Orbitals	47	39	3.99	0.001	−36	18	−15
Left Inferior Frontal Gyrus_Orbitals			3.47	0.001	−33	27	−12
Left Inferior Frontal Gyrus_Orbitals			3.46	0.001	−39	33	−6
Left Superior Temporal Gyrus	21/38	13	3.55	0.001	−48	3	−12
*Left Inferior Frontal Gyrus_Orbitals (cluster level, p = 0.015)	25		3.97	0.001	−36	18	−18

*Notes: for the whole-brain analyses, the threshold was set at $p < 0.001$ (voxel level, uncorrected), and two or more contiguous voxels. For the SVC analyses (noted by *), the threshold was set at $p < 0.001$ (voxel level, uncorrected, two or more contiguous voxels). CP-CN: watching pain pictures vs. watching no pain pictures, in the no-placebo control condition; (CP-PP)-(CN-PN): (no-placebo control condition vs. placebo condition, when watching pain pictures) − (no-placebo control condition vs. placebo condition, when watching no pain pictures); (PP+PN) − (CP+CN): placebo condition vs. no-placebo control condition, regardless of pain or no pain pictures.*

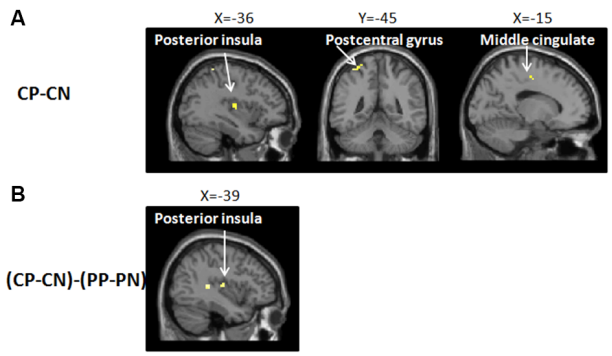

FIGURE 3 | Brain network of **(A)** the main effect in the empathy for pain with CP-CN (i.e., watching pain pictures vs. watching no pain pictures, in the no-placebo control condition). In the no-placebo control condition, some brain regions, including the left postcentral gyrus (−36, −45, 63), left posterior insula (PI; −36, −12, 9), and midcingulate cortex (MCC; −15, −12, 48), showed greater activation in the pain pictures compared to the no pain pictures, p (unc.) < 0.001, two continuous or more voxels; **(B)** the interaction with (CP-PP)-(CN-PN) [i.e., (no-placebo control condition vs. placebo condition, when watching pain pictures) − (no-placebo control condition vs. placebo condition, when watching no pain pictures)]. The activation of the PI (−39, −15, 9) produced a greater attenuation for pain pictures vs. no pain pictures when comparing the no-placebo control condition and the placebo condition, p (unc.) < 0.001, two continuous or more voxels.

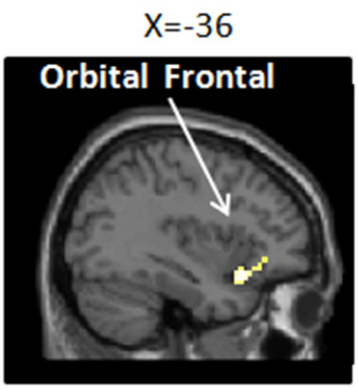

FIGURE 4 | Brain network of the placebo effect of (PP+PN) − (CP+CN; i.e., placebo condition vs. no-placebo control condition, regardless of pain or no pain pictures.). Enhanced activation in the placebo treatment was found in the left inferior orbital frontal gyrus (−36, 18, −15), p (unc.) < 0.001, two continuous or more voxels.

DISCUSSION

The current study revealed the sensory regional activation which occurred in S1, S2, and the PI while watching others in pain, and for the first time, decreased activation of sensory areas (the PI) modulated by the placebo effect was observed in the neural network of empathy for pain.

Some typical regions of direct pain were found activated when observing others in pain, including the postcentral gyrus (the somatosensory cortex, S1, and S2), the PI and the MCC. In previous studies, increased activation in the somatosensory cortex and in the PI has been repeatedly reported and are widely believed to represent the sensory component of pain processing (Bushnell et al., 1999; Hofbauer et al., 2001; Bornhövd et al.,

2002; Rainville, 2002). S1 and S2 are consistently considered as core regions of somatic perception and discrimination, through coding for location, strength, and quality of the stimuli. Specifically, S1 palys a role of identifying the discrimination of the stimuli and S2 is mainly responsible for the integration of the sensation messages (Treede et al., 1999). The PI connects reciprocally with the secondary somatosensory cortex and receives projections from the ventromedial nucleus (posterior part) of the thalamus that are highly specialized to convey information such as pain and temperature (Craig et al., 2000). Researchers considered that the activation in the PI represented a kind of sensory-discriminative characteristic (Brooks et al., 2002; Bingel et al., 2003). Additionally, we found significant MCC activities during empathy for pain. In terms of previous studies, the activation in this region represented the affective component of empathy (Singer et al., 2004; Jackson et al., 2006). In fact, it is believed that ACC/MCC activation was not only related with observing others in pain but also with other emotional situations, such as social exclusion (Masten et al., 2011) and disgust (Wicker et al., 2003; Jabbi et al., 2007). These findings suggest that ACC/MCC might engage in the general affective process of empathy for pain.

More importantly, for the first time, we observed decreased activation in the PI, modulated by placebo manipulation, when observing others in pain. Furthermore, this reduction merely occurred with the pain pictures instead of no pain pictures. The results are in line with previous findings in which placebo analgesia could only modulate thermal pain stimuli/negative emotion pictures representing threat/danger signals and not warm stimuli/neutral pictures (Wager et al., 2004; Zhang et al., 2011). In addition, the analysis showed that in the PI the relieved brain activation by the placebo effect was almost overlapped with the activation discovered when observing others in pain without placebo manipulation. Some evidence suggests that the activation found in the PI, induced by pain stimuli, might be highly responsive to the experience of pain. In one study, researchers applied continuously varied heat pain on subjects' right leg and recorded their brain activation, the results showed that the only significant positive correlation between the absolute cerebral blood flow (CBF) changes and pain ratings within subjects was observed in the dorsal PI (Segerdahl et al., 2015). In another study, patients with epilepsy were given increasing thermal energy and the evoked potentials were recorded with electrodes implanted in both SII and the PI. The result showed that SII responses were more sensitive to the variation of the intensity of stimuli during the no pain level and tended to show a ceiling effect for higher pain intensities, while the PI was not able to detect innocuous stimuli but reliably tracked the dynamic changes of stimuli intensity at pain levels (Frot et al., 2006). Based on these findings, we think, this study provided more powerful evidence that the activation in sensory area, at least in the PI could be highly responsive to empathic pain in the framework of a picture-based paradigm, by using placebo manipulation to modulate empathic pain, compared to other fMRI studies that also reported sensory regional activation during empathy for pain (Jackson et al., 2006; Osborn and Derbyshire, 2010; Lamm et al., 2011).

We observed decreased subjective ratings related to empathic pain and increased activation in a restricted area to be recruited in the OFC under the placebo condition. Previous studies verified that that placebo effect could at least last for several days after the first positive experience of analgesia (Colloca and Benedetti, 2006). For those who had prior experience of the placebo effect, when the context information remains consistent, their responses are considered to be relatively reproducible (Whalley et al., 2008; Morton et al., 2009). Furthermore, repeated acquisition of conditioning enhanced the consequences of consolidation and reinforcement of the placebo belief built upon the prior experience (Benedetti et al., 1998; Colloca and Benedetti, 2006). In our study, we selected placebo responders based on their performance in a prior experiment and later examined the placebo effect in a relatively similar situation, regression analyses demonstrated that participants' placebo performance from the prior experiment could significantly predict their later performance in the fMRI experiment to a high extent. This result demonstrates the performance of the placebo responders from the two experiments was relatively consistent. Additionally, our imaging findings in OFC were in concordance with previous research (Wager et al., 2004; Zhang et al., 2011, 2013). Evidence showed that the increased activity in OFC triggered by the placebo effect was highly related to the endogenous mu-opioid release, which greatly contributed to relieving pain perception and negative emotions (Benedetti et al., 2005; Zubieta et al., 2005; Wager et al., 2007). These findings indicated that we successfully built up the placebo effect in our research. Finally, there is some clinical implication in alleviating empathic pain by placebo modulation. Empathy may facilitate caring behaviors of medical workers but at the same time can exhaust their emotional and cognitive resources and then interfere with their ability to care for the patients (Decety, 2011; Decety et al., 2016). A learning-based placebo effect within a framework of conditional reinforcement and cognition-based reappraisal has a common anxiety-relieving effect. The learning-based placebo modulation only depends on a small recruitment of subgenual cingulate/inferior-OFC, whereas the cognition-based reappraisal usually has an enhanced mobilization of lateral prefrontal cortex resources to meet the individual's cognitive regulation needs (Zhang et al., 2011, 2013). Therefore, if placebo manipulation carried by certain kind of equipment or drug could lead medical workers to believe it can reduce their negative arousal when seeing other in pain, then the effect of analgesic or anxiolytic effect would occur without mobilizing more cognitive resources of the dorsal lateral prefrontal cortex.

We observed significant MCC activation during empathy for pain, while failed to find decreased activities in this area under placebo modulation. On one hand, the lack of decreased activation in MCC could be largely explained by the picture-based paradigm we used. A meta-analytic study has announced that compared with the cue-based paradigm, the picture-based paradigm induced much more somatosensory regional activation other than affective related activation (Lamm et al., 2011). On the other hand, this result may be partly attributed to

the decreased salience of the stimuli following the two-round experiments. Previous studies have illustrated that salience was highly related to the emotional and affective characteristics of the stimuli, which induced significant activation mainly in the ACC/MCC and AI (Downar et al., 2002; Legrain et al., 2011). As a result, compared with the sensory regional activation in the PI, activation in MCC might be much more susceptible to be affected by the significantly decreased salience of stimuli. The general decreased activation in MCC made it hard to detect whether placebo manipulation could modulate activation in MCC. Considering this evidence, here the lack of findings about altered activation in MCC being modulated by the placebo effect does not necessarily mean that MCC activity was not engaged during empathy for pain. In the future we will consider the salience of the stimuli and design an independent experiment to test whether MCC can be modulated by the transferable placebo effect.

It is worth noting the shared neural representations in the pain matrix may not be specific to the sensory qualities of pain, but instead might be associated with more general survival mechanisms such as aversion and withdrawal when exposed to danger and threat (Decety and Michalska, 2010; Decety, 2011; Decety et al., 2012). On the one hand, one study found both pain and rejection activated different multivariate patterns within their overlapped areas, indicating separable neural representations that were co-localized at the gross anatomical level (Woo et al., 2014); The critical agent of discrimination may be driven by the differences in specific activity patterns in regions activated by both physical and social pain, rather than the level of activation of a specific region (Wager et al., 2013). On the other hand, it was found that the fMRI responses triggered by nociceptive stimuli could be largely explained by multimodal neural activities (Mouraux et al., 2011); these multimodal responses are likely to reflect brain processes related to the process of detecting salient sensory events, including the most salient events of nociceptive stimuli, regardless of the sensory modality through which these events are conveyed (Legrain et al., 2011). Even so, there is a likely difference in the neural network between the threat/pain responses and orientation responses to general salient events. If the threat/pain-related responses have protective significance for survival, then they are hard to habituation; In contrast, the general salient stimuli without danger could soon get accustomed to. In the future, we may detect the neural network highly responsive to threat/pain stimuli with a repetition stimuli paradigm (Kim, 2017), through observing the activations in what brain regions by pain/empathy pain stimuli would be significantly reduced under multiple stimulus repetition and in what regions can survive.

To summarize, one contribution of this study is that we used a novel experimental design that could more definitely detect sensory regional brain activation in the process of empathy for pain. Compared with previous experimental designs, for the first time, we successfully detected alteration of the activation of sensory regions during empathy for pain by applying placebo modulation and a picture-based paradigm. This new experiment design is implicated for future research that focuses on the sensory regional activation, instead of affective ones, during empathy for pain. It is also promising to be generalized to other research topics in empathy, for example, empathy for "social pain" (social isolation). In addition, the strategy of combining the "random-controlled" instruction with enhanced placebo belief by conditioning shed some light on clinical research and interventions which want to use placebo manipulation to relieve pain as well as some mental disorders, such as Parkinson's and depression (Andrews, 2001; de la Fuente-Fernández et al., 2001; Mayberg et al., 2002; Benedetti et al., 2004). Even though abundant evidence has already shown that the placebo effect can produce concrete treatment effects on patients apart from the actual medical treatment (de la Fuente-Fernández et al., 2001; Fountoulakis and Möller, 2011; Benedetti, 2014), it is still quite controversial to apply the placebo modulation as a kind of treatment into a clinical situation. One dilemma is that the deceptive instructions had strong placebo power but does not fit the clinical ethical standards. This study revealed a significant placebo effect by avoiding directly deceptive instructions (e.g., the effective treatment might be applied to you or not) and combining corresponding reinforcement conditions (e.g., if you felt pain relieved then you were supposed to belong to the treatment group).

One limitation of the study is that we did not measure other factors affecting placebo effect, such as expectation level and personality traits, which are both very important (Frisaldi et al., 2018). For example, expectations would predict placebo effect independently of personality factors and highly correlate to placebo effects (Corsi and Colloca, 2017; Frisaldi et al., 2017, 2018). Participants' performance on placebo manipulation was found to be correlated with some personality traits, such as suggestibility, acquiescence, dispositional optimism, and resiliency (Corsi and Colloca, 2017; Frisaldi et al., 2018). We will add these measurements in future research in order to pursue multi-faceted evidence on the reliability of the placebo effect and placebo responders. In addition, the brain signals were not recorded when participants were perceiving pain in self and in others in the behavioral experiment, due to the incompatibility of the pain stimulator and the MRI scanner. If activation of the sensory area is relieved in both sessions, then such evidence will be more persuasive regarding whether this activation is pain essential and is shared by empathy for pain. Furthermore, we found significant activation in the MCC during empathy for pain while failing to detect reduced activation in the same region by placebo manipulation. One reason may be that repeated training in the behavioral and fMRI experiments reduced participants' sensitivity to pain pictures. In future studies we will scan brain activities not only in the empathy for pain phase but also during pain in self-phase in the both behavioral and fMRI experiments, thus we may observe whether activation of the sensory area will be relieved in both sessions and whether neural activities such as MCC will be decreased due to repeated trainings. Finally, the present study included more females participated in the task which is twice as many as males both in behavioral experiments and in the fMRI experiment, so it might bring the effect of gender bias. In the future study, we

would employ an equal number of females and males to exclude gender effect.

CONCLUSIONS

In our study, we observed a significant activation in both the sensory areas (the postcentral gyrus and the PI) and MCC during empathy for pain. More importantly, for the first time, we found that placebo modulation could relieve sensory activity in the PI during empathy for pain, which allows for a powerful inference that the reduced activities of the PI sensory areas induced by the placebo effect can be attributed to the empathy for pain itself. By using placebo modulation, this study provides a relatively new approach for future research that focuses on the sensory components during empathy for pain.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to WZ, zhangwc@psych.ac.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Chinese Academy of Science. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WZ, JL, and JZ contributed to the conception and study design. YZ and RL organized the database and wrote sections of the manuscript. YZ performed the statistical analysis. YZ and WZ wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Modulation of Emotional Conflict Processing by High-Definition Transcranial Direct Current Stimulation (HD-TDCS)

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Cognitive control is characterized by selective attention to relevant stimuli while irrelevant, distracting stimuli are inhibited. While the classical color-word Stroop task was implemented to investigate the processes of cognitive control, a variant of it—the face-word Stroop task—allows for directly investigating processes of emotional conflict control. It is thought that the prefrontal cortex (PFC) is especially involved in processes of cognitive control, while the rostral cingulate is mainly associated with the resolution of emotional conflict. In recent years, the role of the dorsolateral PFC (DLPFC) during the performance of the classical Stroop was investigated by means of transcranial direct current stimulation (tDCS) with divergent results. However, investigations to the causal role of the DLPFC during emotional conflict processing are rare. For this purpose, we used a combined high-definition tDCS (HD-tDCS)/electroencephalogram (EEG) setting to investigate the impact of anodal stimulation of the left DLPFC on behavioral and electrophysiological responses during an emotional face-word Stroop task. In two separate sessions, participants (n = 18) received either sham or anodal HD-tdc stimulation while responding to the emotional expression of the face and ignoring the word. Our results show that anodal stimulation of the left DLPFC increases the behavioral interference effect, that is, the already decelerated reaction times (RTs) to incongruent trials further increase while RTs to congruent trials remain largely unaffected. Furthermore, the stimulation modulates brain response to emotional facial expressions during the face-word Stroop generally—independent of the valence of the emotional expression and the congruency of the combined face-word presentation, the N170 decreases during anodal stimulation. These results reveal that the left DLPFC has a causal role in emotional conflict processing during a face-word Stroop.

Keywords: emotional control, tDCS—transcranial direct current stimulation, HD-tDCS, DLPFC (dorsolateral prefrontal cortex), N170 amplitude

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INTRODUCTION

Cognitive control supports flexible, adaptive responses and complex goal-directed behavior. Also called executive control, this process includes selectively attending to relevant information while inhibiting irrelevant information from the environment as well as flexible adjustments in performance (Cohen, 2017). A classical paradigm assessing cognitive control processes is the

color-word Stroop task (Stroop, 1935). The Stroop task has become a standard task to investigate mechanisms of selective attention and top-down control of behavior (MacLeod, 1992; Banich et al., 2001). In the classical version of this task, subjects have to name the ink colors of color words. Compared to naming the ink color of a corresponding written color word (congruent condition), naming the ink color of an incongruent color word (incongruent condition) results in an increase in reaction times (RTs). This effect of slowing in RT is known as the Stroop interference or Stroop effect (Stroop, 1935; MacLeod, 1991). One explanation for the occurrence of this interference effect relates to different stages of automatic processing. The relatively automatic and overlearned process of word reading competes with the less automatic and more controlled process of naming the ink color. Thus, in the incongruent condition it requires more cognitive control to actively inhibit the automatically processed, yet, task-irrelevant information (written word) and selectively attend to the task-relevant information (color of the word; MacLeod, 1991, 1992; Banich et al., 2001). The resulting conflict occurs on a stimulus level (activation of ink color representation conflicts with the activation of the representation corresponding to the semantically meaning of the word; Hock and Egeth, 1970), as well as on motor response level (selection of correct response to ink color conflicts with response to task irrelevant word; Posner and Snyder, 1975).

In the past, neuroimaging and electroencephalogram (EEG) studies defined a distributed neuronal network underlying cognitive control processes during performance of the Stroop task. In particular, two brain areas have been associated with the regulative and evaluative processes of cognitive control—the prefrontal cortex (PFC), especially the dorsolateral and ventrolateral part (Miller and Cohen, 2001) and the anterior cingulate cortex (ACC; Posner and DiGirolamo, 1998). Several studies demonstrated that prefrontal regions execute regulative control processes as maintaining task demands, top-down control, allocation of attention to task-relevant information, demand for control resources, prearrangement of inhibiting task-inappropriate response alternatives and adjustments in behavior (Banich et al., 2000; MacDonald et al., 2000; Egner, 2011). In contrast, the ACC has been mainly associated with evaluative control processes such as monitoring of processing conflicts during error and high conflict trials (Kerns et al., 2004). The interaction between the ACC and PFC emphasizes the dynamic process of cognitive control (MacDonald et al., 2000). It is thought that ACC and PFC form a feedback loop where the ACC evaluates and detects conflicts due to interference or mistakes and signals when adjustments in control is necessary to achieve goal-directed behavior by recruitment of PFC as control implementer (Botvinick et al., 2001, 2004; van Veen et al., 2001).

In everyday life, our ongoing behavior is particularly determined by emotionally salient stimuli (Nummenmaa et al., 2006). In such situations, emotional conflicts emerge from the interference of goal-relevant emotional stimuli with goal-irrelevant emotional stimuli, which normally needs to be suppressed through conflict control mechanisms to optimize goal-directed behavior (Miller, 2000; Carter and van Veen, 2007; Egner et al., 2007). Thus, one has to inhibit the emotional distractor and resolve the "conflict" of emotion (Etkin et al., 2006; Egner et al., 2008). To investigate this emotional conflict control empirically, a variation of the classical Stroop paradigm—the emotional face-word Stroop task—was developed. In this Stroop version, participants are required to indicate the emotional expressions of faces while ignoring emotional words superimposed on the faces. As in the classical version, words can constitute a congruent- (face and word describe same emotional expressions) or incongruent (face and word indicate different emotional expression) condition. Thus, conflict arises when the lexical word information is incongruent to the facial affective stimulus (i.e., the word happy written across a sad face) resulting in the Stroop interference effect (Etkin et al., 2006).

Insights into the underlying brain dynamics during the execution of the emotional Stroop paradigm are determined by fMRI measurements. These data assume that the dorsolateral PFC (DLPFC) and amygdale are associated with emotional conflict detection while the rostral ACC is related to conflict resolution by inhibiting amygdalar responses to emotional task-irrelevant stimuli (Etkin et al., 2006). As indicated by electrophysiological data, the process of emotional interference starts relatively early—with increased amplitude of the face-sensitive N170 component to incongruent compared to congruent stimuli when participants are asked to indicate emotional expression, while during word indication tasks congruent stimuli evoke enhanced N170 amplitude (Zhu et al., 2010). The N170 constitutes an event-related potential (ERP) of enhanced amplitudes to faces compared to non-facial stimuli in an interval of 130 and 200 ms (Itier and Taylor, 2004a). The neural origin of this component was determined in differing but partly simultaneously active face processing brain regions [e.g., lateral inferior occipital cortex and posterior fusiform gyrus (Rossion et al., 2003) and posterior superior temporal sulcus (Itier and Taylor, 2004b)]. Although several studies report N170 amplitude differences between emotional and neutral faces, there is no consensus whether the expression of its amplitude is sensitive to specific facial emotions like sad, happy or angry faces (for meta-analysis, see Hinojosa et al., 2015).

While in fMRI and EEG studies generally the association between brain activation and behavior are drawn on correlational inferences only, noninvasive brain stimulation (NIBS) methods provide the opportunity to directly modulate related brain regions and thereby investigate the role of this brain region in a causal way. Transcranial direct current stimulation (tDCS) is an established NIBS method to modulate cortical excitability. TDCS delivers low currents to the cortex area of interest resulting in the modulation of cortical excitability. The current flows between an active and a reference electrode through the skull to the brain tissue, thereby inducing diminutions or enhancements of cortical excitability (Nitsche et al., 2008). The direction of the tDCS-induced effect depends on the current polarity. Anodal tDCS typically has an excitatory effect while cathodal tDCS decreases the cortical excitability in the region under the electrode (Nitsche et al., 2008). The spatial specificity of this effect is especially important when considering the effectiveness and precision of stimulation and can be

controlled by i.e., the size of electrodes. In conventional tDCS studies, rectangular electrodes with an area of 35 cm^2 are used. While this method displays the standard design, it bears the disadvantage of relative low focal effectiveness. To improve the spatial preciseness, so-called high-definition (HD)-tDCS has been introduced recently (Datta et al., 2009). This stimulation design uses a 4 × 1 ring electrode protocol to modulate neuronal excitability (Datta et al., 2012; Kuo et al., 2013; Heimrath et al., 2015) and allows for the parallel assessment of EEG data.

In the present study, we took advantage of the high focal HD-tDCS design to investigate the role of the DLPFC in emotional conflict control. For this purpose, we measured the behavioral performance of participants during a face-word Stroop task and simultaneously recorded EEG while they underwent anodal HD-tDCS or sham stimulation. Based on the evidence mentioned above, we hypothesize that anodal tDCS will alter cortical excitability of the lDLPFC and in turn, modulates emotional control processing.

MATERIALS AND METHODS

Participants

Eighteen healthy subjects participated in the present study (mean age 24.4 SD = ± 2.6; 10 female). To assess current depressive disorder they completed the Beck Depression Inventory-II (BDI-II; Hautzinger et al., 2006). Additionally, all participants affirmed to have no neurological or psychiatric disease and had normal or corrected-to-normal vision. Participants were stimulated twice on two separate sessions (with at least 5 and a maximum 7 days between)—receiving anodal stimulation at active and sham stimulation at the other session—while measuring their behavioral and electrophysiological performance during a face-word Stroop task. To exclude any stimulation order effect, the order of stimulation condition was pseudorandomized across subjects such that half of the participants started with sham and ended with an anodal stimulation session, while the other half received anodal on the first and sham on the second day. The order of stimulation sessions was predetermined by an odd-even-even-odd stimulation protocol. All participants were naïve to the stimulation conditions as well as the aim of the study and signed informed consent prior to the measurements. The local Ethical Committee of the University of Magdeburg approved the study.

Stimuli

For the emotional face-word Stroop task, nine female and nine male characters were selected from Karolinska face data base (female: AF01, AF02, AF05, AF07, AF14, AF16, AF19, AF20, AF21; male: AM09, AM10, AM11, AM13, AM14, AM17, AM22, AM23, AM29; Lundqvist et al., 1998), each displayed happy, sad and neutral facial expressions resulting in 54 face stimuli. All stimuli were equally sized and oval shaped masked to exclude details like hairstyle (see **Figure 1**). Stimuli were further edited by inserting a written word across the face. Words comprised the German words for happiness, sadness and neutral ("GLÜCK," "TRAUER," "NEUTRAL"), centrally located between face and mouth region, printed in gray capitalized bold letters (see **Figure 1**). Stimuli were either presented congruently (emotion word corresponds to facial expression) or incongruently (emotion word contrasts facial expression), where for the incongruent condition happy faces were always

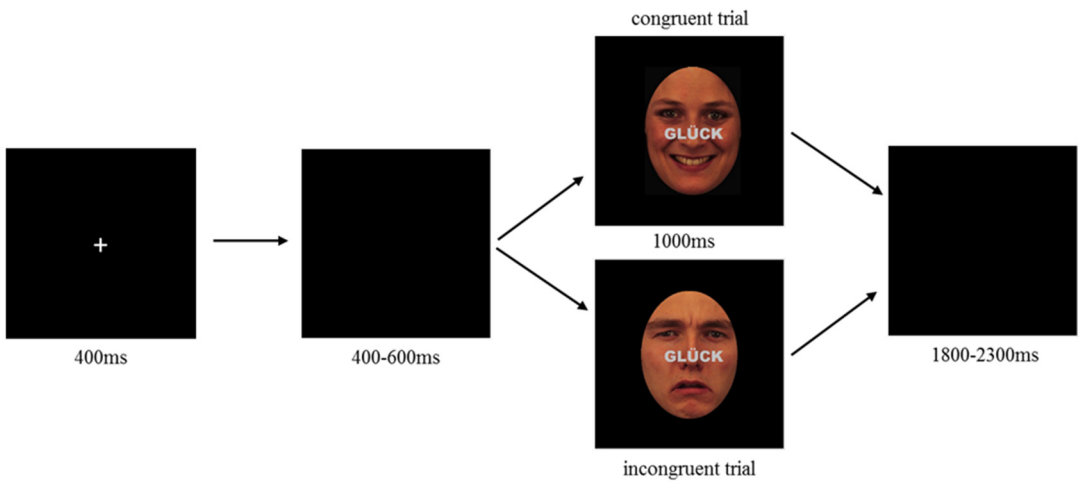

FIGURE 1 | Emotional face-word Stroop paradigm illustrating an example of congruent (top) and incongruent (bottom) trial. Each trial started with the presentation of a fixation cross (400 ms) followed by a blank screen with a random interval between 400 and 600 ms. After blank, a combined emotional face and word was presented as congruent (top) or incongruent (bottom) stimulus lasting for 1,000 ms. Participants were requested to indicate whether the face displayed a neutral, happy or sad expression by pressing the corresponding button on a computer keyboard (buttons: V, B, N). Responses had to be given within 1,000 ms. Target buttons were pseudorandomly assigned to each participant, such that the possible allocation of response button and facial expression was balanced between participants. Each trial ended with a varying inter stimulus interval of 1,800–2,300 ms.

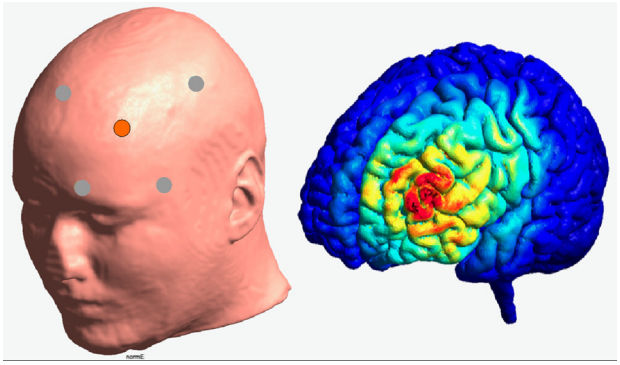

FIGURE 2 | Illustration of the electrode positioning and modeled current density for the HD—stimulation (Jung et al., 2013).

contrasted with the word "sadness" and sad faces always with the word "happiness," while neutral faces were always contrasted with "happiness." Each emotional expression (3) of each character (18) is displayed in each congruency condition (2), resulting in 108 stimuli.

HD-tDCS

Transcranial direct current stimulation was applied to the left DLPFC in a high-definition 4 × 1 ring configuration. For this purpose and according to the international 10–20 system, F3 electrode constituted the active electrode, surrounded by four reference electrodes (Fz, C3, FP1, F7). Brain modeling software (Jung et al., 2013) was used to ensure that this electrode placement is suitable to modulate the activity of the left DLPFC (see **Figure 2**). The sintered Ag/AgCl ring electrode (outer radius 12 mm, inner radius 6 mm) was fixed on a EEG cap and filled with EEG electrolyte gel (Easy Cap, Abralyt 2000) to improve the contact and thus the conductance between electrode and skin. Impedances were under 5 kΩ and were kept constant between electrodes. A battery-driven constant current stimulator (NeuroConn gmbH, Ilmenau, Germany) delivered the current with a strength of 0.5 mA with a linear fade in and fade out of 5 s. Stimulation started 10 min before the measurement to ensure stable stimulation effects in accordance with Nitsche et al. (2008) and ended with the termination of the experiment. In contrast to anodal session, the stimulation during the sham condition was applied for 30 s only. On the 2nd stimulation session, participants were asked to indicate whether and when they received active or sham stimulation.

EEG Recordings

EEG was recorded from Ag/AgCl electrodes at positions F4, F8, Cz, C4, T7, T8, Pz, P3, P4, P7, P8, PO3, PO4, PO7, PO8, Oz and right mastoid according to 10–20 system. Horizontal and vertical electrooculogram (HEOG/VEOG) was measured from two electrodes placed below and lateral to the left eye. Impedances were kept below 5 kΩ. Data of all electrodes were referenced to left mastoid and digitally online filtered with a high pass filter of 0.1 Hz, recorded with Brainamp DC amplifier (Brainproducts) and corresponding recording software (BrainVision Recorder 1.20, Brain Products GmbH, Munich, Germany) at a sampling rate of 1,000 Hz.

Procedure

To investigate the impact of HD-tDCS modulation of the lDPLFC on emotional conflict control, participants performed an emotional face-word Stroop during sham and anodal HD-tDCS. The experiment was conducted in a dimly lit room where participants sat in a comfortable chair with view orientation towards a display located in front of them. After EEG and HD-tDCS preparation, the experiment started with an initial HD-tDCS stimulation (either anodal or sham) of 10 min, thereafter the face-word Stroop and EEG recording started simultaneously to the ongoing stimulation. During the initial stimulation phase, participants performed a practice block to get familiar with the paradigm and response possibilities. During the face-word Stroop, participants had to indicate the emotional expression of the face while ignoring a written word across the face. Stimulus presentation was controlled by Presentation® software (Version 19, Neurobehavioral System, Inc., Berkeley, CA, USA). The stimulation continued during the entire duration of the task where all 108 trials were presented within one block lasting approximately 7 min. Each trial started with the presentation of a fixation cross (400 ms) followed by a blank display with random presentation duration of 400–600 ms, hereafter combined face-word stimuli were presented for 1,000 ms. Each trial ended with a blank display with a random interval of 1,800–2,300 ms. Trials were randomly presented such that there were no restrictions regarding repetition condition (see **Figure 1**).

EEG Data Analysis

To investigate the impact of HD-tDCS modulation of lDPLFC activity on electrophysiological level, the face sensitive N170 was assessed. For this purpose, EEG data were processed using Brain Vision Analyzer (version 2.1, Brain Products GmbH, Munich, Germany). Only trials with correct responses within a time window of 1,000 ms after stimulus onset were selected. In a first preprocessing step, data were bandpass filtered between 1 and 30 Hz using a 2nd order zero-phase IIR Butterworth filter (24 dB/oct) and segmented into 1,200 ms epochs (−200 ms prestimulus interval) relative to the onset of the face stimulus. Those epochs with artifacts were excluded from further analyses. The artifact rejection proceeded semiautomatic in accordance with pre-determined rejection criteria (maximal allowed voltage step of 50 μV/ms, maximal allowed difference of values in intervals 200 μV, lowest allowed activity in intervals of 0.5 μV). Following this artifact rejection procedure, on average 3.78 trials (SD ± 3.50) were excluded in sham condition and 6.44 trials (±4.40 SD) in anodal stimulation condition. Subsequently, artifact-free data were averaged separately for *congruency* and *valence* (i.e., happy congruent, sad congruent, neutral congruent, happy incongruent, sad incongruent, neutral incongruent) for both stimulation sessions. Based on previous research (Zhu et al., 2010; Eimer, 2011) and by visual inspection of grand-average waveforms, data of P7, PO7, P8 and PO8 were pooled. Peak

detection for most negative deflection within a time window between 150 and 250 ms was conducted and subsequently mean amplitude values within a time window of 20 ms around the peak were extracted separately for each participant and each stimulus condition.

Statistical Analysis

Statistical analysis for both, behavioral data as well as EEG data was performed using IBM SPSS software 24. Greenhouse-Geisser adjustment was applied for violations of sphericity. Finally, *post hoc* paired *t*-tests were conducted to further explore significant main or interaction effects.

Behavioral Data

Responses faster than 200 ms and responses exceeding 1,000 ms were excluded from further analysis (sham stimulation: $M = 6.5$, SD $\pm$ 5.97, anodal stimulation: $M = 8.56$, SD $\pm$ 9.04). Further, incorrect responses were not included into the following statistical analysis (sham stimulation: $M = 3.11$, SD $\pm$ 1.63, anodal stimulation: $M = 4.56$, SD $\pm$ 2.99). Subsequently, two separate repeated-measures ANOVAs for the RTs and arcsine transformed error rates (ER) with the within-subject factors *stimulation* (anodal, sham), *valence* of the facial emotional expression (happy, sad, neutral) and *congruency* between target face and word (congruent, incongruent) were performed.

EEG Data

Analogously, missing (no response between 200 and 1,000 ms) as well as incorrect responses were excluded from statistical analysis of EEG data. Mean amplitudes of the N170 were entered into a repeated-measures ANOVA with the within-subject factors *stimulation* (sham, anodal), *valence* of the facial emotional expression (happy, sad, neutral) and *congruency* between face and word (congruent, incongruent).

RESULTS

Behavioral Performance

RT data are presented in **Figures 3**, **4**. The 2 × 3 × 2 repeated measures ANOVA revealed a significant main effect of the factor *congruency* ($F_{(1,17)} = 37.559$, $P = 0.000$) due to faster responses to congruent stimuli ($M = 674.91$ ms, SE = 13.74) compared to incongruent stimuli ($M = 711.98$ ms, SE = 14.51 ms, $t_{(17)} = -6.129$, $P = 0.000$; see **Figure 4A**) and *valence* of facial emotional expression ($F_{(2,34)} = 27.859$, $P = 0.000$) due to faster responses to happy faces ($M = 656.47$ ms, SE = 16.58) compared to sad ($M = 707.83$ ms, SE = 11.70, $t_{(17)} = -5.744$, $P = 0.000$) and neutral faces ($M = 716.04$ ms, SE = 15.30, $t_{(17)} = -7.158$, $P = 0.000$; see **Figure 4B**).

Furthermore, ANOVA revealed a significant interaction between the factors *stimulation* and *congruency* ($F_{(1,17)} = 4.832$, $P = 0.042$). This interaction was driven by a trend for increased RTs for incongruent stimuli during anodal tDCS ($M = 723.05$ ms, SE = 17.04) compared to sham stimulation ($M = 700.90$ ms, SE = 13.87, $t_{(17)} = -1.992$, $P = 0.063$; see **Figure 4C**). Finally, the ANOVA revealed a significant interaction between the factors *congruency* and *valence* of facial emotional expression ($F_{(2,34)} = 8.726$, $P = 0.001$) due to a more pronounced congruency effect for neutral faces [neutral congruent $M = 687.95$ ms, SE = 14.71, neutral incongruent $M = 744.12$ ms, SE = 16.72, $t_{(17)} = -7.545$, $P = 0.000$)] than for happy (happy congruent $M = 642.84$ ms, SE = 16.42, happy incongruent $M = 670.09$ ms, SE = 17.47, $t_{(17)} = -3.892$, $P = 0.001$) and sad faces (sad congruent $M = 693.95$ ms, SE = 13.14, sad incongruent $M = 721.72$ ms, SE = 11.63, $t_{(17)} = -3.366$, $P = 0.004$; see **Figure 4D**). There was no main effect of *stimulation* ($F_{(1,17)} = 1.308$, $P = 0.269$). Further, the interaction between *stimulation* and *emotion* ($F_{(2,34)} = 0.15$, $P = 0.859$) as well as between *stimulation* and *valence* and *congruence* ($F_{(2,34)} = 0.179$, $P = 0.837$) did not reach significance.

The 2 × 3 × 2 repeated measures ANOVA on ER revealed a significant main effect of the factor *congruency* ($F_{(1,17)} = 7.848$, $P = 0.012$) due to fewer errors to congruent stimuli ($M = 0.094$, SE = 0.012) compared to incongruent stimuli ($M = 0.143$, SE = 0.016, $t_{(17)} = -2.802$, $P = 0.012$) and *valence* of facial emotional expression ($F_{(2,34)} = 3.639$, $P = 0.037$) due to fewer errors to happy faces ($M = 0.067$, SE = 0.02) compared to sad ($M = 0.130$, SE = 0.025, $t_{(17)} = -1.849$, $P = 0.082$) and neutral faces ($M = 0.158$, SE = 0.023, $t_{(17)} = -2.546$, $P = 0.021$). Furthermore, ANOVA revealed a significant *valence* × *congruency* interaction ($F_{(2,34)} = 4.069$, $P = 0.026$) due to more pronounced congruency effects for neutral (neutral congruent $M = 0.118$, SE = 0.029, neutral incongruent $M = 0.198$, SE = 0.027, $t_{(17)} = -2.570$, $P = 0.020$) and for happy faces (happy congruent $M = 0.025$, SE = 0.014, happy incongruent $M = 0.111$, SE = 0.034, $t_{(17)} = -2.593$, $P = 0.019$) than for sad faces (sad congruent $M = 0.14$, SE = 0.026, sad incongruent $M = 0.121$, SE = 0.029, $t_{(17)} = 0.798$, $P = 0.436$). There was no main effect of stimulation ($F_{(1,17)} = 2.647$, $P = 0.122$). Further, the interaction between *stimulation* and *emotion* ($F_{(2,34)} = 0.446$, $P = 0.644$), *stimulation* and *congruency* ($F_{(1,17)} = 0.024$, $P = 0.877$) as well as between *stimulation* and *valence* and *congruence* ($F_{(2,34)} = 0.279$, $P = 0.758$) did not reach significance.

EEG Data

Electrophysiological data are presented in **Figures 5**, **6**. The 2 × 3 × 2 repeated measures ANOVA for the N170 amplitude revealed a significant main effect of the factor *stimulation* ($F_{(1,17)} = 6.131$, $P = 0.024$) due to significant decreased N170 amplitude during anodal stimulation ($M = -6.81$ μV, SE = 0.53) compared to sham stimulation ($M = -7.93$ μV, SE = 0.78, $t_{(17)} = -2.476$, $P = 0.024$; see **Figure 6B**). Further, ANOVA revealed a significant main effect of the factor *valence*, due to highest N170 amplitude for sad faces ($M = -7.77$ μV, SE = 0.66) compared to happy faces ($M = -7.24$ μV, SE = 0.63, $t_{(17)} = 2.659$, $P = 0.017$) and neutral faces ($M = -7.12$ μV, SE = 0.63, $t_{(17)} = -3.153$, $P = 0.006$; see **Figure 6C**). The ANOVA revealed no significant main effect of *congruency* ($F_{(1,17)} = 0.283$, $P = 0.601$) as well as no significant interaction effects (*stimulation* × *emotion*: $F_{(2,34)} = 1.024$, $P = 0.370$; *stimulation* × *congruency*: $F_{(1,17)} = 0.00$, $P = 0.985$; *emotion* × *congruency*: $F_{(2,34)} = 1.061$,

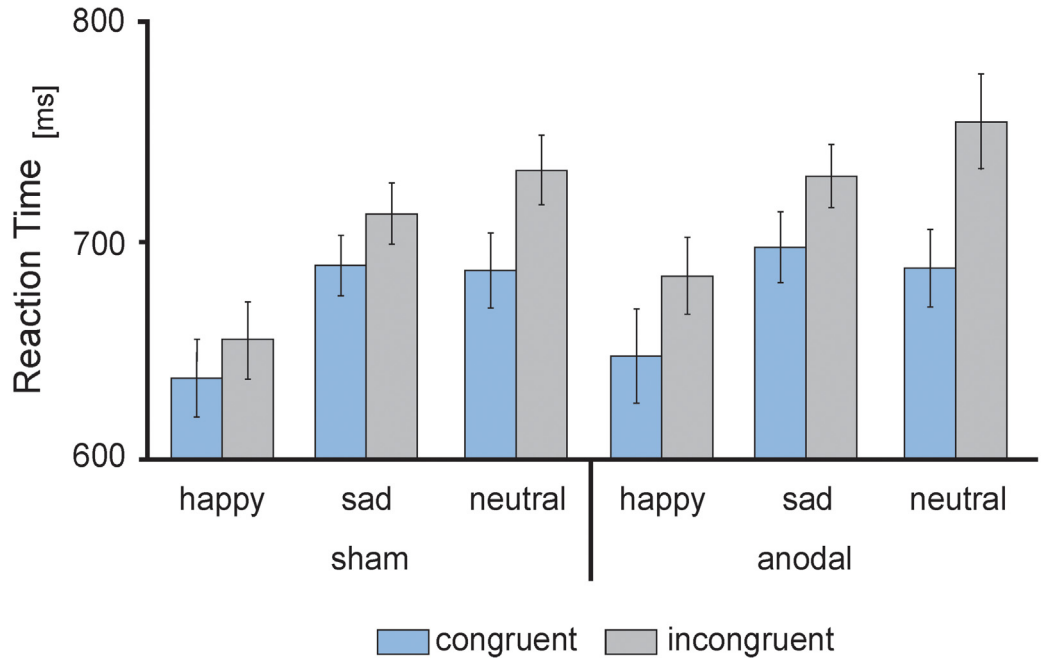

FIGURE 3 | Behavioral performance: mean reaction times (RT) in ms, separately for sham (left) and anodal (right) stimulation for happy, sad and neutral faces during congruent (blue) and incongruent (gray) trials. Error bars represent SEM.

$P = 0.357$, *stimulation* × *emotion* × *congruency*: $F_{(2,34)} = 2.14$, $P = 0.133$).

DISCUSSION

The present study investigates the impact of HD-tDCS on emotional conflict processing. For this purpose, we applied anodal HD-tDCS over the left DLPFC while participants performed an emotional face-word Stroop task and simultaneously measured behavioral and electrophysiological responses. To our knowledge, this is the first study modulating the activity of left DLPFC by means of HD-tDCS while simultaneously recording EEG data during cognitive control.

In result, we show that behaviorally, the face-word Stroop task induced a general interference effect that was additionally modulated by the valence of the processed faces. Importantly, HD-tDCS modulated this interference effect. Under tDCS, participants tended to slow in response times during incongruent trials only, while performance of congruent trials remained unaffected. Finally, the direct electrophysiological data revealed a general effect of the DLPFC stimulation. HD-tDCS consistently decreased the amplitude of the N170 ERPs.

Despite the novel results reported in this study, there are some limitations that have to be acknowledged. First, since this is the first study investigating the influence of HD-tDCS of the lDLPFC on behavioral and electrophysiological data measured during a face-word Stroop task with a rather small sample, further studies are needed to make reliable conclusion. Second, as the performance during a Stroop task depends on attention as well as facial expression discriminations skills, future studies should additionally measure the individual level of the related capabilities to consider results in a more differentiated way and exclude participants with deficits related to these skills. Third, the present study did not control for sequence effects of congruent and incongruent trials, while previous studies (e.g., Botvinick et al., 1999; Kerns et al., 2004; Egner, 2007) revealed a reduction in RTs of trials preceded by high-conflict trials compared to low-conflict trials (Gratton effect, Gratton et al., 1992). In accordance with the conflict-monitoring hypothesis (Botvinick et al., 2001) and with respect to the performance during the Stroop task, the dorsal part of the ACC detects the conflict signal during incongruent trials. In return, this conflict signal triggers adjustment in cognitive control implemented by the PFC especially the dorsolateral part of it (i.e., Botvinick et al., 2004; Kerns et al., 2004). This is an important issue for future research, which could concentrate on the influences of those sequence effects while modulating DLPFC activity by means of tDCS.

Generally, RT as well as ER data of the present study replicate the classical interference effect while performing a Stroop task—incongruent trials lead to longer RTs and higher ER compared to congruent trials. This interference effect is widely proven in classical Stroop paradigms (i.e., Stroop, 1935; Vendrell et al., 1995; Liotti et al., 2000) as well as in the face-word Stroop task (i.e., Etkin et al., 2006; Zhu et al., 2010; Shen et al., 2013; Xue et al., 2015, 2016) and results from a response competition between the distracting but automatically processed

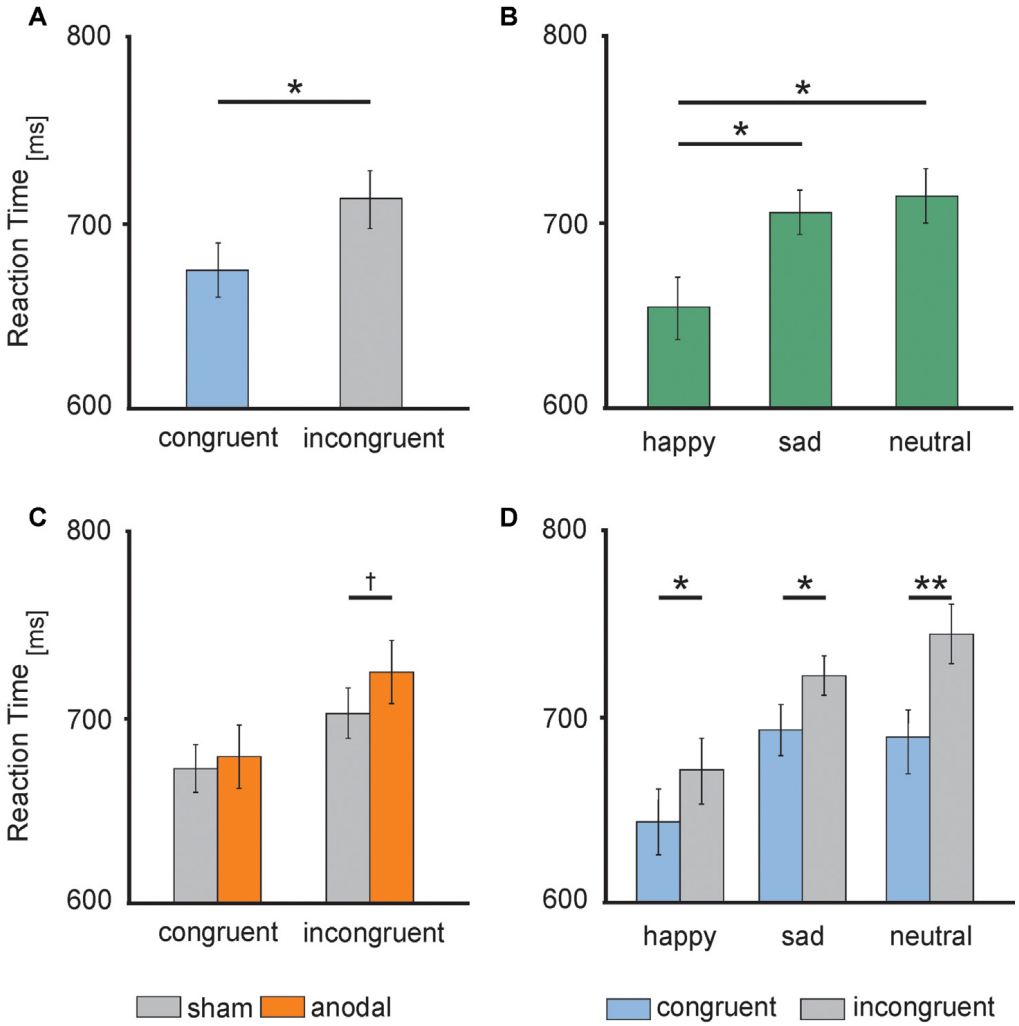

FIGURE 4 | Behavioral performance: **(A)** RTs during congruent (blue) and incongruent (gray) trials. **(B)** RTs to happy (left), sad (middle) and neutral (right) faces. **(C)** RTs during anodal (orange) and sham (gray) stimulation separately for congruent (left) and incongruent (right) trials. **(D)** RTs to happy (left), sad (middle) and neutral (right) faces separately for congruent (blue) and incongruent (gray) trials. Error bars represent SEM. $^{\dagger}p \leq 0.06$, $^{*}p < 0.05$, $^{**}p < 0.001$.

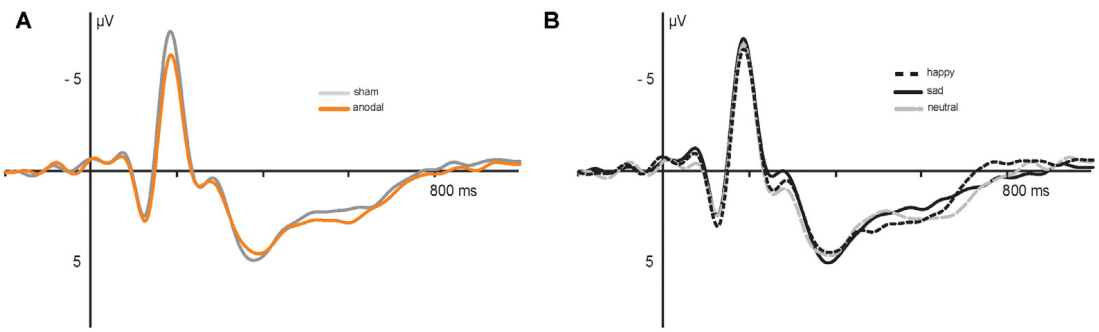

FIGURE 5 | Electrophysiological data: grand average event-related potentials (ERPs) recorded during **(A)** anodal (orange) and sham (gray) stimulation and **(B)** in response to happy (dashed), sad (solid) and neutral (gray) faces.

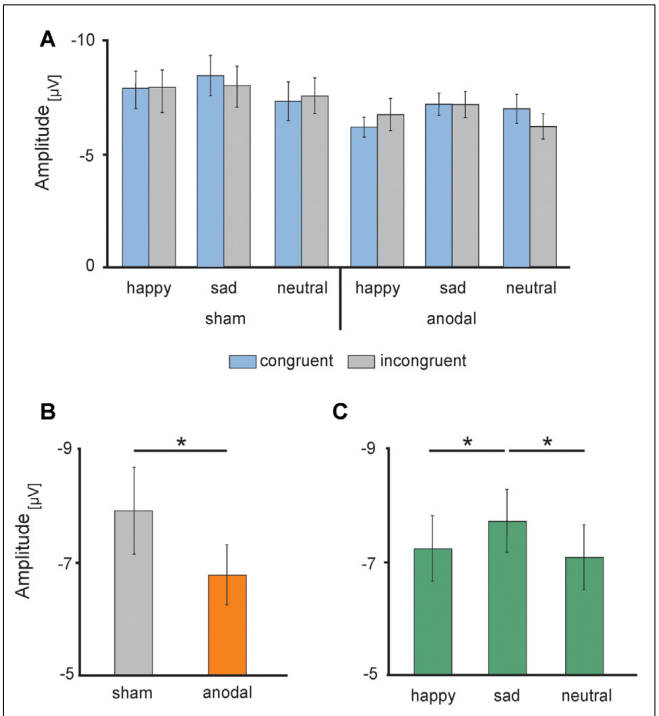

FIGURE 6 | Electrophysiological data: high-definition transcranial direct current stimulation (HD-tDCS) induced changes in the N170 amplitudes **(A)** separately for sham (left) and anodal (right) stimulation for happy, sad and neutral faces during congruent (blue) and incongruent (gray) trials, **(B)** during anodal (orange) and sham (gray) stimulation and **(C)** in response to happy (left), sad (middle) and neutral (right) faces. Error bars represent SEM. *$p < 0.05$.

word stimulus and the target stimulus (facial valence in the present study, ink color in the classical Stroop task). Additionally, our data reveal a general advantage for the processing of happy faces, independent of congruency and stimulation session. This advantage is demonstrated by faster RTs to happy faces compared to sad and neutral faces. Such valence dependencies (i.e., happy face vs. sad face) were less addressed in previous literature. However, an advantage of positive stimuli has been shown in a study by Chechko et al. (2012) where responses to happy faces were faster than to sad and fearful faces, indicating a general processing advantage for positive facial expressions. However, since for incongruent trials neutral as well as sad face stimuli were always combined with the word *happy*, it cannot be completely excluded that this overrepresentation of the word happy further influenced the RTs to happy faces. Nonetheless, this face-word combination of incongruent trials did not influence the stimulation effect, which is consistent across the different valences of facial emotional expressions. Our data show that anodal HD-tDCS over the left DPLFC interacted with the behavioral congruency effect. The effect, however, was limited to incongruent trials. Interestingly, while data in our study indicate a slowing of response times for incongruent trials during anodal stimulation, former studies also reported opposing effects. In particular, two previous studies investigating the influence of conventional anodal tDCS over the left DLPFC on the performance in a classical Stroop (Jeon and Han, 2012) and a modified color-word Stroop task (Loftus et al., 2015). Jeon and Han (2012) demonstrated a general speeding during word naming condition and during the interference condition of the Stroop after 20 min of 1 mA conventional anodal tDCS over F3, corresponding to the left DLPFC. Using 2 mA anodal tDCS for 10 min over the left DLPFC, Loftus et al. (2015) also reported decreased RTs for incongruent trials after tDCS. While already the applied Stroop tasks differ between these studies and the present, both former investigations applied a pre-post design, assessing the effects of conventional tDCS from pre- to post-stimulation. While such repetitive testing might add an additional parameter, also the assessed tDCS influences can differ between online and offline effects (Martin et al., 2014).

Two recent studies investigated the effect of anodal HD-tDCS of the left (Gbadeyan et al., 2016) and right (Gbadeyan et al., 2016, 2019) DLPFC during a visual flanker task. In contrast to our study, cognitive control was enhanced after anodal HD-tDCS. However, considerable methodological differences between these and the current study do not allow for a direct comparison. Particularly, both former studies used a concentric HD-tDCS setup, where the smaller anode was placed in the ring center of a bigger cathode, while we used a 4 × 1 ring electrode placement to stimulate the DLPFC. Additionally, both former studies applied 1 mA while in the present study we used 0.5 mA only. Since current intensity (Hoy et al., 2013; Papazova et al., 2018), as well as stimulation setup, can have a strong impact on tDCS-effects, further systematic investigations are needed to assess these effects in more detail.

While previous research consistently associates the DLPFC with cognitive control processing, divergent assumptions on the implementation of these control processes exist. While some authors assume that the DLPFC solves conflicts by suppressing the processing of task-irrelevant information (i.e., Banich et al., 2019) other affirm that the DLPFC amplifies the processing of task-relevant information (i.e., Egner and Hirsch, 2005). In the present study, modulating the activity of the DLPFC by anodal tDCS increased RTs to incongruent trials and additionally decreased the face selective N170 component, independent of congruency and emotional valence.

It might be assumed that the reduced N170 amplitude represents a reduced processing of task-relevant faces and that, in turn, the stimulation amplifies the processing of the task-irrelevant word by distracting attention from the relevant face stimulus towards the irrelevant word stimulus. While during the congruent condition this enhanced automatic processing of the congruent word would support emotional face identification with no changes in RTs, the enhanced processing of the incongruent word would result in deterioration of task performance during incongruent trials. However, assuming that anodal stimulation results in excitation of the underlying brain region, the present results would contradict results of Banich et al. (2019). In this study, increased DLPFC activity was associated with decreased perceptual processing of task-irrelevant stimuli. An explanation of the discrepancy of results could rely on task demands; while in the present study participants were asked to indicate emotional valence of the face,

they had to indicate the emotional category of the word in the study by Banich et al. (2019).

Finally, when applying tDCS as a tool to investigate brain mechanisms during cognitive processes one has to consider that the general assumption of the dichotic anodal/cathodal effect on brain activity should not be regarded as ultimate. This note for caution is supported by the fact that anodal stimulation does not necessarily result in an excitation. In contrast to the classical anodal excitation–cathodal inhibition theory, recent research demonstrate opposing effects with decreased reactivity after anodal stimulation (Chen et al., 2014) and increased reactivity of brain regions after cathodal stimulation (Zaehle et al., 2011). Furthermore, starting from an optimal level of brain performance in unstimulated condition, anodal/cathodal stimulation does not necessarily result in increase/decrease of the neuronal reactivity of the underlying brain region but may impair processing of it (Baldi and Bucherelli, 2005). Findings of recent studies support this assumption, that the conventional anodal excitation–cathodal inhibition polarity hypothesis cannot be regarded as representative for all tDCS modulation effects (for a review, see Jacobson et al., 2012). In a previous study, cathodal HD-tDC stimulation of the dorsal ACC results in faster responses while participants performed an emotional counting Stroop task (To et al., 2018). Additionally, slowing in RT during a working memory task was reported by Marshall et al. (2005) after anodal and cathodal stimulation of the DLPFC.

Our data show that anodal HD-tDC stimulation over the left DLPFC modulates brain response to facial expressions of emotions and increases the interference effect during a face-word Stroop task. However, from these results, it cannot be reliably concluded that anodal stimulation of left DLPFC influences cognitive control processes by modulating processing of task-relevant-, or by modulating task-irrelevant stimuli by amplifying or suppressing their processing. Furthermore, in contrast to the assumption that anodal stimulation generally results in excitatory effects of the underlying brain region and consequently enhanced cognitive processing, present results suggest that our stimulation setup disturbed the (optimal) DLPFC performance during cognitive control. For this, future studies are necessary to investigate whether HD-tDC stimulation of the DLPFC alters performance during the face-word Stroop task by modulating processing of the task-relevant face or task-irrelevant word.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local ethical committee of the University of Magdeburg, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK and TZ designed the experiment, interpreted the data and wrote the main manuscript. MK and KS performed the experiment, recorded and analyzed the data. H-JH and TZ contributed to the conception of the study. H-JH contributed reagents, materials and analysis tools. All authors reviewed the manuscript, approved the final manuscript and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Effects of Caffeine on Event-Related Potentials and Neuropsychological Indices After Sleep Deprivation

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Objective: Caffeine is a central nervous system stimulant that can effectively alleviate brain fatigue and low cognitive efficiency induced by total sleep deprivation (TSD). Recent studies have demonstrated that caffeine can improve subjective attention and objective behavioral metrics, such as arousal level, reaction time, and memory efficiency. However, only a few studies have examined the electrophysiological changes caused by the caffeine in humans following sleep disturbance. In this study, an event-related potential (ERP) technique was employed to measure the behavioral, cognitive, and electrophysiological changes produced by caffeine administration after TSD.

Methods: Sixteen healthy subjects within-subject design performed a visual Go/No-Go task with simultaneous electroencephalogram recording. Behavioral and ERP data were evaluated after 36 h of TSD, and the effects of ingestion of either 400 mg of caffeine or placebo were compared in a double-blind randomized design.

Results: Compared with placebo administration, the Go hit rates were significantly enhanced in the caffeine condition. A simple effect analysis revealed that, compared with baseline, the Go-P2 amplitude was significantly enhanced after TSD in the caffeine consumption condition. A significant main effect of the drug was found on No-Go-P2, No-Go-N2 amplitude, and Go-P2 latency before and after TSD.

Conclusion: Our findings indicate that caffeine administration has acute effects on improving the efficiency of individual automatic reactions and early cognitive processes. Caffeine was related to the preservation of an individual's arousal level and accelerated response-related decisions, while subjects' higher-level recognition had limited improvement with prolonged awareness.

Keywords: caffeine, ERP, total sleep deprivation, Go/ No-Go, reaction time (RTs)

INTRODUCTION

Sleep deprivation (SD) is common in the current society, with a prevalence of approximately 35% (Bandyopadhyay and Sigua, 2019). SD refers to the state that occurs when there is a loss of sleep and increased wakefulness that is maintained for a certain time (Roca et al., 2012; Kusztor et al., 2019), and total sleep deprivation (TSD) is the elimination of sleep for some time

(at least one night) to significantly prolong wakefulness (Reynolds and Banks, 2010). TSD is one of the main reasons for a low arousal level, reduced cognitive function, and increased reaction times, among other things. Since TSD has serious effects on human cognitive brain function, studies on interventions for mitigating the impact of TSD have become increasingly prevalent in this research field.

Recently, there has been a trend toward the use of caffeine (1,3,7-trimethylxanthine) to alleviate the effects of TSD and maintain arousal levels (Spaeth et al., 2014; Burrows et al., 2020). Worldwide, caffeine is the most widely consumed central nervous stimulant (Colombo and Papetti, 2020). Caffeine has been classified by pharmacologists as a central nervous system stimulant affecting, with increasing doses, the cortex, the medulla, and finally the spinal cord (Arnaud, 1987). Caffeine acts in the brain as a non-specific potent inhibitor of the actions of A1 and A2 Adenosine receptors (Ribeiro and Sebastiao, 2010; Nehlig, 2016). It seems particularly effective in improving alertness in situations of reduced arousal. Caffeine maintains a higher dopamine concentration especially in those brain areas linked with "attention." Depending on the neurotransmitter system, caffeine can affect different brain areas with different functions (Meeusen et al., 2013). Usually, caffeine has delayed effect about 3–4 h of half-life (Knutti et al., 1981, 1982; Nehlig, 2016), caffeine's behavioral effects and the significant increase in psychomotor performance it causes have been documented in a large body of literature, in addition to improvements in attention- (Temido-Ferreira et al., 2019; Alasmari, 2020; Franceschini et al., 2020; Irwin et al., 2020; Jahrami et al., 2020), mood-, and vigor-based tasks (Dietz and Dekker, 2017; Shabir et al., 2018; Alasmari, 2020). Moreover, Beaumont et al. (2005) found that the action of caffeine both shortened response times and reduced the number of errors on psychomotor tests, which indicates that caffeine has a global action on information processing and divided attention management (Beaumont et al., 2005; Wilhelmus et al., 2017).

Although caffeine has been studied for more than a 100 years, more research is necessary to better understand how brain activity is affected by caffeine consumption (Meng et al., 2017; van Son et al., 2018; Franco-Alvarenga et al., 2019; Tarafdar et al., 2019; Ueda and Nakao, 2019). Electrophysiological technology with event-related-potential (ERP) component detection, such as P50, N200, and P300, has been used for the measurement of brain activity. This technology allows for the measurement of neuroelectric activity related to cognitive processes, such as attention allocation and activation of short-term memory. Specific electrical patterns as measured using electroencephalography (EEG) can be evoked by sensory stimulation, such as visual and auditory stimulation. This evoked activity, or ERP, typically consists of several positive and negative peaks (Jin et al., 2015). ERPs are time-locked and can reflect both endogenously and exogenously driven cognitive processes. Concerning ERP components that reflect stimulus processing, a general arousal effect of caffeine would thus be expected to affect all components similarly, acting broadly as a stimulant amplifying all aspects of brain function (Kahathuduwa et al., 2017; Barry et al., 2019). For specific stimuli in certain response inhibition tasks, such as Go and No-Go stimuli in Go/No-Go tasks, corresponding evoked potentials can be generated during brain processing. Go-related potential changes are mainly related to automatic response processing, while No-Go-related potential changes are related to response inhibition.

Several ERP studies have examined the impact of TSD on vigilant attention during target detection and selective attention as it interacts with working and visuomotor memory (Zhang et al., 2014; Jin et al., 2015). These studies have found that TSD reduces early (∼160–200 ms) or late (>250 ms) ERP component amplitudes, or delays the latencies of these components. Jin et al. (2015) found that TSD induces a dose-dependent functional decline in response inhibition (No-Go-N2 and No-Go P3 amplitudes), and 8 h of recovery sleep resulted in a partial recovery or maintenance of response inhibition (Jin et al., 2015).

Tieges et al. (2009) examined the effects of caffeine in a task-switching paradigm and reported that caffeine increased N2 amplitude, but did not affect N2 latency. By contrast, P2 and P3 latencies were reduced, with no amplitude effects, indicating the difficulty in conceptualizing such inconsistent effects between components (Tieges et al., 2009). In an auditory Go/No-Go task, Barry et al. (2007) found that a single oral dose of caffeine (250 mg) resulted in focal rather than global increases in P1, P2, and P3b amplitudes to Go stimuli with no changes in latency, suggesting that caffeine differentially improves aspects of processing related to response production and task performance (Barry et al., 2007). Within the visual Go/NoGo paradigm, ERP studies have suggested that the N2 component reflects stimulus perception (Dulinskas and Ruksenas, 2019; Song et al., 2019), cognitive control, and response inhibition (Magnuson et al., 2019; Quaglia et al., 2019). P300 is the largest positive-going peak amplitude of the waveform within a time window of 300–400 ms and is considered to represent the allocation of attentional resources to rare salient stimuli (Cote et al., 2001; Marhöfer et al., 2015). P300 amplitude and latency are thought to reflect cognitive processing, such as stimulus identification and evaluation (Feng et al., 2019; Wang et al., 2019; Gao et al., 2020; Khedr et al., 2020). Studies have also suggested that higher-order cognitive stimuli-elicited P300 components are generated from the anterior cortex, and these components reflect the response inhibition process (de Bruijn et al., 2020; Paul et al., 2020). However, Deslandes et al. (2006) and Tieges et al. (2009) have found no significant alteration of ERP indices or other neuropsychomotor results following caffeine administration after TSD, indicating that there is still a lack of knowledge of caffeine's effects on the human brain.

By comparing ERPs related to response inhibition tasks before and after TSD, we can understand how the brain's automatic response or response inhibition is affected by TSD. In the present study, we utilized ERP techniques to analyze behavioral, cognitive, and electrophysiological changes produced by caffeine administration after TSD. Based on previous studies, we hypothesized that TSD would induce a decrease in amplitude and a prolonged latency of the N2/P3 components. We also hypothesized that caffeine consumption would attenuate the decline in response accuracy and prolongation of reaction time

(RT) caused by TSD. Because caffeine mainly enhances the alertness level of individuals, we supposed that ingesting caffeine after TSD can improve the process of automatic response and response inhibition, which will be reflected in increased amplitude and prolonged latency of ERP involving Go or No-Go stimulation. We chose 36 h of TSD to induce a moderate intensity of fatigue in subjects, to better observe the effect of caffeine intervention. To address these problems clearly, a visual Go/No-Go task with simultaneous EEG recording was used to evaluate caffeine's effect on brain function before and after 36 h of TSD.

MATERIALS AND METHODS

Subjects

Sixteen healthy male undergraduate students (age range 18–28 years, mean 25.9 ± 2.3 years) recruited from Beijing Normal University participated in this study. All subjects were right-handed and healthy, and we specifically excluded any potential subjects with diseases of the peripheral or central nervous system, cardiovascular disease and/or hypertension, cataracts and/or glaucoma, pulmonary problems, audiological problems, or alcohol or drug abuse. All subjects had normal vision and the standard full-length Raven's test was employed to measure subjects' IQ (mean 112 ± 8.7). All subjects had no psychiatric disorders (Peebles et al., 2001). All subjects scored < 60 (mean 12 ± 5) on the Symptom Checklist-90 (SCL-90; Kenemans et al., 1991). Finally, subjects were asked to be free of tobacco smoking and caffeine intake and have a regular sleep pattern with at least 8 h of sleep per night for at least 1 week before the experiment. We asked subjects about a prior history of caffeine use. Subjects who reported a prior history of caffeine intake habit (one cup per day) were excluded from our study. The experiment was fully explained to all subjects, and written informed consent was obtained before the start of the experiment. The experiment was approved by the ethics committee of the Beijing Institute of Basic Medical Science. The experiment was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. The subjects were paid $200 for participating in the study.

Experimental Design and Task Procedures

The visual Go/No-Go task was presented on a screen with a resolution of 1280 × 768 pixels, as shown in **Figure 1A**. At the beginning of each trial, a small white cross (+) on a black background appeared in the center of the screen for 50 ms, followed by the stimulus. Each stimulus was presented for a duration of 200 ms with an inter-stimulus interval of 750 ms. The time window for responses was <1,000 ms. The cross was displayed onscreen whenever a stimulus was not displayed. The stimulus had two arrow types (left and right, 78 × 18 pixels each, white visual stimulus on a black background) that were presented in a block task in a pseudorandom way. The task had two blocks with 200 trials in each block. In one block, the subjects were asked to respond to the left arrow [target stimulus (Go)] and withhold responding to the right arrow [non-target stimulus (No-Go)], while in the other block, the response pattern was reversed. The Go stimuli occurred with a 67% probability; the sequence of Go/No-Go stimuli is pseudorandom to ensure that No-Go stimuli do not appear in a continuous sequence. Response within 50 ms after presentation of the stimuli is regarded as invalid (Casement et al., 2006). Missed stimuli were not considered for further study. The subjects were instructed to respond as quickly as possible while maintaining a high level of accuracy and to maintain their attention on the fixation mark during the task blocks.

Subjects underwent a training session to ensure that they understood the Go/No-Go task, and to ensure that their performance was above 90%. The subjects slept for 7–9 h in a bed at the laboratory. The sleep time was assessed *via* a questionnaire and recorded by the experimenter. Subjects were tested in two sessions with a one-month interval. For the first session, the subjects arrived at the laboratory at 22:00 to ensure a full night's sleep before TSD. At 8:00 the following morning, after a routine sleep, the subjects performed the Go/No-Go task. The subjects were not allowed to sleep for the following 36 h, during which they took either 400 mg of placebo (starch) or caffeine at the 28th hour, and the same drug was taken again at the 32nd hour. After 36 h, subjects were asked to complete the Go/No-Go task again. Subjects were accompanied and supervised by the experimenters throughout the experiment to ensure that they completed the relevant experimental tasks, such as taking medicine, testing, and maintaining wakefulness. Throughout the experiment, the subjects were required to stay in the laboratory at all times, and were only allowed to have conversations, read, play computer games, and do other non-violent activities. They were not allowed to smoke or drink coffee, hot chocolate, alcohol, or other stimulating drinks. The second session was the same as the first session, except that the subjects received the drug they did not receive in the first session. For example, if the subject received a placebo in the first session, then caffeine was taken in the second session. Subjects received either caffeine or placebo, in a randomized, double-blind design (**Figure 1B**). The visual Go/No-Go task was performed with simultaneous EEG recording.

EEG Recording

The study was designed following international Pharmaco-EEG group standards. Continuous EEG recordings were obtained using a SynAmps2 amplifier (Compumedics Neuroscan, Charlotte, NC, USA). The subjects wore an Ag/AgCl electrode cap that had electrodes at the 32 sites specified by the international 10-20 system, and the reference electrodes were the digitally-linked bilateral mastoids (Duffy et al., 2013). The sampling frequency was 1,000 Hz, and the electrode impedances were maintained below 5 kΩ. The subjects were seated comfortably in a quiet, light-attenuated, and magnetic-free room. EEG was recorded from 20 monopolar derivations (Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, T3, T4, T5, T6, P3, Pz, P4, O1, Oz, and O2).

ERP Preprocessing

The raw EEG data were analyzed offline using Scan 4.3 (Neuroscan Products). The eye movement artifacts of the EEG data were corrected using the time-domain regression

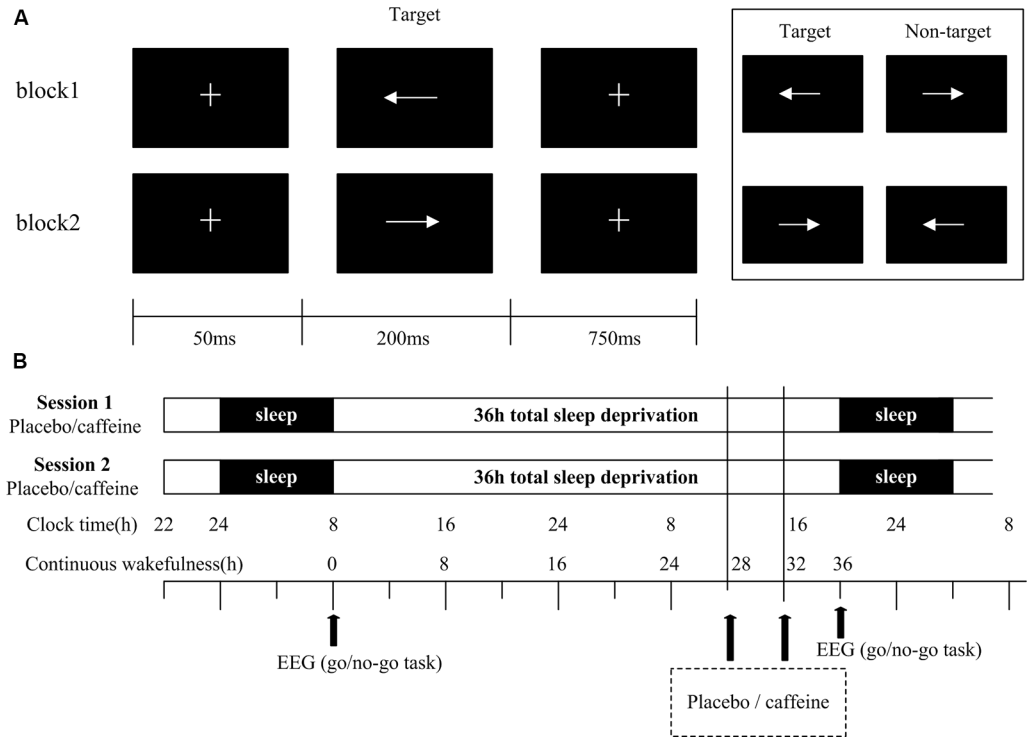

FIGURE 1 | Go/No-Go task and study protocol. **(A)** Schematic representation of the Go/No-Go task, showing a single trial of two blocks. Each block consisted of 200 trials. **(B)** In the study protocol, subjects underwent two 36 h periods of total sleep deprivation (TSD). The black arrows indicate the time points of electroencephalogram (EEG) recordings and drug administration (400 mg of caffeine or placebo).

analysis method, which was implemented with Scan 4.5 software (Casement et al., 2006). Epochs with a length of 900 ms that ranged from −100 ms to 800 ms with respect to the onset of the stimuli were then extracted from the continuous EEG data. Trials with incorrect responses or RTs outside the acceptable time range (50–800 ms) were excluded. The stimuli-locked ERP was baseline-corrected for the range of −100 ms to 0 ms before stimuli onset. The range of parameters for artifact removal was from −100 ms pre-artifact to 100 ms post-artifact, and the amplitude was between −100 μV and 100 μV. A band-pass filter from 0.5 Hz to 40 Hz was then used to filter the epoch data. The frequency slope of the filter was 24 dB/oct. Stimuli-locked data averages were computed separately for each participant and each drug condition.

The ERP components P2 (120–200 ms), N2 (200–350 ms), and P3 (300–550 ms) of the stimulus trials were identified and quantified. The grand-average peak amplitudes and latencies of the three components were calculated separately at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4. These areas are the ones usually activated by the stimuli (Choo et al., 2005; Verweij et al., 2014; Jin et al., 2015; Lei et al., 2015; Feng et al., 2019; Ueda and Nakao, 2019; Wang et al., 2019; Khedr et al., 2020).

Behavior Performance and ERP Component Analysis

The number of trials per subject for our behavioral and ERP analysis was 264 at go-trial and 136 at no-go-trial, respectively.

All behavior performance analyses were conducted using SPSS 22 software for Windows. The behavioral outcome variables included the mean RT for correct hits, hit rates (correct button presses for Go stimuli), and the percentage of false alarms (FA, incorrect button presses in response to No-Go stimuli), which were used as indices of individual behavior performance. A repeated measure ANOVA was employed to analyze the drug effects (placebo and caffeine) and the time effects (baseline and 36 h-TSD) on the behavioral data (van Son et al., 2018; Daou et al., 2019).

The repeated measure ANOVA was also used for the analysis of ERP indices. ANOVAs were performed on the P2, N2, and P3 components of the scalp electrodes in the Go/No-Go task. Greenhouse-Geisser corrections were applied when the data do not conform to the hypothesis of the spherical test.

The "eta squared" method provided by IBM SPSS 22 was employed for estimates of effect size.

RESULTS

Behavioral Performance

The hit rates in Go trials showed a significant difference based on a main effect of the drug ($F_{(1,31)}$ = 5.054, p = 0.037, ES = 0.188) and a main effect of time ($F_{(1,31)}$ = 8.209, p = 0.009, ES = 0.273), but no interaction effects (drug × time; $F_{(1,31)}$ = 1.899, p = 0.180, ES = 0.080). A simple effect analysis showed no significant difference in the hit rates between placebo and

caffeine conditions at baseline; however, there was a significantly increased hit rate with caffeine compared with placebo after TSD ($p = 0.028$).

The RTs in Go trials showed a significant difference based on a main effect of drug ($F_{(1,31)} = 5.541$, $p = 0.031$, ES = 0.223) and a main effect of time ($F_{(1,31)} = 5.462$, $p = 0.034$, ES = 0.220). A simple effect analysis revealed a significantly increased RT in caffeine compared with that in placebo at baseline ($p = 0.050$); however, there was no significant difference after TSD.

The FA rates of No-Go trials showed no significant difference in the main effects or interaction effects ($p > 0.05$).

The standard deviations and means of the Go-hit rates, Go-RTs, and FA rates before and after TSD are presented in **Table 1**. To more clearly observe the effects of taking caffeine, performance metrics under caffeine, and placebo conditions were compared, as shown in **Figure 2**.

ERP

The means and standard deviations of the P2, N2, and P3 components' amplitudes and latencies at the nine electrode sites in the Go trials are presented in **Table 1**, and the average waveforms are shown in **Figure 3**. The means and standard deviations of the P2, N2, and P3 components' amplitudes and latencies elicited during the No-Go trials at the nine electrode sites are presented in **Table 1**, and the average waveforms are shown in **Figure 4**. The scalp topography shows the differences in P2/P3 before and after TSD. It can be seen from the scalp topography that the energy differences of the P2 and P3 components before and after TSD is greater after ingesting caffeine than after taking placebo. The larger changes are in frontal regions of the brain.

In **Figure 3**, it can be seen that, compared with the placebo condition, the P2, N2, and P3 components in the caffeine condition have larger amplitude changes before and after TSD in Go trials, especially in the frontal area (F3, Fz, and F4). To compare the effects of caffeine on the ERP components in the anterior, middle, and posterior brain regions, we performed ANOVAs of the Fz, Cz, and Pz channels located at the midline of the brain.

Changes in ERP Component P2

The Go-P2 amplitude in the Fz channel showed significant main effects of drug ($F_{(1,31)} = 13.211$, $p = 0.001$, ES = 0.329) and time ($F_{(1,31)} = 6.13$, $p = 0.020$, ES = 0.185); however, an interaction effect was not found ($F_{(1,31)} = 3.719$, $p = 0.064$, ES = 0.121). Furthermore, *Post hoc* multiple comparisons found that, compared with baseline, the Go-P2 amplitude was significantly enhanced after TSD in the caffeine consumption condition ($p = 0.001$). In TSD conditions, compared with placebo, caffeine caused a significant enhancement of the Go-P2 amplitude ($F_{(1,31)} = 7.027$, $p = 0.015$, ES = 0.251). Both before and after TSD, the amplitude of Go-P2 in the caffeine condition was significant smaller than that in the placebo condition (before: $p < 0.001$; after: $p = 0.049$), and the difference of amplitude between after TSD was smaller than that at baseline in caffeine condition ($p = 0.001$).

During Go trials, the Go-P2 latency in the Fz channel showed a significant difference based on the main effect of the drug ($F_{(1,31)} = 5.360$, $p = 0.028$, ES = 0.166) and a main effect of time ($F_{(1,31)} = 25.503$, $p < 0.001$, ES = 0.486); *Post hoc* multiple comparisons showed that there was no significant difference between placebo and caffeine at baseline ($p = 0.710$), however, there was a significantly shorter Go-P2 latency in the caffeine condition compared with placebo after TSD ($p = 0.002$).

ANOVAs of the Go-P2 amplitude and latency in the Cz and Pz channels did not yield significant results.

In the Fz channel, during No-Go trials, significant main effects of drug ($F_{(1,31)} = 18.766$, $p < 0.001$, ES = 0.410) and time ($F_{(1,31)} = 8.564$, $p = 0.007$, ES = 0.241) on No-Go-P2 amplitude were found; an interaction effect was also found ($F_{(1,31)} = 8.910$, $p = 0.006$, ES = 0.248). Furthermore, a simple effect analysis found that during resting wakefulness, the two baseline conditions (caffeine vs. placebo) showed significant differences in the No-Go-P2 amplitude ($p < 0.001$); there was no significant difference in the No-Go-P2 amplitude between caffeine and placebo conditions after TSD ($p = 0.237$). Moreover, compared with baseline, the No-Go-P2 amplitude was significantly enhanced in the caffeine consumption condition after TSD ($p < 0.001$).

In the Cz channel, there were significant main effects of drug ($F_{(1,31)} = 18.004$, $p < 0.001$, ES = 0.400) and time ($F_{(1,31)} = 5.874$, $p = 0.022$, ES = 0.179) on the No-Go-P2 amplitude. Furthermore, *Post hoc* multiple comparisons revealed that, compared with baseline, the No-Go-P2 amplitude was significantly enhanced in the caffeine consumption condition after TSD ($p = 0.002$). Both before and after TSD, the amplitude of No-Go-P2 in the caffeine condition was smaller than that in the placebo condition (before: $p < 0.001$; after: $p = 0.039$), and the difference of amplitude between after TSD was smaller than that at baseline in caffeine condition ($p = 0.002$).

ANOVAs of the No-Go-P2 latency in the Fz, Cz, and Pz channels and of the No-Go-P2 amplitude in the Pz channel did not yield significant results.

TABLE 1 | Summary of behavioral performance (mean ± deviation).

	Placebo			Caffeine		
	Baseline	**36 h-TSD**	***p*-value**	**Baseline**	**36 h-TSD**	***p*-value**
Go-hit rates	0.914 ± 0.077	0.851 ± 0.104	0.003*	0.929 ± 0.089	0.898 ± 0.098#	0.158
Go-RTs (ms)	285.852 ± 22.725	295.746 ± 31.467	0.006*	295.947 ± 35.466#	305.389 ± 40.520	0.172
No-Go-FA rates	0.124 ± 0.069	0.158 ± 0.068	0.109	0.080 ± 0.059	0.111 ± 0.069	0.085

*Note: *Baseline vs. 36 h-TSD, $p < 0.05$; #Placebo vs. Caffeine, $p < 0.05$.*

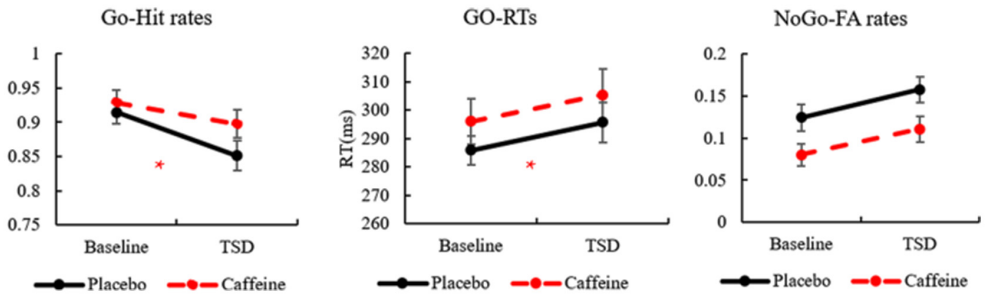

FIGURE 2 | The standard errors and means of Go-hit rates, Go-reaction times (RTs), and No-Go-false alarm (FA) rates. *Caffeine vs. Placebo, $p < 0.05$.

Changes in ERP Component N2

ANOVAs of the Go-N2 amplitude and latency in the Fz channel did not yield significant results.

A significant main effect of time on Go-N2 amplitude was found ($F_{(1,31)} = 5.208$, $p = 0.031$, ES = 0.162) in the Cz channel; *Post hoc* multiple comparisons found that during resting wakefulness, the two baseline conditions (caffeine vs. placebo) showed no significant difference in Go-N2 amplitude. However, there was a significant decrease in amplitude in the caffeine condition compared with placebo after TSD ($p = 0.04$).

ANOVAs of the Go-N2 latency in the Cz and Pz channels and of the Go-N2 amplitude in the Pz channel did not yield significant results.

In the Fz channel during No-Go trials, significant main effects of drug ($F_{(1,31)} = 7.118$, $p = 0.013$, ES = 0.209) and time ($F_{(1,31)} = 10.178$, $p = 0.004$, ES = 0.274) on No-Go-N2 amplitude were found along with an interaction effect ($F_{(1,31)} = 7.062$, $p = 0.013$, ES = 0.207). Furthermore, a simple effect analysis found that, compared with baseline, the No-Go-N2 amplitude was significantly enhanced in the caffeine consumption condition after TSD ($p = 0.001$). Before TSD, the amplitude of No-Go-N2 in the caffeine condition was smaller than that in the placebo condition (before: $p < 0.001$;), and the difference of amplitude between after TSD was smaller than that at baseline in caffeine condition ($p = 0.001$).

Significant main effects of drug ($F_{(1,31)} = 13.307$, $p = 0.001$, ES = 0.330) and time ($F_{(1,31)} = 14.093$, $p = 0.001$, ES = 0.343) on the No-Go-N2 latency in the Fz channel were found with no interaction effect. Furthermore, *Post hoc* multiple comparisons found that, compared with baseline, the No-Go-N2 latency shortened significantly in the caffeine consumption condition after TSD ($p = 0.006$). Both before and after TSD, the latency of No-Go-N2 in the caffeine condition was shorter than that in the placebo condition (before: $p < 0.001$; after: $p = 0.034$), and the difference of amplitude between after TSD was smaller than that at baseline in caffeine condition ($p = 0.001$).

In the Cz channel, significant main effects of drug ($F_{(1,31)} = 3.557$, $p = 0.050$, ES = 0.116) and time ($F_{(1,31)} = 16.727$, $p < 0.001$, ES = 0.383) on the No-Go-N2 amplitude were found, along with an interaction effect ($F_{(1,31)} = 4.638$, $p = 0.040$, ES = 0.147). Furthermore, a simple effect analysis found that, compared with baseline, the No-Go-N2 amplitude reduced significantly in the caffeine consumption condition after TSD ($p < 0.001$). Before TSD, the amplitude of No-Go-N2 in the caffeine condition was smaller than that in the placebo condition (before: $p < 0.009$; after: $p = 0.924$), and the difference of amplitude between after TSD was smaller than that at baseline in caffeine condition. ANOVAs of the No-Go-N2 latency in the Cz and Pz channels and of the No-Go-N2 amplitude in the Pz channel did not yield significant results.

Changes in ERP Component P3

There was significant main effect of time on Go-P3 amplitude in the Fz ($F_{(1,31)} = 6.74$, $p = 0.015$, ES = 0.200), Cz ($F_{(1,31)} = 7.806$, $p = 0.009$, ES = 0.224), and Pz ($F_{(1,31)} = 8.316$, $p = 0.008$, ES = 0.235) channels; however, there were no significant main effects of drug in any of the three channels. The amplitude of No-Go-P3 was the same as that of Go-P3. In the Fz channel, there was a main effect of time in the latencies of Go-P3 ($F_{(1,31)} = 5.144$, $p = 0.032$, ES = 0.160) and No-Go-P3 ($F_{(1,31)} = 6.860$, $p = 0.014$, ES = 0.203), and an ANOVA of the No-Go-N2 latency in other channels did not yield significant results.

Combining the above results, **Figure 5** shows the amplitudes and latencies of the ERP components with the main effect of the drug, highlighting the effect of caffeine on the peak ERP.

DISCUSSION

In the present article, we report an investigation of the effects of time (baseline and TSD) and drug (placebo and caffeine) on executive brain function using a visual Go/No-Go task with simultaneous EEG recordings. We recorded both behavioral and ERP indices in two TSD sessions to observe how automatic responses and response inhibition were altered during TSD and to what extent caffeine administration could maintain executive brain function. By examining the effects of caffeine on different ERP components, we found that the P2 ERP component in Go trials showed an increased differential wave in the TSD condition following caffeine administration compared to placebo. After TSD, the N2 and P3 components showed decreased amplitude and prolonged latency compared to baseline. However, the latency of Go-P2 in the caffeine condition was less prolonged than it was in the placebo condition; this suggests that caffeine

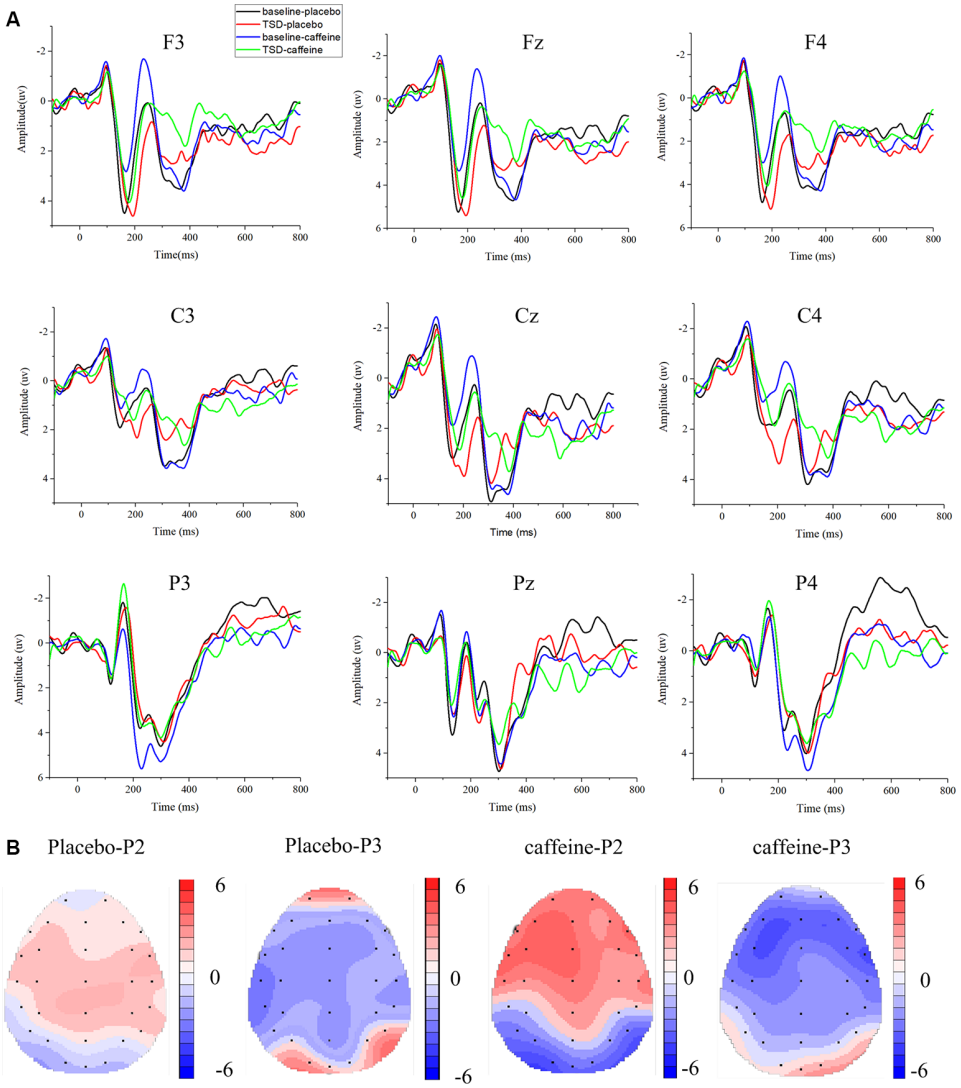

FIGURE 3 | Differences between event-related potential (ERP) component amplitudes and topographic analysis following caffeine or placebo treatment at baseline and after TSD in Go trials. **(A)** Stimulus-locked average certainty ERP responses following placebo or caffeine administration at baseline and after TSD. **(B)** Significant differences in P2 and P3 components in scalp topography between baseline and after TSD. Headpoles of the paired *t*-test approach ($p < 0.05$; Bonferroni corrected) map the scalp distribution of statistical differences between baseline and after TSD (placebo-P2 most significant: Pz channel, two-tailed paired *t*-test, $t = 2.316$, $p = 0.028$; placebo-P3 most significant: C3 channel, two-tailed paired *t*-test, $t = -3.78$, $p = 0.001$; caffeine-P2 most significant: F3 channel, two-tailed paired *t*-test, $t = 3.897$, $p = 0.01$; caffeine −P3 most significant: F3 channel, two-tailed paired *t*-test, $t = -3.082$, $p = 0.005$). Colors represent the *t*-values of the statistical comparisons (color bar indicates *t*-values), and the black points represent electrodes. The larger the *t*-value, the greater the difference between the values before and after TSD. Placebo-P2: P2 changes after placebo administration; placebo-P3: P3 changes after placebo administration; caffeine-P2: P2 changes after caffeine administration; caffeine-P2: P2 changes after caffeine administration.

administration may enhance cognitive processing related to response selection and inhibition.

Our study showed that the ERP components can reflect different arousal levels (TSD vs. awake). From the behavioral analysis, we found a significant decrease in hit rates and an increase in FA rates after 36 h of TSD, compared with the baseline level. Our previous study showed that the most significantly changed indices among the behavioral measurements after TSD, the RTs of Go trials, and FA rates in the No-Go trials, revealed a significant increase in performance impairment after TSD. Consistent with observations, these results revealed poor inhibitory control after 36 h of TSD and demonstrated that TSD greatly impairs higher-level cognitive functions (Tremblay et al., 2014). After caffeine administration, the hit rates in Go trials increased significantly following TSD. However, no significant changes in RTs were found in this study. These results indicate that the deterioration of performance following TSD, which was related to increased sleepiness, could be improved by caffeine administration in the Go/No-Go tasks.

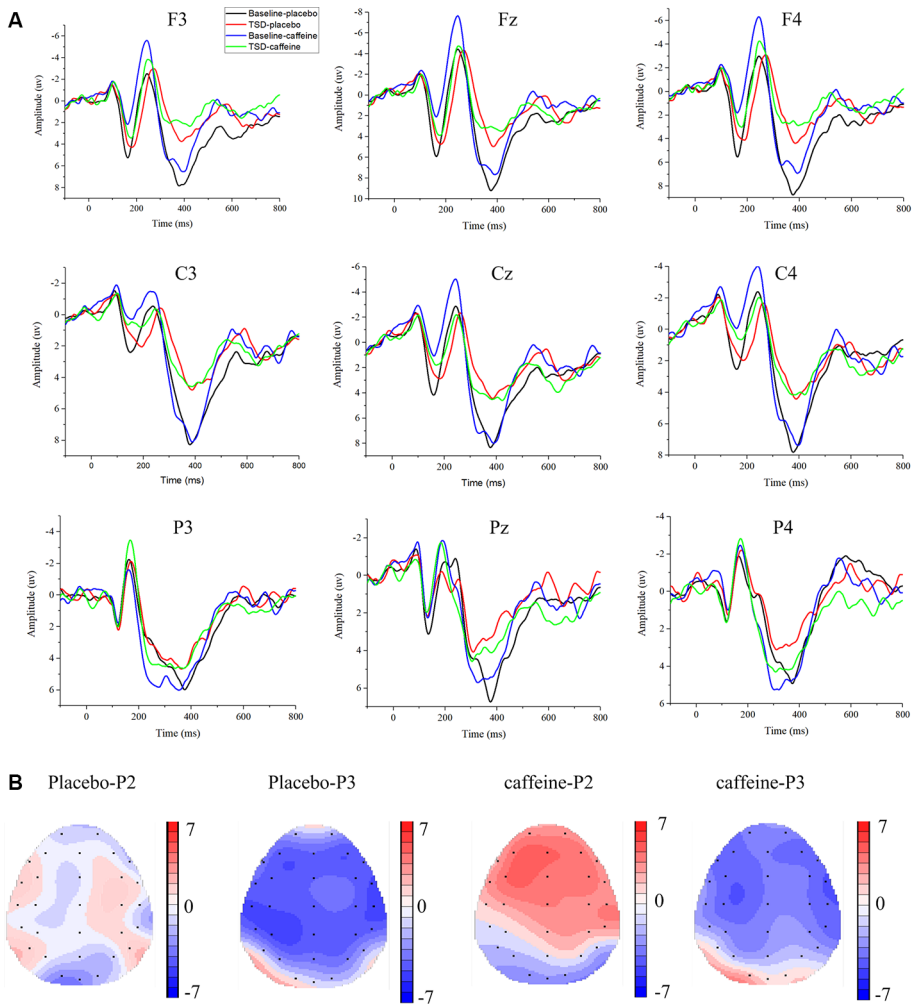

FIGURE 4 | Differences between ERP component amplitudes and topographic analysis following caffeine or placebo treatment at baseline and after TSD in No-Go trials. **(A)** Stimulus-locked average certainty ERP responses following placebo or caffeine administration at baseline and after TSD. **(B)** Significant differences in P2 and P3 components in scalp topography. Headpoles of the paired *t*-test approach ($p < 0.05$; Bonferroni corrected) map the scalp distribution of statistical differences between baseline and after TSD (placebo-P2 most significant: C4 channel, two-tailed paired *t*-test, $t = 1.987$, $p = 0.035$; placebo-P3 most significant: P3 channel, two-tailed paired *t*-test, $t = -4.056$, $p < 0.001$; caffeine-P2 most significant: Fz channel, two-tailed paired *t*-test, $t = 4.310$, $p < 0.001$; caffeine-P3 most significant: C3 channel, two-tailed paired *t*-test, $t = -4.156$, $p < 0.001$). Colors represent the *t*-values of the statistical comparisons (color bar indicates *t*-values), and the black points represent electrodes. Placebo-P2: P2 changes after placebo administration; placebo-P3: P3 changes after placebo administration; caffeine-P2: P2 changes after caffeine administration; caffeine-P2: P2 changes after caffeine administration.

An interesting finding of the present study is that the P2 component amplitude during Go trials increased after caffeine administration. Although the exact cognitive process underlying the P2 component is still widely debated, the consensus is that the P2 component reflects processes before attention. P2 is believed to reflect the post-synaptic activity of a specific neural process, and it represents aspects of higher-order perceptual processing, modulated by attention, linguistic contextual information, memory, and repetition effects (Liu et al., 2014). The exact function and neural source of the P2 component are not yet known, but some evidence has indicated that P2 may reflect general neural processes that occur when a visual (or other sensory) input is compared with an internal representation or expectation in the memory or language cortex (Stancak et al., 2018). Therefore, the larger amplitude of the P2 ERP component in Go trials may reflect the improved pre-attention brain function produced by caffeine administration after TSD.

The relevance of N2 and P3 components in individual attention processes has been established in the literature. In our study, the No-Go-P3 component showed prolonged latency after TSD, suggesting that TSD induced difficulty in inhibiting an inappropriate response. However, the increased latency of No-Go-P3 induced by TSD was not significantly improved by caffeine administration. We concluded that, rather than maintaining response inhibition, individuals maintained automatic responses. Our results regarding the No-Go-N2 and No-Go-P3 amplitudes provided evidence that the mechanism

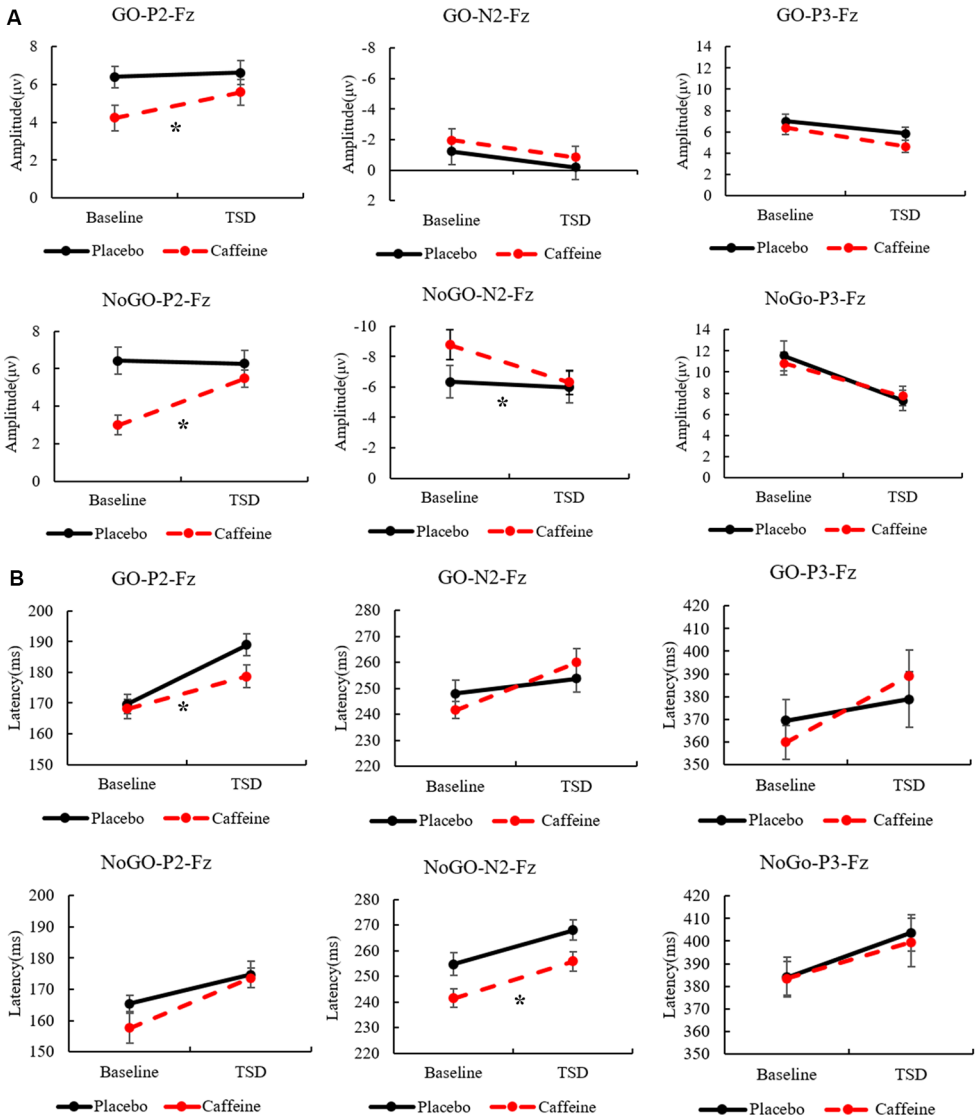

FIGURE 5 | The standard errors and mean values of the amplitude **(A)** and latency **(B)** of ERP components. Solid black line, Placebo; Red dotted line, Caffeine. TSD, total sleep deprivation; Go-P2-Fz, Go trials, P2 components, Fz channel; No-Go-P2-Fz, No-Go trials, P2 components, Fz channel. *Indicates significant differences in the drug.

inhibiting inappropriate responses was not fully maintained, as we had speculated. These findings suggest that simple cognitive responses are easily maintained following caffeine administration, while higher-level cognitive brain functions that are related to No-Go-P3 are difficult to maintain. An alternative explanation could be that these changes are the result of an energy allocation (EA) function of sleep (Schmidt, 2014). In the EA model, the homeostatic drive to sleep is governed by an accumulation of biological deficits, or unfulfilled biological functions, favored by natural selection to utilize the state of sleep to complete such processes. Indeed, the ability to upregulate many sleep-related biological operations in waking during periods of prolonged sleep loss could explain the historical difficulty in identifying specific deficits resulting from TSD (Roca et al., 2012; Kusztor et al., 2019). During 36 h of TSD, however, the EA model predicts that energy requirements to counteract sleep deficits are directed away from advanced perception energy resources (Schmidt, 2014). The N2 and P3 ERP components measured with EEG electrodes are established neurophysiological signals with relevance to individual and working memory processes in healthy humans, patients, and even animals. In the present experiment, however, following caffeine ingestion, the P3 component measurement demonstrated some differences, and even conflicting results, from the N2 component. The variability among subjects for factors such as temperature, recent work, and the individual's mood may account for these results. A previous study showed that the influence of caffeine on neurophysiological response is

related to the individual's alertness level (Wilhelmus et al., 2017). Findings related to ERP components deserve further exploration and investigation of the specific mechanisms responsible for these results to draw a firm conclusion in future research.

CONCLUSION

These results suggest that caffeine may be beneficial to cognitive processes related to response selection and inhibition. Higher-level cognitive brain functions appeared to be improved by the administration of caffeine (Han et al., 2015; Satterfield et al., 2018). By utilizing an electrophysiological technique, the most notable results of the present study were concerning changes to the P2 component. After TSD, there was an obvious change in the N2 and P3 component amplitudes. Also, a change in the P2 amplitude was seen following caffeine ingestion. This could be explained by the fact that caffeine is related to individual arousal and accelerated response-related decisions rather than higher-level recognition (Bocca and Denise, 2006; Czisch et al., 2012). Thus, the ingestion of caffeine seems to counteract the TSD effect, which did not occur in the placebo condition. EEG studies have shown an absolute increase in the P2 amplitude after caffeine ingestion compared with the N2 and P3 components after 36 h of TSD. It reflects neuroelectric activity related to cognitive processes such as attention allocation and activation of short-term memory. Caffeine is related to the preservation of an individual's arousal level and accelerated response-related decisions, while subjects' higher-level recognition has limited improvement with prolonged awareness.

Limitations

A limitation of this study was that only young male subjects were chosen. Therefore, the findings may not be generalizable to women and older people. Additionally, the sample size was small. Further, due to the one-month interval between the two TSD tests, there is a difference between the two baseline measurements, which may affect the results. The subject was under a time pressure to respond to the stimuli, which may have been faster than the actual response (Gajewski and Falkenstein, 2013). Follow-up studies should focus on the role of individual differences in ERP after TSD and caffeine consumption. The presentation time of stimuli was 200 ms, which will disturb the ERP effects because the offset potentials fail in the range of the analyzed components like the N2. Additionally, the sequential assignment of well-rested and TSD states during each testing session is a non-optimal design for studying TSD effects. Also, by the time we scanned our subjects after caffeine administration, one half-life of the caffeine had elapsed, suggesting that the drug would have been significantly eliminated from the bloodstream by the time that data were obtained. In this regard, any verdicts on the significance of the results of this study should be made with caution. Finally, individuals' sleep-wake rhythm is a factor that may also have impacted the 36 h of TSD, and we intend to explore this in the future.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Beijing Institute of Basic Medical Science. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XC designed the experiments and interpreted data. XC, LZ, and GA performed the behavior experiments. DY performed the ERP experiments. RF, CL, and JW performed processing and analysis of the data. XC and LZ wrote the manuscript. QM and YS provided the overall guidance. All authors read and approved the final manuscript.

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frontiers in Behavioral Neuroscience

BRIEF RESEARCH REPORT
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The Influence of Music Tempo on Inhibitory Control: An ERP Study

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The purpose of the present study is to investigate the influence of music tempo on inhibition control. An electroencephalogram (EEG) was recorded when participants performed a Go/No-go task while listening to slow (54 bpm), medium-paced (104 bpm), fast (154 bpm), or no music. The behavioral results showed that the accuracies for the No-go trials were lower in the fast than in the slow tempo music conditions, while the accuracies for the Go trials were also lower in the fast tempo than in no music conditions. The event-related potential (ERP) study results showed that larger N2 and P3 amplitudes were elicited by No-go than by Go conditions. Moreover, the difference N2 (N2d) amplitudes observed by No-go vs. Go condition were larger in fast music than in medium-paced, slow, and no music conditions, indicating more consumption of cognitive resources in the process of conflict monitoring under the fast music condition. However, no such differences were observed among medium-paced, slow, and no music conditions. In addition, the difference P3 (P3d) amplitudes, an index of response inhibition, were not significant among these four music conditions. The present study showed a detrimental influence of music tempo on inhibition control. More specifically, listening to fast music might impair an individual's ability to monitor conflict when performing the inhibitory control task.

Keywords: music tempo, inhibitory control, Go/No-go paradigm, N2, P3

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INTRODUCTION

The popularity of music in the field of psychological research has been increasing. More and more researchers regard music as the product of a general-purpose cognitive architecture and then discuss it from different perspectives of musical elements (e.g., mode, rhythm, tempo, etc.; Sutton and Lowis, 2008; Levitin et al., 2018; Navarro et al., 2018). An investigation into these elements of music not only has strong operability and practical significance but also is the basis for our understanding of the effects of music on human cognition.

Music tempo, which is measured in terms of beats per minute (bpm), is a representative of the basic dimension of music (Karageorghis et al., 2011). Moreover, it has been found that the tempo of music can affect not only human's cognition such as attention, time perception, decision-making (North et al., 1998; Amezcua et al., 2005; Day et al., 2009), but also human's consumption, diet, or driving behaviors. For example, it was found that participants made faster stimulus evaluation and response in fast than in slow tempo music conditions during a visual selective attention task (Amezcua et al., 2005). The decision accuracy was also higher in fast than in slow tempo music conditions during a multi-attribute decision-making task (Day et al., 2009). Moreover, previous studies have shown that the in-store traffic in a supermarket

could be speeded up and the daily gross sales volume increased when the background music played in fast tempo relative to that played in slow tempo (Milliman, 1982). Furthermore, the background music of fast tempo could shorten restaurant patrons' dining time (Milliman, 1986), with drinking speed increased (McElrea and Standing, 1992). Brodsky (2002) investigation into the impact of music tempo on simulated driving performance and vehicle control showed that the fast-paced music would increase the simulated driving speed and perceived speed estimate. Moreover, vehicular collision, lane crossings, and disregarded red traffic lights were more frequent during simulated driving in fast-paced than in low-paced background music conditions. Brodsky (2002) suggested that fast music could consume a driver's attentional resources and impaired their motor control.

Actually, most of our daily activities, such as consumption, shopping, diet, or driving behaviors as mentioned above, are associated with human's executive functions (also called cognitive control; Burkhard et al., 2018). Moreover, previous studies have demonstrated a close relationship between executive functions and musical training (Zuk et al., 2014). However, much less is known about the influence of music tempo on executive functions. Given the considerations mentioned above, the present study aimed to investigate the influences of music speed on executive functions. More specifically, we adopted event-related potentials (ERPs) and Go/No-go paradigm to investigate the temporal features underlying the influences of music speed on inhibition control. As an important subcomponent of executive functions, inhibition control is the ability to suppress inappropriate thoughts and responses (Diamond, 2013). Inhibitory control is frequently measured by using the Go/No-go paradigm, in which subjects were asked to respond to the "Go" stimulus and withhold their responses to the "No-go" stimulus (Falkenstein et al., 1999; Luijten et al., 2011).

Thus, in the present study, an electroencephalogram (EEG) was recorded when the participants performed the Go/No-go task while listening to slow (54 bpm), medium-paced (104 bpm), fast (154 bpm), or no music. Moreover, we put our focus on two ERP components, N2 and P3, both of which have been widely observed in the Go/No-go task. Specifically, the N2 amplitudes were larger for No-go trials relative to Go trials, reflecting the process of conflict monitoring (Nieuwenhuis et al., 2003). Moreover, the P3 amplitudes were also larger for No-go trials relative to Go trials, indexing the process of response inhibition (Falkenstein et al., 1999). In order to highlight the No-go N2 and the No-go P3 effects, the difference N2 (N2d) and P3 (P3d) waveforms were observed by subtracting the Go from the No-go conditions (Falkenstein et al., 1999; Gajewski and Falkenstein, 2013; Burkhard et al., 2018). Thus, we aimed to explore whether or not music tempo could affect the inhibitory control as evidenced by behavioral and neural indices. If music tempo influenced the inhibitory control, then different Go and No-go accuracies as well as the N2d and P3d amplitudes would be expected among music of different tempos. Otherwise, no behavioral and neural differences would be observed.

MATERIALS AND METHODS

Participants

To establish the sample size, *a priori* statistical power analysis for a repeated-measures design was conducted using G*Power 3.1.9.2 (Faul et al., 2007). According to the software, a total sample size of $n = 19$ would be required to obtain a medium effect size of Cohen's $f = 0.25$ ($a = 0.05$, power = 0.8; Cohen, 1988). To ensure a sufficient number of participants, a sample size of 26 participants (10 females, mean age = 19.5 years, SD = 1.4) were selected in the present study. All subjects were right-handed, with normal or corrected-to-normal visual acuity and no history of neurological diseases or color blindness. Ethical approval for the study was obtained from the Research Ethics Committee of the Hunan Normal University. The participants also signed an informed consent form before the experiment and were given appropriate rewards upon completion of the experiment.

Materials

The first movement of Beethoven's "Moonlight Sonata" was selected at the original 54 bmp for slow tempo musical excerpt. Similar to the previous studies (Brodsky, 2002; Bishop et al., 2014), this original musical excerpt was recomposed to 104 bmp for the medium and 154 bmp for the fast musical excerpts using the Adobe Audition CS6 (Adobe Systems Inc., San Jose, CA, USA) software. All the participants in this experiment are not familiar with these three musical excerpts. Dynamic earphones (Air Pods 2) with noise cancellation function were used for the participants to listen to the music. In addition to these three music conditions, there is also a no music condition, in which the participants performed the Go/No-go task with no audio input. The music loudness value is set to 70 dB SPL, which could be adjusted by the subjects at will to ensure maximum comfort.

Procedure

This study adopted the Go/No-go paradigm, which is a classical paradigm to investigate inhibition control (Diamond, 2013). The stimuli in this task were two kinds of shapes with different colors: a white rectangle, a purple rectangle, a white triangle, and a purple triangle. All the white stimuli were Go trials (75%) and all the purple stimuli were No-go trials (25%), with each type of stimulus presented randomly. Each trial was initiated by a small black cross presented for a duration ranging from 500 to 1,000 ms. Afterwards, one of the four types of stimuli was presented for 500 ms, which then was followed by a gray screen presented for 800 ms (see **Figure 1**). The participants were required to press a key on Go trials and not to press a key on No-go trials while listening to slow tempo, medium tempo, fast tempo, and no music. Thus, the present study included four blocks (the slow tempo, medium tempo, fast tempo, and no music blocks). Each block contained 240 trials (180 Go and 60 No-go trials), and the order of these four blocks was balanced across the participants. At the end of each block, a self-reported rate of this music was required on a scale of 1–9 in terms of induced pleasure (unpleasant to pleasant), arousal (calm to intense), and preference (dislike to like). After the rating, there was also a break of at least 5 min.

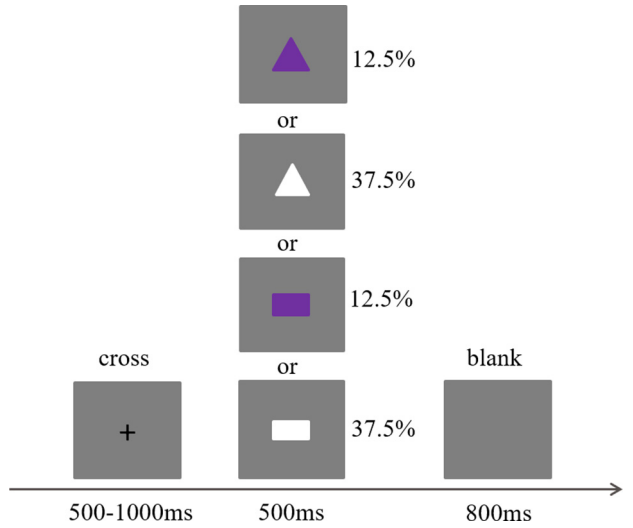

FIGURE 1 | Task parameters for the Go/No-go paradigm. The task was presented using E-Prime v. 2.0 (Psychology Software Tools Inc., Pittsburgh, PA, USA) software running on an IBM-compatible computer. The presentation of trials was randomly switched, and each subject was required to press the buttons when presented go (white rectangle or white triangle) trials and give no response to No-go (purple rectangle or purple triangle) trials.

Data Recording and Processing

An EEG was recorded from 64 scalp sites using tin electrodes mounted in an elastic cap (Neuro Scan Inc.,) with an online reference to the CPz. During the offline analysis, the EEG was re-referenced to the average of the right and the left mastoids. All interelectrode impedances were maintained under 5 KΩ. The EEG signals were amplified with a 0.1–30-Hz bandpass filter and were continuously sampled at 500 Hz/channel. The EEG was averaged in 800 ms epochs (200-ms baseline) that were time-locked to the presentation of the stimulus mark. According to previous ERP literatures regarding the Go/No-go task (Huster et al., 2010) and through the inspection of the topographic maps and grand-averaged ERP waveforms, we analyzed two specific components, N2 (260–320 ms) and P3 (400–500 ms) with the following regions: frontal (F3, F1, Fz, F2, and F4), fronto-central (FC3, FC1, FCz, FC2, and FC4), central (C3, C1, Cz, C2, and C4), centro-parietal (CP3, CP1, CPz, CP2, and CP4), and parietal (P3, P1, Pz, P2, and P4) regions. A three-way repeated analysis of variance (ANOVA) was conducted on the mean amplitudes of N2 and P3, with music tempo (four levels: 54 bpm, 104 bpm, 154 bpm, and no music), stimulus type (Go and No-go trials), and brain regions (five levels: frontal, fronto-central, central, centro-parietal, and parietal) as within-subject factors. The difference N2 and P3 waveforms were observed by subtracting the Go from the No-go conditions. In addition, one-way ANOVA was conducted on the behavioral accuracy and reaction times (RTs) with music tempo as within-subject factor. The degrees of freedom of the F-ratio were corrected by Greenhouse–Geisser. False discovery rate correction was applied for *post hoc* multiple comparisons.

RESULTS

Behavioral Results

The ANOVA for No-go accuracy showed a significant main effect of music tempo ($F_{(3,75)} = 4.48$, $p = 0.017$, $\eta_p^2 = 0.15$). The *post hoc* multiple comparisons revealed that the accuracies were lower in fast than in slow music conditions. The ANOVA for Go accuracy ($F_{(3,75)} = 8.93$, $p = 0.001$, $\eta_p^2 = 0.26$) and RT ($F_{(3,75)} = 42.43$, $p < 0.001$, $\eta_p^2 = 0.71$) also showed a significant main effect of music tempo. The accuracy in the no music condition was higher than those in the fast-paced ($p = 0.006$), the medium-paced ($p < 0.001$), and the slow-paced ($p = 0.006$) music conditions. RTs in the fast-paced music condition were shorter than those in the medium-paced and in the slow-paced music conditions ($ps < 0.004$), in which RTs were also shorter than those in the no music condition ($ps < 0.001$; **Table 1**).

In addition, the ratings on music-induced pleasure, arousal, and preference showed no significant main effects on arousal ($F_{(2,50)} = 1.78$, $p = 0.18$, $\eta_p^2 = 0.07$) and preference ($F_{(2,50)} = 2.34$, $p = 0.11$, $\eta_p^2 = 0.086$). A significant main effect on pleasure was observed ($F_{(2,50)} = 5.93$, $p = 0.005$, $\eta_p^2 = 0.19$), with higher scores for medium than for slow tempo musical excerpts ($p = 0.006$). However, no significant differences were observed between medium and fast ($p = 0.19$) or slow and fast ($p = 0.08$) tempo musical excerpts.

ERP Results

The ANOVA for N2 amplitudes showed a significant main effect on stimulus type ($F_{(1,25)} = 50.35$, $p < 0.001$, $\eta_p^2 = 0.67$), and the No-go condition elicited more negative N2 than the Go condition (see **Figure 2A**). Moreover, the interaction between stimulus type and music tempo was significant ($F_{(3,75)} = 4.95$, $p = 0.005$, $\eta_p^2 = 0.17$). The difference N2 amplitudes, obtained by subtracting the Go from the No-go conditions, were larger in the fast-paced music condition (−5.19 μV) than those in the medium-paced (−3.48 μV, $p = 0.05$), slow-paced (−2.51 μV, $p < 0.001$), and no music (−3.16 μV, $p = 0.045$) conditions. However, no significant differences were observed among the medium-paced, slow-paced, and no music conditions ($ps > 0.26$).

TABLE 1 | Results of the one-way repeated-measures analysis of variance (ANOVA) for the accuracy of Go and No-go trials and the reaction time (RT) of Go trials.

Conditions	Fast (154 bpm) Mean (SD)	Medium-paced (104 bpm) Mean (SD)	Slow (54 bpm) Mean (SD)	No music Mean (SD)	*F*
Accuracy of No-go trials (%)	93.78 (0.06)	95.32 (0.03)	96.35 (0.03)	96.28 (0.04)	4.48*
Accuracy of Go trials (%)	94.64 (0.08)	95.86 (0.04)	95.23 (0.07)	99.25 (0.02)	8.93**
RT to Go trials in ms	333.10 (24.67)	340.76 (23.24)	346.91 (25.85)	376.10 (38.19)	42.43***

*Notes: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.*

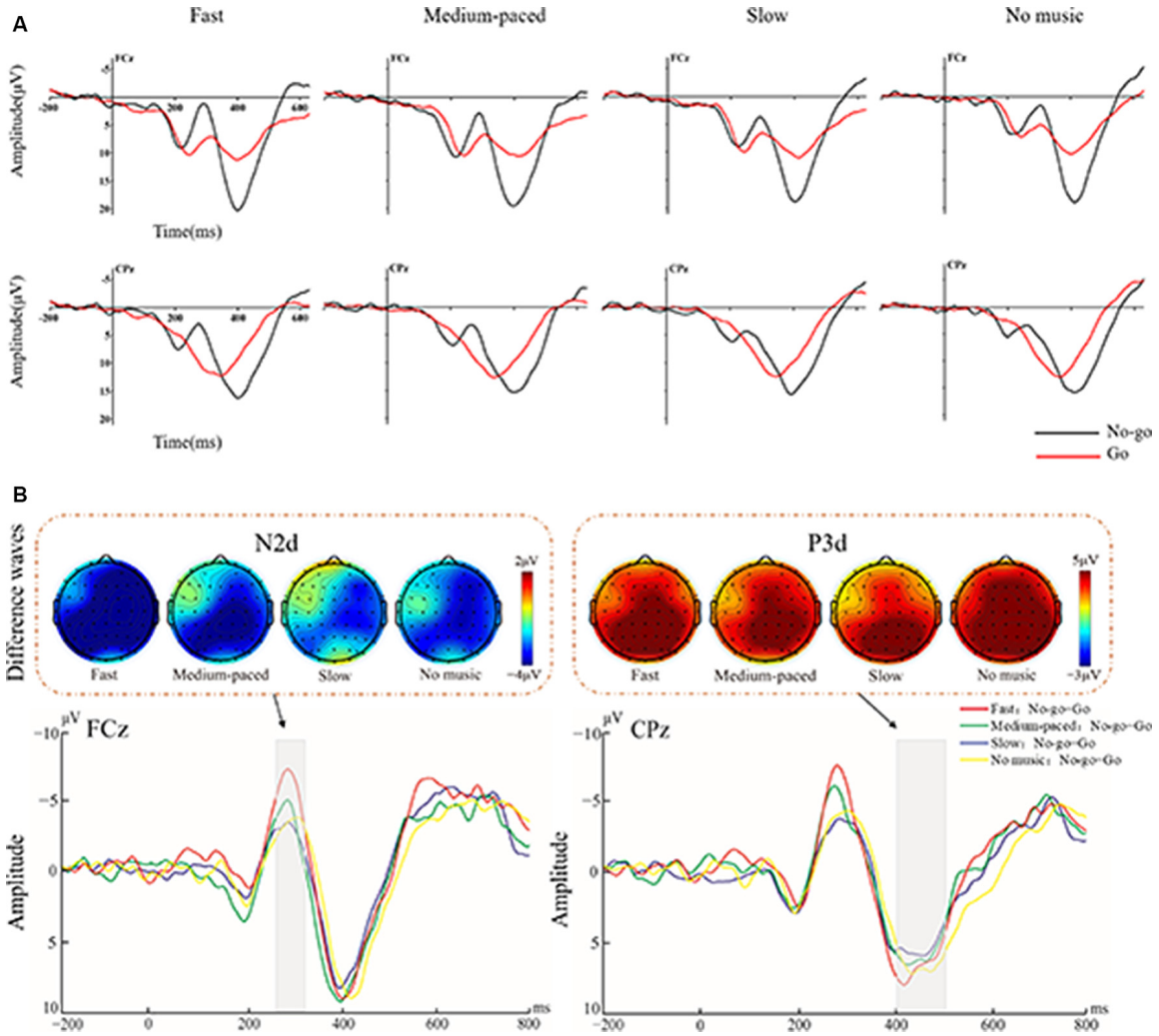

FIGURE 2 | (A) Averaged event-related potentials (ERPs) at electrode FCz and CPz for Go (red lines) and No-go (black lines) trials separated by conditions of music tempo (fast, medium-paced, slow, and no music). **(B)** The different waves (No-go minus Go) at FCz and CPz for the different tempos are shown in the lower panel. The amplitudes of the N2d and P3d components for tempos are indicated by different line colors: fast, red lines; medium-paced, green lines; slow, blue lines; and no music, yellow lines. The topographical maps of the N2d (left panel) and P3d (right panel) components for different tempos are shown in the upper panel.

The interaction between stimulus type and brain region was also significant ($F_{(4,100)}$ = 4.88, p = 0.02, η_p^2 = 0.16). The N2d amplitudes were largest at the centro-parietal region. In addition, there was no significant interaction effect among music tempo, stimulus type, and regions ($F_{(12,300)}$ = 1.88, p = 0.13, η_p^2 = 0.07).

The ANOVA for P3 amplitudes showed a significant main effect on stimulus type ($F_{(1,25)}$ = 54.14, p < 0.001, η_p^2 = 0.68), and the No-go condition elicited larger P3 amplitudes than the Go condition (see **Figure 2B**). The interaction between stimulus type and brain region was significant ($F_{(4,100)}$ = 7.13, p = 0.008, η_p^2 = 0.22). The P3d amplitudes were largest at the parietal region. However, no significant interaction effects were observed between stimulus type and music tempo ($F_{(3,75)}$ = 1.005, p = 0.39, η_p^2 = 0.04) and among stimulus type, music tempo, and brain region ($F_{(12,300)}$ = 1.53, p = 0.2, η_p^2 = 0.06).

DISCUSSION

The current study examined the influences of different tempos of music on inhibitory control by using the Go/No-go paradigm. The behavioral results showed that the accuracies for No-go trials were lower in the fast than in slow tempo music conditions, while the accuracies for Go trials were also lower in the fast tempo than in no music conditions. These behavioral results might indicate an impaired inhibitory control when listening to fast tempo music.

Consistent with previous studies (Nieuwenhuis et al., 2003), the present study showed larger N2 amplitudes in No-go than in Go conditions, irrespective of the type of background music. Moreover, we also observed a significant interaction effect between stimulus type and music tempo. The N2d amplitudes, obtained by subtracting the Go from the No-go conditions,

were larger in the fast tempo music condition than in the three other conditions. The N2 component in the inhibitory control tasks was suggested to reflect the detection of response conflict (Nieuwenhuis et al., 2003) and also a recruitment of attentional resource for the following response inhibition (Van Veen and Carter, 2002; Yuan et al., 2012). Jodo and Kayama (1992) found that the No-go N2 amplitudes were larger under high than under low time pressure condition. The participants in the high time pressure condition were required to make Go responses within a shorter period, which thus resulted in fast responses to Go trials. Jodo and Kayama (1992) suggested that the faster responses to the Go trials could enhance the Go responses, which would be more difficult to be withheld on the appearance of the No-go trials. Thus, increased efforts were required to inhibit the Go response to No-go trials, which thus contributed to enhanced N2 amplitudes (Jodo and Kayama, 1992). In the current study, the behavioral responses to Go trials were faster in the fast tempo music condition than those in the three other conditions. This result was consistent with the previous study showing that faster responses were induced by listening to fast than to slow tempo music during a visual selective attention task (Amezcua et al., 2005). Thus, more cognitive efforts would be required to produce appropriate No-go response in a fast tempo music condition, which contributed to larger N2d amplitudes.

Moreover, consistent with previous studies (Falkenstein et al., 1999; Gajewski and Falkenstein, 2013), larger P3 amplitudes were observed for No-go trials relative to Go trials in the present study. It has been generally considered that the P3 predominantly represents motor or response inhibition (Enriquez-Geppert et al., 2010). However, we did not observe the interaction effect between stimulus type and music tempo. In other words, the P3d amplitudes were similar among the four music conditions. This finding suggested that the tempo of music did not affect the later response inhibition.

However, it should be noted that the tempo of the music is one of the potential factors for inducing emotion (Kim et al., 2018). Thus, the emotion effect induced by music tempo cannot be completely ruled out when investigating the influence of music tempo on inhibitory control and thus would form a contamination for the present study. However, the self-reported rate of music in terms of induced pleasure, arousal, and preference could rule out this possibility because there were no significant differences on arousal and preference rating among these three types of music conditions. Although a significant main effect on pleasure was observed, no significant differences were observed between medium and fast or between slow and fast tempo music conditions. Thus, the ERP effects at the N2d were more likely specific to the tempo of music rather than the induced pleasure, arousal, and preference.

Taken together, the present study, using ERPs, demonstrated an obvious effect of music tempo on inhibition control. More specifically, listening to fast music would impair an individual's ability to monitor conflict. To our knowledge, this is the first time that the influences of music tempo on inhibitory control are directly investigated. In the future, the present findings should be replicated and verified by other experimental paradigms, especially the two-choice oddball task, which can provide the RT index of behavioral inhibitory control that the Go/No-go task does not have (Yuan et al., 2008, 2012).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Hunan Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RX and JieC designed the study. RX, JieC, CL and JiejC wrote the manuscript and carried out all data analyses. RX, CL and JiejC conducted data collection. All authors contributed to and approved the final version of the manuscript.

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Cultivating Affective Resilience: Proof-of-Principle Evidence of Translational Benefits From a Novel Cognitive-Emotional Training Intervention

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Available evidence highlights the importance of emotion regulation (ER) in psychological well-being. However, translation of the beneficial effects of ER from laboratory to real-life remains scarce. Here, we present proof-of-principle evidence from a novel cognitive-emotional training intervention targeting the development of ER skills aimed at increasing resilience against emotional distress. This pilot intervention involved training military veterans over 5–8 weeks in applying two effective ER strategies [Focused Attention (FA) and Cognitive Reappraisal (CR)] to scenarios presenting emotional conflicts (constructed with both *external* and *internal* cues). Training was preceded and followed by neuropsychological, personality, and clinical assessments, and resting-state functional MRI data were also collected from a subsample of the participants. Results show enhanced executive function and psychological well-being following training, reflected in increased working memory (WM), post-traumatic growth (PTG), and general self-efficacy (GSE). Brain imaging results showed evidence of diminished bottom-up influences from emotional and perceptual brain regions, along with evidence of normalized functional connectivity in the large-scale functional networks following training. The latter was reflected in increased connectivity among cognitive and emotion control regions and across regions of self-referential and control networks. Overall, our results provide proof-of-concept evidence that resilience and well-being can be learned through ER training, and that training-related improvements manifested in both behavioral change and neuroplasticity can translate into real-life benefits.

Keywords: emotion regulation training, transfer effects of intervention, affective resilience, emotional well-being, emotional memory recollection, emotion-cognition interactions, large-scale functional brain networks, resting state fMRI

INTRODUCTION

The increasing prevalence of emotional disturbances, such as anxiety and depression, in the adult population is a major public health concern. It is estimated that by 2030 anxiety and depression will be among the most prevalent causes of disability worldwide. Because of their high prevalence (with over 40 million Americans having anxiety disorders alone), these emotional disturbances are associated with overwhelming long-term costs, which may affect the overall quality of life even decades later (Howard et al., 2014). Complicating the issue, these mental health problems often go untreated because the dominant models of delivering mental health treatment in clinical settings prevent many individuals from accessing such services (Kazdin, 2019). Moreover, deficient emotion regulation (ER), which is one of the core problems in emotional disorders, may persist even after treatment and remission, hence increasing the likelihood of relapse and the persistence of emotional distress (Kanske et al., 2012). Psychological resilience, which involves adaptive emotional responses in the face of adversity, can provide a protective buffer against the harmful effects of stressful events. Resilience is influenced by a combination of internal personal attributes and external factors (family and social networks support). Among the most important personal attributes associated with resilience is the ability to self-regulate emotional responses and adaptively engage cognitive/executive control. Here, we provide proof-of-concept evidence regarding the effectiveness of a novel training alternative that captures the complexity of ER in everyday life. Our training program is grounded in the *emotion regulation choice* framework (Sheppes et al., 2014) and is based on a multidimensional approach involving behavioral, personality, clinical, and brain imaging assessments.

Self-regulation influences the ability to control thoughts, emotions, and actions to achieve a desired outcome, and encompasses cognitive, emotional, neural, and behavioral levels (Mischel et al., 1989; Blair and Diamond, 2008). Deficient regulation of emotion (or emotion dysregulation) is one of the core problems in emotional disturbances, such as anxiety and depression, and may persist after therapeutic treatment and remission (Kanske et al., 2012). Self-regulation capacities indexing differences in vulnerability to anxiety and stress are related to both *psychological* and *neural* factors, highlighting the need to develop self-regulatory solutions based on an integrative understanding of psychological factors and their interactions, along with an understanding of the associated neural mechanisms. *Psychological* factors include both cognitive control [working memory (WM), inhibitory control] and ER skills (Naragon-Gainey et al., 2017), as also demonstrated by our own work (Hu and Dolcos, 2017; Moore et al., 2018). *Neural* factors include network-level (Power et al., 2011) targets for cognitive control ("*cognitive control networks*"), involving dorsolateral prefrontal cortical (dlPFC) and lateral parietal (LP) regions, and emotion/ER networks ("*salience/survival network*"), involving basic emotion processing regions, such as the amygdala (AMY), and regions of emotion integration and regulation, such as the ventrolateral PFC (vlPFC), medial PFC (mPFC), and anterior cingulate cortex (ACC; Hopfinger et al., 2000; Seeley et al., 2007; Dosenbach et al., 2008). The role of these networks in self-regulation has been identified based on both functional and structural neuroimaging studies. For instance, we have recently shown increased activity in the cognitive control network and reduced activity in regions of the salience network, when engaging specific ER strategies (Denkova et al., 2015; Iordan et al., 2019; Dolcos et al., 2020a). Also, increased gray matter volume in cognitive control regions provides protection against symptoms of anxiety (Dolcos et al., 2016; Hu and Dolcos, 2017; Moore et al., 2018).

Important to consider in this context are possible links between psychological and neural aspects in self-regulation, which highlight the importance of flexible adaptive behavior (Naragon-Gainey et al., 2017). For instance, increased focus on distressing thoughts and memories observed in affective disorders may be linked to an inability to flexibly switch attentional focus between internal and external environments, which may be the main cause for getting "*stuck in the rut*" (Nolen-Hoeksema, 1991; Cooney et al., 2010; Holtzheimer and Mayberg, 2011). This is consistent with evidence pointing to alterations in the *default* or resting-state functional connectivity (rsFC) of the large-scale brain networks linked to cognitive/executive and emotional dysfunctions, with increased coupling among regions on the *default mode network* (DMN) and functional decoupling of DMN from regions of the *frontoparietal control network* (FPCN; Hopfinger et al., 2000; Raichle et al., 2001; Fox et al., 2005; Dosenbach et al., 2008; Kaiser et al., 2015).

Recent cognitive neuroscience research offers some initial promising evidence that ER may be enhanced through cognitive training (Denny and Ochsner, 2014), although such evidence is limited. Cognitive training and interventions that train specific psychological abilities, such as mindfulness-based attention and multitasking performance, can induce changes in brain structure and function (Denny and Ochsner, 2014; Verghese et al., 2016; Valk et al., 2017; Cohen and Ochsner, 2018; Dolcos et al., 2020c). Evidence from these interventions complements clinical studies showing volume reductions in specific brain regions following traumatic life events (Sekiguchi et al., 2015), and provide evidence for possible enhancements induced by customized cognitive training. However, most of the work on ER training is limited because it has focused on practicing one specific strategy (Sekiguchi et al., 2015; Cohen and Ochsner, 2018; Dolcos et al., 2020c). In our view, such a "*one size fits all*" approach minimizes the complexity of ER, which inherently involves interactions of person, situation, and ER strategy factors (Aldao et al., 2015).

Our view is consistent with the *emotion regulation choice* framework, which proposes that ER involves two major cognitive stages, an attentional selection stage and a semantic meaning stage (Sheppes et al., 2014). The initial attentional stage consists of an early disengagement from emotional information before it undergoes elaborated processing. This is typically achieved through attentional deployment strategies, such as focused attention (FA), which involve disengaging attention from the emotional information before it is represented in working memory by focusing on neutral thoughts or details

(Van Dillen and Koole, 2007). The subsequent semantic meaning stage involves later engagement with the emotional information that passes the early attentional selection stage (Sheppes et al., 2014). The most common semantic strategy is cognitive reappraisal (CR), which involves engaging with and modifying the meaning of emotional information through semantic processing (e.g., Gross, 2002). These early vs. later strategies have differential benefits. Specifically, blocking emotional information early, through attentional deployment, before it gathers force, allows modulation of high-intensity emotional information, by engaging relatively simple cognitive processes, whereas the elaborated semantic processing that occurs during CR allows processing, evaluating, and remembering emotional information, which are crucial for long-term goals and for adaptation (Sheppes et al., 2014). Psychological resilience and well-being require flexible adaptation of ER strategies to fit differing situational demands (Gross, 2007; Kashdan and Rottenberg, 2010; Watkins, 2011). Therefore, it is important to examine interactive effects of regulation strategies that are most beneficial for a given person in a given situation.

The following additional concepts are also central to consider in this context: *self-efficacy* (SE), *cognitive flexibility* (CF), and *working memory* (WM). The concept of SE, originating in the Social Cognitive Theory (SCT; Bandura, 1986), refers to individuals' beliefs about their own competence to exert control over events that matter (Bandura, 1997). Such beliefs influence cognitive, affective, motivational, and decisional processes that support individuals in achieving their goals and are crucial determinants of initiating and maintaining changes in behavior (Bandura, 1986). Individuals with high SE engage in more effortful, persistent, and resilient coping efforts, which may enable them to identify important opportunities within stressful circumstances and promote individual growth (Bandura, 1997, 2001). Importantly, recent evidence identifying SE as a mechanism influencing the effects of stress on mental health, along with suggestions regarding the malleability and transfer of SE beliefs across functional domains, point to the importance of considering SE as a key concept in interventions aimed at improving mental health (Bandura, 1986; Maciejewski et al., 2000; Zinken et al., 2008; Schönfeld et al., 2019).

Regarding CF, given the complexity and shifting nature of contextual demands in everyday life, individuals may need to flexibly engage multiple regulation strategies, both within and across emotional episodes (ER flexibility; Kashdan and Rottenberg, 2010; Aldao et al., 2015; Ford et al., 2019). A rich repertoire of ER strategies, along with their flexible implementation linked to current contextual demands, have been associated with enhanced adaptation and better coping (Cheng, 2001; Bonanno et al., 2004; Kashdan and Rottenberg, 2010; Bonanno and Burton, 2013; Aldao et al., 2015; Koole et al., 2015; Levy-Gigi et al., 2016). Inflexibility, on the other hand, characterized by rigid attempts to control psychological reactions to discomfort, has been associated with increased distress and detrimental effects on self-efficacy (Gamez et al., 2014; Levin et al., 2014; Jeffords et al., 2018; Tavakoli et al., 2019).

Flexible engagement of ER strategies is also an important predictor of post-traumatic growth (PTG). PTG theory suggests that growth occurs by developing regulation strategies that encourage constructive thinking and allow individuals to engage with trauma-related emotions and memories (Tedeschi and Calhoun, 2004). Reappraisal, a strategy focused on engaging with and changing the meaning of the emotional content, has been consistently associated with PTG, but recent ER research supports a more nuanced, context-dependent view. For instance, reappraisal seems to be preferred when dealing with low-intensity traumatic events, and attention focus/distraction is preferred for coping with high-intensity distressing emotions (Sheppes et al., 2014; Orejuela-Dávila et al., 2019). Moreover, the use of reappraisal or distraction at different phases in the trauma recovery may have different effects, reflected in increased PTG or reduced post-traumatic stress (Levy-Gigi et al., 2016).

Finally, WM also plays a critical role in the ability to successfully engage ER and reduce symptoms of distress (Schmeichel and Demaree, 2010). Defined as the capacity-limited resource that temporally maintains and manipulates information in the service of higher functions, WM is an executive function that plays a key role in the regulation of cognitive and emotional processes at both early and later stages of processing (Baddeley, 2003). Evidence linking WM to the early stage control of visual attention shows that WM capacity contributed to the ability to focus one's eyes away from a salient visual stimulus, and predicted the ability to ignore the "unattended" message in a dichotic-listening task (Conway et al., 2001; Kane et al., 2001). Moreover, WM capacity has been linked to the ability to engage later-stage ER strategies, such as reappraisal and suppression (Schmeichel et al., 2008; McRae et al., 2012). Finally, increased WM capacity is essential in reducing the detrimental impact of apprehensive thoughts, which tend to be "permanent residents" in the WM of anxious individuals (Eysenck et al., 2007).

The main goal of the present study was to investigate the effectiveness of a comprehensive cognitive-emotional training program aimed at developing healthy and flexible ER skills to increase resilience and well-being and improve executive function. This training program builds upon evidence, including from our own research, regarding cognitive and emotional control and their link to the associated neural mechanisms, and capitalizes on evidence regarding the effectiveness of two ER strategies in reducing emotional distress: focused attention (FA) and cognitive reappraisal (CR; Ochsner and Gross, 2005). This combination of strategies is based on evidence regarding their effectiveness in both healthy functioning and in clinical conditions, which allows for optimal adaptive responses when facing real-life emotional challenges (Kanske et al., 2012; Denkova et al., 2015; Iordan et al., 2019; Dolcos et al., 2020a,b). For instance, FA can be quickly deployed when individuals may unexpectedly encounter highly emotional stimuli (earlier stages of emotion processing) and CR can draw on a combination of cognitive control processes (later stages of emotion processing) to change one's emotional appraisals and responses (Gross, 1998). Also, both strategies can be applied to *external* (percepts) and to *internal* (memories, thoughts) stimuli, as well as to developing problem-solving skills. Hence, these two aspects (i.e., external vs. internal) were both trained using a picture processing task and a writing task, respectively. Of particular relevance is also

evidence regarding their effectiveness in influencing emotional memories, which is a topic less explored in the ER literature. For instance, we recently demonstrated the effectiveness of FA during both encoding of memories for emotional pictures and retrieval of emotional autobiographical memories (Denkova et al., 2015; Iordan et al., 2019; Dolcos et al., 2020a).

The effectiveness of the training was assessed using neuropsychological, personality, and clinical assessments, along with measures of rsFC, before and after the training. We tested the following hypotheses regarding the neurobehavioral effects of the present ER intervention: (1) behavioral improvements following training would be reflected in measures of both cognitive/executive and affective domains, and possibly in measures indexing more general abilities, such as self-efficacy, and positive psychological growth; (2) regarding brain imaging, we expected normalization of the rsFC in the large-scale functional networks following training, possibly reflected in decreased connectivity among DMN regions and increased connectivity between DMN and FPCN regions. We also explored evidence for diminished bottom-up influences, possibly linked to decreased rsFC of perceptual regions and AMY, as well as possible changes in the connectivity between basic emotion processing regions (AMY) and emotion control (PFC) regions.

MATERIALS AND METHODS

Participants

Nineteen military veterans (with a deployment assignment to Iraq and/or Afghanistan in the preceding 5 years) enrolled in post-secondary education at the time of the study (mean age = 30.9; *SD* = 7.9; 95% males, 79% White/European American, 11% Black/African American, 5% Asian/Asian-American, and 5% Other) were recruited to participate in the present pilot intervention. Participants were assigned to one of two training programs: (1) a cognitive-emotional regulation training (CERT) program (N = 9); or (2) a psychosocial training (PSYCT) program (N = 10), ensuring equal proportions of participants with posttraumatic stress disorder (PTSD) – i.e., scores 33 or above on the PTSD Checklist – PCL-5 in each condition (Weathers et al., 2013). Branch of service was also considered when assigning participants to the two programs. All participants provided written informed consent under a protocol approved by the Institutional Review Board (IRB) of the University of Illinois at Urbana-Champaign.

General Procedures

The intervention took place over 5–8 weeks, and participants in both conditions received equal amount of training/therapy per week (90 min), over two 45-min sessions for the CERT intervention and all in one session for the PSYCT intervention. The CERT participants had individual sessions led by an advanced doctoral student in cognitive neuroscience, where they learned how to apply the two ER strategies (i.e., FA and CR) to hypothetical scenarios (see **Figure 1** below) in computerized tasks, and the PSYCT participants had group sessions with an advanced doctoral candidate in clinical psychology. All participants completed a set of self-report measures and a battery of cognitive tasks before and after the training. Ten participants (five from each group) also received structural and resting-state functional brain scans before and after the intervention.

Training/Intervention Procedures

CERT Group

Participants in this group were individually guided by the researcher to perform computer-based tasks that simulated situations that required ER (**Figure 1**). Specifically, two types of situations were involved: external situations, where emotional challenges would arise from negative events in the surrounding

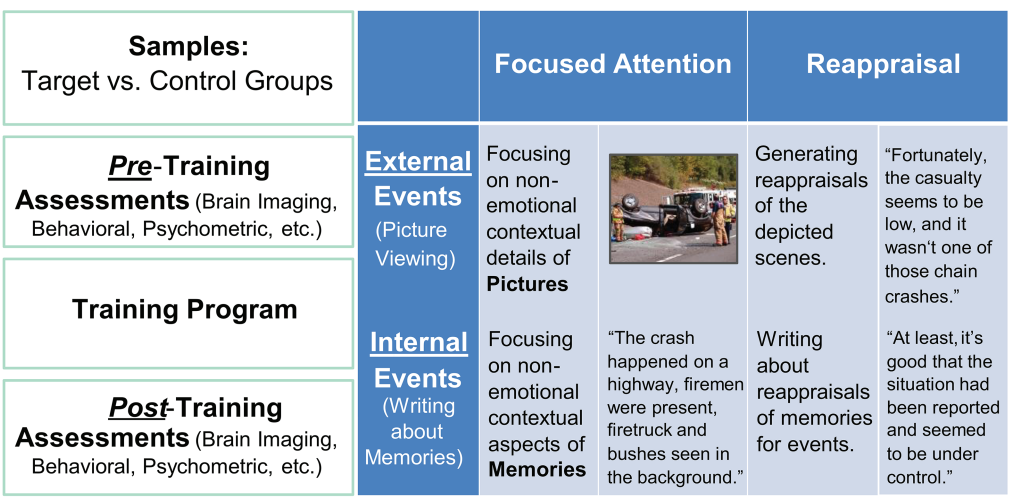

FIGURE 1 | Illustration of the Intervention Approach. Big-picture details (left-side panel) and specific details regarding the implementation of ER training in the CERT group (right-side panel).

environment, and internal situations, where emotional challenges would come from intruding negative autobiographical memories. The external ER was simulated using a picture-viewing task, where participants were instructed to apply ER strategies while viewing emotionally disturbing images. The internal ER was simulated using a timed writing task, where they were instructed to write about pre-identified emotional episodes from their autobiographical memories, in ways consistent with ER strategies. The autobiographical memories were identified using established procedures that have been effectively employed in our previous research to collect emotional autobiographical memories (Denkova et al., 2011, 2012, 2013a,b, 2015; Iordan et al., 2019). In the present study, participants were prompted with cues of a wide range of life events and were instructed to select and provide short descriptions of 12 most negative and 12 most positive events that reminded them of specific, unique, and personal events that they would like to work on during the training. Training primarily focused on the identified negative events. Due to the potential sensitive nature of past experiences of our subject population, a highly personalized approach was adopted, where participants were encouraged to identify six unpleasant episodes that they were comfortable working with on a regular basis, throughout the duration of the training. Because of the highly individualized nature of these memories, participants varied in the way they rated the emotional intensity associated with their own unpleasant memories, but overall they rated them as intense (mean intensity/arousal = 5.57; *SD* = 1.35) on a seven-point Likert scale (1 = "*Not at all*," 7 = "*Very much*"). In each session, participants were guided to confront the presented emotional challenges, and practiced the application of both FA and CR to reduce the emotional impact created by the tasks.

In order to facilitate mastery over the strategies and encourage transfer effects to occur, participants were trained to switch between FA and CR, between the two types of tasks (involving internal thoughts and memories and external stimuli) and three temporal dimensions (present, past memories, and future worries). Several gradients were built into the session schedules. The training started out by familiarizing participants with one strategy at a time in a session, focusing on guiding participants to apply FA or CR to one internal and one external event selected by the participant. As the training advanced, each session posed increasingly complex situational demands, by guiding participants to first apply the same strategy to different events and eventually deploy different strategies on different events within a session, thereby achieving an increasing level of flexibility. Flexibility training culminated with sessions that engaged both strategies to work with worries for expected future events.

PSYCT Group

This intervention was developed by two of the authors (CW and HB), who are clinical psychologists and one of them (CW) is a military veteran. The Control intervention focused on the provision of skills (e.g., goal setting, problem solving) that were considered likely to be useful to military student veterans. This intervention emphasized skills that student veterans had likely already acquired in the military (e.g., time management) and explored how the skillset could be translated to an academic setting. Skills were presented and practiced in a group format, with participants given assignments to practice the skills between sessions. The intervention included elements of several evidence-based psychological treatments that were considered likely to be useful to military student veterans. Specifically, the intervention included elements of problem-solving therapy (Nezu, 2004), acceptance and commitment therapy (Hayes et al., 2006), cognitive therapy for depression (Beck, 1979), social skills training (Bellack et al., 1981), and behavioral activation treatment (Cuijpers et al., 2007). The treatment was provided in a group format (with group sizes ranging from 4 to 8), once per week for 90 min. Each week focused on a different aspect of psychoeducation and/or skill development (e.g., identifying values and cognitive distortions, clarifying goals, expressing anger, and recognizing thoughts, sensations, and behaviors associated with emotions).

Symptom, Personality, and Neuropsychological Assessments

Posttraumatic Stress Disorder status was assessed using the PCL-5 (Weathers et al., 2013), which consists of 20 items that present challenges associated with a stressful experience (e.g., "*Repeated, disturbing dreams of the stressful experience*?"). Participants are instructed to report how much they are bothered by these challenges using a five-point scale (0 = "*Not at all*"; 4 = "*Extremely*"). An overall PCL-5 score is computed by summing the item ratings.

Anhedonic Depression was assessed using an abbreviated version of the Mood and Anxiety Symptom Questionnaire – Anhedonic Depression Scale (MASQ-AD; Bredemeier et al., 2010), which contains eight items asking participants how often they feel various positive and negative experiences (e.g., "*Felt really bored*"; "*Felt unattractive*"). Participants responded using a five-point scale, corresponding to how frequently they have experienced a variety of different symptoms during the past week (1 = "*Not at all*"; 5 = "*Extremely*"). Item ratings were summed to calculate the final MASQ-AD score. Some versions of this questionnaire ask participants how often they experience thoughts of suicide, but this question was omitted from our presentation due to IRB restrictions.

Trait Worry was assessed using an abbreviated version of the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990; Kertz et al., 2014), which consists of eight items, each presenting a statement concerning how often participants worry (e.g., "*I do not tend to worry about things*"). To each item, participants responded using a five-point scale, describing how applicable the statement was to them (1 = "*Not at all typical of me*"; 5 = "*Very typical of me*"). Item ratings were summed to calculate the final PSWQ scores.

Trait Affect was assessed using the Positive and Negative Affective Schedule (PANAS; Watson et al., 1988), which includes a list of 20 adjective descriptors of 10 positive (e.g., "*interested*," "*enthusiastic*") and 10 negative (e.g., "*irritable*," "*upset*") affects. Items were rated on a five-point scale (1 = "*Very slightly or not at all*"; 5 = "*Extremely*") according to the extent to which

"[the person] *feels this way over a longer period of time*." This version of the PANAS was supplemented by adding three positive affect words ("*pleased*," "*cheerful*," and "*happy*") and five negative affect words ("*frustrated*," "*down*," "*anxious*," "*grouchy*," and "*sad*"), for a total of 28 items (Boden et al., 2012). Positive and negative affect scores were summed for affect totals.

Post-Traumatic Growth was assessed using the PTG Inventory (PTGI; Tedeschi and Calhoun, 1996), which consists of 21 items that assess changes in peoples' lives following a crisis or disaster. Each item presents participants a statement describing a potentially positive change in one's mental state linked to the crisis (e.g., "*I can better appreciate each day*"; "*I changed my priorities about what is important in life*"). Participants rated the extent that they believed the statement applied to them, using a six-point scale (0 = "*I did not experience this change as a result of my crisis*"; 5 = "*I experienced this change to a very great degree as a result of my crisis*"). An overall PTGI score was created by summing the item ratings.

General Self-Efficacy was assessed using the General Self-Efficacy scale (GSE; Schwarzer and Jerusalem, 1995), which consists of 10 items assessing participants' optimism and self-belief concerning difficult tasks and overcoming adversity. Participants were presented statements addressing how they tend to solve problems (e.g., "*When I am confronted with a problem, I can usually find several solutions*") and were instructed to respond using a four-point scale corresponding to how much they believe the statement applies to them (1 = "*Not at all true*"; 4 = "*Exactly true*"). An overall GSE score was tallied by summing the values for each item.

Emotional Approach Coping was assessed using the Emotional Approach Coping scale (EAC; Stanton et al., 1994), which is an eight-item questionnaire designed to measure emotional coping. It contains two subscales, one on emotional processing (EP), addressing the extent that participants process their emotions in a healthy manner (e.g., "*I acknowledge my emotions*"), and a second subscale on emotional expression (EE), addressing whether participants are comfortable expressing their emotions (e.g., "*I let my feelings come out freely*"). For questions on each subscale, participants indicate how often they engage their emotions in these manners (1 = "*I usually do not do this at all*"; 4 = "*I usually do this a lot*"). Final EP and EE scores are calculated by summing the item ratings associated with each subscale. A total EAC score, reflecting the ability to acknowledge, understand, and express emotions, is also calculated, with lower scores representing poorer emotional coping.

Working memory was assessed using two versions of the Two-Back Working Memory task, one focusing on the spatial locations of the letter stimuli (Two-Back Space) and the other focusing on the identity of the letter stimuli (Two-Back Letter; Bredemeier and Berenbaum, 2013). For each version, participants were presented with a series of letter stimuli appearing at different spatial locations on the computer screen, one at a time, and responded *via* keyboard. Participants were instructed to maintain the two prior stimuli in their working memory. For the spatial version of the task, participants indicated whether the current stimulus was in the same or different location as the one presented two trials ago. For the letter version, participants responded to whether the current stimulus was the same as or different from the one presented two trials ago. Each stimulus was presented for 500 ms (with a 2,000 ms intertrial interval), and each participant completed five blocks of 20 stimuli for both space and letter tasks. Working memory performance was assessed as the percent accuracy and the average response time (RT) to correct trials. The first two trials were excluded from analyses, as they lack prior stimuli for comparison.

Attention and Executive Functions were measured using the Stroop test (Stroop, 1935). In this task, participants named the color of words while ignoring the content of the words (i.e., color words). The words used were all color words (e.g., red, blue, yellow, and green). The test takes advantage of individuals' abilities to read words more quickly and automatically than naming colors.

Brain Imaging Data Acquisition

MRI scanning was conducted on a 3T Siemens PRISMA scanner. Sagittal localizer and 3-D MPRAGE anatomical images were first obtained (TR = 2,300 ms; TE = 2.32 ms; FOV = 230 × 230 mm; volume size = 192 slices; voxel size = 0.9 × 0.9 × 0.9 mm^3). Functional images consisted of a series of axial images acquired using an echoplanar sequence (TR = 2,000 ms; TE = 25 ms; FOV = 230 × 230 mm; volume size = 38 slices; voxel size = 2.5 × 2.5 × 3 mm^3, number of volumes = 298), while participants stayed eyes-open.

Data Analyses

Behavioral Data Analyses

The effects of interventions on cognitive and affective well-being were assessed by measuring participants' pre- vs. post-intervention scores on the neuropsychological and questionnaire assessments. For each assessment, the simple main effects of the CERT and PSYCT training were first assessed by submitting participants' scores to paired *t*-tests, done separately for each training group. Next, to compare the pre vs. post differences between the two groups, two-way mixed-ANOVAs were performed, with Time (Pre vs. Post) as the within-subject factor, and Group (CERT vs. PSYCT) as the across-subject factor. All the behavioral data were analyzed using the SPSS software (IBM Corp. 2017. version 25.0).

Brain Imaging Data Analyses

Preprocessing

Functional images collected at both timepoints (i.e., pre- and post-intervention) were despiked using 3dDespike in AFNI (Cox, 1996), before being submitted to preprocessing in SPM12,[1] where they first underwent slice timing and two-pass realignment. The resulting motion parameters were later used to calculate scan-to-scan head displacement used for denoising. Co-registration was done in two steps: first between functional and anatomical images within each session, then between all images collected pre- and post- intervention. To take advantage

[1]http://www.fil.ion.ucl.ac.uk/spm

of the repeated scans, the Longitudinal Registration toolbox (Ashburner and Ridgway, 2013) in SPM12 was used to first create mid-point average anatomical images for each participant, which were then segmented and submitted to groupwise Dartel template creation (Ashburner, 2007). Using this Dartel template, functional images were resampled to the MNI space on an isotropic 3 mm grid combining transformations estimated at previous steps in a single interpolation. Lastly, images were smoothed with a 6 mm FWHM Gaussian filter. Notably, smoothed data were used to define voxel time series at each voxel, whereas unsmoothed data were used to generate tissue type regressors used during denoising as well as to define seed timeseries for the chosen Regions of Interest (ROIs). After preprocessing, images were processed through denoising steps to further remove noises and artifacts, including (1) demeaning and detrending across each session, (2) nuisance regressions, which used a combination of motion regressors (six realignment parameters and their first-order derivatives), aCompCor (Behzadi et al., 2007) regressors (signals from top five principal components generated from each of the tissue maps of white matter and cortico-spinal fluids, along with their first-order derivatives), and main condition effects (computed by convolving images in a session with a canonical hemodynamic response function to further remove simple session-related co-activation confounds), (3) a simultaneous (Hallquist et al., 2013) bandpass filter of (0.008, 0.09) Hz, and (4) scrubbing based on framewise displacement (Power et al., 2011) with a threshold of 0.5 mm. Denoising steps were implemented in the CONN toolbox (v18b; Whitfield-Gabrieli and Nieto-Castanon, 2012). Denoised images were visually inspected to ensure the effectiveness of the procedures by observing the normality of the functional connectivity distributions, the relative independence between functional connectivity values and nodal distances, and that there were no substantial differences between the two experimental groups.

Functional Connectivity Analysis

A seed-based approach was implemented to examine the effects of interventions on the rsFC, based on clear a priory interest in regions involved in bottom-up emotion processing (i.e., amygdala, AMY) and top-down cognitive/emotional control processing, as follows: dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), and medial PFC (mPFC; Moore et al., 2018). Two complementary atlases were used to define the masks of the seeds: the anatomically-based FSL Harvard-Oxford atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007) was used to define the seed mask for the subcortical structure, AMY, and the CONN network atlas (derived from ICA analyses of 497 subjects in a dataset from the Human Connectome Project) was used to define the seed masks for the cortical regions, with the lateral prefrontal cortex (PFC) node in the Frontoparietal network roughly corresponding to the dlPFC, the inferior frontal gyrus node in the Language network roughly corresponding to the vlPFC, and the Default Mode network node in the medial PFC, located anterior and ventral to the rostral ACC, roughly corresponding to the mPFC.

Seed timeseries were extracted from the unsmoothed data aggregated across all voxels within each seed ROI, and voxel timeseries were extracted from the smoothed data at each voxel in the rest of the brain. Functional connectivity values were calculated as the Pearson correlation coefficients between the selected ROI seeds and voxels in the rest of the brain, which were then Fisher-transformed into *z*-scores to allow subsequent statistical testing. At the second level, analyses focused on investigating Group × Time interaction effects, where differential functional connectivity changes were identified in the two groups as a result of the intervention, as well as a main effect of Time, where functional connectivity changes were identified across both groups. To this end, a general linear model was constructed, with Time being the within-subject factor and Group being the between-subject factor, each with two levels. Interaction effects were tested using the contrast [CERT(Post-Pre) − PSYCT(Post-Pre)], and the main effects contrast [CERT(Post-Pre) + PSYCT(Post-Pre)]. Unless otherwise specified, statistical significance was set at a voxel-level threshold of $p < 0.005$ (uncorrected) combined with a cluster-level threshold of $p < 0.05$ (FDR-corrected). These analyses were performed in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012).

RESULTS

Evidence of Enhanced Well-Being and Executive Function Following ER Training

Table 1 summarizes the means and SDs of behavioral measures. As hypothesized, we identified behavioral patterns of increased abilities associated with the CERT training within domains relevant to adaptive cognitive and emotional processing. Specifically, the CERT group showed significant pre vs. post increases in GSE [$t(8) = 2.910$, $p = 0.020$, $d = 0.970$; **Figure 2**]. Additionally, participation in the CERT group promoted positive growth-focused mindsets with regard to participants' traumatic events [PTGI: $t(8) = 1.994$, $p = 0.041$, one-tailed, $d = 0.665$]. While both changes support the efficacy of CERT training, only the benefits in GSE were found to be specific to the CERT group. This was demonstrated by a two-way mixed-design ANOVA examining the effect of Time (Pre vs. Post) and Training Group (CERT vs. PSYCT), which revealed a significant Time × Training Group interaction effect [$F(1,17) = 7.196$, $p = 0.016$, $\eta_p^2 = 0.297$], further supporting the effectiveness of our training in increasing self-efficacy and positive psychological change.

Second, also as hypothesized, participants in the CERT group also showed post-training improvements in executive function (**Figure 3**), and these increases were observed in both Two-Back Letter and Space WM tasks. These findings were confirmed by paired samples *t*-tests for both the Two-Back Letter and Two-Back Space tasks, which both showed a decrease in reaction time in the CERT group [Letter: $t(8) = -3.172$, $p = 0.013$, $d = -1.06$; Space: $t(8) = -2.535$, $p = 0.035$, $d = -0.845$]. Although a two-way mixed-design ANOVA did not identify significant Time × Training Group interactions for either the

TABLE 1 | Descriptive statistics linked to each intervention.

	PSYCT		CERT	
	Pre	Post	Pre	Post
Measures:				
PTSD PCL-5	22.4 (12.9)	18.7 (15.2)	21.8 (11.9)	22.1 (17.0)
MASQ-AD	17.7 (6.4)	16.4 (7.2)	17.7 (6.0)	19.3 (6.6)
PSWQ	24.4 (8.8)	20.0 (10.0)*	23.1 (8.6)	22.7 (8.8)
PANAS-Pos	33.1 (7.1)	32.9 (7.8)	29.3 (9.5)	27.8 (8.2)
PANAS-Neg	14.6 (3.0)	13.7 (2.8)	15.9 (5.1)	15.9 (5.4)
PTGI	38.6 (27.8)	42.8 (30.1)	26.9 (24.6)	38.4 (25.3)†
EAC-Total	21.6 (4.6)	22.7 (5.9)	18.9 (4.0)	20.3 (6.7)
EAC-EP	11.7 (4.1)	12.6 (3.2)	10.1 (2.1)	11.2 (3.3)
EAC-EE	9.9 (3.5)	10.1 (3.6)	8.8 (3.2)	9.1 (3.2)
GSE	33.5 (4.0)	31.7 (2.3)	30.6 (3.4)	32.6 (3.3)*
2-Back Letter	1,022 (141)	939 (191)	1,111 (194)	921 (192)*
2-Back Space	865 (187)	840 (162)	921 (241)	775 (175)*
Stroop	87 (19)	52 (19)	66 (17)	81 (48)
Demographics:				
Age (yr.)	29.2 (1.5)		32.0 (4.3)	
Male (%)	100		89	
Ethnicity (%)				
White	70		89	
Black	20		0	
Asian	10		0	
Other	0		11	
Education (yr.)	13.8 (0.6)		13.9 (0.5)	

*Values represent means (SDs). Two-Back values reflect reaction times (RTs) in milliseconds (ms), and Stroop values reflect RT differences (ms) between incongruent and congruent trials. Significance markings, † and *, indicate significant pre vs. post differences. PSTD PCL, Posttraumatic Stress Disorder Checklist; MASQ-AD, Mood and Anxiety Symptom Questionnaire – Anhedonic Depression Scale; PSWQ, Penn State Worry Questionnaire; PANAS, Positive and Negative Affective Schedule (Pos, Positive subscale; Neg, Negative subscale); PTGI, Post Traumatic Growth Inventory; EAC, Emotional Approach Coping (EP, Emotional Processing subscale; EE, Emotional Expression subscale); GSE, General Self Efficacy. *significant at $p < 0.05$ (two-tailed); †significant at $p < 0.05$ (one-tailed).*

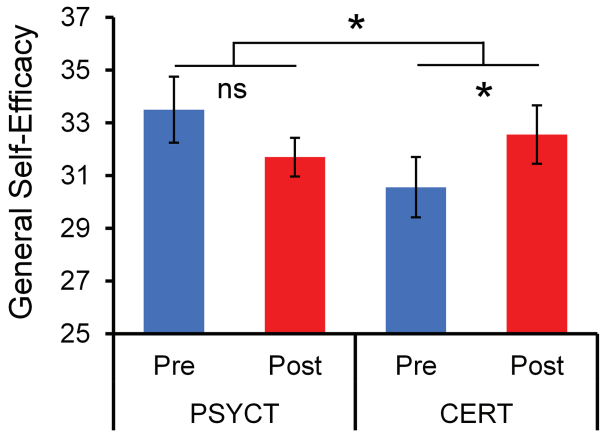

FIGURE 2 | Increased General Self-Efficacy (GSE) following Cognitive – Emotional Regulation Training (CERT). Paired *t*-tests revealed a significant pre- to post-training increase in the GSE score that was specific to the CERT group ($N = 9$). This was confirmed by a two-way ANOVA Time (Pre vs. Post) × Group (PSYCT vs. CERT) interaction ($N = 19$). *significant at $p < 0.05$ (two-tailed); ns, non-significant.

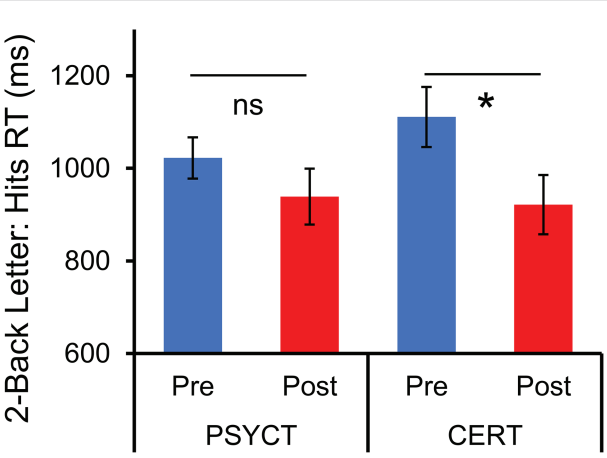

FIGURE 3 | Increased Working Memory Performance following CERT Intervention. Figure shows the results of the Two-Back Letter task, and the same patterns were also observed for the Space task (not shown). Paired t-tests of pre- and post-training reaction times (RT) within the Two-Back WM tasks revealed significant improvements (faster time), which were exclusive to the CERT group. *significant at $p < 0.05$ two-tailed; ns, non-significant.

Letter [$F(1,17) = 1.38$, $p = 0.257$, $\eta_p^2 = 0.077$] or Space [$F(1,18) = 2.62$, $p = 0.122$, $\eta_p^2 = 0.146$] tasks, the effect of training on WM was significant only in the CERT group, but not in the PSYCT group [Letter: $t(9) = 1.279$, $p = 0.233$, $d = -0.404$; Space: $t(9) = 0.650$, $p = 0.532$, $d = -0.206$]. These results indicate that improvements in executive domains were exclusive to the CERT training group. No other significant changes linked to the interventions were identified (all $p_s > 0.05$).

Changes in Resting-State Functional Connectivity Following ER Training

Further supporting the effectiveness of the CERT intervention, brain imaging results showed significant changes in the rsFC (**Table 2**), overall, supporting the idea that the our ER training facilitated functional decoupling of bottom-up emotion and perception processing regions from regions of the DMN, along with enhanced functional coupling among top-down cognitive control regions and between regions of default-mode and control networks. First, for the subcortical seed regions, the AMY showed overall decreased rsFC with cortical regions involved in higher-level cognition and lower-level perception, following training (**Figure 4**). Specifically, across both groups, there was decreased rsFC between the left AMY seed and clusters in the cortical midline regions, including the medial frontal (mPFC/ACC) and parietal cortices. Interestingly, in the CERT group, the left AMY showed larger decrease in the rsFC with a cluster in the left visual cortex.

Second, for the cognitive control cortical regions, the left dlPFC showed decreased rsFC with a cluster in the left occipital pole, which was seen across both CERT and PSYCT groups. However, the left dlPFC showed larger increase in rsFC with a cluster in the cingulate/paracingulate cortex as

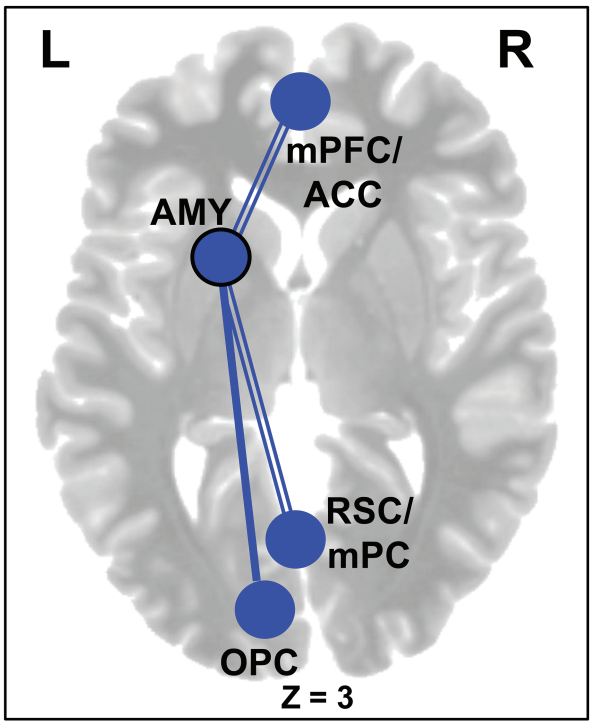

FIGURE 4 | Decreased amygdala (AMY) rsFC following Training. Subjects across both CERT and PSYCT groups showed reductions in left AMY-medial prefrontal frontal cortex (mPFC) and left AMY-RSC/mPC rsFC following training (double lines); similar reduced rsFC was also identified for the right AMY (not shown), at a lower threshold (see **Table 2**). Interaction effects additionally revealed larger post-training reduction in rsFC between the left AMY seed and the left OPC, in the CERT group (single line; see also **Table 2**). Blue nodes and edges reflect decreases in rsFC. Black node outline indicates the seed region. mPFC, Medial Prefrontal Cortex; ACC, Anterior Cingulate Cortex; AMY, Amygdala; RSC, Retrosplenial Cortex; mPC, Medial Parietal Cortex; OPC; Occipito-parietal Cortex; and L/R, Left/Right Hemispheres.

well as with a cluster in the right posterior segment of the inferior frontal cortex (IFC), in the CERT group (**Figure 5**, left panel). Moreover, increased rsFC was also found between the right dlPFC and a cluster in the posterior part of the left middle frontal cortex, which was also larger, in the CERT group. Regarding the vlPFC seeds, there was increased rsFC between the right vlPFC seed and a cluster in the posterior segment of the right IFC, as well as clusters in the bilateral occipito-temporal cortex (OTC), all of which were larger in the CERT group. Finally, regarding the mPFC seed, there was increased rsFC with clusters in the right lateral parietal cortex (LPC), across both groups, and with a cluster in the left LPC, which was stronger in the CERT group (**Figure 5**, right panel).

Overall, these findings pinpoint training-dependent changes in bottom-up as well as top-down processes that are less driven by the emotional salience and basic perceptual processing, along with enhanced *in-tune* responses among cognitive and emotion control regions and across self-referential and cognitive control networks.

DISCUSSION

This report presents proof-of-principle evidence for the effectiveness of a novel cognitive-emotional training intervention targeting the acquisition of ER skills aimed at increasing resilience against emotional distress in military veterans. There were two main novel results: (1) behavioral results showed evidence for enhanced psychological well-being and executive function following training, reflected in increased GSE, PTG, and WM; (2) brain imaging results showed evidence of diminished bottom-up influences from emotional and perceptual brain regions, along with evidence of normalized rsFC in the large-scale functional networks following training, reflected in increased connectivity among cognitive and emotion control regions and across DMN and FPCN networks. These findings are discussed below.

Enhanced Well-Being and Executive Function Following ER Training

First, CERT, but not PSYCT, was associated with increased GSE. GSE is not constrained to specific types of tasks or situations, but rather reflects more general beliefs in one's competence to manage a broad range of tasks and challenges (Luszczynska et al., 2005). Therefore, successful performance of a range of behaviors and activities in a variety of situations is expected to build such a generalized sense of efficacy (Schwarzer and Luszczynska, 2007). The enhanced GSE as a result of engaging in the complex CERT is in line with previous intervention programs that have shown an efficacy-enhancing impact of a range of mastery experiences (Schunk, 1989; Bandura, 1997). Increased GSE is a very desirable outcome, given that SE is seen as the most crucial and proximal predictor of behavior (Bandura, 1997, 2002). SE has a self-regulatory function in dealing with stress and negative affect, being linked to better psychological adjustment, lower distress, fewer symptoms of burnout, and fewer symptoms of depression over time, along with reduced social anxiety, depression, and externalizing symptoms and better posttraumatic recovery (Brouwers and Tomic, 2000; Benight and Harper, 2002; Benight and Bandura, 2004; Bisschop et al., 2004; Gallagher et al., 2011, 2020; Singh and Bussey, 2011). It is assumed that SE impacts the appraisal and interpretation of stressful situations (transactional stress theory) and exerts beneficial effects through constructive regulation of motivational, affective, and decisional processes (Lazarus and Folkman, 1984; Bandura, 1997; Simmen-Janevska et al., 2012). This leads individuals with higher levels of self-efficacy to consider anxiety and stress symptoms as more controllable and temporary (Cervone, 2000; Leganger et al., 2000). We expect that, with a larger sample, the increased self-efficacy in our CERT group will also be associated with multiple benefits on well-being.

Second, both CERT and PSYCT were associated with increased PTG. One essential component of PTG is the ability to manage distressing emotions elicited by the traumatic event. The PTG model proposed by Tedeschi and Calhoun (2004) suggests that the process of rebuilding disrupted beliefs involves significant cognitive processing that allows engagement with trauma-related

TABLE 2 | Brain regions showing changes in functional connectivity following training.

Brain region	Side	BA	MNI coordinates			Peak *t*-value	Cluster size
			x	*y*	*z*		
L Amygdala							
Main Effects							
↓ mPFC/ACC	R	32	15	39	−12	7.25	182
	R	10	14	41	−11	7.10	
	R	9	11	47	19	4.73	
↓ RSC/mPC	M	29	−6	−39	12	6.69	105
	M	23	−9	−54	12	5.05	
	M	31	−1	−64	27	4.07	
Interaction Effects							
↓ Precentral gyrus	M	4	0	−18	69	10.70	163
	L	5	−15	−44	85	6.69	
↓ Occipito-parietal Ctx.	L	19	−12	−81	45	7.43	106
	L	7	−18	−74	55	4.92	
R Amygdala							
Main Effects							
↓ RSC*	M	29	−3	−42	9	6.32	131
↓ Occipital Ctx.*	M	23	−6	−58	10	4.19	
↓ Cerebellum*			−1	−48	−15	4.52	
L dlPFC							
Main Effects							
↓ Lateral occipital Ctx.	L	18	−24	−93	0	7.77	113
↓ Occipital pole	L	17	−12	−100	−12	4.90	
Interaction Effects							
↑ dACC	M	32	9	18	39	7.55	128
↑ Medial frontal Ctx.	M	8	6	26	46	6.09	
	M	6	5	11	58	5.74	
↑ Inferior frontal Ctx.	R	44	52	15	3	5.19	80
R dlPFC							
Interaction effects							
↑ Middle frontal Ctx.	L	8	−42	12	45	8.79	72
↑ Medial occipital Ctx.	M	18	9	−87	−6	7.62	83
↑ Occipital pole	R	17	20	−96	−14	5.51	
R vlPFC							
Main Effects							
↑ Occipito-parietal Ctx.*	M	19/7	9	−75	39	7.43	186
↑ Occipital Pole*	M	18	12	−94	27	5.50	
↑ Occipital Ctx.*	R	18	15	−96	24	5.11	
Interaction Effects							
↑ Inferior Frontal Ctx.	R	9	39	12	24	7.00	92
↑ Occipito-temporal Ctx.	R	37	60	−57	0	7.36	109
↑ Occipito-temporal Ctx.	L	37	−63	−54	−9	6.86	74
Medial PFC							
Main Effects							
↑ Inferior parietal lobule	R	40	42	−45	57	6.47	97
↑ Superior parietal lobule	R	7	18	−66	55	5.83	
↑ Occipito-parietal Ctx.	M	19/7	−6	−81	39	7.90	76
	L	19	−18	−85	42	6.39	
Interaction Effects							
↑ Inferior parietal lobule	L	40	−42	−45	57	8.16	203

*The table contains peak coordinates for clusters identified as showing significant changes in the resting-state functional connectivity (rsFC) across the cognitive-emotional regulation training (CERT) and psychosocial training (PSYCT) groups (i.e., Main Effects of Time) or stronger for the CERT group (i.e., Time × Group Interaction Effects). In the case of the main effects, up arrows indicate increases in the post-training rsFC and downward arrows indicate decreases in the post-training rsFC. In the case of the interaction effects, upward arrows indicate stronger rsFC increases in the CERT group than in the PSYCT group and downward arrows indicate stronger rsFC decreases in the CERT group than in the PSYCT group, following training. For main effects, the t-values represent Post vs. Pre differences, averaged across the CERT and PSYCT groups, and for interaction effects, t-values represent of Post vs. Pre differences between the two groups. Unless otherwise noted *, regions listed were identified with a $p < 0.005$ threshold and FDR cluster-size corrected ($q_{FDR} < 0.05$). *significant at a threshold of $p < 0.01$, $q_{FDR} < 0.05$.*

BA, brodmann area; MNI, montreal neurological institute; Ctx., cortex; PFC, prefrontal cortex; mPFC, medial prefrontal frontal cortex; ACC, anterior cingulate cortex; RSC, retrosplenial cortex; mPC, medial parietal cortex; MFC, middle frontal cortex; dlPFC, dorsolateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; IFC, inferior frontal cortex; vlPFC, ventrolateral prefrontal cortex; M, medial; and L/R, Left/right hemispheres.

emotions and memories. Recent research examining the relation between ER and PTG suggests that strategies that involve engagement with the emotional stimuli, such as reappraisal, might influence PTG by helping individuals extract meaning from their traumatic experiences (Larsen and Berenbaum, 2015). Whereas reappraisal seems to be the choice for dealing with low-intensity situations, attentional deployment strategies are less cognitively demanding and seem to be preferred in high-intensity situations in individuals who had experienced a recent traumatic event (e.g., in the last 6 months, Strauss et al., 2016; Orejuela-Dávila et al., 2019). Both of our training programs involved significant cognitive processing. CERT, which offered our participants the flexibility to choose between FA and CR, allowed both engagement with diverse negative stimuli (pictures, memories, and worries) and disengagement of attention from the negative aspects of these stimuli, and facilitated PTG. The beneficial effect of ER training on PTG is in line with available evidence showing a positive correlation between self-reported engagement of adaptive ER strategies and PTG in undergraduate students (Thomas et al., 2019).

Third, participants in the CERT group also showed post-training improvements in WM, and these increases were observed in both Letter and Space tasks, while the PSYCT group participants did not show such increases. Individuals with emotional disorders such as anxiety and depression show a bias toward processing of negative emotional information (threat, sadness, etc.), leading to excessive rumination on past negative events and worry about the uncertainty of the future (for a review, see Mogg and Bradley, 2018). Our brain systems have a limited capacity, and thus when people get stuck on negative (and task-irrelevant) information, they have fewer resources to invest to complete the demands of the tasks at hand, shift attention, and process information efficiently (Derakshan and Eysenck, 2009). This gives rise to patterns of cognitive inflexibility (for a review, see Stange et al., 2017). When executive functions of WM become inefficient and rigid, people are more likely to experience interference and find it difficult to achieve their goals efficiently (Berggren and Derakshan, 2013).

Recent research suggests a strong link between WM, attentional control, and cognitive reappraisal (Shipstead et al., 2014). In fact, some authors argue that WM capacity refers specifically to attention control (Kane et al., 2001). Successful WM needs efficient use of attentional control to hold information temporarily and to manipulate the content in order to execute ER tasks, which require overriding habitual responses. Moreover, evidence from cross-sectional and training studies have established that WM ability and ER are connected, and that this connection is likely mediated by attention control (Schmeichel et al., 2008; McRae et al., 2012; Schweizer et al., 2013). The two ER strategies trained in the CERT group involve a number of mental operations, such as keeping in mind the specific ER strategy, monitoring/resolving the conflict between habitual and targeted reactions, selection among possible alternatives, and the modulation of behavior that, repeated over the course of the training, have helped participants improve their WM (Ochsner et al., 2012).

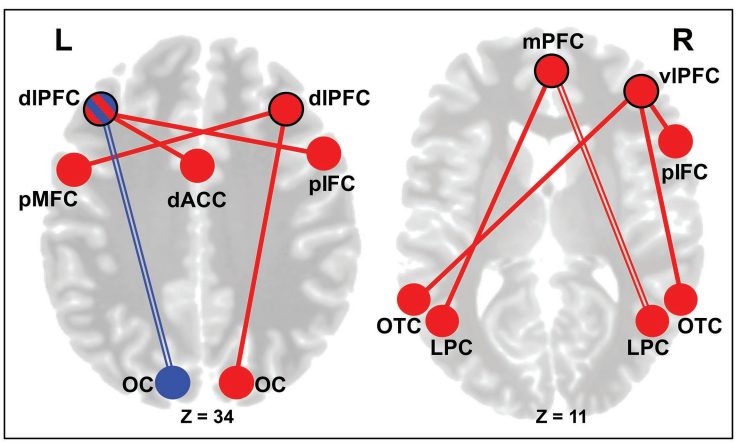

FIGURE 5 | Changes in the rsFC of Control Regions following Training. Left panel: altered dorsolateral prefrontal cortex (dlPFC) rsFC following training. Subjects across both CERT and PSYCT groups showed reductions in rsFC between the left dlPFC seed and areas of the left visual cortex, following training (blue double line). CERT training was also associated with stronger increases in the rsFC between the left dlPFC seed and the dorsal anterior cingulate cortex (dACC), and between the left dlPFC seed and a posterior portion of the right inferior frontal cortex (red solid lines). Additionally, the CERT training was also associated with larger increases in the rsFC between the right dlPFC seed and areas of the right visual cortex, and between the right dlPFC seed and a posterior area of the left middle frontal gyrus (red solid lines). Right panel: increased ventrolateral prefrontal cortex (vlPFC) and mPFC rsFC following training. The CERT training was associated with stronger increases in the rsFC between the right vlPFC seed and a posterior area of the inferior frontal cortex (IFC; pIFC), as well as between the right vlPFC seed and the bilateral occipito-temporal cortex (OTC). Regarding the mPFC, there was increased post-training rsFC between the mPFC seed and the right LPC across both CERT and PSYCT groups (red double line), and the CERT training was also associated with larger increases in the rsFC between the mPFC seed and the left LPC (red solid line). Blue reflects decreases in functional connectivity, red reflects increases, and their combination (left dlPFC node) reflects both. Black node outlines indicate the seed regions. dlPFC, dorsolateral prefrontal cortex; MFC, middle frontal cortex; vlPFC, ventrolateral prefrontal cortex; IFC, inferior frontal cortex; mPFC, medial prefrontal cortex; dACC, dorsal anterior cingulate cortex; OC, occipital cortex; OTC, occipito-temporal cortex; LPC, lateral parietal cortex; and L/R, left/right hemispheres.

Finally, it should also be noted that an important aspect of the present training linked to the engagement of memory processes is not only related to WM *per se*, as discussed above, but also related to "*working with memory*." This is because our ER training also affected the way participants encoded and retrieved emotional episodic memories. Indeed, there is evidence that both ER strategies affect emotional memory during both stages (Denkova et al., 2015; Dolcos et al., 2020a), with the overall tendency for reduction of the impact of emotion on memory (but see Dillon et al., 2007). In particular, by focusing away from the most emotional aspects of *external* stimuli, the engagement of FA is associated with reduced recollection of memory for emotional pictures (Dolcos et al., 2020a). Similarly, FA is also effective in decreasing the impact of recollected emotional autobiographical memories, both when retrieved in isolation and when retrieved as *internal* emotional distraction during an ongoing cognitive task (Denkova et al., 2015; Iordan et al., 2019). Hence, it is reasonable to expect that training participants to use ER strategies with external and internal stimuli have longer-lasting effects on the encoding and retrieval of memories for emotional events.

Changes in Resting-State Functional Connectivity Following ER Training

The brain imaging findings from our pilot investigation provide further evidence for the effectiveness of the intervention in the CERT group. First, reduced functional connectivity between AMY and midline cortical structures (both frontal and parietal) is consistent with the idea of normalized bottom-up emotional influences on activity in DMN brain regions (Zilverstand et al., 2017). DMN has been linked to a range of self-referential processing (internal thought, memory retrieval, future planning, and emotion regulation), and hence reduced rsFC from a basic emotion processing region suggests diminished influences that would emotionally color the affective state of participants when turning their focus on the internal environment, which is typically associated with a negative emotional bias in emotional disturbances (Nolen-Hoeksema, 1991; Raichle et al., 2001; Fox et al., 2005; Schacter et al., 2007; Cooney et al., 2010; Denkova et al., 2015). Interestingly, these effects were observed across the participants from CERT and PSYCT groups, which suggests similar mechanisms of change in the expected direction. However, further supporting diminished default interactions between the AMY and perceptual areas, the reduced AMY-visual cortex rsFC was larger in the CERT group. This finding is consistent with the differences in training between the CERT and PSYCT groups. Whereas the PSYCT training primarily took the form of interpersonal communications about higher-level ideas (e.g., goals, values, and skills), the CERT training emphasized cognitive mechanisms (e.g., FA), including processing of visual stimuli, in combination with advanced cognitive processing (i.e., CR), meant to diminish the impact of emotional stimulation at different stages of emotion processing. Hence, reduced coupling between regions involved in bottom-up emotion signaling specifically observed in the CERT group suggests that this training equips participants with skills that reduce the impact of bottom-up emotional influences. This is particularly important in preparing them to respond quickly in emotionally intense situations, where more effortful emotion regulation might be difficult to deploy immediately (Sheppes et al., 2014; Orejuela-Dávila et al., 2019).

Turning to brain regions involved in cognitive/emotional control, reduced rsFC of the left dlPFC with the visual cortex is also consistent with diminished bottom-up influences from perceptual brain regions, a change that was also observed across the CERT and PSYCT groups. The overall greater increased connectivity of dlPFC ROIs, bilaterally, with vlPFC and dACC areas following the CERT intervention suggests strengthened default cross-talk among areas associated with cognitive/executive and affective control regions promoted by our ER training. This is important, given the central role of the dlPFC as part of the FPCN, which is involved in interfacing between focusing on internal and external stimulation, together with brain regions (vlPFC and ACC) circumscribed by other networks (salience and cingulo-opercular; Fuster, 1997; Smith and Jonides, 1999; Hopfinger et al., 2000; Corbetta and Shulman, 2002; Seeley et al., 2007; Dosenbach et al., 2008). This allows flexible behavior involving adaptive switches between paying attention to external stimulation and being aware of our internal states, needs, thoughts, and memories (Sridharan et al., 2008; Zabelina and Andrews-Hanna, 2016). Finally, increased rsFC connectivity among subregions of the right IFC (anterior and posterior), along with stronger increased connectivity between mPFC and lateral parietal cortical areas, in the CERT group, are also consistent with enhanced functional coupling among control brain regions and normalized cross-network interactions, respectively, promoted by the CERT training.

Interestingly, our expected increased connectivity between the AMY and ER brain regions was not confirmed. Our expectation was based on task-related evidence of increased functional coupling between basic emotion processing (AMY) and emotion control (lateral and medial PFC) regions, possibly indexing the need to regulate (Dolcos et al., 2006; Denkova et al., 2015). This is consistent with the idea that such coupling is necessary for the latter regions to exert control on the AMY response, when facing external or internal emotional challenges (Dolcos et al., 2006; Denkova et al., 2015). However, it may be the case that such couplings may only be transiently increased by current challenges and not necessarily also implemented in longer-term changes reflected by measures of rsFC. Further research is needed to clarify this matter.

Caveats

A caveat of the current study is the limited sample, as there were only 19 participants in total. Future research should further confirm the proof-of-principle results of this pilot study in larger samples. Despite the smaller sample size, our findings showed strong improvements in post-traumatic growth, self-efficacy, and working memory, although there were no significant decreases in anxiety and depression as a result of the training. It is possible that changes in our primary outcomes of psychological distress have not been detected at the behavioral level due to the relatively small sample sizes of the groups in our pilot study. Nevertheless, some of the factors of behavior change, such as self-efficacy, might be more sensitive to the

particular type of training offered by our interventions, and they may act as buffering mechanisms that contribute to the protection against symptoms of distress. Moreover, changes in the rsFC following both CERT and PSYCT training indicate a normalization of bottom-up emotional influences on activity in self-referential processing regions, suggesting that both types of training helped participants experience diminished negative affect when focusing on internal thoughts and worries. Second, the combination of FA and CR in the CERT was the most effective proof-of-concept strategy for testing our approach grounded in interactive person-situation-strategy processes and the emotion regulation choice framework (Sheppes et al., 2014). However, their relative contribution to the observed effects is not clear. Although it is reasonable to expect that FA contributed to improved WM and CR to the enhanced PTG, future research using multiple control groups is needed to disentangle the unique contribution of each of these strategies.

CONCLUSION

Reduced ability to control emotional responses is a major marker of affective disturbances. Despite the small sample, the present pilot study provides proof-of-principle evidence for a sustainable cognitive emotion-regulation training intervention that goes beyond costly traditional models of therapeutic treatment by targeting the development of healthy and flexible ER skills in a sample of military veterans. Using a combination of behavioral and brain imaging methods, this study showed enhanced executive function and psychological well-being following training, reflected in increased working memory, post-traumatic growth, and general self-efficacy. Moreover, brain imaging results showed evidence of diminished bottom-up influences from emotional and perceptual brain regions, along with evidence of normalized functional connectivity in the large-scale functional networks following training, reflected in increased connectivity among cognitive and emotion control regions and across regions of self-referential and control networks. Overall, our results provide proof-of-concept evidence that resilience and well-being can be learned through ER training, and that training-related improvements manifested in both behavioral change and neuroplasticity can translate into real-life benefits.

DATA AVAILABILITY STATEMENT

The data sets analyzed for the current report are available upon requests made to the corresponding authors, pending approval from participants and the Institutional Review Board (IRB).

ETHICS STATEMENT

The study was approved by the IRB office at the University of Illinois at Urbana-Champaign, and all participants provided written informed consent. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

SD and FD designed the study, with input from YH, CW, and HB. YH and CW collected the data. SD, FD, and YH planned the analytical approach, with input from HB. YH performed the analyses, with help from PB and KH and input from FD and SD. SD and FD wrote the first draft of the manuscript, and then revised it based on contributions from YH, PB, KH, and CW, and feedback from HB. All authors contributed to the article and approved the submitted version.

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Resting State Cortico-Limbic Functional Connectivity and Dispositional Use of Emotion Regulation Strategies: A Replication and Extension Study

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Neuroimaging functional connectivity analyses have shown that the negative coupling between the amygdala and cortical regions is linked to better emotion regulation (ER) in experimental task settings. However, less is known about the neural correlates of ER traits or dispositions. The present study aimed to: (1) replicate the findings of differential cortico-limbic coupling during resting-state depending on the dispositional use of emotion regulation strategies. Furthermore, the study aimed to: (2) extend prior findings by examining whether differences in cortico-limbic coupling during resting-state predict experiential and neuronal ER success in a standard ER task. To this end, $N = 107$ healthy adults completed the Emotion Regulation Questionnaire (ERQ), underwent an 8-min resting-state fMRI acquisition, and completed a reappraisal task during fMRI. Functional connectivity maps of basolateral and centromedial amygdala nuclei were estimated with a seed-based approach regarding associations with regions of the prefrontal cortex and were then correlated with ERQ scores as well as experiential and neuronal ER success. All hypotheses and the analysis plan are preregistered at https://osf.io/8wsgu. Opposed to prior findings, we were not able to replicate a correlation of dispositional ER strategy use with functional connectivity between the amygdala and PFC regions ($p > 0.05$, FWE-corrected). Furthermore, there was no association of experiential and neuronal reappraisal success with functional connectivity between amygdala and insula as well as PFC ($p > 0.05$, FWE-corrected). The present preregistered study calls into question the reported association between individual differences in resting-state cortico-limbic connectivity and dispositional use of ER strategies. However, ongoing advances in functional brain imaging and distributed network approaches may leverage the identification of reliable functional connectivity patterns that underlie successful emotion regulation.

Keywords: emotion regulation, resting-state, amygdala, preregistration, cortico-limbic connectivity

INTRODUCTION

Emotion regulation (ER) is defined by the activation of a goal to change an unfolding emotional response and can be described as any process by which individuals modify their emotional experiences, expressions, and physiology (Gross, 1998, 2015). Being able to effectively regulate one's emotional reactions is of crucial importance for appropriate social interactions and an essential feature of mental and physical health (Gross and Munoz, 1995; English et al., 2012; Kanske et al., 2012; Hu et al., 2014; Johnstone and Walter, 2014; Kret and Ploeger, 2015). The influential Process Model of Emotion Regulation and its extension (Gross, 1998, 2015) categorizes strategies of emotion regulation according to the time point in the emotion generation process, at which they are being implemented. Cognitive change (e.g., reappraisal) appears early in the process (antecedent-focused) and refers to altering the value of the emotion eliciting stimulus, whereas response modulation (e.g., expressive suppression) takes effect later and aims at altering the emotional response. The most studied reappraisal strategy is reinterpretation, which implies changing the meaning of a stimulus (Ochsner et al., 2002). Another reappraisal strategy is detachment (distancing) where one is taking the perspective of an uninvolved observer to reduce the subjective relevance of the stimuli (Kalisch et al., 2005; Walter et al., 2009). It has been assumed that cognitive reappraisal (reinterpretation and detachment) as antecedent-focused strategies are most effective because the emotional response has not fully unfolded and the negativity of an event itself is altered, whereas response-focused strategies such as expressive suppression often fail in fully modifying the emotional response since they are initiated later in the emotion-generative process (for a review see Gross, 2002). Nevertheless, people implement both strategies in their daily lives and results are pointing to expressive suppression being advantageous in some contexts (Bonanno et al., 2004; Bonanno and Burton, 2013), while reappraisal may also turn out unsuccessful (Aldao et al., 2015). Research that investigates the underlying mechanisms influencing these long and short-term outcomes of both strategies is still ongoing.

Until recently, this research has roughly followed two approaches (Tull and Aldao, 2015): A task-related, experimental approach (hereinafter referred to as task-related ER) and an approach investigating individual differences in ER abilities and dispositional use of strategies, respectively (hereinafter referred to as dispositional ER). The task-related approach uses experimental tasks, in which participants are instructed to use one or more ER strategies to decrease or increase (mostly negative) emotions and investigates effects on different emotional (experiential), behavioral and psychophysiological outcomes. The dispositional approach frequently relies on self-report questionnaires to evaluate ER abilities and dispositional use of ER strategies. One of the most widely used self-report measures of reappraisal (with an emphasis on reinterpretation) and expressive suppression is the Emotion Regulation Questionnaire (ERQ, Gross and John, 2003). Based on the Process Model of Emotion Regulation, the ERQ evaluates the dispositional use of these two strategies.

In experimental settings, task-related reappraisal is effective in changing emotional experiences, behavior, and physiological responses (Webb et al., 2012). The authors report detachment ($d+ = 0.45$) being significantly more advantageous than reinterpretation ($d+ = 0.36$). Expressive suppression proved to be effective in the regulation of emotional experiences and behavioral, but not physiological responses (Webb et al., 2012). In contrast, a recent meta-analysis on psychophysiological outcomes of task-related ER reports mixed findings with low to medium effect-sizes for both reappraisal and expressive suppression and mostly non-significant meta-analytical effects (Zaehringer et al., 2020). Concerning dispositional ER, the dispositional use of reappraisal, measured with the ERQ, has been linked to interpersonal functioning and psychological as well as physical well-being (Gross and John, 2003). Moreover, Aldao et al. (2010) could meta-analytically show that dispositional reappraisal is negatively associated with symptoms of psychopathology. In contrast, dispositional suppression was positively associated with psychopathology with medium to large effect sizes (Aldao et al., 2010; Hu et al., 2014), worse interpersonal functioning, and greater risk of depression (Gross and John, 2003). Hence, concerning emotional experiences, both strategies have shown to be successful in the short-term regulation of emotions, while there are mixed findings of short-term physiological outcomes. Reappraisal is advantageous concerning long-term (self-reported) psychological outcomes.

Neuroscientific studies of healthy but also impaired ER can contribute to the understanding of the mechanisms and underlying processes leading to these outcomes. Mostly, this research is investigating neuronal activity in brain regions implicated in cognitive control (i.e., the prefrontal cortex, PFC) and brain regions implicated in emotional processing (i.e., amygdala and insula) as well as the coupling between these structures. Functional brain imaging studies repeatedly showed that activation in the PFC [i.e., the anterior cingulate cortex (ACC), medial (m)PFC, and dorsolateral (dl) PFC] and reduction of amygdala activation is associated with a detachment in ER tasks (Kalisch et al., 2005; Walter et al., 2009; Erk et al., 2010; Koenigsberg et al., 2010; Schardt et al., 2010; Ochsner et al., 2012; Dörfel et al., 2014. During expressive suppression, activity within similar PFC regions and the supplementary motor area (SMA) has been reported (Phillips et al., 2008; Vrtička et al., 2011; Dörfel et al., 2014). In contrast, suppression has been associated with significant increases in the amygdala and insula activity (Goldin et al., 2008; Hayes et al., 2010; Vanderhasselt et al., 2013; Dörfel et al., 2014). Therefore, it can be assumed that the interaction between PFC regions and regions of emotional processing is different for the two strategies.

For successful ER, it is assumed that dorsal PFC regions exert an inhibitory effect on regions of emotional processing *via* ventral PFC regions (Ochsner et al., 2002; Wager et al., 2008; Lee et al., 2012; Buhle et al., 2014). Consequently, in reappraisal tasks, task-related functional connectivity has been reported between the amygdala and the PFC (Banks et al., 2007; Erk et al., 2010; Schardt et al., 2010; Winecoff et al., 2011; Sripada et al., 2014; Paschke et al., 2016). Moreover, the functional coupling

of the amygdala with ventral and dorsal PFC regions were significantly correlated to experiential (self-reported) emotion regulation success (Banks et al., 2007; Paschke et al., 2016). Lee et al. (2012) suggested that functional coupling between the amygdala and prefrontal regions as well as pregenual ACC during cognitive reappraisal depends on individual differences in the capacity for reducing negative emotion. In line with this, studies including patients with psychological disorders with reduced ability to regulate emotions (e.g., depression and anxiety) have found deficits in functional and effective connectivity between the amygdala and frontal brain regions (Erk et al., 2010; Cullen et al., 2011; Niedtfeld et al., 2012; Clauss et al., 2014; Mochcovitch et al., 2014; Radaelli et al., 2015; Picó-Pérez et al., 2017). Additionally, there is evidence that not only task-related connectivity but also alterations in resting-state functional connectivity of (among others) PFC, amygdala, and insula are associated with depression and anxiety (Menon, 2011; Zhang et al., 2014; Barch, 2017). Resting-state functional brain connectivity (rsFC) reflects intrinsic connectivity, which is correlated temporal patterns among brain regions during rest. The resting-state networks closely match networks that have been continuously reported by different task conditions pointing to an intrinsic functional brain architecture important for task-specific brain activation (Smith et al., 2009). This also applies to ER-related brain networks (i.e., default mode network, the executive control network, and the salience network, see Beckmann et al., 2005; Damoiseaux et al., 2006; Seeley et al., 2007). Hence, it can be suggested that activity in task-related ER networks and resting-state connectivity between PFC and the amygdala show associations.

Gabard-Durnam et al. (2016) propose that experiences of stimulus-elicited coactivations in ER brain regions form these resting-state connectivity patterns (long-term phasic molding hypothesis), particularly during development in childhood and adolescence. The authors found that in a sample of children and adolescents, stimulus-elicited amygdala-mPFC connectivity predicted rsFC 2 years later. Likely, the dispositional, daily use of a specific ER strategy and the experience of (un)successful ER alters the functional architecture of these brain networks, which is represented in rsFC. In turn, it can be assumed that functional connectivity influences dispositional, daily strategy choice as well as strategy implementation.

Successful task-related ER (defined by a decrease in self-reported emotional experiences as well as a deactivation of brain regions engaged in emotion processing), as well as dispositional ER, should, therefore, be associated with rsFC between amygdala and PFC. However, few studies so far have directly investigated this. Picó-Pérez et al. (2018) found rsFC between the amygdala and PFC regions as well as the insula to be distinctly associated with dispositional use of suppression and reappraisal, respectively, as measured by the ERQ (Gross and John, 2003). In contrast, Uchida et al. (2015) could not find associations with self-reported dispositional ER (measured with the Difficulties in Emotion Regulation Scale, DERS, Gratz and Roemer, 2004). In a study by Morawetz et al. (2016), task-related ER (reinterpretation) success, defined by affect ratings, was positively correlated with rsFC between right amygdala and the left ventrolateral (vl)PFC as well as the insula. Uchida et al. (2015) demonstrated that greater reappraisal (reinterpretation) success, again measured by affect ratings, showed a significant negative correlation with rsFC of the right amygdala with mPFC. However, the two latter studies only focused on experiential ER success (affect ratings), and did not report results on neuronal ER success (defined by deactivations in regions of emotional processing). Additionally, to our knowledge, findings of these few existing studies have not been validated by replications.

Following this, the present study aimed at replicating and extending findings of associations between ER and rsFC of the amygdala and PFC. To define the replication attempts, we draw upon the definitions proposed by Zwaan et al. (2018), who differentiate between direct and conceptual replication studies. Direct replication is described as a study that attempts to recreate the critical elements (e.g., samples, procedures, and measures) of an original study. The authors underline that "a direct replication does not have to duplicate all aspects of an original study. Rather it must only duplicate those elements that are believed necessary for producing the original effect." Conceptual replication is defined as a study with theoretically meaningful changes "to the original procedures that might make a difference concerning the observed effect size" (p. 3).

The present study specifically pursued three objectives: (1) we aimed at an investigation of whether individual differences in *dispositional reappraisal and expressive suppression* (defined by self-reported habitual use as measured with the ERQ) can explain variance in rsFC between amygdala and PFC. To do so, we reanalyzed own existing data (Diers et al., 2014; Scheffel et al., 2019) from three related ER experiments containing measures of dispositional use of reappraisal and suppression (*via* ERQ) and fMRI resting-state scans to replicate the findings by Picó-Pérez et al. (2018). We aimed at a direct replication according to the definition outlined above. Due to using existing data, there were methodological differences between our investigation and the Picó-Pérez et al.'s (2018) study which will be outlined in the "Materials and Methods" section and in **Supplementary Table S23**. However, these differences are mostly technical and do not lead to a different operationalization of the constructs.

(2) We aimed at investigating whether individual differences in task-related, *experiential reappraisal success* (as defined by a decrease in self-reported arousal during a reappraisal task) explain variance in rsFC between the amygdala and PFC. To this end, we reanalyzed existing data from the aforementioned experiments, which focused on detachment as a reappraisal strategy. This investigation is inspired by the study of Uchida et al. (2015). Because there are important differences concerning the operationalization of the constructs and the experimental procedure between our study and the Uchida study (see **Supplementary Table S24**), the current investigation can be a conceptual replication at best.

(3) Extending the findings of Uchida et al. (2015), we aimed at an investigation of associations between task-related, *neuronal reappraisal success* (as defined by a decrease of amygdala activity

during emotion regulation) and rsFC between the amygdala and PFC, again using existing data of the aforementioned data sets.

Replication Attempt and Extension of Existing Studies on rsFC and Dispositional as well as Task-Related Emotion Regulation Success

Picó-Pérez et al. (2018) reported that dispositional reappraisal was negatively correlated with rsFC between left basolateral amygdala and left insula as well as dACC, and between right basolateral amygdala and SMA/dACC as well as the left insula. For dispositional suppression, a positive correlation was found with rsFC between the right basolateral amygdala and dACC, a negative correlation with rsFC between the left centromedial amygdala and SMA. The study was conducted with 48 healthy participants (23 females) with a mean age of 39.7 years. Participants filled out the Spanish version of the ERQ and underwent a resting fMRI scan. Detailed methods in comparison to our replication attempts can be found in **Supplementary Table S23**.

Uchida et al. (2015) report a significant negative correlation of task-related experiential reappraisal success with rsFC between the right amygdala and mPFC. This study investigated 62 participants (32 females, mean age 22.3 years), reflecting a broad range of ER ability due to preselection according to DERS scores (Gratz and Roemer, 2004). The participants underwent a fMRI reappraisal task, where they were instructed to either attend to neutral or negative pictures or reinterpret the pictures to reduce their negative feelings (reinterpretation as reappraisal strategy). At the end of each trial, participants rated their negative emotional reactions (affect rating). Reappraisal success (reappraisal score) was defined as the difference between the affect rating for the Attend Negative condition minus the Reappraise Negative condition during scanning. Additionally, the participants underwent a resting fMRI scan. The authors did not report associations between rsFC and the fMRI responses during the reappraisal task (neuronal emotion regulation success). Detailed methods in comparison with our replication attempt can be found in **Supplementary Table S24**.

Based on the two studies described above, we developed the following hypotheses: Regarding aim 1, we took into account the connectivity results of Picó-Pérez et al. (2018) with and without global signal regression (GSR) and hypothesized that there is a significant negative correlation of *dispositional reappraisal use* with rsFC between (1a) left basolateral amygdala and left insula, (1b) left basolateral amygdala and dACC, (1c) right basolateral amygdala and left insula, (1d) right basolateral amygdala and the SMA/dACC. Additionally, we hypothesized that there is a negative correlation of *dispositional suppression use* with rsFC between (1e) left centromedial amygdala and the SMA, and (1f) right basolateral amygdala and dACC. Concerning aim 2, we took into account the results of both, Uchida et al. (2015) and Picó-Pérez et al. (2018), and hypothesized that there is a negative correlation of task-related *experiential reappraisal success* with rsFC between (2a) left amygdala and left insula, (2b) right amygdala and left insula, (2c) the amygdala and dorsomedial (dm) PFC, (2d) amygdala and ventromedial PFC, and (2e) a correlation of *experiential reappraisal success* with rsFC between the amygdala and dlPFC. Lastly, we hypothesized that there is a correlation between task-related *neuronal reappraisal success* with rsFC between (3a) the amygdala and insula, (3b) amygdala and dmPFC, and (3c) amygdala and dlPFC. Hypotheses, methods, and analysis plan were preregistered and can be found at https://osf.io/8wsgu.

MATERIALS AND METHODS

This study is a reanalysis of data collected within a larger project on neural correlates and individual differences of ER and its aftereffects (SFB 940 Project A5). To achieve a reliable sample size, we combined three samples from three slightly different ER experiments. Please note that results regarding research questions on task-related effects as well as associations with genetic polymorphisms are published elsewhere (Diers et al., in preparation; Gärtner et al., 2019; Scheffel et al., 2019). Results on the research question of this publication have not been reported in any of these publications. We report how we determined our sample size, all data exclusions (if any), all manipulations, and all measures in the study (Simmons et al., 2012). Data, scripts, and analysis routines can be found at https://osf.io/8wsgu.

Mostly due to the analysis of existing data, our procedures deviated from the methodological procedures of the original studies, differences can be found in detail in **Supplementary Tables S23, S24**.

Participants

The sample size was defined based on feasibility considerations. This resulted in a target sample size of over 48 participants per experiment. At the end of the data collection, 136 healthy participants took part in the study, $N = 42$ in Experiment 1, $N = 47$ each in Experiment 2 and 3. Participants were mostly students from the local university community. All participants were right-handed, pre-screened for magnetic resonance imaging (MRI) contraindications (e.g., metal plates or implants), and had no current or prior medical, neurological, or psychiatric illness or treatment. The experimental protocol was approved by the ethics committee of the TU Dresden (EK 10012012). Participation was voluntary and written consent was obtained. Participants received financial compensation for their time and effort.

After inspection of the data, $N = 29$ had to be excluded because of missing resting-state sessions or due to missing significant parts of the amygdala in resting-state images. Data of $N = 107$ participants (64 female; age: 24.4 $\pm$ 4.2 years, range: 18–48) were analyzed ($N = 27$ in Experiment 1, $N = 40$ in Experiments 2 and 3, respectively). Please note that the sample size of some calculations is smaller due to missing questionnaire data or task-related fMRI data (see **Table 1** below). Given our sample size, a power analysis with G*Power (Faul et al., 2009) indicated that for correlational analyses, we were able to detect an r of 0.31 with a power of 0.80 (two-tailed, $\alpha = 0.05/4$ corrected for multiple comparisons for analyses on four amygdala nuclei).

TABLE 1 | Sample characteristics and descriptive results of dispositional emotion regulation.

	N	M (±SD)
Age	106	24.4 (±4.2)
Gender (male/female)	106	42/64
ERQ reappraisal (α = 0.74)	101	4.8 (±0.8)
ERQ suppression (α = 0.76)	102	3.4 (±1.2)

Note: α = Cronbach's Alpha; differences in N are due to missing demographic or questionnaire data of single participants.

Study Procedure

All three experiments contained two sessions 1 week apart from each other. In the first session, a functional MRI (fMRI) measurement during an experimental emotion regulation task (ERT), self-reported arousal ratings (AR) after each experimental run, a structural MRI (sMRI) measurement, and a stimuli re-exposure fMRI run were performed. In the second session, a resting-state fMRI (RS-fMRI) and another stimuli re-exposure fMRI run were completed. Additionally, the participants filled in questionnaires measuring individual differences on several traits and abilities (see "Emotion Regulation (ER) Task and Experiential Reappraisal Success" section). Please refer to **Supplementary Figure S1** for a detailed description of the experimental procedure.

Emotion Regulation (ER) Task and Experiential Reappraisal Success

Participants performed an ER task with negative (categories: animal, body, disaster, disgust, injury, suffering, violence, and weapons) and neutral (categories: objects, persons, and scenes) pictures. Pictures were taken from the International Affective Picture System (IAPS, Lang et al., 2008) and the Emotional Picture Set (EmoPicS, Wessa et al., 2010). Pictures were divided into subsets and randomly assigned to conditions. Valence (V) and arousal (A) were comparable between the experiments: For negative pictures, values were V = 2.67–2.81 and A = 5.54–5.74 (Experiment 1), V = 2.65–2.71 and A = 5.69–5.85 (Experiment 2), and V = 2.65–2.71 and A = 5.55–5.85 (Experiment 3). For neutral pictures, values were V = 4.98–5.16 and A = 2.86–3.04 (Experiment 1), V = 5.13–5.17 and A = 2.94–2.96 (Experiment 2), and V = 5.13–5.19 and A = 2.85–2.96 (Experiment 3).

The ER tasks differed slightly across the three experiments. However, all had in common that participants went through a Permit and a Detach condition (Diers et al., 2014, in preparation; Gärtner et al., 2019; Scheffel et al., 2019). During the Permit condition, participants should take a close look at the pictures and permit any emotions, that might arise. During the Detach condition, they were asked to "take the position of a non-involved observer, thinking about the picture objectively." Strategies were trained outside the MRI scanner.

Each experimental trial consisted of a stimulation period and a relaxation period. In the stimulation period, a picture was presented for 8 (Experiments 1 and 3), or 10 s (Experiment 2). Within the initial 2 s of this period, a semi-transparent overlay containing the instruction was presented in the center of the picture. Afterward, a fixation cross was presented (relaxation period). After each trial (Experiment 1) or block (Experiments 2 and 3), participants rated their emotional arousal. The difference between arousal ratings for the conditions Negative Permit and Negative Detach was determined as *experiential reappraisal success*.

After the ER experiment, participants were asked whether they followed the instructed strategies. All participants stated that they did so. For a more detailed description of the three experiments, please see **Supplementary Methods**.

Psychometric Measurements (Dispositional Emotion Regulation and Affect)

Participants completed several questionnaires on personality traits, ER abilities, need for cognition, thought suppression, mindfulness, acceptance, worry, and anxiety (for a complete list of measures, see https://osf.io/8wsgu). The following questionnaires were used in the present study: The German version of the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003; German version: Abler and Kessler, 2009) to determine *dispositional reappraisal and suppression use*, and the Positive and Negative Affect Schedule (PANAS, Watson et al., 1988; German version: Janke and Glöckner-Rist, 2014) to determine positive and negative affect.

MRI Data Acquisition

Functional and structural imaging was performed on a 3.0 Tesla Siemens Magnetom Trio scanner (Siemens AG, Erlangen, Germany), using a 12-channel head coil. Functional data were obtained using a T2*-weighted echo-planar imaging sequence. The field of view (FOV) had a size of 192 × 192 mm^2 with a matrix size of 64 × 64, flip angle 80°, slice gap 1 mm, repetition time (TR) = 2410 ms, and echo time (TE) = 25 ms. Forty-two axial slices were acquired with a voxel size of 3.0 × 3.0 × 2.0 mm^3. Stimuli were presented using Presentation (Neurobehavioral Systems, Albany, CA, USA). For each subject, anatomical (T1-weighted) images were acquired using an MPRAGE sequence consisting of 176 sagittal slices with a thickness of 1 mm (TR: 1,900 ms, TE: 2.26 ms, flip angle 9°, FOV: 256 × 256 mm^2, matrix size 256 × 256, voxel size: 1 × 1 × 1 mm^3; Diers et al., 2014; Gärtner et al., 2019; Scheffel et al., 2019).

Data Analysis

Resting-State Functional Connectivity

Seed and ROI Definition

The selection of the seed regions were based on Baur et al. (2013) and corresponded to left basolateral amygdala (BLA), right BLA, left centromedial amygdala (CMA), and right CMA for the resting-state analyses (see **Figure 1A**). For all four nuclei, maximum probability maps were created using the SPM Anatomy toolbox v.2.2c (Eickhoff et al., 2005). The probability threshold was set to 40% for each voxel to provide sufficient areal coverage of the anatomical structure (Eickhoff et al., 2006; Baur et al., 2013). Note that following Picó-Pérez et al. (2018), the CMA comprised centromedial and superficial divisions of the left and right amygdala.

The ROI mask for the PFC was restricted to a 56,833-voxel mask (2 × 2 × 2 mm^3; see **Figure 1B**) created with the Wake

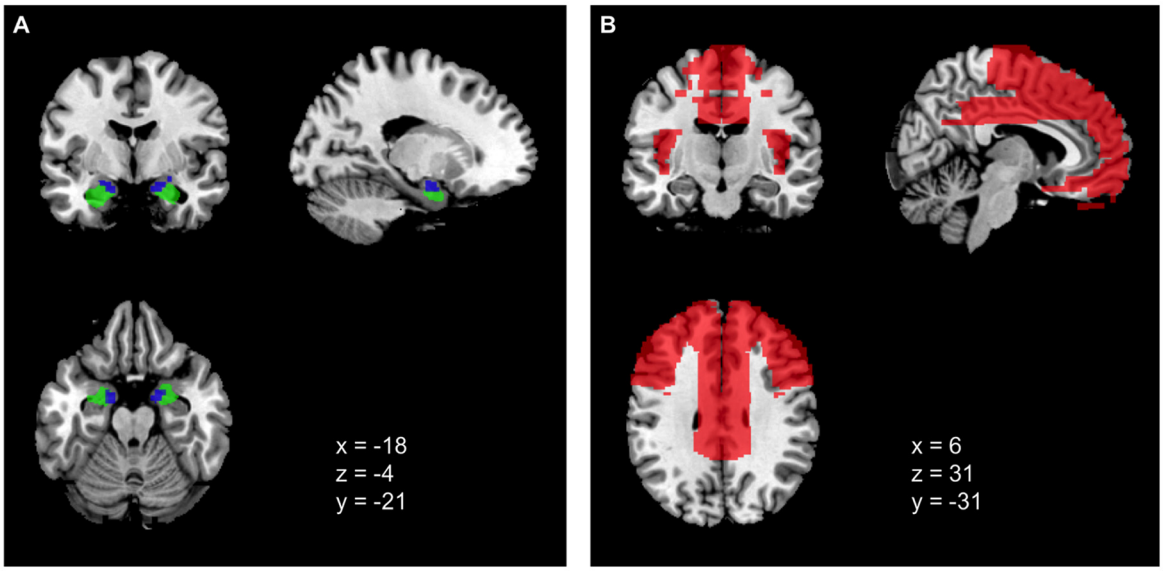

FIGURE 1 | (A) Amygdala seed regions, blue = CMA, green = BLA. **(B)** Prefrontal cortex (PFC) ROI mask encompassing different regions of the frontal lobe, cingulate gyri, and insula (see Picó-Pérez et al., 2018).

Forest University (WFU) Pick-atlas toolbox (Maldjian et al., 2003). Following the procedure described by Picó-Pérez et al. (2018), the mask comprised different regions of the frontal lobe (i.e., inferior frontal, middle frontal, superior frontal, medial frontal and orbital gyri), the cingulate gyri and the insulae. Although we used the same regions, our ROI mask differed in size with the ROI mask by Picó-Pérez et al. (2018). Our contact with the authors did not solve the issue.

Data Preprocessing and Analysis

Preprocessing and statistical analyses of resting-state MRI data were carried out using the CONN toolbox (version 18b) pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012), SPM 12[1] and Matlab 2019b (MathWorks, Natick, MA, USA). Preprocessing of the functional scans included spatial realignment and unwarping, slice-time correction, and outlier detection (ART-based scrubbing). Next, DARTEL (Ashburner, 2007) was used to create a study-specific anatomical template. Subject-specific normalization parameters were estimated for anatomical images. These parameters were then applied to the functional scans. Lastly, smoothing using an 8 mm Gaussian kernel was done. Before first-level analyses, a denoising procedure was applied to remove motion artifacts, physiological and other artifactual effects from the fMRI-signal. This procedure included the component-based correction method (Comp-Cor, Behzadi et al., 2007) and temporal band-pass filtering of 0.008–0.09 Hz. To avoid potential ramping effects at the beginning of the session, CONN models the entire acquisition and includes an additional confounding variable as a covariate in the denoising procedure. The six-movement parameters and a matrix containing the ART-detected outliers were included as first-level nuisance covariates. Preprocessing of the structural scans included segmentation and normalization to the MNI reference brain.

For first-level analysis, a general lineal model (GLM) was created which includes the four noise-corrected amygdala-seed time series as predictors. To check the whole brain, basic rsFC of the four amygdala nuclei were computed both for the whole sample as well as for the three experiments. All second-level analyses for hypotheses testing were restricted to the PFC mask. For second-level analysis of aim 1, separate multiple regression models were performed for each of the four amygdala seeds (left CMA, right CMA, left BLA, and right BLA). Dispositional reappraisal and suppression use served as predictors of interest to test for voxel-wise correlations between the seed-to-ROI connectivity values and ERQ subscales. For second-level analyses of aim 2, multiple regression models were performed for left and right amygdala seeds, respectively (each comprising the mean of both CMA and BLA nuclei) for hypotheses (2a) and (2b), and for each of the four amygdala seeds (*F*-Test for any effects among the four seeds) for hypotheses (2c) to (2e). Experiential reappraisal success (one predictor) served as a predictor of interest. For second-level analyses of aim 3, multiple regression models were performed for each of the four amygdala seeds (*F*-Test for any effects among the four seeds) for hypotheses (3a) to (3c). Neuronal reappraisal success (extracted mean activity from left BLA, right BLA, left CMA, right CMA during Negative Permit > Negative Detach, see "Task-Related Neuronal Reappraisal Success–Data Preprocessing and Statistical Analysis" section) served as predictors of interest, and the mean of all four predictors was computed during second-level contrast analysis. For all analyses, the number of Experiments (1, 2, 3) served as a covariate. The significance threshold was set

[1]https://www.fil.ion.ucl.ac.uk/spm/software/spm12/

to $p < 0.05$, family-wise error corrected (FWE) for multiple comparisons. For exploratory analyses, we lowered the threshold to $p < 0.001$ (uncorrected) and report respective results in the **Supplementary Material**.

Task-Related Neuronal Reappraisal Success—Data Preprocessing and Statistical Analysis

Preprocessing and statistical analyses of functional MRI data were carried out using SPM 8[2], SPM 12[1], and Matlab 2019b (MathWorks, Natick, MA, USA). The first four volumes of each run were discarded. Preprocessing included motion correction, coregistration of individual functional and anatomical images, spatial normalization (deviating from the preregistration) of the anatomical data to the MNI template, application of the estimated transformation parameters to the coregistered functional images using a resampling resolution of $2 \times 2 \times 2$ mm^3, and spatial smoothing of the functional images (FWHM 8 mm). For first-level analysis, a GLM was created with regressors based on experimental conditions (Experiment 1: View Neutral, View Negative, Permit Negative, Detach Negative; Experiment 2: Permit Neutral, Permit Negative, Detach Neutral, Detach Negative; Experiment 3: Permit Neutral, Permit Negative, Detach Neutral, Detach Negative, Intensify Neutral, Intensify Negative), as well as six additional motion regressors of no interest. Instructions and pictures were set together as one event. Temporal patterns were modeled as boxcar function (8 s duration (Experiment 1 and 3) and 10 s duration (Experiment 2), respectively) to cover sustained responses. All regressors were convolved with the canonical hemodynamic response function (HRF). All runs of the imaging experiments were combined within one fixed-effects model.

To obtain scores for *neuronal reappraisal success*, the mean activity of the amygdala for the contrast Negative Permit > Negative Detach was extracted for each participant using MarsBaR[3]. Therefore, maximum probability maps of the left BLA, right BLA, left CMA, and right CMA were created using the SPM Anatomy toolbox v.2.2c (Eickhoff et al., 2005). The probability threshold was set to 40% for each voxel to provide sufficient areal coverage of the anatomical structure (Eickhoff et al., 2006; Baur et al., 2013).

Dispositional ER and Task-Related Experiential Responses (Self-report)–Statistical Analysis

Analyses on task-related experiential responses (arousal ratings) and trait measures were conducted using R[4]. A Shapiro-Wilk test was performed to test variables for normal distribution. ERQ subscales (dispositional reappraisal and suppression use) were normally distributed ($p > 0.05$, see **Supplementary Table S1**). A paired *t*-test was conducted to check whether participants reported using reappraisal strategies to an equal extent than suppression strategies. The PANAS subscale positive affect and task-related experiential responses were not normally distributed ($p < 0.05$, see **Supplementary Table S1**). Wilcox signed-rank tests with continuity correction were conducted to check whether participants experienced positive and negative affect to an equal amount and to test whether task-related experiential responses were significantly lower after using detachment, compared to permitting all upcoming emotions.

[2]https://www.fil.ion.ucl.ac.uk/spm/software/spm8/
[3]http://marsbar.sourceforge.net/
[4]https://www.r-project.org/

RESULTS

Dispositional ER and Task-Related Experiential Responses (Self-report)

The mean dispositional reappraisal and suppression scores (ERQ) are presented in **Table 1** (for a comparison of all predictor variables across the three experiments see **Supplementary Table S2**). Participants reported using reappraisal ($M = 4.8$, $SD = 0.8$) to a significantly stronger extent than suppression ($M = 3.4$, $SD = 1.2$; $t_{(100)} = 9.1$, $p < 0.001$). Regarding positive and negative affect (PANAS), participants showed a significant higher experience of positive affect as compared to negative affect ($V = 5241$, $p < 0.001$). Correlation analyses showed a significant association between both PANAS subscales ($r = -0.29$, $p = 0.003$), but none between ERQ and PANAS subscales ($p > 0.05$).

In the ER experiment, participants reported significantly lower task-related experiential responses after detachment from negative pictures, $M = -15.4$, $SD = 68.9$, compared to permitting emotions, $M = 13.6$, $SD = 59.8$, $V = 722.5$, $p < 0.001$. Therefore, the implementation of the instructed ER strategies in the Experiment was successful (see Scheffel et al., 2019).

Resting-State Functional Connectivity Results

Basic, Whole-Brain Functional Resting-State Connectivity (Without PFC Mask and Covariate)

Functional connectivity patterns of basolateral (BLA) and centromedial (CMA) amygdala seeds and regions within the whole brain for the whole sample without covariate are presented in **Supplementary Figure S5**. Overall, there were significant ($p < 0.05$ FWE-corrected) associations of left and right BLA and CMA nuclei with the amygdala, nucleus caudate, precentral and postcentral gyrus, Rolandic operculum, middle cingulum, angular gyrus, middle temporal gyrus, middle occipital gyrus, hippocampus, superior temporal pole and inferior parietal gyrus (see **Supplementary Table S15** for a complete list of all associations).

Because of the differences between experiments (see **Supplementary Table S2**), we repeated all analyses separately for each experiment. The results are reported in **Supplementary Figures S2** (Experiment 1), **S3** (Experiment 2), **S4** (Experiment 3), and **Supplementary Tables S3** (Experiment 1), **S7** (Experiment 2), **S11** (Experiment 3).

Aim 1: Replication Dispositional Emotion Regulation and Functional Resting-State Connectivity

Whole Sample Results (With PFC Mask and Covariate)

Functional connectivity patterns of left and right basolateral (BLA) and centromedial (CMA) amygdala seeds and regions within the PFC mask are presented in **Supplementary Table S19**.

Overall, there were no significant associations of left and right BLA and CMA with any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. We found meaningful associations (clusters $k \geq 10$ voxels) with superior orbitofrontal gyrus, SMA, inferior orbitofrontal gyrus, middle orbitofrontal gyrus, inferior frontal gyrus triangularis, superior frontal gyrus, insula, and Rolandic operculum.

Regarding dispositional emotion regulation, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, neither dispositional reappraisal nor suppression use was positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected and found meaningful associations of dispositional emotion regulation (clusters $k \geq 10$ voxels) with rsFC between brain regions: Reappraisal use was positively correlated with rsFC between right CMA and left insula, right BLA and right middle cingulum as well as left inferior frontal gyrus triangularis. Suppression use was positively correlated with rsFC between left CMA and right superior medial frontal gyrus, right inferior frontal gyrus opercularis, and left middle cingulum; and between right CMA and left middle frontal gyrus as well as right superior frontal gyrus. Furthermore, suppression scores were positively correlated with rsFC between left BLA and left superior temporal gyrus and right inferior frontal gyrus; and right BLA and right superior frontal gyrus. The results are presented in **Table 2** and **Supplementary Table S20**.

Because of differences between experiments (see **Supplementary Table S2**) we repeated all analyses separately for each experiment. The results are reported in the following.

Experiment 1

Regarding dispositional emotion regulation, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, neither reappraisal nor suppression use was positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S4**.

Experiment 2

Regarding dispositional emotion regulation, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, neither reappraisal nor suppression use was positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S8**.

Experiment 3

Regarding dispositional emotion regulation, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, neither reappraisal nor suppression use was positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S12**.

Aim 2 and Aim 3: Extension to Experiential and Neuronal Reappraisal Success

The analyses were repeated with *experiential and neuronal reappraisal success*, respectively, as predictors of interest. Regarding experiential reappraisal success, there were no significant correlations with rsFC of the left and right amygdala to any region within the PFC mask ($p > 0.05$ FWE-corrected)[5]. For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected and found meaningful associations (clusters $k \geq 10$ voxels). Experiential reappraisal success was positively correlated with rsFC between left amygdala and left middle cingulum and left inferior frontal gyrus opercularis, and positively associated with rsFC between right amygdala and left middle cingulum (see **Table 3** and **Supplementary Table S21**).

Regarding *neuronal reappraisal success*, there were no significant correlations with rsFC of the left and right amygdala to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. However, we found no meaningful associations (all clusters $k < 10$ voxels, except one association with superior frontal gyrus; see **Table 4** and **Supplementary Table S22**).

Experiment 1

Regarding *experiential reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, changes in arousal ratings were not positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S5**.

Regarding *neuronal reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, mean activity of the amygdala for the contrast Negative Permit > Negative Detach was not positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S6**.

Experiment 2

Regarding *experiential reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, changes in arousal ratings were not positively

[5]Because values for experiential reappraisal success differed significantly between the three experiments (see **Supplementary Table S2**), we repeated the analyses with *z*-standardized values for this variable. However, there were still no significant correlations with rsFC of left and right amygdala to any region within the PFC mask ($p > 0.05$ FWE-corrected).

TABLE 2 | Significant clusters associated with the four amygdala nuclei as seeds restricted to PFC mask for reappraisal and suppression (aim 1).

Region	H	x	y	z	k	T	p-uncorr	p-FWE
Reappraisal								
Left centromedial amygdala								
No suprathreshold clusters								
Right centromedial amygdala								
Insula	L	−34	12	−14	49	4.16	<0.001	0.264
Left basolateral amygdala								
No suprathreshold clusters								
Right basolateral amygdala								
Middle Cingulum	R	4	−38	44	41	3.79	<0.001	0.602
Inferior Frontal Gyrus Triangularis	L	−54	38	20	10	3.64	<0.001	0.758
Suppression								
Left centromedial amygdala								
Superior Medial Frontal Gyrus	R	14	58	30	17	3.76	<0.001	0.645
Inferior Frontal Gyrus Opercularis	R	60	16	38	10	3.66	<0.001	0.744
Middle Cingulum	L	−8	−44	32	29	3.50	<0.001	0.882
Right centromedial amygdala								
Middle Frontal Gyrus	L	−30	20	44	34	4.30	<0.001	0.176
Superior Frontal Gyrus	R	18	26	40	14	3.75	<0.001	0.647
Left basolateral amygdala								
Superior Temporal Gyrus	L	−40	20	−16	11	3.67	<0.001	0.752
Inferior Frontal Gyrus Opercularis	R	56	16	36	15	3.50	<0.001	0.893
Right basolateral amygdala								
Superior Frontal Gyrus	R	18	24	40	23	4.29	<0.001	0.187

Note. The significance threshold for seed-to-voxel analyses set at p < 0.001 uncorrected. Only clusters with k ≥ 10 are reported. Coordinates are given in MNI space. Amy, amygdala; R, right; L, left; H, Hemisphere.

TABLE 3 | Significant clusters associated with experiential reappraisal success with respective amygdala seeds restricted to PFC mask (aim 2).

Region	H	x	y	z	k	T/F	p-uncorr	p-FWE
Left amygdala (BLA + CMA)								
Middle Cingulum	L	−14	8	32	17	3.76	<0.001	0.663
Inferior Frontal Gyrus Opercularis	L	−38	10	12	19	3.67	<0.001	0.756
Right amygdala (BLA + CMA)								
Middle Cingulum	L	−12	14	32	21	3.88	<0.001	0.510
Precentral Gyrus	R	46	6	28	39	3.63	<0.001	0.765
Amygdala (Any nucleus)								
No suprathreshold clusters								

Note. The significance threshold for seed-to-voxel analyses set at p < 0.001 uncorrected. Coordinates are given in MNI space. Amy, amygdala; R, right; L, left; H, Hemisphere; Only clusters with k ≥ 10 are reported.

TABLE 4 | Significant clusters associated with neuronal reappraisal success for amygdala nuclei as seeds restricted to PFC mask (aim 3).

Region	H	x	y	z	k	F	p-uncorr	p-FWE
Amygdala (Any nucleus)								
Superior Frontal Gyrus	R	16	48	48	12	5.52	<0.001	0.894

Note. The significance threshold for seed-to-voxel analyses set at p < 0.001 uncorrected. Coordinates are given in MNI space. Amy, amygdala; R, right; L, left; H, Hemisphere; Only clusters with k ≥ 10 are reported. Because of differences between experiments (see **Supplementary Table S2***) we repeated all analyses separately for each experiment. The results are reported in the following.*

or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S9**.

Regarding *neuronal reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, mean activity of the amygdala for the contrast Negative Permit > Negative Detach was not positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S10**.

Experiment 3

Regarding *experiential reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, changes in arousal ratings were not positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S13**.

Regarding *neuronal reappraisal success*, there were no significant correlations with rsFC of any of the four amygdala seeds, that is, mean activity of the amygdala for the contrast Negative Permit > Negative Detach was not positively or negatively correlated with rsFC between left and right BLA and CMA to any region within the PFC mask ($p > 0.05$ FWE-corrected). For exploratory purposes, we lowered the threshold to $p < 0.001$ uncorrected. The results are reported in **Supplementary Table S14**.

DISCUSSION

The first aim of this investigation was to directly replicate the study by Picó-Pérez et al. (2018). We analyzed associations of *dispositional emotion regulation* (ER), which is the habitual use of reappraisal and suppression measured *via* self-report (Abler and Kessler, 2009), with functional resting-state connectivity (rsFC) between the amygdalae and PFC by reanalyzing data from 107 participants of an ER study. None of the hypotheses could be confirmed, that is, we could not statistically confirm associations of dispositional reappraisal and suppression use with rsFC between left and right basolateral and centromedial amygdala, respectively, and regions in the PFC (ACC and SMA) and the insula. Thus, we failed to replicate the results of Picó-Pérez et al. (2018).

Second, we extended the investigation of resting-state functional networks and ER to associations with *experiential reappraisal success*. This investigation was based on findings by Uchida et al. (2015). Following the recommendations of Zwaan et al. (2018), we aimed at a conceptual replication and hypothesized that experiential reappraisal success (measured *via* arousal ratings) is associated with rsFC between left and right amygdala and left insula, with rsFC between left and right amygdala and dmPFC, with rsFC between the amygdalae and vmPFC, as well as with rsFC between the amygdala and dlPFC. Again, none of our hypotheses could be confirmed.

Lastly and to extend the research question to *neuronal reappraisal success*, we added a third analysis. Data of the same sample was analyzed to examine the hypotheses of associations between neuronal reappraisal success (defined by amygdala downregulation during reappraisal in an ER task) with rsFC between the amygdalae and insula, rsFC between the amygdalae and dmPFC, and rsFC between the amygdalae and dlPFC. We were not able to find any significant correlations here either.

To clarify whether there were any basic problems in detecting resting-state networks in our sample, we conducted a whole-brain functional connectivity analysis without any additional predictors and the covariate. This revealed that left and right basolateral and centromedial amygdala were negatively coupled with dlPFC, vlPFC, dmPFC, and dorsal ACC regions, and positively coupled with vmPFC, SMA, subgenual ACC as well as posterior cingulate gyrus and insula/vlPFC (see **Supplementary Figure S5** and **Supplementary Table S15**). Overall, there is an overlap of these regions with the regions reported by Picó-Pérez et al. (2018), albeit not in the same direction. Similar connectivity maps have been reported by others (Roy et al., 2009; Weis et al., 2019 and Tetereva et al., 2020). We, therefore, assume that our resting state measurement has been successful in principle. However, when we included the number of Experiment as a covariate in this basic functional connectivity analysis, none of the clusters showed significant coupling with the amygdala anymore. Separate analyses of basic, whole-brain rsFC of the amygdala nuclei revealed variability between the three different sub-samples of our study (see **Supplementary Figures S2–S4**). However, this variability points to differences in strength rather than in the composition of the network.

There are several differences in methodology between the study of Picó-Pérez et al. (2018) and our study. Mainly, the differences refer to acquisition parameters of the functional MR images resulting, for instance, in a much lower spatial while slightly higher temporal resolution in Picó-Pérez et al. (2018). There were also differences in the preprocessing of fMRI data and statistical procedures (see **Supplementary Table S23**). Most importantly, we were not able to directly replicate the size of the PFC ROI for small volume correction. Although we followed the procedure laid out in the original study by Picó-Pérez et al. (2018), which resulted in an ROI of 17,391 voxels ($2 \times 2 \times 2$ mm^3) in the original study, our mask contained 56,833 voxels ($2 \times 2 \times 2$ mm^3). A visual comparison further points to some differences in coverage of the PFC, although the regions targeted by our hypotheses were included. Nevertheless, corrections for multiple comparisons had to be performed for a much smaller ROI in the Picó-Pérez study, which might have led to a higher possibility for smaller effects to reach statistical significance (see **Figure 1**). Moreover, differences are obvious regarding sample size and composition. The original study sample comprised 48 participants with a mean age of 39.6 years, while the participants in our study ($N = 107$) were much younger with a mean age of 24.4 years. Since emotion control, motives, as well as the choice of strategies change with age (e.g., Scheibe and Carstensen, 2010), this difference in mean age between the samples certainly plays a role. Because of the larger sample size, our study offers greater statistical power, which could have led to a reduced likelihood of false-positive findings.

Nevertheless, concerning aim 1, we did not achieve an exact but direct replication following Zwaan et al. (2018). A different definition of replications offers Brandt et al. (2014). They define close replications as studies that "aim to recreate a study as closely as possible so that ideally the only differences between the two are the inevitable ones" (p. 218). Concerning this strict definition, we did not achieve a close replication of the Pidó-Pérez study. However, we do not consider the differences in data acquisition and preprocessing to produce the failed replication, but the differences between the samples might at least partly explain the divergent results. However, we think that a replication of the same results should be rather independent of the detailed methodology.

Concerning aim 2, the methodological differences between our study and Uchida et al. (2015) are more pronounced. While the samples' mean age is very similar (see **Supplementary Table S24**), the sample size is larger in our study. Additionally, Uchida et al. (2015) selected their participants according to their ER abilities to achieve an equal

distribution of their abilities. This was not the case in our study. Thus, the original study ensured a higher variability of their main construct, which might have increased the possibility of finding an effect. Concerning the operationalization of experiential reappraisal success, the original study instructed reinterpretation as ER strategy and measured trial-by-trial affect ratings (Uchida et al., 2015), whereas in our replication attempt distancing was used as ER strategy and trial-by-trial ratings were only implemented in one of our data sets. Additionally, all of our experiments used arousal ratings. With these different operationalizations of a central construct, our replication attempt could be considered as conceptual (Zwaan et al., 2018) at best. In other words, "on a continuum from 'close' to 'conceptual'" (Brandt et al., 2014) our replication attempt might be placed at the very end of the continuum. Thus, we can only conclude that the findings of the original study could not conceptually be replicated, the results do not extend to a different reappraisal strategy nor arousal instead of affect outcomes. Minor differences between the original and the replication can be found in data acquisition and processing, however, we consider these negligible (see **Supplementary Tables S23, S24** for a detailed comparison).

Our findings not only contrast with the two studies on which we based our *a priori* hypotheses (Uchida et al., 2015; Picó-Pérez et al., 2018), they also contradict several other studies that have identified patterns of intrinsic functional connectivity that differ between the dispositional use of ER strategies or are associated with experiential and neuronal reappraisal success (Morawetz et al., 2016; Pan et al., 2018; Burr et al., 2020). Common to these studies is that regions in the default mode network have been identified. Particularly, the latest study by Burr et al. (2020) used the largest sample up to date (N = 1,316) in a data-driven, theory-free approach and found that intrinsic connectivity of the default mode network was associated with dispositional use of suppression (but not reappraisal). Critically, the authors used general functional connectivity (GFC, Elliott et al., 2019) to leverage shared features of task and resting-state fMRI and circumvent reported reliability issues of resting-state measures (e.g., Noble et al., 2019). Thus, instead of focusing on connectivity in *a priori* regions of interest between cortical and subcortical areas, distributed networks of brain regions might be a more promising target in future studies as they take into account the complexity of the underlying neuronal processes.

Limitations

Several limitations have to be noted. First, to achieve a larger sample size and power, we combined three samples from three slightly different ER experiments. Although all experiments included the conditions and instructions relevant for the present study, subtle effects of experimental variation cannot be ruled out (e.g., Experiment 3 included an intensify instruction that was not present in Experiments 1 and 2). Therefore, we included Experiment, as a covariate in all our analyses (see also **Supplementary Table S2** for a comparison of all predictor variables across experiments). Related to the study design, the resting-state measurement took place in a separate session approximately 1 week after the ER task. Although the investigated effects are supposed to be independent of each other (resting-state vs. task-related), unknown effects of time cannot be excluded since the experimental protocol was not randomized.

Second, the results regarding experiential reappraisal success are limited, because in Experiments 2 and 3 arousal ratings were recorded retrospectively after each block. In the overall research question of the larger study we were interested in aftereffects of ER (see for instance Walter et al., 2009). However, an arousal rating after picture offset in the relaxation period would alter time courses of the HRF (Burklund et al., 2014), thus, no trial-by-trial arousal rating was used while accepting the disadvantages of a retrospective arousal rating. **Supplementary Table S2** presents the arousal ratings separately for each experiment. Indeed, the arousal ratings were higher for the trial-by-trial rating in Experiment 1 compared to the retrospective ratings in Experiments 2 and 3.

Third, the fixation of presented pictures was not controlled for *via* eye-tracking. Therefore, we do not have an objective measure to assess whether participants fixated negative images as instructed. This could have led to a failed activation of brain regions related to emotional processing during the negative stimulation period and, subsequently, to difficulties in detecting a reappraisal success. However, analyses of brain activation during reappraisal of negative pictures as compared to viewing negative pictures revealed downregulation of amygdala activation as well as activation in prefrontal regions in a previous analysis of the same data (Scheffel et al., 2019) replicating earlier findings (Walter et al., 2009; Buhle et al., 2014; Dörfel et al., 2014; Paschke et al., 2016).

Finally, we have no information on whether detachment is the participants' preferred ER (reappraisal) strategy. Some participants may use other forms of reappraisal in their everyday life, for example, reinterpretation. While performing the task, they might be more successful with their preferred instead of the instructed strategy. However, we tried to address this by a training session on the implementation of detachment before the scanner session.

CONCLUSION

In conclusion, the present replication study calls into question the reported findings on individual differences in resting-state cortico-limbic functional connectivity related to dispositional use of ER strategies and even task-related, experiential, and neuronal reappraisal success. The most parsimonious explanation for the lack of replication is that these differences are either small or non-existent, and/or swamped by sample effects and methodological differences. However, we remain optimistic that continued developments towards improving methodology in resting-state measurement (enhancing reliability) and distributed network approaches will help to eventually reveal reliable patterns of functional connectivity underlying successful emotion regulation.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during this study can be found at the Open Science Framework (https://osf.io/p7hb5/).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the TU Dresden (EK 10012012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG and DD contributed to the design of the study. AG and CS organized the database and performed the statistical analysis. DD, CS, and AG wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.00128/full#supplementary-material.

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Automatic Reappraisal-Based Implementation Intention Produces Early and Sustainable Emotion Regulation Effects: Event-Related Potential Evidence

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Implementation intention has proven effective in regulating intense emotions but is found to be difficult when instructed regulation is used. Here, we aim to test whether automatic reappraisal-based implementation intention (RII) downregulates intense negative emotion more efficiently than controlled reappraisal (CR) using a two-phase event-related potential (ERP) experiment. In the regulation phase, both RII and CR decreased subjective experiences of negative emotion relative to passive watching, irrespective of emotional intensity. Moreover, RII reduced the central–parietal late positive potential (LPP) amplitudes for both intensities in the 300–1,700-ms epoch after picture onset, whereas CR reduced LPP amplitudes just in the 500–700-ms interval. Moreover, the application of RII but not CR produced a reliable long-term LPP attenuation compared to passive watching in the unexpected re-exposure phase. These findings demonstrate that reappraisal-based implementation intention yields an earlier and more sustainable emotion regulatory effects than controlled reappraisal.

Keywords: cognitive reappraisal, implementation intention, emotional intensity, event-related potentials, late positive potential

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INTRODUCTION

Cognitive reappraisal involves construing an emotional situation in nonemotional terms during emotion regulation (Sheppes and Gross, 2011). This self-regulation strategy has been established to effectively downregulate subjective emotional experiences (Ochsner et al., 2004; Ray et al., 2010), emotion-expressive behavior (Gross, 1998), and amygdala activation (Chen et al., 2017). However, recent studies indicate that the controlled reappraisal (CR) initiated by explicit and conscious instructions is less effective and more effortful in high than in low emotional intensity (Sheppes et al., 2014; Shafir et al., 2015). For example, CR resulted in weaker modulation of self-reported negative experience compared with distraction (Shafir et al., 2015) or attentional deployment (Sheppes et al., 2014) even though CR was as effective as these strategies in downregulating low-intensity negative emotions.

Previous studies have suggested that automatic cognitive processes operate earlier than controlled cognitive processes (Beck and Clark, 1997; Hahne and Friederici, 1999). Consistently, increasing evidence shows that automatic self-regulation is activated quickly and resists to ego-depletion efficiently (Webb and Sheeran, 2003; Fitzsimons and Bargh, 2004; Gallo et al., 2009). Given that one self-regulation strategy can operate in controlled or automatic forms (Gross, 1998; Braunstein et al., 2017), automatic emotion regulation may interrupt the development of an emotional impulse earlier than controlled emotion regulation. According to the process model of emotion regulation (Gross, 1998), the earlier an emotional impulse is interrupted, the less experiential and physiological emotional responses are generated (**Figure 1**). Consequently, the emotional regulatory effects of automatic cognitive reappraisal should be more prominent than CR, particularly during intense emotional situations. Additionally, previous research indicates that automatic cognitive processing leads to long-term retention of associated skills (Schneider and Chein, 2003), suggesting that automatic emotion regulation may provide long-term emotion regulation effects.

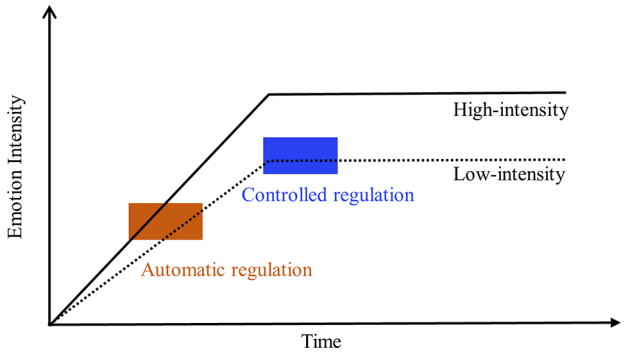

FIGURE 1 | The hypothesis of emotion-regulatory speed and effect of automatic regulation vs. controlled regulation in downregulating low- and high-intensity emotion. The size of the rectangle reflects the regulatory effects of automatic regulation (khaki) and controlled regulation (blue) on low- or high-intensity emotional responses.

However, no research has attempted to examine whether the short- and long-term regulatory effects of automatic reappraisal are impacted by emotional intensity and the underlying temporal mechanisms. Given that event-related potentials (ERPs) have been widely used as the temporally fine-grained indices of the effects of reappraisal, we designed an ERP study including regulation and re-exposure phases to examine the short- and long-term regulatory effects of automatic reappraisal, respectively. Specifically, we collected self-report ratings of valence and arousal and used the centro-parietal late positive potential (LPP) as an ERP index, since LPP has been suggested to be sensitive to both emotional intensity (Shafir et al., 2016) and cognitive reappraisal process (Hajcak et al., 2006, 2010). The centro-parietal LPP starts 300 ms after stimulus onset, showing enhanced amplitudes as the processing of emotional intensity increases (Hajcak et al., 2009). Importantly, 300–1,700 ms of centro-parietal LPP is typically used to show the regulatory effects of cognitive reappraisal (Foti and Hajcak, 2008; Thiruchselvam et al., 2011; Shafir et al., 2015; Qi et al., 2017). Besides, we used the frontal LPP as an objective index of cognitive effort, since previous ERP studies observed an enhanced LPP at frontal sites during implementing controlled reappraisal relative to passive watching (Bernat et al., 2011; Moser et al., 2014; Shafir et al., 2015).

Furthermore, we used the implementation intention paradigm to initiate automatic reappraisal. Implementation intentions refer to the if–then plans that specify when, where, and how individuals will strive towards particular goals (Gallo et al., 2009). Implementation intention paradigm has been suggested to be effective in automatically reducing subjective and physiological responses to negative emotional stimuli (see meta-analysis by Webb et al., 2012), without taxing self-regulatory resources (Gallo and Gollwitzer, 2007) or increasing conscious perception on the regulatory processing (Gallo et al., 2012). For example, Gallo et al. (2012) found that participants who formed reappraisal-based implementation intention (RII, e.g., "if I see blood, then I will take a perspective of a physician!") rated disgusting pictures as less unpleasant than participants in the watching or mere goal-intention groups, without consciously perceiving themselves as being more successful. More importantly, indirect evidence indicates that automatic emotion regulation supported by implementation intention results in earlier attenuation of neural activity than controlled emotion regulation. Gallo et al. (2009) found that participants who formed an implementation intention showed a lower positivity in the P1 (60–150 ms) when viewing threatening pictures as compared to participants given a goal intention and to no-goal control participants. In contrast, the regulatory effects of CR generally appear during the LPP phase (>300 ms; Foti and Hajcak, 2008; MacNamara et al., 2009; Moser et al., 2014; Qi et al., 2016).

Moreover, because we were interested in differences between automatic and controlled forms of reappraisal, we focused on one type of cognitive reappraisal (i.e., perspective-taking reappraisal) to avoid the confounding of types of reappraisal. Perspective-taking reappraisal askes participants to alter the impact of the emotional stimulus by adopting a third-person perspective, which has been suggested to have a larger effect size in modulating emotional outcomes than the other types of cognitive reappraisal (e.g., reappraising emotional response or emotional stimulus; see Webb et al., 2012 for more details). In terms of how a stimulus is appraised, perspective-taking reappraisal is a case of detached reappraisal (also called as self-focused) that reinterprets one's subjective relationship to emotional events in a detached and unemotional way (Qi et al., 2017). Consistent with the meta-analysis by Webb et al. (2012), our recent ERP study also found that detached reappraisal supported by implementation intention led to lower physiological responses to disgusting stimuli than positive reappraisal supported by implementation intention that requires a reinterpretation of an emotionally charged situation in a constructive manner (Ma et al., 2019).

The regulation phase of this study guided participants in the passive watching, RII, and CR groups passively view,

automatically regulate, and controllably regulate disgust images, respectively. In the regulation phase, we first hypothesized that RII would result in earlier and enhanced attenuation of the centro-parietal LPP than CR, which in turn was expected to be more effective during intense emotional situations. Behaviorally, we hypothesized that relative to the passive watching (control condition), RII would result in less negative experience irrespective of low or high intensity, whereas CR would only result in less negative experience in low (but not high)-intensity condition. Given the automatic characteristics of RII (Gallo and Gollwitzer, 2007; Gallo et al., 2009), we also hypothesized that RII relative to CR would require less cognitive control, as indicated by stronger attenuation of the frontal LPP. The re-exposure phase began 20 min later, during which all groups passively viewed the same pictures. The re-exposure task was designed to explore whether RII had long-term effects on self-reported arousal and the central–parietal LPP.

Moreover, we chose disgust as the target emotion because it reliably induces both enhanced subjective emotional ratings and LPP responses (Schienle et al., 2008; Wheaton et al., 2013). We restricted this study to women who are more susceptible to negative emotions (Yuan et al., 2009) and generally show higher disgust sensitivity than men (Schienle et al., 2002, 2005; Curtis et al., 2004).

MATERIALS AND METHODS

Participants

Seventy-five (25 participants per group) healthy, right-handed female undergraduates (M_{age} = 19.85, SD = 1.39) participated in this study, with normal or corrected-to-normal vision. Because this experiment mainly focused on the LPP responses, we determined the sample size based on the recent majority of ERP studies in the field of cognitive reappraisal (e.g., Shafir et al., 2016; Qi et al., 2017). Written informed consent was obtained before the experiment. This study was approved by the local ethical committee of the Faculty of Psychology at Southwest University.

We also examined the group differences (watching, RII, and CR) in emotional states, emotion-related traits, and ages using one-way between-subjects ANOVAs. Results demonstrated no significant group differences (ps $>$ 0.05) in the scores of positive/negative affect (PANAS, Watson et al., 1988), Spielberg State Anxiety Inventory, the Spielberg Trait Anxiety Scale (Spielberger, 1970), and the ages, suggesting that the three groups have no significant difference in the emotional baseline.

Materials and Presentation

In order to find sufficient numbers of low- and high-intensity disgust pictures, we first collected pictures from both the International Affective Picture System (IAPS, Lang et al., 1999) and the Chinese Affective Picture System (CAPS, Lu et al., 2005). Specifically, two authors working in the domain of affective neuroscience for at least 2 years first collected the low- (e.g., slight cuts on hands) and high-intensity (e.g., severe facial burns) disgust pictures based on subjective experiences.

Furthermore, because of the two different sources (i.e., IAPS and CAPS) used for picture selection and the potential impact of cultural difference on ratings of IAPS pictures (Huang and Luo, 2004), we re-rated the collected pictures by an independent sample. Fifteen psychology graduate or doctoral students assessed the valence (1 = very unpleasant; 9 = highly pleasant) and arousal (1 = low; 9 = high) scores, and the degree they felt sadness, fear, joy, anger, and disgust on scales (1 = little; 9 = very) of each disgust picture presented in a randomized order. Results revealed a significant interaction effect between the emotional intensity and the emotion degree ratings, $F_{(4,472)} = 115.69$, $p < 0.001$, $\eta_p^2 = 0.49$. *Post hoc* Bonferroni tests showed that disgust (low/high, M = 5.55/7.21) was the most prevalent emotion for both low- and high-intensity pictures in comparison with sadness (low/high, M = 3.84/4.5, $p < 0.001$), anger (low/high, M = 3.49/4.23, $p < 0.001$), happiness (low/high, M = 2.27/1.73, $p < 0.001$), and fear (low/high, M = 3.65/5.93, $p < 0.001$), and that for each emotion rating, the differences between high and low pictures were significant (ps < 0.001). These findings suggest that the picture set we offered here can elicit low- and high-intensity disgust effectively.

The picture set comprised 150 pictures, including 60 low-intensity and 60 high-intensity disgust pictures with low valence (low/high, M = 2.86/1.87, SD = 0.47/0.36) and high arousal (low/high, M = 5.72/7.46, SD = 0.79/0.64) ratings, and 30 neutral pictures with medium valence (M = 5.12, SD = 0.52) and low arousal (M = 3.39, SD = 0.66) rating. Thirty low- and 30 high-intensity disgust pictures and 30 neutral pictures were selected from the picture set and were used in this study. These pictures were presented on a color monitor using E-prime 2 stimulus presentation software. Viewing distance was held constant at ∼150 cm, and both horizontal and vertical visual angles were kept below 6°.

Design and Procedure

This experiment used a 3 × 3 mixed design with the instruction type (watching, RII, and CR) as a between factor and emotional-intensity category (high, low, and neutral) as a within factor. Upon arrival, participants completed informed consent. Participants were then seated in a quiet room and completed emotion-related questionnaires. With these preparations completed, we began the two-phase ERP study.

In the following regulation phase, each group first underwent a 12-trial (four trials per picture type) practice phase. During this phase, participants were required to speak out how they implemented their instructions and were corrected as needed. The RII group received the following instructions to form an implementation intention: "I will not get disgusted! And if I see blood, then I will take a perspective of a physician!" Participants were not given a specific time (∼1 min) to form their implementation intentions but were asked to read and repeat the instructions very carefully. Passive watching instructions involve paying close attention to the pictures and letting natural thoughts and feelings to arise. Controlled reappraisal instructions involved changing their perspective to decrease emotional reactivity to disgust pictures, for example, by assuming the perspective of a medical professional watching an instructional presentation. The experimenter explained how to use SAM to participants after giving instructions. Each group of participants reported that they

understood and were familiar with the instructions and SAM when finishing the 12 practice trails.

The formal ERP task began after the practice stage. The watching and RII groups received the same instructions of passively watching images, and the CR group received the explicit instructions of cognitive reappraisal. RII group received no further emotion regulatory instruction. After receiving the instruction, participants started the picture presentations by pressing the "S" key. Each regulation or control task consisted of 30 low-intensity, 30 high-intensity negative, and 30 neutral pictures. Within each group and for each participant, the pictures were presented in a randomized manner. Each trial began with a fixation cross for 2–4 s, followed by a picture for 4 s. After the offset of each picture, participants rated their level of emotional valence and arousal using SAM.

After ∼20-min resting, an unexpected re-exposure task was delivered where subjects were presented with the images from the earlier regulation task. For all of three experimental groups, the re-exposure task simply instructed participants to attend to each image and to report their emotional experiences naturally.

EEG Recording and Analysis

We recorded electroencephalogram (EEG) at 500 Hz using an elastic cap (Brain Products) with 64 sensors according to the extended 10-20 system, with two additional mastoid electrodes and a ground electrode on the medial frontal aspect. We used the electrode FCz as an online reference and kept impedance below 5 kω. Raw EEG data were amplified with a 0.01–100 Hz band-pass and were filtered with a notch filter at 50 Hz.

Offline signal processing was carried out using EEGLAB (Delorme and Makeig, 2004). During the offline analysis, we first downsampled the EEG signal at 250 Hz and performed bandpass filter (0.01–40 Hz). We then removed nonbrain electrodes, rejected artifactual channels by the clean_rawdata plugin in EEGLAB, rereferenced the EEG data to the average activity of the left and right mastoids, and rejected epochs with nonstereotyped artifacts. We removed eye-movement artifacts using independent component analysis (ICA) approach. To improve the decomposition, the ICA was performed on the bandpass-filtered (1–40 Hz) raw data (excluding bad channels; Groppe et al., 2009; Winkler et al., 2015). The demixing matrix obtained at 1 Hz data was then applied to the 0.01 Hz filtered data. Eye-movement-related ICA components were marked by visual inspection and finally removed from the continuous EEG data.

For LPP analysis, the continuous EEG was epoched into segments. Baseline correction was then performed by subtracting the mean of a 200-ms prepicture period from the entire duration of picture presentation (4,000 ms). The centro-parietal LPP was measured as the average activity of CPz and Pz, where it is frequently observed (Hajcak et al., 2010; Shafir et al., 2015; Shafir and Sheppes, 2018). In order to better test the time points at which two forms of reappraisal modulated the centro-parietal LPP, the period (300–1,700 ms) of centro-parietal LPP was divided into seven equal 200-ms time segments (300–500, 500–700, 700–900, 900–1,100, 1,100–1,300, 1,300–1,500, and 1,500–1,700 ms). The method of dividing centro-parietal LPP into small time segments (i.e., 200 ms) is frequently used in previous ERP studies focusing the timing effects of cognitive reappraisal (e.g., Thiruchselvam et al., 2011; Paul et al., 2013; Shafir et al., 2015; Qi et al., 2017). Following Moser et al. (2014) and Shafir et al. (2015), the frontal LPP was measured as the average activity of FC1, FC2, and FCz between 700 and 1,100 ms following picture onset.

RESULTS

Behavioral Measure of the Negative Experience

For subjective ratings of valence or arousal, we conducted a 3 × 3 ANOVA with emotional intensity (high, low, and neutral) as a repeated-measures factor and instruction type (RII, CR, watching) as a between-participants factor to examine the effects of emotional intensity and to test the efficacy of RII and reappraisal in low and high emotional intensities. As expected, we found that the main effects of emotional intensity were significant for both arousal and valence ratings [arousal/valence, $F_{(2,144)}$ = 360.78/374.91, ps < 0.001, η_p^2 = 0.83/0.84). Bonferroni planned comparisons showed that high-intensity pictures (arousal/valence, M = 6.62/6.95, SD = 0.11/0.10) were experienced as more negative than low-intensity pictures (M = 5.39/5.76, SD = 0.09/0.06, ps < 0.001) and neutral pictures (M = 3.74/4.24, SD = 0.11/0.08, ps < 0.001). Low-intensity pictures were also experienced as more negative than neutral pictures (ps < 0.001), suggesting a successful experimental manipulation of high- and low-intensity emotion (**Figures 2A,B**).

Furthermore, we found no significant interaction between Emotional-Intensity and Instruction-Type on arousal ratings ($F_{(4,144)}$ = 1.23, p = 0.30, η_p^2 = 0.033), but a significant main effect of Instruction-Type ($F_{(2,72)}$ = 8.45, p < 0.001, η_p^2 = 0.19). Follow-up Bonferroni comparisons showed that RII (M = 4.94, SD = 0.77) and CR (M = 5.06, SD = 0.77) were both effective in reducing arousal ratings compared with the watching group (M = 5.74, SD = 0.77), yet with no difference between these two regulatory groups (p > 0.1; **Figure 3A**). Moreover, we found a significant interaction between Emotional-Intensity and Instruction-Type on valence ratings, $F_{(4,144)}$ = 4.20, p = 0.003, η_p^2 = 0.105. Follow-up Bonferroni comparisons showed that RII (low/high, M = 5.52/6.54, SD = 0.60/0.97, ps < 0.001) and CR groups (M = 5.62/6.74, SD = 0.53/0.77, ps = 0.004) significantly reduced unpleasantness of both low- and high-intensity disgust pictures compared with the watching group (M = 6.13/7.56, SD = 0.58/0.86), also with no significant difference between RII and CR (ps > 0.1; **Figure 3B**). No significant group differences were found in the valence ratings of neutral pictures (ps > 0.5).

In the re-exposure task, we examined whether self-reported ratings of valence and arousal varied as a function of instruction history (RII, CR, and watching) and emotional intensity (high, low, and neutral). For arousal ratings, we found no significant interaction effect between instruction history and emotional intensity ($F_{(4,144)}$ = 0.68, p = 0.61), but significant main effects of instruction history and emotional intensity ($F_{(2,72)}$/$F_{(2,144)}$ = 7.93/290.87, ps ≤ 0.001, η_p^2 = 0.18/0.80).

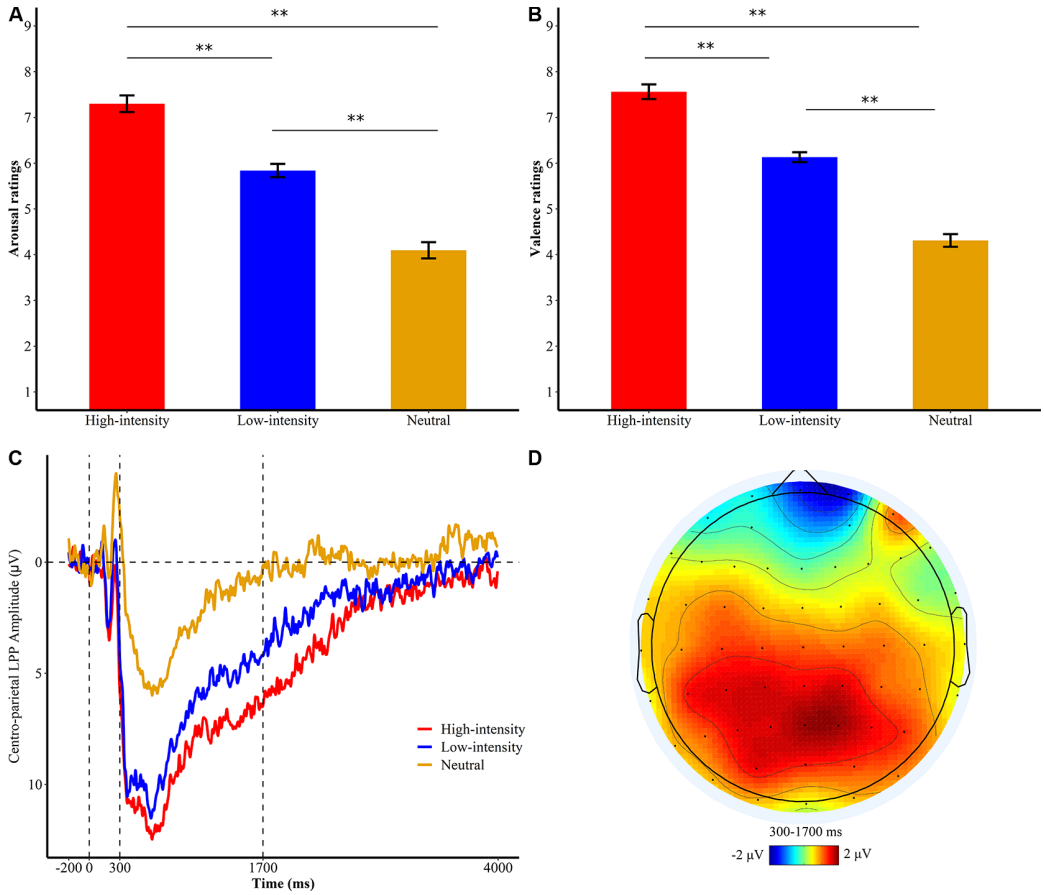

FIGURE 2 | Subjective ratings of **(A)** emotional arousal and **(B)** valence of the passive watching group. $^{**}p < 0.001$; bars represent standard error. **(C)** Centro-parietal late positive potential (LPP) amplitudes for different levels of emotional intensities of the watching group during the first exposure phase. Waveforms are averaged across CPz and Pz electrodes. The *x*-axis runs from the beginning of the baseline (−200 ms before picture onset) to the end of the picture presentation (4,000 ms). **(D)** Topographical distribution of the difference wave of high intensity minus neutral in the watching group.

Bonferroni planned comparisons showed that RII (M = 4.64, SD = 0.83) reduced arousal ratings compared with both CR (M = 5.16, SD = 0.83, p = 0.068) and watching (M = 5.54, SD = 0.83 $p < 0.001$) groups (**Figure 4A**). For valence ratings, we found a significant interaction effect between instruction history and emotional intensity, $F_{(4,144)} = 4.23$, $p = 0.003$, $\eta_p^2 = 0.11$ (**Figure 4B**). Follow-up Bonferroni comparisons showed that for both low- and high-intensity disgust pictures (but not neutral pictures, $ps > 0.5$), RII (low/high, M = 5.32/6.24, SD = 0.59/1.08) significantly reduced valence ratings compared with both CR (M = 5.77/7.24, SD = 0.58/0.83, $ps < 0.02$) and watching (M = 5.96/7.45, SD = 0.56/0.94, $ps \leq 0.001$) groups.

Neural Measures of Regulatory Modulation and Effort: Centro-parietal and Frontal-LPP Analysis

To test whether the neural modulation differences between RII and CR differ across low- and high-intensity levels, we employed a 7 × 3 × 3 ANOVA with time window (time segment) and emotional intensity (high, low, and neutral) as within-participants factors and instruction type (RII, CR, and watching) as a between-participants factor. Consistent with results of subjective ratings, the main effect of emotional intensity was also significant on LPP responses, $F_{(2,864)} = 44.62$, $p < 0.001$, $\eta_p^2 = 0.383$. High-intensity pictures (M = 6.54, SD = 5.83) elicited larger LPP amplitudes than low-intensity pictures (M = 4.84, SD = 5.52, $p = 0.026$) and neutral pictures (M = −0.08, SD = 7.80, $p < 0.001$), and low-intensity pictures elicited a larger LPP amplitude than neutral pictures ($p < 0.001$; **Figure 2C**).

Importantly, we found a significant time window × emotional intensity × instruction type interaction ($F_{(24,864)} = 1.89$, $p = 0.006$, $\eta_p^2 = 0.05$), and a significant main effect of instruction type, $F_{(2,72)} = 5.36$, $p = 0.007$, $\eta_p^2 = 0.13$. In order to examine whether RII would decrease centro-LPP amplitudes earlier than CR and whether its effects would be impacted by emotional intensity, we then performed two-way ANOVAs in each time segment with emotional intensity (high, low) as a within-participants factor and instruction type (RII, reappraisal, and watching) as a between-participants factor. We observed no significant interaction effects between instruction

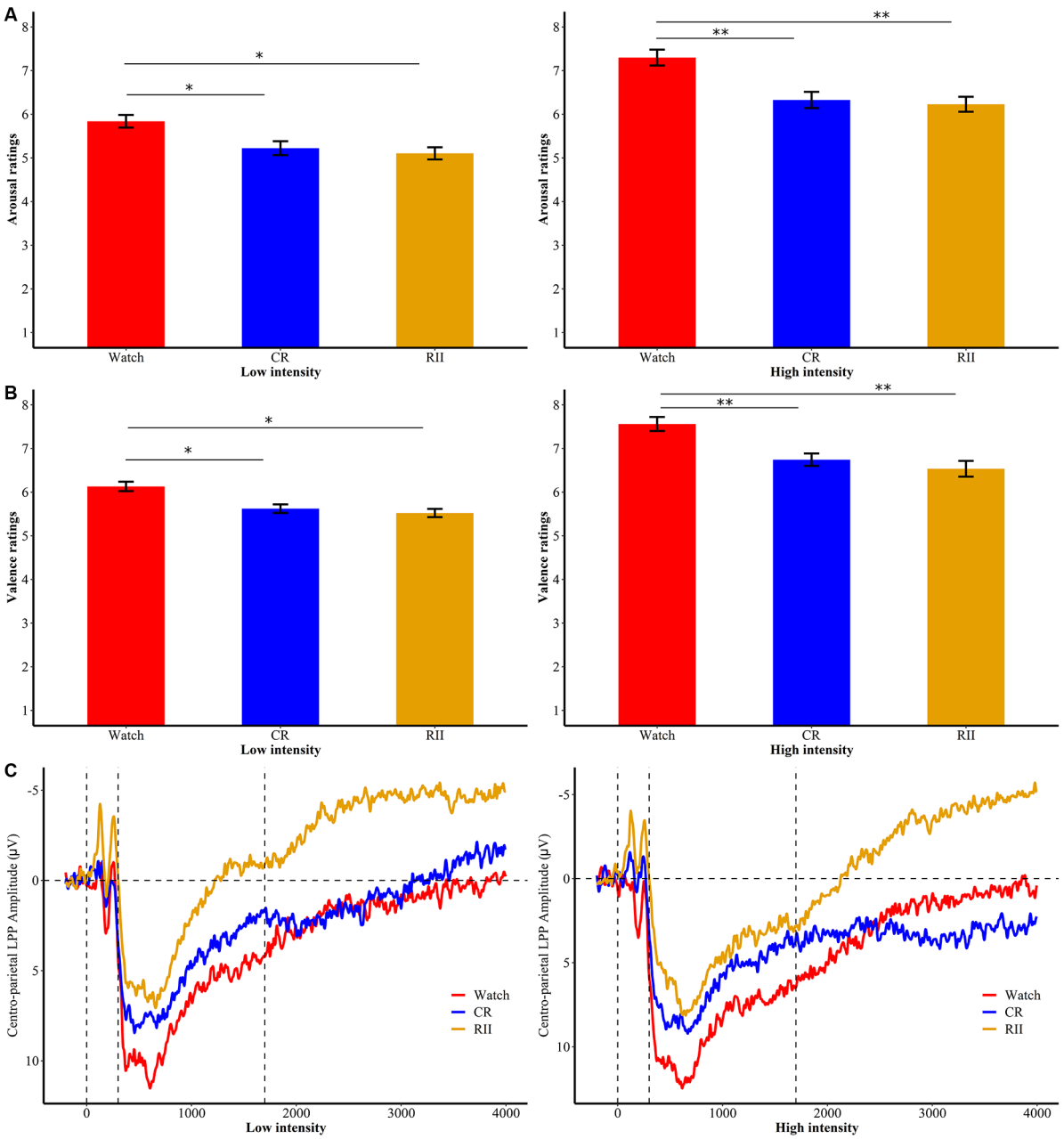

FIGURE 3 | Subjective ratings of emotional **(A)** arousal and **(B)** valence for RII, CR, and watch groups in low- and high-intensities of the first exposure. $^{*}p < 0.05$; $^{**}p < 0.001$; bars represent standard error. RII, reappraisal by implementation intention; CR, controlled reappraisal. **(C)** Centro-parietal LPP amplitudes for RII, CR, and watch groups in high and low emotional intensities of the first exposure. Waveforms are averaged across CPz and Pz electrodes. The *x*-axis runs from the beginning of the baseline (−200 ms before picture onset) to the end of the picture presentation (4,000 ms).

type and emotional intensity across the seven time segments, $Fs_{(2,72)} < 0.96$, $ps > 0.1$ but significant main effects of instruction type across the first six time segments, $Fs_{(2,72)} > 3.24$, $ps < 0.05$. Because of multiple statistical comparisons for the main effects of instruction type, we applied Finner's procedure to control type I error (Finner, 1993), which is a stepwise method to control the familywise error rate that has more power than the classical Bonferroni correction. Planned comparisons showed that RII led to lower centro-LPP amplitudes relative to the watching group during all the seven time segments (300–1,700 ms; $ps < 0.04$; **Figure 3C**). In contrast, CR led to significantly lower centro-LPP amplitudes than watching only during the second segment (500–700 ms, $ps = 0.03$; **Figure 3C**). Moreover, the significant results of RII across seven time segments, when corrected for multiple comparisons, were still significant, whereas the significant result of CR disappeared. The *t* values, *p* values,

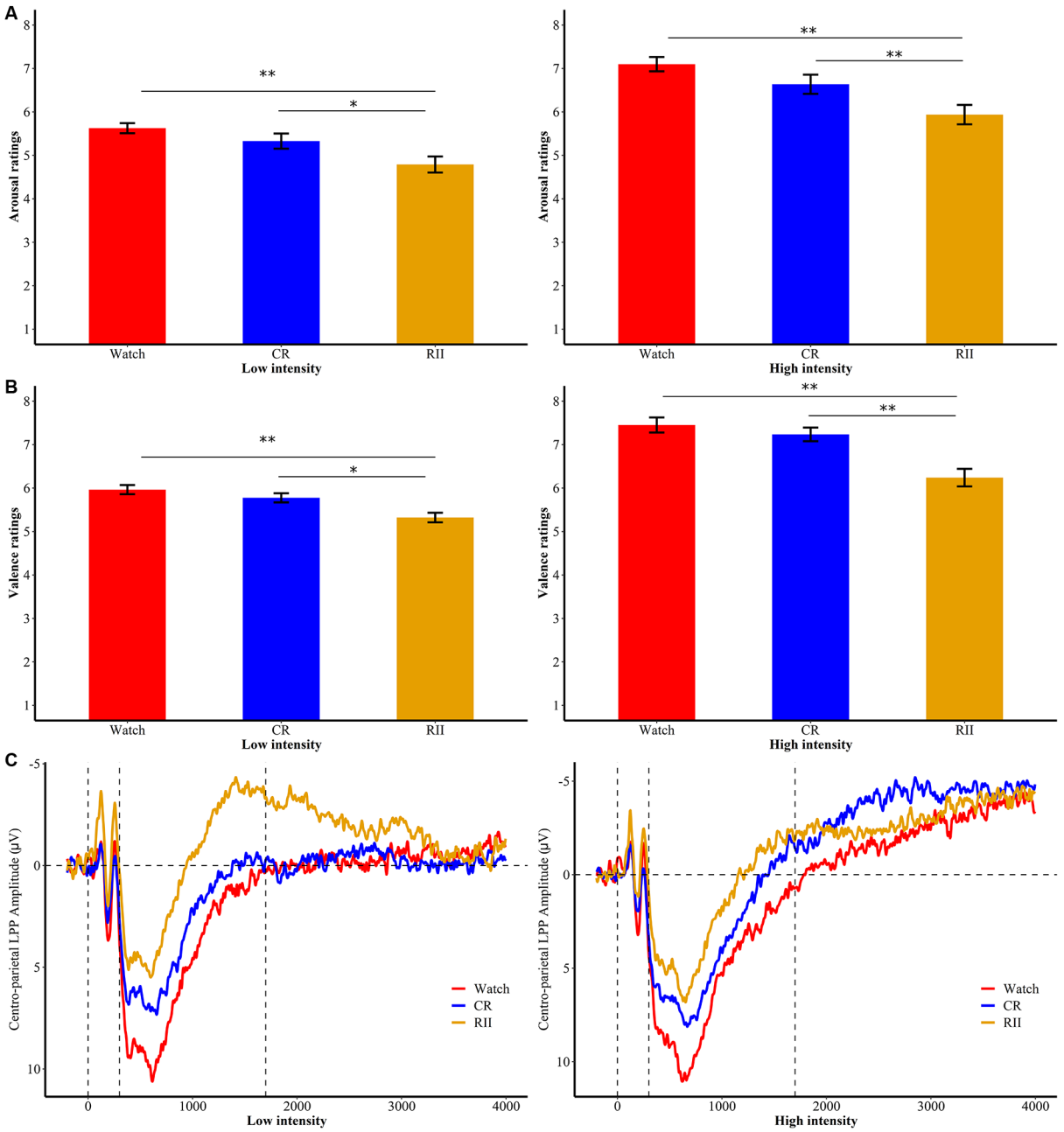

FIGURE 4 | Subjective ratings of **(A)** emotional arousal and **(B)** valence for RII, CR, and watch groups in high and low emotional intensities of the re-exposure task. $^{*}p < 0.05$; $^{**}p < 0.001$; bars represent standard error. RII, reappraisal by implementation intention; CR, controlled reappraisal. **(C)** Centro-parietal LPP amplitudes for RII, CR, and watch groups in high and low emotional intensities of the re-exposure task. Waveforms are averaged across CPz and Pz electrodes. The *x*-axis runs from the beginning of the baseline (−200 ms before picture onset) to the end of the picture presentation (4,000 ms).

means, and standard deviations of LPP of three groups across the seven time segments are presented in **Tables 1**, **2**. No other significant difference was observed between the three groups.

Concerning the centro-parietal LPP during the unexpected re-exposure task, we also conducted a 7 × 2 × 3 ANOVA with time window (seven time segments) and emotional intensity (high, low, and neutral) as within-participants factors and instruction history (RII, CR, and watching) as a between-participants factor. Results yielded no interaction effect with instruction history ($Fs \leq 1.1$). However, we found a marginally significant main effect of instruction history, $F_{(2,72)} = 3.09$, $p = 0.052$, $\eta_p^2 = 0.079$. Planned comparisons showed that RII ($M = -0.27$, $SD = 5.33$, $p = 0.051$), but not CR ($M = 2.18$, $SD = 5.33$, $p = 1.0$), led to lower centro-LPP amplitudes than watching group ($M = 3.41$, $SD = 5.33$; **Figure 4C**). No other significant or

TABLE 1 | Means (standard deviations) and pair-wise comparisons of the central–parietal late positive potential (LPP) between watch and controlled reappraisal (CR) groups in each 200-ms interval of the 300–1,700-ms time epoch.

Time (ms)	Watch	CR	*t*-value	*p*-value	Finner's *p*-value
300–500	9.46 (5.47)	7.13 (5.81)	1.46	0.15	0.38
500–700	11.15 (4.79)	8.16 (4.91)	2.17	0.03	0.19
700–900	9.46 (5.21)	7.33 (4.87)	1.49	0.14	0.38
900–1,100	7.38 (5.09)	5.27 (4.73)	1.52	0.13	0.38
1,100–1,300	6.45 (5.63)	4.40 (5.09)	1.35	0.18	0.38
1,300–1,500	6.13 (5.88)	3.81 (5.20)	1.48	0.14	0.38
1,500–1,700	5.48 (6.14)	2.96 (5.84)	1.49	0.14	0.38

TABLE 2 | Means (standard deviations) and pair-wise comparisons of the central–parietal late positive potential (LPP) between watch and reappraisal-based implementation intention (RII) groups in each 200-ms interval of the 300–1,700-ms time epoch.

Time (ms)	Watch	RII	*t*-value	*p*-value	Finner's *p*-value
300–500	9.46 (5.47)	4.58 (6.41)	2.89	0.006	0.0277
500–700	11.15 (4.79)	6.80 (5.37)	3.02	0.004	0.0277
700–900	9.46 (5.21)	5.70 (5.58)	2.46	0.018	0.0369
900–1,100	7.38 (5.09)	3.41 (6.21)	2.47	0.017	0.0369
1,100–1,300	6.45 (5.63)	1.92 (7.07)	2.50	0.016	0.0369
1,300–1,500	6.13 (5.88)	1.25 (7.86)	2.49	0.016	0.0369
1,500–1,700	5.48 (6.14)	0.93 (8.85)	2.12	0.04	0.040

marginal differences between the three groups were observed ($ps > 0.1$).

We then conducted analyses to estimate the differential requirement of RII and controlled reappraisal for cognitive effort measured by frontal LPP. For both the first exposure and re-exposure tasks, we employed a 3 × 3 ANOVA with emotional intensity (high, low, and neutral) as a within-participants factor and instruction type or instruction history (RII, CR, and watching) as a between-participants factor. We found neither significant interaction effects between emotional intensity and instruction type/instruction history ($Fs \leq 1.0$, $ps > 0.1$) nor for the main effect of instruction type ($F_{(2,72)} = 1.24$, $p = 0.29$). However, we found a marginally significant main effect of instruction history, $F_{(2,72)} = 2.93$, $p = 0.06$, $\eta_p^2 = 0.075$. Planned comparisons showed that pictures with RII-history ($M = -1.86$, $SD = 5.91$, $p = 0.034$) but not with CR-history ($M = 1.52$, $SD = 5.91$, $p = 0.89$) elicited a lower amplitude of frontal LPP than pictures with Watching-history ($M = 1.75$, $SD = 5.91$; **Figures 5A,B**).

DISCUSSION

Finding more effective emotion regulation strategies is a continuing concern within the field of emotion. Although cognitive reappraisal has been suggested to be powerful in downregulating negative emotion, its implementation process (Shafir et al., 2015) and use frequency (Sheppes et al., 2011) have been suggested to be impacted by emotional intensity. The present two-phase ERP experiment revealed that reappraisal-based implementation intention produced an earlier and more sustainable emotion regulatory effects than controlled reappraisal.

During the first exposure task, we found that CR and RII reduced both the low- and high-intensity disgust experience effectively relative to the watching group. Consistent with previous findings, these behavioral findings suggest that automatic cognitive reappraisal (i.e., RII) as effective as controlled reappraisal (Shafir et al., 2015) in reducing both the low- and high-intensity adverse subjective experience. However, relative to the watching group, RII significantly reduced LPP amplitude across the entire time epoch (300–1,700 ms), whereas CR only reduced lower LPP amplitude within one time segment (500–700 ms). Furthermore, the neural regulatory effects of CR disappeared after corrections for multiple comparisons. We argue that the neural regulatory effects of RII have two advantages over that of CR. First, emotion regulation effects of RII on LPP amplitude were earlier than that of CR. In both low and high intensities, RII attenuated the centro-parietal LPP at the 300-ms picture presentation, whereas emotion regulation effects of CR started at 500 ms. Second, RII elicited a more sustainable attenuation of the centro-parietal LPP than CR in both low and high intensities. The modulating effect of RII lasted for a longer period (low/high, 300–1,700 ms) than CR (low/high, 500–700 ms), which supports our prediction that RII leads to a more sustainable emotion-regulatory effect than CR.

It may be argued whether RII participants in the first exposure task simply used attentional distraction as an effective method (i.e., "I will look away if I see a disgusting image"). However, the patterns observed for RII during the present re-exposure task significantly differed with those in the literature for attentional distraction. On the one hand, Thiruchselvam et al. (2011) found that upon unexpected re-exposure, pictures with a distraction (but not reappraisal) history elicited a larger LPP than images with a watching history and did not differ from pictures with a negative-watch history on self-reported ratings of valence and arousal. On the other hand, our unexpected re-exposure task showed that RII participants still self-reported lower ratings of emotional valence and arousal than CR and watching groups

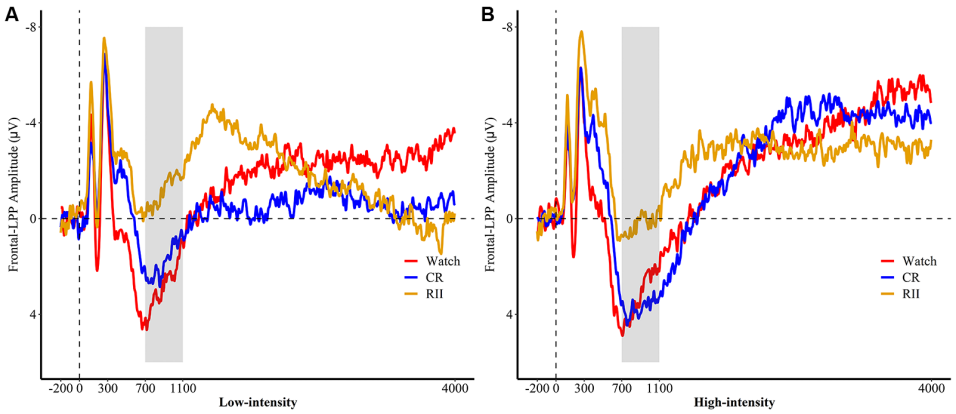

FIGURE 5 | Picture-locked event-related potentials (ERP) in **(A)** low and **(B)** high emotional intensities for the re-exposure task, pooled at fronto-central sites (FC1, FC2, FCz). Picture onset is identified with a dotted line on *x*-axis. The *x*-axis runs from the beginning of the baseline (−200 ms before picture onset) to the end of the picture presentation (4,000 ms). RII, reappraisal by implementation intention; CR, controlled reappraisal.

in both low and high intensities. In line with previous research (Thiruchselvam et al., 2011), we found no significant differences in subjective ratings between CR- and watching-history groups in both low and high intensities, confirming that the emotion-regulatory effects of CR on subjective experiences easily drop off with time. Moreover, the present results also demonstrated that only pictures with RII history (but not with CR history) elicited a lower amplitude of the centro-parietal LPP during the entire time window (300–1,700 ms). The subjective and ERP findings suggest that RII may integrate some advantages of distraction and reappraisal, as evidenced by that RII not only reduced the centro-parietal LPP amplitude earlier than CR during the first exposure task but also produced long-term emotion regulation effects during the unexpected re-exposure task.

Moreover, during the unexpected re-exposure task, results showed that RII also led to a lower amplitude of frontal LPP than the watching group, confirming the effortless characteristics of RII (Gallo and Gollwitzer, 2007; Gallo et al., 2009, 2012). To our surprise, we did not find a significant increase in frontal LPP amplitude during CR relative to watching groups, which is inconsistent with previous studies (Bernat et al., 2011; Moser et al., 2014; Shafir et al., 2015). A likely explanation is that previous studies of CR mainly used a within-participants design, requiring participants to switch between regulation and watch trials within one task (e.g., Moser et al., 2014). The trial of these studies commonly includes a blank or fixation (800 ms–1 s) between the cue and picture. In theory, participants have to retrieve information related to reappraisal into their explicit memory after viewing a cue of reappraisal. The memory preparation of reappraisal may be more effortful than that of simply passive watching. In contrast, the between-participants design only required participants to either passively watch pictures or reappraise their emotions during the entire task (e.g., Gallo et al., 2012). Participants did not need to switch their working memory back and forth between reappraisal and watching strategy frequently. Therefore, the between-participants design may be less effortful for participants to implement CR compared with the within-participants design of CR. In brief, the design to initiate CR, rather than CR itself, maybe cognitive costly (Richards, 2004).

Several limitations should be noted. First, the present study only focused on perspective-taking reappraisal and only used negative pictures involving blood to elicit disgust responses. These manipulations may result in the present task lacking ecological validity to understand the true ability of an individual to implement the automatic or controlled forms of cognitive reappraisal strategy. For example, it is unknown whether and how the results generalize to other forms of disgust, other negative emotions, and positive emotions. Second, the sample was entirely female, which may also limit the generalizability of our findings.

In summary, we first demonstrated that automatic reappraisal-based implementation intention yields an earlier and more sustainable emotion regulatory effects than controlled reappraisal, and such regulatory effects are not impacted by emotional intensity. These findings extend the process model of emotion regulation (Gross, 1998), suggesting that automatic and controlled forms of even one strategy have varying temporal trajectories.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethical committee of the Faculty of Psychology at Southwest University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC, JYa, and JYu conceived and designed the experiments. SC and KY performed the experiments and analyzed the data. SC, JYa, and JYu wrote the article. All authors reviewed the manuscript.

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Erratum: Automatic Reappraisal-Based Implementation Intention Produces Early and Sustainable Emotion Regulation Effects: Event-Related Potential Evidence

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Automatic Reappraisal-Based Implementation Intention Produces Early and Sustainable Emotion Regulation Effects: Event-Related Potential Evidence
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Due to a production error in the abstract, the last half of the sentence beginning with "Here, we aim to test" and the first half of the subsequent sentence were deleted. The text has been corrected to read as follows:

"Here, we aim to test whether automatic reappraisal-based implementation intention (RII) downregulates intense negative emotion more efficiently than controlled reappraisal (CR) using a two-phase event-related potential (ERP) experiment. In the regulation phase, both RII and CR decreased subjective experiences of negative emotion relative to passive watching, irrespective of emotional intensity."

The publisher apologizes for this mistake. The original version of this article has been updated.

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Emotions, Alexithymia, and Emotion Regulation in Patients With Psoriasis

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Psoriasis is a chronic dermatological condition that is frequently associated with problematic patterns of emotional reactivity (the way in which patients react to stimuli), alexithymia (their ability to recognize and label the emotional reaction), and emotion regulation (the ability to enhance or reduce their own emotional reaction). A research in the peer-reviewed scientific literature was conducted in order to identify articles describing the association of psoriasis and affective problems. In particular, we first evaluate studies that have investigated abnormal emotional reactivity (in terms of duration, frequency, or type of the experienced emotions) and its impact on patients' quality of life; next, we review the role of alexithymia and emotion regulation in modulating the relationship between emotional reactivity and quality of life in this population. From a critical analysis of the reviewed studies, we highlight that altered emotional processing might be particularly important in the characterization of this condition. In particular, we show that this condition is related to an emotional reactivity characterized by negative emotions that have a stronger impact on patients' quality of life when emotion regulation abilities are weak, especially if patients have alexithymia. Finally, we present suggestions for future directions in both clinical and research fields.

Keywords: psoriasis, emotional reactivity, alexithymia, emotion regulation, stress

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease affecting approximately 2% of the population (Schmid-Ott et al., 2007) and characterized by cutaneous lesions that may appear on any part of the body. This condition can be very challenging and has such a strong impact on patients' physical appearance in that embarrassment over appearance is rated as the most debilitating feature of the disease (Vardy et al., 2002). Psychological stress, in turn, has a negative impact on psoriasis symptoms leading to a self-perpetuating mechanism that might be difficult to interrupt (Basavaraj et al., 2011). In such a scenario, emotional reactivity (i.e., the emotional response provoked by the perception and the valuation of a given situation; Gross and Jazaieri, 2014) and emotion regulation (i.e., the ability to modify the perceived emotion in terms of its quality, intensity, or duration; Gross and Jazaieri, 2014) become particularly crucial. Importantly, the way in which we experience and regulate our emotions is strictly dependent on the ability to recognize and distinguish them from other bodily sensations (Chen et al., 2011), thus, deficit in such domain (i.e., alexithymia) can also worsen the affective experience of psoriasis patients.

In what follows, we provide a review of the literature tapping into emotional processing in psoriasis with the aim of characterizing it in terms of emotional reactivity, alexithymia, and emotion regulation. Even though these constructs can be correlated with each other, here, we highlight how their abnormal functioning is associated with different dermatological, psychological, or life quality outcomes. Finally, we discuss the implications for clinical practice and research.

METHODS

We conducted a search of PubMed's database of articles containing the word "psoriasis" and one of the following terms: emotional reactivity, alexithymia, social exclusion, stigmatization, stress, anxiety, depression, and emotion regulation. Additional records were identified through manual searches of references of identified articles. Thirty-seven studies were selected (see **Table 1**).

EMOTIONAL REACTIVITY

Emotional reactivity is the constellation of behavioral and physiological changes triggered by the evaluation of a given situation in relation to one's own active goals (Gross and Jazaieri, 2014). It can assume the form of a discrete emotion (i.e., an intense and short-lived response; Sander, 2013) or a feeling (i.e., the conscious experience of the emotion state; Tsuchiya and Adolphs, 2007), or it can be chronically altered in affective clinical disorders (i.e., fear in anxiety or sadness in depression). Pathological forms of emotional reactivity are typically characterized in terms of *emotion intensity* (e.g., emotional hyporeactivity), *emotion duration* (e.g., prolonged negative emotions), *emotion frequency* (e.g., frequent aggressive episodes), or *emotion type* (e.g., displaying inappropriate emotions) (Gross and Jazaieri, 2014). Psoriasis patients tend to experience a wide range of negative emotions that can be altered in several of these qualities (Sampogna et al., 2012). Below, we provide a detailed review of emotions (anger, disgust, and shame), feelings (stigmatization and social exclusion), and affective clinical disorders (anxiety and depression) that have been studied in relation to psoriasis.

Anxiety

Psoriasis is characterized by anxiety (i.e., the feeling of apprehension, uncertainty, and fear) as showed by the high prevalence of anxiety disorders (13.1%; Lamb et al., 2017) diagnosed in these patients (Cepuch et al., 2014; Fleming et al., 2017). Self-reported anxiety seems to be higher in women with psoriasis with respect to men and is positively correlated with the severity of the disease (Pujol et al., 2013). Recently, higher level of anxiety and depression has been found in these patients, even in a sample of psoriasis patients with cognitive deficits (Innamorati et al., 2018).

Stigmatization, Shame, and Disgust

Given its impact on patients' physical appearance, psoriasis is often associated with a feeling of stigmatization, especially when it appears early in patients' life (Schmid-Ott et al., 2007). Stigmatization is higher when the disease has an early onset and when the extent of bleeding and feeling of rejection are greater (Ginsburg and Link, 1989). It has been shown that high levels of stigmatization are caused by disease's severity and, in turn, provoke a significant decrement of quality of life (Vardy et al., 2002). Moreover, stigmatization seems to (i) be the most powerful predictor of depressive symptoms in these patients (Hrehorów et al., 2012; Łakuta et al., 2017); (ii) be significantly related to psychological distress and degree of disability (Richards et al., 2001); and (iii) interfere with work and daily activities (Ginsburg and Link, 1993). Patients suffering from stigmatization tend not to have a partner, to have lower education, to have a higher level of social inhibition, to show a type D personality (van Beugen et al., 2017), to have higher stress and pruritus intensity, and to have lower quality of life (Hrehorów et al., 2012). In a recent study (Ponsi et al., 2019), we showed that in patients with psoriasis with respect to controls, higher sympathetic system activation during an experimental paradigm designed to induce the feeling of social exclusion (i.e., cyberball paradigm) was related to a higher need for social reconnection (i.e., the need to invest in new social interactions).

When chronic stigmatization is associated with an anxious ambivalent attachment style, dermatological patients' view of themselves can be severely influenced, and they can manifest negative feelings of self-disgust (Jafferany and Patel, 2019). Psoriasis patients show higher sense of skin-related shame and disgust, which correlates with a less positive evaluation of being touched by their parents when they were kids (Lahousen et al., 2016). Interestingly, it has been shown that not only psoriasis patients but also their significant ones tend to avoid disgusted faces more than do controls (van Beugen et al., 2016). Shame—which is associated with the severity of psoriasis symptoms and also with depression and anxiety—seems to be higher in women than men, and it is more frequent in patients with a low level of education (Sampogna et al., 2012).

Depression

It has been shown that the risk of developing depression in psoriasis patients (prevalence of 9.9% of Major Depressive Disorder; Lamb et al., 2017) seems to be mediated by the presence of other comorbidities, except in younger patients with severe psoriasis where the presence of the disease directly predicts the onset of depression (Jensen et al., 2016). Psychological distress, negative beliefs about one's own appearance, and lower levels of emotional and social support are factors that predispose to the development of depression in psoriasis (Wojtyna et al., 2017). Also, compared with patients with other dermatological conditions such as acne or alopecia areata, psoriasis patients show higher scores of depression, and suicidal ideation (Pompili et al., 2016).

TABLE 1 | Description of the studies identified by the review.

N	Authors Year	Type of study	Number of patients	Number of control participants	Emotional reactivity/ regulation/ alexithymia/ stress	Measures behavioral/ self-report	Outcome
1	Cepuch et al., 2014	Cross-sectional	105	Absent	Emo	Self-report	High prevalence of anxiety
2	Pujol et al., 2013	Longitudinal (2 sessions)	164	Absent	Emo	Self-report	Anxiety is higher in women and correlates with the severity of the disease
3	Innamorati et al., 2018	Cross-sectional	50	50	Emo	Self-report	Higher anxiety and depression than controls
4	Vardy et al., 2002	Cross-sectional	100	100	Emo	Self-report	In psoriasis, the relationship between disease severity and quality of life is mediated by the feeling of stigmatization
5	Łakuta et al., 2017	Cross-sectional	148	Absent	Emo	Self-report	Stigmatization seems to be the most powerful predictor of depressive symptoms in these patients
6	Richards et al., 2001	Cross-sectional	115	Absent	Emo	Self-report	Stigmatization is related to psychological distress and degree of disability
7	Ginsburg and Link, 1989	Cross-sectional	100	Absent	Emo	Self-report	Stigmatization is higher when psoriasis has an early onset and the extent of bleeding is wider and feeling of rejection is stronger
8	Ginsburg and Link, 1993	Cross-sectional	100	Absent	Emo	Self-report	Stigmatization interferes with work and daily activities
9	van Beugen et al., 2017	Cross-sectional	514	Absent	Emo	Self-report	Stigmatization was associated with higher impact on daily life; lower education; higher disease visibility, severity, and duration; higher levels of social inhibition; having a type D personality; and not having a partner
10	Hrehorów et al., 2012	Cross-sectional	102	Absent	Emo	Self-report	Stigmatization is assiciated with: pruritus intensity, stress, depressive symptoms and lower quality of life
11	Ponsi et al., 2019	Cross-sectional	16	17	Emo ER	Behavioral and physiological	Higher sympathetic activity during social exclusion which brings to higher need for social reconnection
12	Lahousen et al., 2016	Cross-sectional	171	171	Emo	Self-report	Shame and disgust correlated with a less positive evaluation of being touched by their parents when they were kids
13	van Beugen et al., 2016	Cross-sectional	50 + 50 (significant ones psoriasis)	50 (alopecia) 50 (significant ones alopecia) 50 controls	Emo	Behavioral	Patients with psoriasis and their significant ones avoid disgusted faces more than controls
14	Sampogna et al., 2012	Cross-sectional	936	Absent	Emo	Self-report	Shame is higher in women than men. Shame and anger are more frequent in patients with low level of education
15	Jensen et al., 2016	Cross-sectional	42511	Reference population: 4724748	Emo	Clinical diagnosis	Developing depression after psoriasis is mediated by the presence of other comorbidities
16	Wojtyna et al., 2017	Cross-sectional	219	Absent	Emo	Self-report	Depression is predicted by: psychological distress, negative beliefs about one's own appearance, and lower levels of emotional and social support
17	Pompili et al., 2016	Cross-sectional	112	77 (melanoma) 53 (allergy)	Emo	Self-report	Psoriasis is more frequently associated with suicidal ideation and attempt
18	Aydin et al., 2017	Cross-sectional	85	86 (healthy)	Emo	Self-report	Higher anger related to lower self-esteem
19	Matussek et al., 1985	Cross-sectional	38	113 (depression) 32 (healthy)	Emo	Self-report	High in outward aggression and low in autoaggression
20	Picardi et al., 2003	Cross-sectional	40	116 (other dermatological)	Alexi	Self-report	Higher alexithymia

(Continued)

TABLE 1 | Continued

N	Authors Year	Type of study	Number of patients	Number of control participants	Emotional reactivity/ regulation/ alexithymia/ stress	Measures behavioral/ self-report	Outcome
21	Innamorati et al., 2016	Cross-sectional	100	97 (healthy)	Emo Alexi	Self-report	The effect of psoriasis on quality of life is mediated by difficulties in emotion regulation, anxiety, depression, and food craving Higher alexithymia
22	Talamonti et al., 2017	Cross-sectional	250	215 (healthy)	Alexi	Self-report	Higher alexithymia Association between alexitimia and female gender and involvment of sensitive body areas
23	Korkoliakou et al., 2014	Cross-sectional	100	100 (healthy)	Emo Alexi	Self-report	Higher alexithymia
24	Korkoliakou et al., 2017	Cross-sectional	108	Absent	Emo Alexi	Self-report	Psoriasis with alexithymia is related to higher somatization, interpersonal sensitivity, anxiety, and phobic anxiety than Psoriasis witout alexithymia
25	Consoli et al., 2006	Longitudinal	92	Absent	Alexi	Self-report	Patients with low emotional awareness are more reactive to stress and more responsive to treatment
26	Vari et al., 2013	Cross-sectional	33	33 (healthy)	ER	Self-report	Higher use of emotion supression
27	Ciuluvica et al., 2019	Cross-sectional	91	101 (healthy)	ER	Self-report	Higher use of emotion supression More impulse control difficulties, and non-acceptance of emotional responses
28	Ciuluvica et al., 2014	Cross-sectional	23	18 (dermatological) 27 (healthy)	ER	Self-report	Suppression is negatively related with quality of life, while reappraisal is positively related with patients well being
29	Almeida et al., 2017	Cross-sectional	228	Absent	ER	Self-report	Higher difficulties in ER negatively correlates with treatment satisfaction and positively correlates with: discomfort due to the disease; psychopathological symptoms; missed work/school days
30	Picardi et al., 2005	Cross-sectional	33	73 (dermatological)	Alexi ER	Self-report	More likely to have alexithymia. Lower perceived social support and higher insicure attachment
31	Larsen et al., 2017	Longitudinal	163	Absent	Alexi ER	Self-report	Lower self-management is associated with higher alexithymia
32	Mastrolonardo et al., 2006	Cross-sectional	25	50	ER	Behavioral	Higher increase of heart rate and diastolic blood pressure during stress induction
33	Mastrolonardo et al., 2007	Cross-sectional	25	50	ER	Behavioral	No change in cortisol levels and stress perception after stress induction
34	Panasiti et al., 2019	Cross-sectional	16	17	ER	Behavioral	Patients perform better and show reduced sympathetic system activity when the cognitive load associated to the emotional task is high
35	Jose and Menon, 2017	Cross-sectional	10	10 (acne) 10 (melanoma)	Stress	Self-report	More sensitive to stress
36	Simonić et al., 2013	Cross-sectional	45	191 (dermatologic)	Stress	Self-report	Psoriatic arthritis report less positive and more negative (stressful) life events during late childhood
37	O'Leary et al., 2004	Cross-sectional	141	Absent	Stress	Self-report	Perceived stress is associated with a poorer level of quality of life, higher levels of anxiety and depression

Anger

It has been shown that in dermatologic conditions, aggression is associated with anxiety, and with a lower level of optimism and social support (Coneo et al., 2017). In psoriasis, anger (subclinical condition) frequency correlates with severity and length of the disease, and it is higher in patients with a low level of education (Sampogna et al., 2012). Psoriasis patients are characterized by a higher level of trait anger respect to controls; moreover, when they have low self-esteem, they show more anger toward people or objects and have enhanced difficulties in anger control (Aydin et al., 2017); conversely, they score very low in autoaggression (Matussek et al., 1985). Notably, however, one study reported that psoriasis patients exhibited fewer verbal aggression responses after anger-inducing procedures (Niemeier et al., 1999).

ALEXITHYMIA

Alexithymia is a subclinical trait defined by difficulties in the following: (i) identifying, describing, and communicating one's own feelings; (ii) differentiating them from emotionally unrelated bodily sensations; (iii) emotional awareness related to psychosomatic symptoms; and (iv) imagination, daydreaming, and introspection (Martin and Pihl, 1985; Taylor et al., 1991). Crucially, identifying emotions is believed to be related to the ability to regulate them (Chen et al., 2011).

Neuroscientific evidence links alexithymia to (i) aberrant emotion processing (i.e., decreased activation of limbic structures in response to negative emotional stimuli and angry vs. neutral faces; Kano et al., 2003; Van der Velde et al., 2013; (ii) reduced gray matter volume in emotional processing brain areas (Xu et al., 2018); and (iii) reduced connectivity within the default mode network (DMN), in brain areas involved in emotional awareness and increased connectivity of the DMN with areas involved in sensory input and emotion control (Liemburg et al., 2012).

The association between alexithymia and various medical disorders suggests that it may represent a risk factor for their development, probably because it enhances stress responses through autonomic dysregulation (i.e., the alexithymia–stress hypothesis; Martin and Pihl, 1985). In particular, alexithymic people seem not to cope effectively with stressors because of a stress response that is typically altered in its cognitive (i.e., lack of emotional awareness), behavioral (i.e., maladaptive coping and lack of emotional expression), and physiological (i.e., increased arousal) components (Martin and Pihl, 1985). This altered response to stress might prolong the exposure to stressors and, on the long run, exacerbate the somatovisceral response (Martin and Pihl, 1985).

Also, alexithymia presents hypo-reactive physiological responses rather than hyper-reactive ones (Van der Velde et al., 2013) and seems to be associated with poorer interoception and the tendency to misattribute bodily signals (Palser et al., 2018). Misinterpretation of bodily sensations associated with negative emotions might be another mechanism through which alexithymia worsens clinical conditions (Lumley et al., 1996; Tuzer et al., 2011).

Alexithymia is often associated with psoriasis (Picardi et al., 2003, 2005; Innamorati et al., 2016) (prevalence of 24.8%, Sampogna et al., 2017), especially in women and in cases in which the plaques extend to sensitive body areas (like the face, the hands, or the genitals) (Talamonti et al., 2017). These patients show a higher level of somatization, interpersonal sensitivity, anxiety, and phobic anxiety respect to non-alexithymic patients (Korkoliakou et al., 2014, 2017). Some researchers suggested that alexithymia might be a condition that patients acquired in order to avoid dealing with unwanted emotions (Panayiotou et al., 2015). Consistently with this point of view, emotional awareness, an emotional skill distinct but often correlated to alexithymia, consisting in the ability to integrate and differentiate emotions, predicts better response to treatment in psoriasis patients (Consoli et al., 2006). The reported studies measured alexithymia using the Toronto Alexithymia Scale (TAS−20; Bagby et al., 1994).

EMOTION REGULATION

Emotion regulation is a multi-componential process that comprehends the implicit and explicit strategies through which we act on the emotional experience in order to enhance or reduce it (Gross and John, 2003). Maladaptive emotion regulation is a component of many psychopathological diseases such as depression (Ehring et al., 2010) and post-traumatic stress disorder (McLean and Foa, 2017).

Compared with controls, patients with psoriasis are characterized by higher use of emotional suppression (Vari et al., 2013; Ciuluvica et al., 2014, 2019), an emotion regulation strategy considered rather primitive that consists in inhibiting the expression of the ongoing emotional response once it has been generated (Gross and John, 2003). Interestingly, this is the same strategy used by recovered-depressed patients (Ehring et al., 2010). Conversely, higher use of reappraisal (Ciuluvica et al., 2014), an emotion regulation strategy that is more adaptive than suppression and consists in re-thinking the situation to alter its meaning and emotional impact (Gross and John, 2003), has shown to be positively related with patients' well-being (Ciuluvica et al., 2014). In patients with psoriasis, higher difficulty in emotion regulation, as measured by the difficulty in emotion regulation strategies (DERS) scale, negatively correlates with treatment satisfaction and positively correlates with (i) the discomfort due to the disease; (ii) the number of reported psychopathological symptoms; and (iii) the frequency of missed work/school days (Almeida et al., 2017). Moreover, subtypes of psoriasis patients also show different patterns of emotion regulation: early-diagnosed patients have higher difficulties in behaving according to their goals when distressed (Almeida et al., 2017); obese patients with psoriasis show higher difficulties respect to obese patients without psoriasis (Innamorati et al., 2016). It has also been shown that the ability of impulse control (subclinical condition) when experiencing negative emotions is lower in this condition (Innamorati et al., 2016). Two subscales of the DERS, namely, emotional clarity and emotion acceptance, which are believed to measure concepts that are very close to alexithymia, also show higher scores among these patients (Innamorati et al., 2016). In agreement, in two recent studies, we showed that psoriasis patients scored higher than controls in the "Lack of Emotional Clarity" subscale of the DERS, indicating that patients have more difficulties than controls in correctly identifying their own emotions (Panasiti et al., 2019; Ponsi et al., 2019).

It has been hypothesized that low abilities in emotion regulation in psoriasis patients might increase the impact of poor social support on the severity of the disease (Picardi et al., 2005). Moreover, lower self-management, a psychological construct composed of medical management, role management, and emotional management, is associated with higher alexithymia in patients with moderate to severe psoriasis (Larsen et al., 2017).

It has to be noticed that most of the studies present in the scientific literature, at least to our knowledge, employed self-report measures or questionnaires. The lack

of behavioral and physiological evidence regarding emotion regulation deficits in this population is crucial. Two studies reported some indirect measure by submitting patients to a standardized stressful procedure (mental arithmetic and the Stroop Color-Word Naming Test). They found higher heart rate and diastolic blood pressure in psoriasis patients (Mastrolonardo et al., 2006), which, however, was not accompanied by differences in stress perception or salivary cortisol levels (Mastrolonardo et al., 2007). Importantly, we recently showed that when presented with a working memory task with emotional distractors (i.e., the Emotional N-Back), psoriasis patients perform better and show reduced sympathetic system activity when the cognitive load associated with the task is high versus low and thus found it easier not to pay attention to the emotional distractors (Panasiti et al., 2019).

To sum up, the impact of emotion regulation abilities on the course of psoriasis seems crucial: patients' well-being is negatively associated with suppression and is positively associated with reappraisal. Suppression and rumination are indeed more strongly linked to psychopathological outcomes than reappraisal and acceptance strategies (Kobylińska and Kusev, 2019). To our knowledge, there are no studies exploring the employment of acceptance strategies in psoriasis.

Stress Managing

The experience of stress can impact each of the three aspects of emotional processing that we mentioned in this review (i.e., emotional reactivity, alexithymia, and emotion regulation): (i) exposure to stressors is correlated to higher experience of negative emotions (Feldman et al., 1999); (ii) higher basal cortisol level during stress anticipation is associated with higher alexithymia (de Timary et al., 2008); and (iii) acute stress impairs emotion regulation during fear conditioning (Raio et al., 2013).

Stress managing is pivotal in psoriasis patients because impaired emotional processing could affect not only the response to stressful events but also the quality of the general emotional response in psoriasis. Patients with psoriasis are more sensitive to stress with respect to other dermatological conditions such as acne or melanoma (Jose and Menon, 2017), and patients with psoriatic arthritis report less positive and more negative (stressful) life events during late childhood (Simonić et al., 2013). Stressful events are indeed very often reported by patients as the cause of the appearance or the exacerbation of the disease (Griffiths and Richards, 2001). Perceived stress in patients is significantly associated with a poorer level of quality of life and higher levels of depression and anxiety (O'Leary et al., 2004) and might be associated with dermatological worsening of the plaques (Basavaraj et al., 2011).

CONCLUSION AND FUTURE DIRECTIONS

From our review, it is apparent that emotional reactivity, alexithymia, and emotion regulation have a profound impact on the management of psoriasis symptoms. On the one hand, emotional reactivity in patients with psoriasis seems to be characterized by negative emotions such as anger (Matussek et al., 1985; Sampogna et al., 2012; Aydin et al., 2017), shame (Sampogna et al., 2012; Shah and Bewley, 2014; Lahousen et al., 2016), disgust (Lahousen et al., 2016), and feelings like social exclusion (Vardy et al., 2002; Schmid-Ott et al., 2007; Lahousen et al., 2016; van Beugen et al., 2017; Łakuta et al., 2017) and also by psychopathological disorders such as anxiety (Pujol et al., 2013; Cepuch et al., 2014; Fleming et al., 2017) and depression (Jensen et al., 2016). This emotional pattern seems to affect slightly more women (Sampogna et al., 2012; Pujol et al., 2013; Talamonti et al., 2017) than men and to be a risk factor for a wide range of negative outcomes spanning from lower quality of life (Vardy et al., 2002; O'Leary et al., 2004; Vari et al., 2013) to suicide (Pompili et al., 2016).

On the other hand, the ability to regulate emotions seems to be a protective factor that improves quality of life (Vari et al., 2013), treatment satisfaction, and the impact of negative emotions (Almeida et al., 2017). This is especially true when patients do not suffer from alexithymia. The effect of presence of alexithymia or low emotional awareness in these patients is not completely clear: on the one hand, it seems to help them in ignoring unwanted emotions (Panayiotou et al., 2015) and improve the treatment outcome (Consoli et al., 2006); on the other hand, it seems to worsen the impact of emotions on quality of life (Picardi et al., 2005; Almeida et al., 2017). From this literature review, it appears clear that treatments for psoriasis should also include techniques that address emotional reactivity, alexithymia, and emotion regulation because affective symptoms, together with dermatological ones, play a fundamental role in the resolution of this condition. One promising candidate would be the emotion regulation therapy (ERT), which is a manualized intervention that aims at (i) increasing emotional and motivational awareness; (ii) developing emotion regulation abilities; and (iii) generating new learning experiences (Renna et al., 2017).

Our review also highlights some limitations of the approaches that have been used so far for studying emotional processes in psoriasis. First of all, only few studies (Mastrolonardo et al., 2006, 2007; van Beugen et al., 2016; Panasiti et al., 2019; Ponsi et al., 2019) reported behavioral and physiological evidence. Although we acknowledge that self-report measures are important to understand the conscious evaluation that patients have of themselves, we also believe that implicit measures are crucial to understand what are the abilities that are truly compromised in these patients. Future studies should include these measurements and compare them with self-report measures in order to obtain a fine-grained picture of emotional processing in these patients. Second, many studies (15 of the 37 we reviewed) did not test a control group; this practice does not allow to disentangle whether what is observed is specific of this skin condition or is also true in the general population. Furthermore, very few studies tested a clinical control group with other dermatological conditions. Including such control groups would be very important to understand the altered psychological mechanisms behind psoriasis and to define efficient psychological treatments.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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OPINION
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Emotion Regulation in Essential Hypertension: Roles of Anxiety, Stress, and the Pulvinar

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Excessive emotional arousal can impair individuals' ability to function and achieve their goals. This is especially true when this heightened arousal emerges from an emotional stimulus that is irrelevant to current goals and hence should be ignored (Ochsner et al., 2012). One clinical population that has yet to be investigated in the context of emotion regulation comprises patients with essential hypertension (EH). EH is defined as systolic blood pressure (BP) higher than 140 mmHg and/or diastolic BP higher than 90 mmHg (James et al., 2014). EH is the most important risk factor for cerebrovascular diseases, a major cause of death in industrialized societies (Mendis et al., 2011; Mozaffarian et al., 2016). Frequent complications of EH include atherosclerotic coronary artery disease, congestive heart failure, stroke, Alzheimer's disease and chronic kidney disease, and therefore constitutes a leading cause of severe disability and premature death (Mendis et al., 2011; James et al., 2014; Mozaffarian et al., 2016).

Patients with EH exhibit "exaggerated" reactions to emotional and stressful stimuli (Jern et al., 1995; Deter et al., 2007), as well as high levels of anxiety (Liu et al., 2017). Recent evidence further suggests that patients with EH exhibit altered structure, function and connectivity within a neural network that has been associated with emotion regulation, which includes prefrontal and limbic regions (defined as the amygdala, insula, and cingulate cortex; Gianaros and Sheu, 2009; Jennings and Zanstra, 2009). Taken together, these different lines of investigation suggest possible abnormalities among patients with EH in neurocognitive inhibitory dysfunction, as related to emotion regulation, depression, anxiety, stress regulation, and emotion control processes. Yet to date very little research has examined possible deficits in cognitive control mechanisms, which may be the basis for the aforementioned emotion-related abnormalities in EH.

DEFICIENT EMOTIONAL BEHAVIOR IN ESSENTIAL HYPERTENSION

Research has established that the tendency to exhibit enhanced cardiovascular responses to stress and aversive situations predicts later development of EH (Matthews et al., 2004; Gianaros and Sheu, 2009; Gianaros et al., 2012). Such responses include BP elevations that are higher than what is required for adaptive motor reaction to possible stressors (Lang et al., 1998, 2000). Researchers have posited that these "exaggerated" cardiovascular responses may be caused by abnormal neural circuits related to vascular control and reactivity to

stress, eventually influencing the brainstem nuclei that control autonomic nerve movement to the myocardium and vasculature (Gianaros and Sheu, 2009; Gianaros et al., 2012). Patients with EH exhibit structural and functional abnormalities in neural networks that include fronto-parietal, limbic, and brainstem regions (Gianaros and Sheu, 2009; Gianaros et al., 2009; Jennings and Zanstra, 2009). Initial studies among healthy individuals demonstrate a relation between enhanced BP reactions and enhanced neural activation in limbic and brainstem regions in response to mental stress (Gianaros and Sheu, 2009; Gianaros et al., 2012). Based on these studies, researchers have suggested that brain abnormality in groups at high risk of developing EH is related to exaggerated BP responses to stress, which may play a *causal* role in the development of EH (Jennings and Zanstra, 2009). They speculate that such recurring "exaggerated" cardiovascular responses may promote structural changes in the vascular tissues and thus ultimately lead to the development of EH (Gianaros and Sheu, 2009).

ENHANCED ANXIETY AND DEPRESSION IN ESSENTIAL HYPERTENSION

The association between chronic stress and EH is well-established (Lucini et al., 2005; Huang et al., 2013). Epidemiological studies have found that the association between anxiety and EH is bidirectional, such that individuals with EH are more likely to have anxiety and vice versa (Ginty et al., 2013; Liu et al., 2017).

There is also evidence for a relation between depression and EH (Davidson et al., 2000; Ginty et al., 2013). Depression is associated with changes in the autonomic regulation of the heart that are also associated with EH (Grippo and Johnson, 2009). In addition, depressive symptoms are related to inflammatory factors (Howren et al., 2009) that may affect the development of EH (Montecucco et al., 2011). Accordingly, integrated treatment for depression and EH has led to lower BP as well as fewer depressive symptoms, compared to usual EH treatment (Bogner et al., 2013; McClintock and Bogner, 2017). Nevertheless, observations of EH's association with anxiety and depression are inconsistent (Cheung et al., 2005; Hildrum et al., 2011; Wiltink et al., 2011). It is therefore crucial to further investigate and shed light on the underlying mechanisms.

ARE ABNORMAL EMOTIONAL REACTIONS IN ESSENTIAL HYPERTENSION MEDIATED BY DYSFUNCTIONAL NEUROCOGNITIVE INHIBITION MECHANISMS?

Studies with clinical and sub-clinical populations exhibiting anxiety and depression symptoms point to deficits in inhibition and control systems. Dysfunctional inhibitory mechanisms have been suggested as underlying cognitive control deficits in depression (Goeleven et al., 2006; Owens et al., 2013) and anxiety (Berggren and Derakshan, 2014). Correspondingly, abnormalities in prefrontal-limbic neural pathways have been shown both in depression (Drevets, 2000) and in anxiety (Bishop, 2008). For example, frontal and limbic activation during implementation of cognitive inhibition (manipulated by a Go/No-Go task) predicted post-treatment improvement of depression symptoms (Langenecker et al., 2007).

Do similar neurocognitive inhibitory dysfunctions mediate abnormally enhanced BP reactions? To date, most research examining the mechanisms responsible for EH has focused on the peripheral nervous system and peripheral BP (Jennings and Zanstra, 2009). Yet recent studies point to deficiencies in central regulatory factors such as central control of baroreceptor function and regulation mechanisms within midbrain areas (Gianaros and Sheu, 2009; Jennings and Zanstra, 2009; Gianaros et al., 2012). In addition, brain abnormalities such as altered cerebral blood flow, white matter hyperintensities, decreased gray matter volume, and brain atrophy are also associated with EH (for review, see Jennings and Zanstra, 2009). Additional evidence shows that EH is related to cognitive impairment, deficits in executive function and processing speed as well as dementia (Hughes and Sink, 2016).

There is evidence of abnormalities in prefrontal-limbic neural pathways among patients with EH and those at high risk (Gianaros et al., 2009, 2012). Further evidence shows that central aortic and peripheral BP measures are related to cognitive functions (Hughes and Sink, 2016; Aronow, 2017). A large sample study ($N = 493$) found that higher BP was related to impairment in several cognitive processes, among them poorer color-word Stroop processing, which is commonly used to assess the ability to inhibit cognitive interference (Pase et al., 2013). Taken together, these studies indirectly suggest that deficient neurocognitive inhibitory control mechanisms may form the basis for the abnormally enhanced emotional reactions seen in groups at high risk for developing EH. In a first attempt to examine whether inhibitory control mechanisms influence BP reactions among healthy volunteers and to determine the neural basis of this modulation, Okon-Singer et al. (2014) manipulated attention to distracting highly aversive pictures while simultaneously measuring neural activation using fMRI and peripheral BP. The results demonstrated that attention modulates BP and neural reactions to aversive stimuli in a network that includes prefrontal, parietal, limbic, and brainstem regions previously shown to be related both to emotion control and to BP reactivity. These results indicate that neurocognitive control mechanisms modulate BP reactions among healthy individuals and indirectly suggest that abnormalities in these systems may underlie abnormal BP emotional reactions (Okon-Singer et al., 2014). Based on these findings, it is plausible to hypothesize that among patients with EH, abnormalities in prefrontal and parietal areas associated with inhibitory control results in deficits in emotion regulation, which leads to enhanced activity in the amygdala, insula and cingulate cortex. This enhanced activity, in turn, leads to elevated symptoms of anxiety and depression, as well as exaggerated BP reactions to stress and aversive stimuli (see **Figure 1**). However, this hypothesis should be taken with caution and directly examined in future studies.

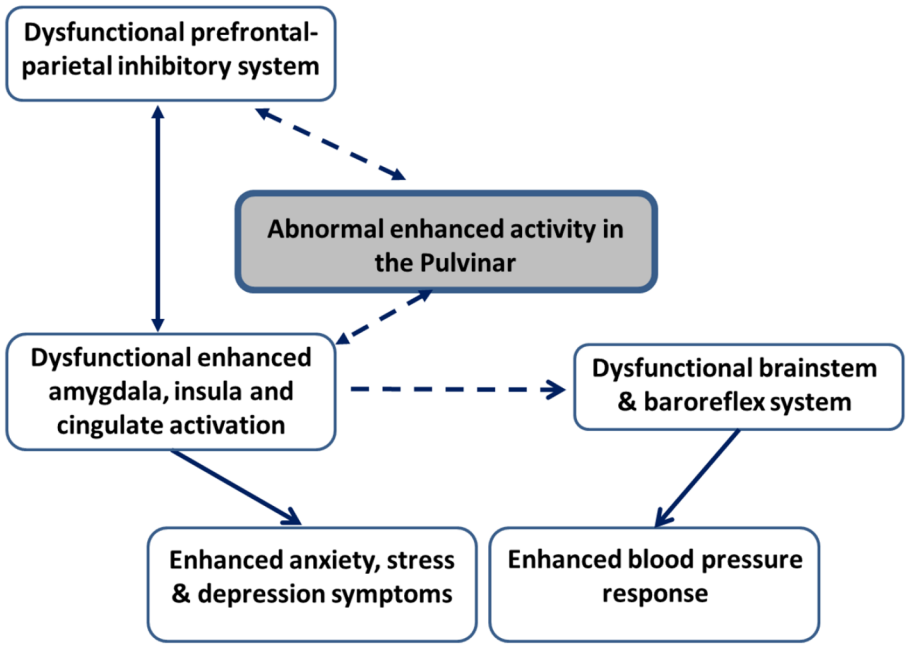

FIGURE 1 | Schematic illustration of the neural pathways hypotheses in patients with essential hypertension and groups at high risk to develop hypertension. Hypothesized connectivity is represented with dashed lines. Known connectivity is represented with continuous lines. Enhanced activation in the pulvinar in face of stimuli interpreted as threatening is expected to result in enhanced activity in limbic regions, including the amygdala, insula, and cingulate regions both directly and indirectly, via the influence of the pulvinar on dysfunctional inhibitory activation in prefrontal and parietal areas. This enhanced limbic activation, in turn, is expected to lead to enhanced symptoms of anxiety, stress, and depression. In addition, enhanced limbic activation is hypothesized to result in dysfunctional brainstem and baroreflex regulatory mechanisms, which are expected to result in exaggerated blood pressure reactions to aversive stimuli.

THE PULVINAR MAY PLAY AN IMPORTANT ROLE IN ABERRANT EMOTION REGULATION IN ESSENTIAL HYPERTENSION

Recent models highlight the role of the thalamic pulvinar nucleus in emotion regulation, specifically in the interplay between emotion and attention in early emotion regulation mechanisms (Pessoa, 2017). This view is based on two types of evidence: First, the pulvinar has substantial anatomical connections with diffused brain regions, including retinal, striatal and extrastriatal cortices, frontal, parietal, orbital and temporal cortices, the superior colliculus, and the amygdala (Grieve et al., 2000) and was recently suggested as a central node in a functional network related to emotion-cognition interactions (Pessoa, 2017). Specifically, while the pulvinar is considered to be an area of the brain irrelevant to the study of higher cognition and is therefore often disregarded (Silverstein and Ingvar, 2015), it has extensive connections to visual and fronto-parietal areas important for attention and to the amygdala, which is important for emotion (Grieve et al., 2000; Buchsbaum et al., 2006; Tamietto et al., 2012). Evidence suggests that the pulvinar may play an important role in selective orienting of visual attention to relevant stimuli (Fischer and Whitney, 2012), including selective attention to emotional/aversive stimuli (Padmala et al., 2010; Frank and Sabatinelli, 2014). Pulvinar connectivity has also been implicated in emotion processes underlying anxiety. In an effective connectivity analysis, Tadayonnejad et al. (2016) demonstrated a causal relation between the pulvinar and higher order visual and frontal areas among participants with social anxiety in an emotional face-processing paradigm. Second, there is evidence for pulvinar involvement in emotional tasks, including tasks that involve threat detection. For example, Hakamata et al. (2016) showed that individuals with attention bias to aversive information exhibited higher pulvinar activation with unattended fearful faces than with unattended neutral faces, as well as enhanced effective connectivity from the pulvinar to fronto-parietal areas. Based on data from patients with brain injuries, we (Arend et al., 2015) suggested that the pulvinar may determine whether a certain stimulus is considered to be emotional and therefore receive prioritized processing. In line with our suggestion, Hakamata et al. (2016) concluded that the pulvinar may be involved in gating unattended aversive information depending on individual threat-related attention bias. These researchers later added data to bolster these findings (Hakamata et al., 2018). The pulvinar has also been linked to stress and post-traumatic stress disorder (Drabant et al., 2012; Terpou et al., 2018). Indirect evidence further indicates that the pulvinar is related to action and BP reactions (Kemper et al., 2001; Renard et al., 2014).

Although the pulvinar is thought to play a critical and active role in EH, the underlying mechanisms and links between these

findings remain unclear. Based on its anatomical and functional connectivity, we hypothesize that pulvinar may influence both BP and anxiety and depression symptoms via limbic regions (**Figure 1**). Specifically, pulvinar activation may lead to enhanced limbic activation, which in turn results in higher anxiety and depression behaviors, as well as exaggerated BP reactions to aversive stimuli, possibly due to abnormalities in brainstem and baroreflex mechanisms. This hypothesis should be directly examined in future studies.

CONCLUSIONS AND OUTLOOK

In the current paper, we highlighted the gap in knowledge about factors underlying deficient emotion regulation in EH, a context that is of high clinical significance. By bringing together separate yet related strands of research, we conclude that aberrant emotion regulation in EH may share common neurocognitive mechanisms with stress and anxiety. Furthermore, we suggest that the role of the thalamic pulvinar nucleus in EH, anxiety, stress, and emotion regulation may be a promising area for investigation.

Future studies may also investigate individuals at high risk of developing EH, such as individuals with prehypertension or individuals with a genetic risk. Indeed, recent findings (Schaare et al., 2019) demonstrate lower gray matter in thalamic, amygdala, prefrontal and parietal regions in prehypertension. Furthermore, recent technological advances provide continuous non-invasive methods for measuring and analyzing BP, which can also assist in future investigations (Wiener et al., 2020). It is our hope that future studies will address these questions, so that in the long-term new treatments can be developed and help individuals with EH to more effectively combat daily life stressors and reduce their impact on physical and mental health.

AUTHOR CONTRIBUTIONS

AW and HO-S: initiated the idea, literature review, and writing. CR: literature review and writing. NN and AV: contribution to the conception of the work and involved in the writing.

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Trait Anxiety Attenuates Response Inhibition: Evidence From an ERP Study Using the Go/NoGo Task

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Neuropsychology and cognitive neuroscience have shown that anxious individuals have deficits in response inhibition. However, existing knowledge about the influence of trait anxiety on response inhibition is still inconsistent. The aim of this study was to investigate response inhibition between groups with high trait anxiety (HTA) and low trait anxiety (LTA). Here, we used event-related potential (ERP) indexes as biomarkers to examine the effect of trait anxiety on response inhibition using the Go/NoGo task. Behavioral results indicated that the HTA group made significantly lower accuracy than did the LTA group in the NoGo condition but not the Go condition. Meanwhile, the HTA group needed significantly longer overall response time (RT) than the LTA group did. ERP analyses revealed that the HTA group had smaller and later frontal NoGo-N2 as well as larger and later parietal NoGo-P3 compared to the LTA group. The two response inhibition-related ERP components are distinct neurophysiological indexes that, first, the NoGo-N2 is a component involved in the motor plan prior to the motor execution inhibitory process. Second, the NoGo-P3 reflects later monitoring and evaluation of the inhibition process. Accordingly, the current ERP findings suggest that HTA individuals' response inhibition deficits are the consequence of abnormal premotor inhibition control and inefficient evaluation and monitoring. In addition, we also found that the peak amplitude of NoGo-N2 and NoGo-P3 were significantly correlated with the State–Trait Anxiety Inventory (STAI) scores after correction for multiple comparisons. To sum up, these results support the notion that trait anxious individuals have response inhibition deficits in the Go/NoGo task.

Keywords: response inhibition, trait anxiety, event-related potential, Go/NoGo, N2, P3

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INTRODUCTION

According to Eysenck's attentional control theory (Eysenck et al., 2007), anxiety might be associated with dysfunction of inhibitory control. From this perspective, neuropsychology and cognitive neuroscience studies have revealed that the medial prefrontal regions [including the anterior cingulate cortex (ACC)] are crucial substrates of the human anxiety circuitry (Sehlmeyer et al., 2009) and that deficits in these areas are associated with impaired inhibition control (Sehlmeyer et al., 2010). Although previous studies have shown that individuals with state anxiety (e.g., experimentally induced anxiety; see Aylward et al., 2017), anxiety with substance use (Karch et al., 2007), and clinical anxious patients (Grillon et al., 2017) have deficits in response

inhibition, the question remains on whether and at what extent anxiety-related personality traits (e.g., trait anxiety) can also modulate response inhibition. Recent studies have demonstrated that trait anxiety interrupts top-down goal-driven processes such as response inhibition, resulting in failures in the inhibition function that enable executive control over prepotent motor responses (Pacheco-Unguetti et al., 2012; Su-Hao et al., 2014). Thus, this abnormal inhibitory function may consequently alter the level of cognitive control as well as cognitive performance in anxious population (Sehlmeyer et al., 2010) and appear to be a promising predictive marker of trait anxiety (Grillon et al., 2017). Response inhibition is a critical executive function in accordance with situation changes in everyday life, and this function involves attention and flexibility, which are largely influenced by anxiety levels (Pacheco-Unguetti et al., 2012). Moreover, investigating the response inhibition in anxiety may deepen our understanding of comorbid anxiety symptoms including impulsivity (Jakuszkowiak-Wojten et al., 2015) and substance use disorders (Karch et al., 2007). Therefore, it is important to investigate the influence of trait anxiety on response inhibition and its associated neural mechanism, which can broaden our understanding of the inhibitory control of anxious individuals and further unravel the psychological and etiological mechanisms of anxiety.

Among many inhibition tasks such as the two-choice oddball task (Wang et al., 2011; Yuan et al., 2012, 2017; Ren et al., 2019), this study employed the Go/NoGo task due to its wide application and easy performance (Helton, 2009). In this paradigm, subjects should response fast to frequently presented "Go" targets while ignoring rare "NoGo" stimuli using motor inhibition (Aron and Poldrack, 2005). Such withholding of a prepotent response generates a prototypical index of response inhibition (Helton, 2009; Bari and Robbins, 2013). To our knowledge, previous studies have examined the influence of trait anxiety on response inhibition in the Go/NoGo task and resulted in conflict results. For example, Sehlmeyer et al. (2010) found that trait anxious subjects maintain a high level of cognitive control effort reflected by electrophysiological measurements which might facilitate response inhibition. Some researchers explained that trait anxious individuals are cautious about errors and aware of their cognitive control failures. Thus, they might allocate excessive cognitive resources in response inhibition task (McWilliams and Cox, 2001; Righi et al., 2009; Sehlmeyer et al., 2010). However, some other studies found that attenuated response inhibition in trait anxiety due to the dysfunction in the frontal cortex (Yang and Li, 2014) and cognitive control deficits in anxiety resulted in impaired response inhibition (Pacheco-Unguetti et al., 2012). These results suggested that trait anxiety might attenuate rather than facilitate the response inhibition. Consistent with this idea, recent studies suggested that trait anxiety interferes with the top-down mechanisms required for the suppression of prepotent responses, resulting in failures in the response inhibition (Ansari and Derakshan, 2010, 2011). Furthermore, this abnormal response inhibition process might consequently reduce the level of cognitive control to prepare and to evaluate the outcome of actions reflected by electrophysiological measurements in trait anxious population (Yang and Li, 2014). In our opinion, the declining level of cognitive control supports the assumption that impairment of inhibitory control leads to reduced neural processing efficiency related to cognitive control in trait anxious individuals. Although the neural processing efficiency related to cognitive control in response inhibition account does not make predictions with respect to the effects of trait anxiety on behavioral performance (Basten et al., 2011), several studies proposed that less flexibility in response control in trait anxious individuals is driven by their repetitive compulsive behaviors which might induce an inability to inhibit prepotent responses reflected by behavioral performance measurements, for example, high-anxiety individuals may show an inefficient or inflexible response style with repetitive movements with rigid routines (Bannon et al., 2002; Martial et al., 2005). Thus, we assume that trait anxiety might attenuate the response inhibition that shifts motor action tendencies, resulting in cognitive failures. However, the detailed underlying mechanisms of trait anxiety modulate response inhibition related to cognitive control deficiency are far less elucidated (e.g., as mentioned above, the different patterns of electrophysiological activity related to cognitive control level in trait anxiety were not predictive of overt behavioral performance during response inhibition) and should be taken into consideration in our study.

The goal of the present study was to verify whether and at what extent the attenuated response inhibition processes in trait anxious individuals due to the impairment of cognitive control processes as shown on the electrophysiological level can also be demonstrated on the behavioral level, so as to enrich the understanding of the influence of trait anxiety on response inhibition. To this end, we chose the event-related potential (ERP) technique for its exquisite temporal resolution (Amodio et al., 2014). Two frontocentral ERP components have been associated with different subprocesses of response inhibition in the Go/NoGo task (Beste et al., 2010), based on which we compared the ERP differences between individuals with high and low trait anxiety (HTA and LTA, respectively). The first component is the frontal–midline N2, peaking approximately from 200 ms to 400 ms post stimulus. The N2 displays larger amplitudes in the NoGo compared to Go conditions (Eimer, 1993). In general, the N2 enhancement for NoGo stimuli (NoGo-N2) has been interpreted as a premotor inhibitory process that suppresses the incorrect response prior to reaction stage (Falkenstein et al., 1999). The latency of NoGo-N2 reflects the success or failure of inhibitory control (Roche et al., 2005). The amplitudes of NoGo-N2 have been found to be negatively correlated with psychiatric symptoms such as obsessive–compulsive disorder (Herrmann et al., 2003; Kim et al., 2007), depression (Katz et al., 2010), and attention-deficit/hyperactivity disorder (Woltering et al., 2013); also, a high false alarm rate (the number of mistaken responses made on NoGo trials) is associated with small and delayed NoGo-N2 (Falkenstein et al., 1999). The second component is the parietal P3, peaking approximately from 300 ms to 600 ms post-stimulus, which also displays larger amplitudes in the NoGo compared to Go conditions (Falkenstein et al., 1999).

The P3 enhancement to NoGo stimuli (NoGo-P3) has been considered as an extra enhanced cognitive control effort for later monitoring and evaluation of the outcome of inhibition process (Schmajuk et al., 2006; Huster et al., 2013). In addition, the prolonged NoGo-P3 latency might reflect the extent of evaluation processing (Roche et al., 2005). Taken together, the superior response inhibition in subjects was characterized by larger and shorter NoGo-N2 as well as smaller and shorter NoGo-P3 (Zhang et al., 2015).

Based on current knowledge in the Go/NoGo task, several studies found that the attenuated response inhibition in anxious population was due to decreased activation of the frontal area and that the hypoactivity of the frontal cortex might lower premotor inhibition but enhance the cognitive control effort for monitoring and evaluation of inhibition outcomes (Kim et al., 2007; Yang and Li, 2014). The latter two processes are reflected by the NoGo-N2 and NoGo-P3. Regarding this, we predicted in this study the following. On the behavioral level, the HTA group would exhibit lower accuracy (ACC) in the NoGo condition compared with the LTA group; on the electrophysiological level, the HTA group would show smaller and later NoGo-N2 as well as larger and later NoGo-P3 compare with the LTA group.

MATERIALS AND METHODS

Participants

In view of the fact that anxiety and depression are highly comorbid (Hirsh and Inzlicht, 2008; Nelson et al., 2016) and depressive individuals also have inhibitory deficits in the Go/NoGo task (Kaiser et al., 2003; Ruchsow et al., 2008), we only recruited nondepressed participants with HTA vs. LTA in this study.

All the freshman students (n = 6,903) in Shenzhen University were required to complete the Trait form of Spielberger's State–Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983; Shek, 1993). Among them, 788 questionnaires were missed. As a result, the total effective sample of questionnaires was 6,115, and the effective rate was 88.6%. In this sample, individuals with STAI-T scores in the upper and lower 25% of the distribution were considered as HTA and LTA subjects (Gu et al., 2010; Luo et al., 2014; Xia et al., 2017). The Beck Depression Inventory second edition (BDI-II; Beck et al., 1996) was used to assess self-reported symptoms of depression. Only the participants with BDI-II scores <13 were considered in this study (note that while BDI-II < 13 indicates minimal depression, BDI-II ≥ 14 indicates mild, moderate, or severe depression; see Beck et al., 1996). From those who met these criteria, we randomly recruited 56 students as paid participants (28 in the LTA group and 28 in the HTA group). There was no significant difference between the two groups with respect to age, handedness, and BDI-II scores (see **Table 1**).

Exclusion criteria for both groups were: (1) any Axis I and II disorders according to the Diagnostic and Statistical Manual (DSM-IV; APA, 1994); (2) seizure disorder; (3) history of head injury with possible neurological sequelae; and (4) substance abuse or dependence in the past 6 months.

TABLE 1 | Demographic data of participants with high trait anxiety (HTA) and low trait anxiety (LTA).

Characteristics	LTA (n = 28)	HTA (n = 28)	Statistics
Mean age, years	20.10 ± 1.13	19.80 ± 1.02	$t_{(54)} = 1.01$, $p = 0.153$
Sex, male/female	14/14	14/14	
Handedness, right/left	28/0	28/0	
STAI-T	31.79 ± 5.43	55.68 ± 4.30	$t_{(54)} = -17.928$, $p < 0.001$
BDI-II	4.32 ± 1.42	4.96 ± 1.59	$t_{(54)} = -1.568$, $p = 0.123$

STAI-T, the trait form of Spielberger's State–Trait Anxiety Inventory; BDI-II, Beck Depression Inventory (second edition). Descriptive data are presented as mean ± standard deviation.

Procedures

Each trial started with a 200- to 300-ms fixation, followed by targets (Go stimuli: M, N or O, Q) and nontargets (NoGo stimuli: O, Q or M, N) that were presented for 150 ms (see also Kim et al., 2007). A black blank screen appeared after the stimulus and lasted for 1,000 ms. Participants were required to press a button with their right index finger on the response box as quick as possible when the Go stimuli appeared while with hold the motor responses when the NoGo stimuli appeared. The Go and NoGo trials were presented in random order with a probability of 2:1 to build a prepotent response of "Go" (see also Yang et al., 2010). The total experiment consisted of two blocks, with 240 trials in each block (Go stimulus: 160 trials; NoGo stimulus: 80 trials). In order to avoid the confounding factor of letter shape, the Go and NoGo stimuli were counterbalanced across subjects (**Figure 1**).

EEG Recording and Analysis

Brain electrical activity was recorded referentially against the left mastoid and re-referenced off-line to the average of the left and right mastoids, by a 64-channel amplifier with a sampling frequency of 250 Hz (Brain Products, Gilching, Germany). Electroencephalography (EEG) data were collected with electrode impedances kept below 5 kΩ. Ocular artifacts were removed from EEGs using a regression procedure implemented in Neuroscan software (Scan 4.3).

The recorded EEG data were filtered (0.01−30 Hz; slope 12 dB/oct; zero phase) and segmented beginning 200 ms prior to the onset of stimuli. All epochs were baseline-corrected with respect to the mean voltage over the 200 ms preceding the onset of stimuli, followed by averaging in association with Go and NoGo conditions. Trials contaminated with large artifacts (peak-to-peak deflection exceeded ±100 μV) were excluded from the averaging. As a result, 21 ± 8 trials and 13 ± 7 trials were rejected in each subject for Go and NoGo conditions, respectively. The rejected trials were less than 10% of the total trials (see also Gu et al., 2010; Xia et al., 2017). Trial numbers did not show significant difference between experimental conditions.

We analyzed the peak amplitudes and peak latencies of the frontal–midline N2 and parietal P3; the measures were averaged based on waveforms of different sets of electrodes according to grand-mean ERP topographies and relevant literatures (Kim et al., 2007; Huang et al., 2009; Righi et al., 2009). The N2 peak was detected to occur at 250–350 ms post stimuli at the electrode

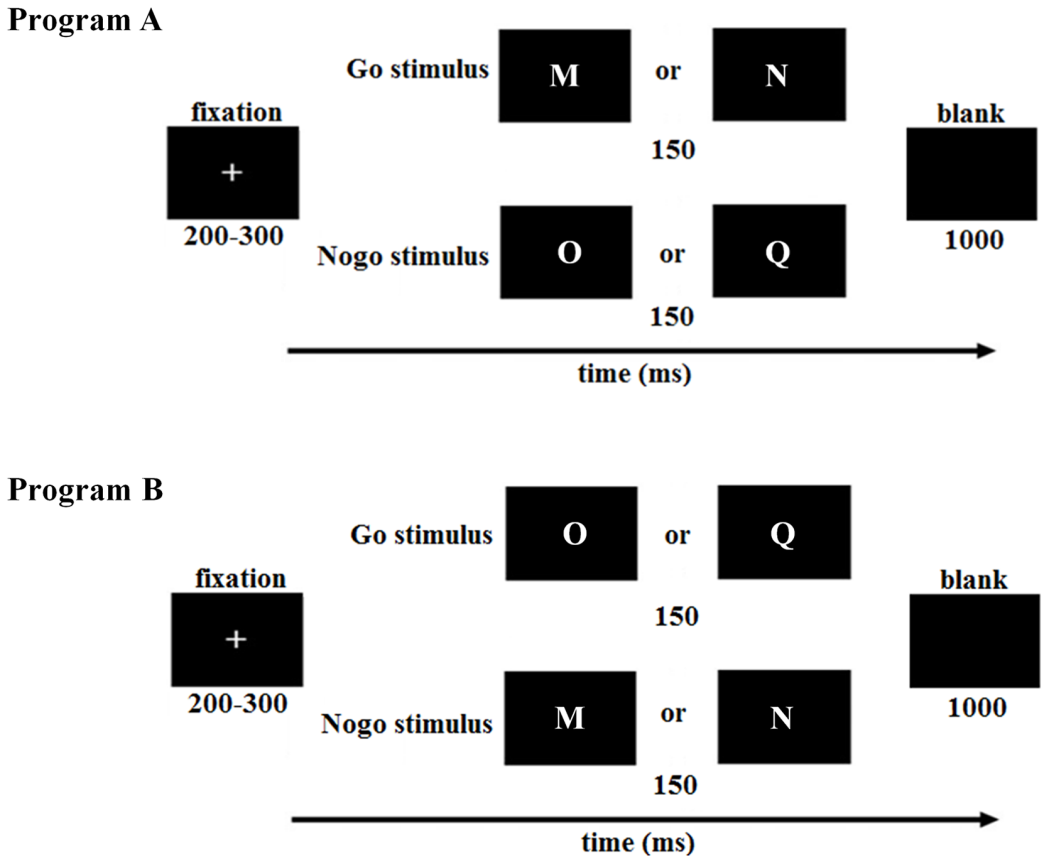

FIGURE 1 | Illustration of the Go/NoGo paradigm in this study. To counterbalance the Go and NoGo stimuli across subjects, the first half of low trait anxiety (LTA) and high trait anxiety (HTA) subjects was assigned to program **(A)**, while the second half was assigned to program **(B)**. LTA, the low-trait anxiety group; HTA, the high-trait anxiety group.

sites of Fz, F1, F2, FCz, FC1, FC2, Cz, C1, and C2, while the P3 peak was detected within a time window of 340–420 ms (Go condition) or 430–530 ms (NoGo condition) at the electrode sites of Pz, P1, P2, CPz, CP1, CP2, and POz.

Statistics

Statistical analysis was performed using SPSS Statistics 21.0 (IBM, Somers, NY, USA). Descriptive data were presented as mean ± standard error. The significance level was set at 0.05.

Two-way repeated-measures ANOVAs were performed on measurements of behavioral [ACC and response time (RT)] and ERP data (N2 and P3 amplitude/latency), with response assignment (Go vs. NoGo) as the within-subject factor and group (HTA vs. LTA) as the between-subject factor. Significant interactions were analyzed using simple effects model. Partial eta-squared (η_p^2) was reported to demonstrate the effect size in ANOVA tests.

Two-tailed Pearson's r correlation was performed between the two self-reported measures (BDI-II and STAI-T) and behavioral/ERP indexes. Correction for multiple comparisons was based on Holm's stepwise method.

RESULTS

For the sake of brevity, the experimental effects that did not reach significance were omitted.

Behaviors

Accuracy

The interaction of response assignment by group was significant ($F_{(1,54)} = 4.107$; $p = 0.048$; $\eta_p^2 = 0.071$; **Figure 2A**). Simple effect analysis indicated that the ACC in the NoGo trials was lower in the HTA group (76.05 ± 2.96%) compared with that in the LTA group (86.75 ± 2.96%; $F_{(1,54)} = 6.525$, $p = 0.013$). However, this group difference did not achieve significance level in the Go trials ($F_{(1,54)} < 1$; HTA = 93.07 ± 2.06% ; LTA = 95.78 ± 2.06%).

The main effect of group was significant ($F_{(1,54)} = 4.926$; $p = 0.031$; $\eta_p^2 = 0.084$). The HTA group (84.56 ± 2.14%) made lower ACC than the LTA group did (91.26 ± 2.14%).

Response Time

The main effect of group was significant ($F_{(1,54)} = 7.733$; $p = 0.007$; $\eta_p^2 = 0.125$; **Figure 2B**). The LTA group (overall RT: 274.77 ± 10.93 ms; Go RT for correct response:

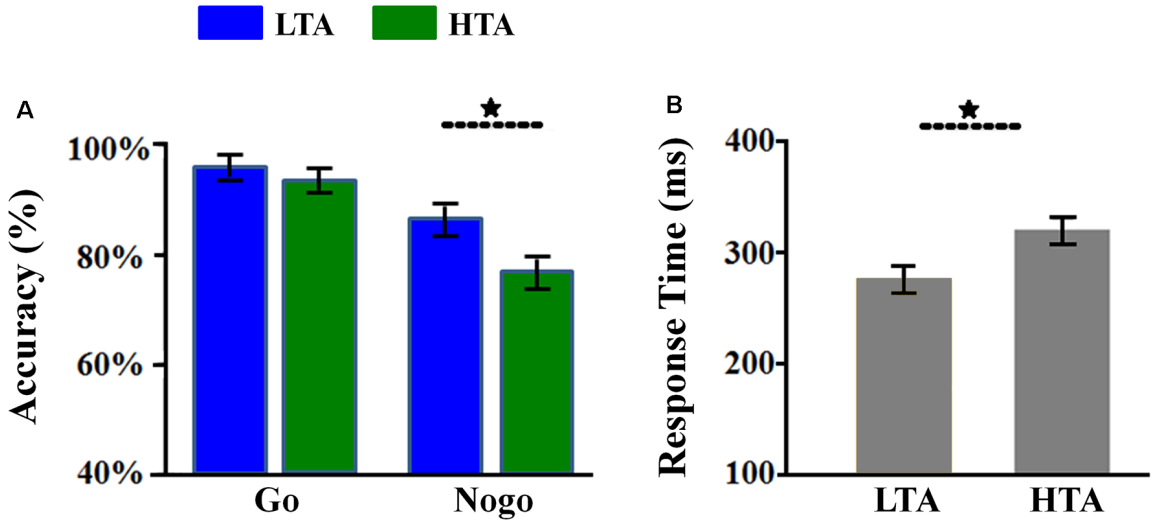

FIGURE 2 | Behavioral results. **(A)** The Go accuracy and NoGo accuracy in the two groups. **(B)** The overall response time (RT) in the two groups. Bars represent standard error of the mean. LTA, the low-trait anxiety group; HTA, the high-trait anxiety group. *$p < 0.05$.

295.82 ± 14.36 ms) responded much faster than the HTA group did (overall RT: 317.75 ± 10.93 ms; Go RT for correct response: 322.25 ± 14.36 ms).

ERPs

N2

For peak amplitude, the interaction effect of response assignment by group was significant ($F_{(1,54)} = 4.418$; $p = 0.040$; $\eta_p^2 = 0.076$; **Figure 3**). Simple effect analysis indicated that the N2 amplitude in the NoGo condition ($F_{(1,54)} = 9.567$; $p = 0.003$) was lower in the HTA group (−1.35 ± 0.31 μV) compared with the LTA group (−2.71 ± 0.31 μV). However, this group difference did not achieve significant level in the Go condition ($F_{(1,54)} < 1$; HTA = 0.76 ± 0.28 μV; LTA = 0.77 ± 0.28 μV). The main effect of group was significant ($F_{(1,54)} = 6.567$; $p = 0.013$; $\eta_p^2 = 0.108$). The HTA group (−0.29 ± 0.19 μV) had a smaller N2 than the LTA group did (−0.97 ± 0.19 μV).

For peak latency, the interaction effect of response assignment by group was significant ($F_{(1,54)} = 7.946$; $p = 0.007$; $\eta_p^2 = 0.128$; **Figure 3**). Simple effect analysis indicated that the N2 latency in the NoGo condition ($F_{(1,54)} = 11.475$; $p = 0.001$) was longer in the HTA group (336.71 ± 8.08 ms) compared with LTA group (298.00 ± 8.08 ms), However, this group difference did not achieve significance level in the Go condition ($F_{(1,54)} < 1$; HTA = 264.50 ± 7.12 ms; LTA = 268.75 ± 7.12 ms). The main effect of group was significant ($F_{(1,54)} = 5.121$; $p = 0.028$; $\eta_p^2 = 0.087$). The HTA group (300.61 ± 5.38 ms) had a longer peak latency of the average N2 than the LTA group did (283.38 ± 5.38 ms).

P3

For peak amplitude, the interaction effect of response assignment by group was significant ($F_{(1,54)} = 4.534$; $p = 0.038$; $\eta_p^2 = 0.077$; **Figure 4**). Simple effect analysis indicated that the P3 amplitude in the NoGo condition ($F_{(1,54)} = 11.496$; $p = 0.001$) was higher in the HTA group (6.63 ± 0.33 μV) compared with the LTA group (5.04 ± 0.33 μV). However, this group difference did not achieve significance level in the Go condition ($F_{(1,54)} < 1$; HTA = 3.55 ± 0.33 μV; LTA = 3.37 ± 0.33 μV). The main effect of group was significant ($F_{(1,54)} = 7.125$; $p = 0.01$; $\eta_p^2 = 0.117$). The HTA

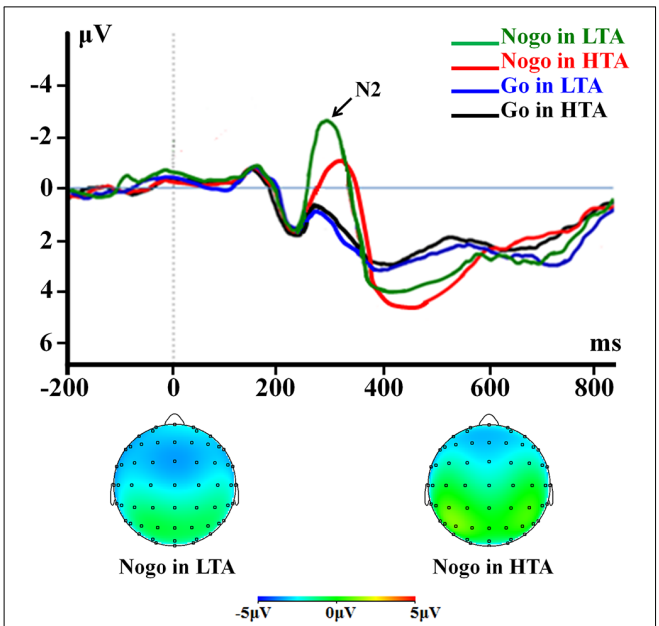

FIGURE 3 | The N2 component time-locked to the Go and NoGo conditions. Event-related potentials (ERPs) were calculated by averaging the data at the electrodes of Fz, F1, F2, FCz, FC1, FC2, Cz, C1, and C2.

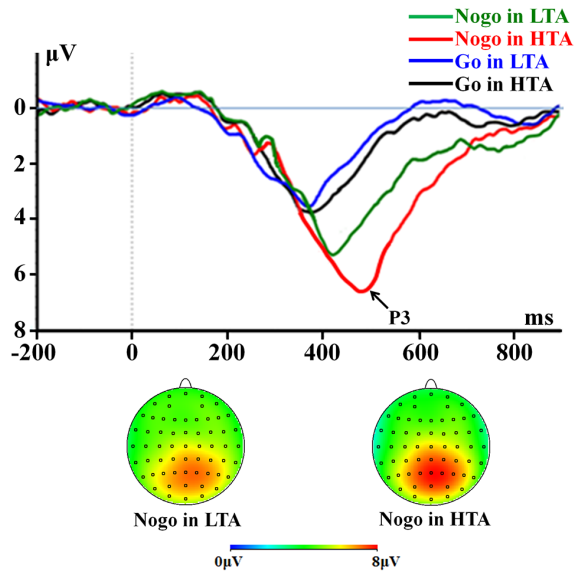

FIGURE 4 | The P3 component time-locked to the Go and NoGo conditions. ERPs were calculated by averaging the data at the electrodes of Pz, P1, P2, CPz, CP1, CP2, and POz.

group (5.09 ± 0.24 μV) had a larger P3 than the LTA group did (4.20 ± 0.24 μV).

For peak latency, the interaction effect of response assignment by group was significant ($F_{(1,54)} = 6.603$; $p = 0.013$; $\eta_p^2 = 0.109$; **Figure 4**). Simple effect analysis indicated that the P3 latency in the NoGo condition ($F_{(1,54)} = 16.664$; $p < 0.001$) was longer in the HTA group (473.86 ± 11.82 ms) compared with LTA group (405.64 ± 11.82 ms). However, this group difference did not achieve significance level in the Go condition ($F_{(1,54)} < 1$; HTA = 376.75 ± 11.17 ms ; LTA = 372.93 ± 11.17 ms). The main effect of group was significant ($F_{(1,54)} = 12.076$; $p = 0.001$; $\eta_p^2 = 0.183$). The HTA group (425.30 ± 7.33 ms) had a longer peak latency of the average P3 than the LTA group did (389.29 ± 7.33 ms).

Correlation

According to the results reported above, we conducted Pearson correlation analyses between the two self-reported scores (STAI-T and BDI) and the five behavioral/ERP indexes which showed interaction between response assignment and group (e.g., the ACC in the NoGo condition and the peak amplitudes as well as peak latencies of NoGo-N2 and NoGo-P3). In total, we performed 10 (2 × 5) correlations.

The results showed two significant correlations after correction for multiple comparisons. The peak amplitudes of NoGo-N2 ($r = 0.383$, $p = 0.004$, corrected $p = 0.036$; note that since NoGo-N2 is a negative-going component, the positive correlation means that higher STAI-T scores were associated with smaller NoGo-N2 amplitudes) and NoGo-P3 were correlated with the STAI-T ($r = 0.404$, $p = 0.002$, corrected $p = 0.02$).

In addition, we also conducted Pearson correlation analyses between the behavior and ERP which showed interaction between response assignment and group (e.g., the ACC in the NoGo condition and the peak amplitudes as well as peak latencies of NoGo-N2 and NoGo-P3). In total, we performed 4 (1 × 4) correlations.

The results showed one significant correlation after correction for multiple comparisons. The peak amplitudes of NoGo-N2 were correlated with ACC ($r = -0.409$, $p = 0.002$, corrected $p = 0.02$).

DISCUSSION

Debate exists on the influence of trait anxiety on response inhibition. This study applied the Go/NoGo paradigm to compare the response inhibition between HTA and LTA participants. On the behavioral level, we found that the HTA group made significantly lower ACC than the LTA group did in the NoGo condition. Meanwhile, the overall RT was longer in the HTA group than in the LTA group. Our behavioral results are consistent with the study conducted by Pacheco-Unguetti et al. (2012) that showed impaired response inhibition processes due to inflexibility in response control in anxiety. However, our behavioral results are inconsistent with some other studies showing no behavioral effect of trait anxiety in the Go/NoGo paradigm (Karch et al., 2007; Ruchsow et al., 2008; Righi et al., 2009). These discrepancies may be due to the difference in experimental parameters. For example, the study conducted by Righi et al. (2009) required subjects to inhibit their response to only one special stimulus, and all stimuli were presented for 250 ms. However, in this study, subjects were required to discriminate between two pairs of stimuli, and these stimuli were presented for 150 ms, which enhanced the difficulty of inhibiting the NoGo stimuli. In addition, the ratio between Go and NoGo trials may modulate the behavioral results (Kim et al., 2007). In our study, we used a 2:1 Go/NoGo ratio while Karch et al. (2007) and Ruchsow et al. (2008) used a 1:1 ratio.

As mentioned in the "Introduction" section, we speculate that the attenuated response inhibition behavioral effect in trait anxious individuals is driven by their repetitive compulsive behaviors. The core symptoms of repetitive compulsive behaviors (e.g., rigid routines, hesitation, and inflexibility) have been thought to be related to response inhibition deficits (Bannon et al., 2002), and this deficit might serve as a behavioral maker underlying inhibitory dysfunction of anxiety findings (Martial et al., 2005; Kim et al., 2007). Moreover, several evidences suggested that repetitive compulsive behaviors and trait anxiety are highly positive related (Black, 2008; Rodgers et al., 2012; Goodwin, 2015). It has been found that HTA individuals showed an inability to inhibit certain stimuli or certain prepotent responses compared with LTA individuals due to the repetitive compulsive behaviors (Martial et al., 2005). Meanwhile, HTA participants are less flexible in response control (e.g., inability to set shift) than the LTA group due to repetitive compulsive behavior inducing slowness and hesitation (Hughes et al., 2008; Dar and Iqbal, 2014; Yilmaz, 2015), resulting in a decrease in speed in the task. Note that this study also found that the Go RT was slightly longer in the

HTA group than in the LTA group. In the current study, both the ACC and the RT indicate that HTA individuals are inferior to LTA individuals in response inhibition, leading to decreased NoGo ACC and longer RT. However, a non-negligible limitation of the current study is that we did not include any behavioral measure of the repetitive compulsive level, such as the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989) and Repetitive Behaviors Scale (Lam and Aman, 2007). Follow-up research is necessary to further address this issue.

On the electrophysiological level, the first ERP finding is that trait anxious participants showed smaller and later NoGo-N2 compared to low-anxiety participants. Consistent with this result, previous Go/NoGo studies found that a smaller and/or later NoGo-N2 was evoked in individuals with obsessive–compulsive disorder (Herrmann et al., 2003; Kim et al., 2007), depression (Katz et al., 2010), and attention-deficit/hyperactivity disorder (Woltering et al., 2013). As mentioned in the introduction, the NoGo-N2 reflects the inhibitory process of a motor plan prior to the motor execution stage (Eimer, 1993; Falkenstein et al., 1999; Herrmann et al., 2003; Karch et al., 2007; Kim et al., 2007; Huster et al., 2013), and this inhibitory process is usually located at the premotor level rather than at the motor level (Falkenstein et al., 1999). The N2 enhancement to the NoGo stimulus has been suggested to reflect the suppression of incorrect response prior to the motor action (Falkenstein et al., 1999; Zhang et al., 2015), and a shorter-latency NoGo-N2 has been observed in successful withholding to NoGo stimuli compared with unsuccessful attempts to inhibit (Roche et al., 2005). In addition, neuroimaging studies have revealed that the neural sources of NoGo-N2 are located in the ACC and inferior/orbitofrontal prefrontal cortex (Kiefer et al., 1998; Bokura et al., 2001; Bekker et al., 2005). In our opinion, the smaller and later NoGo-N2 in the frontocentral electrode sites observed in anxious individuals here indicates that trait anxiety is associated with dysfunction in the frontal prefrontal cortex (including the ACC), which are crucial neural substrates known to be involved with the anxiety circuitry (Sehlmeyer et al., 2010). Taken together, the current finding of anxiety-modulated NoGo-N2 suggests that the premotor inhibitory process of trait anxious individuals is impaired, which might disrupt behavioral responses and inhibition.

The second ERP finding is that trait anxious participants were associated with an enhanced and latency-prolonged NoGo-P3 component. The NoGo-P3 is usually considered as the later monitoring and evaluation of the inhibition process outcome (Beste et al., 2010; Huster et al., 2013). The P3 enhancement to NoGo stimuli has been considered as more effort being devoted to monitoring of behavioral outcome (Sehlmeyer et al., 2010), while the prolonged NoGo-P3 latency is thought to be indicative of deliberative or "deeper" evaluation (Roche et al., 2005). Several studies related to response inhibition revealed that anxious individuals need to allocate more cognitive resources and make more control effort to withhold a response compared with healthy individuals, leading to a larger and/or longer NoGo-P3 (Karch et al., 2007; Ruchsow et al., 2007). Consistent with this idea, the current finding shows that the NoGo stimulus evoked larger and later NoGo-P3 in anxious individuals, suggesting that anxiety impairs inhibitory control system and makes us unable to evaluate and monitor the inhibition of incorrect responses in an efficient manner, leading to enhanced cognitive control effort or extra processing resources in the brain of anxious people.

Finally, one limitation should be pointed out for an appropriate interpretation of the current result. This study only measured the response inhibition in young, anxious adults (approximately 20 years old). Seeing that the cognitive characteristics of anxious people might differ between the young-adult group and other age groups (Krasucki et al., 1998; Goldberg et al., 2003), the generalizability of the current findings awaits to be tested in future work.

To sum up, this study has revealed that HTA participants have response inhibition deficits in the Go/NoGo paradigm, demonstrating a negative relationship between trait anxiety and response inhibition. The ERP results indicate that the psychological processes of premotor (reflected by NoGo-N2) and later evaluation of inhibition processes (reflected by NoGo-P3) both contribute to impaired response inhibition in anxiety. Specifically, HTA individuals' response inhibition deficits are due to deficits of premotor inhibition control and inefficient evaluation and monitoring of NoGo stimuli. These findings would provide valuable knowledge about the underlying mechanism of the maladaptive response inhibition in trait anxious people.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Institute of Psychology, Chinese Academy of Sciences (H14019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LX and DZ designed the study. LX conducted the experiment and analyzed the data. LX, LM, JW, WZ, and DZ contributed to the manuscript.

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Predicting Late Adolescent Anxiety From Early Adolescent Environmental Stress Exposure: Cognitive Control as Mediator

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Early exposure to stressful life events is associated with greater risk of chronic diseases and mental health problems, including anxiety. However, there is significant variation in how individuals respond to environmental adversity, perhaps due to individual differences in processing and regulating emotional information. Differences in cognitive control – processes necessary for implementing goal directed behavior – have been linked to both stress exposure and anxiety, but the directionality of these links is unclear. The present study investigated the longitudinal pathway of environmental stress exposure during early adolescence on later adolescent anxiety, and the possible mediating mechanism of cognitive control. Participants were 674 Mexican-origin adolescents ($mean_{age}$ = 10.8 years, 50% male) enrolled in the California Families Project, an ongoing longitudinal study of Mexican-origin families. In the current analysis, we examined self-reports of environmental stressors at age 14 (Time 1), cognitive control at age 16 (Time 2), and anxiety at age 18 (Time 3). Structural equation modeling revealed that environmental stressors (Time 1) had both direct and indirect effects on later anxiety (Time 3) through their effects on cognitive control (Time 2), even when accounting for prior levels of anxiety (Time 2). Cognitive control accounted for 18% of the association between environmental stressors and adolescent anxiety: an increase in stressors decreased cognitive control ($\beta = -0.20$, $p < 0.001$), however, cognitive control buffers against anxiety ($\beta = -0.10$, $p = 0.004$). These findings deepen our understanding of the mechanisms underlying the development of anxiety and highlight the importance of cognitive control as a potential protective factor.

Keywords: cognitive control, executive function, self-regulation, mental health, stress

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INTRODUCTION

Exposure to stressful life events is associated with greater risk of developing chronic diseases and mental health disorders, including anxiety – the most prevalent psychiatric disorder experienced by youth (Pérez-Edgar and Fox, 2005; Pine, 2007; Rapee et al., 2009). However, there is significant variation in how individuals respond to environmental adversity, and those individual differences

might be related to the processing and regulation of information. These cognitive control processes necessary for implementing goal-directed behavior – an umbrella term for a collection of related yet distinct processes that are also labeled effortful control, executive function, and self-regulation, depending on the field of study (Zhou et al., 2012) – have been significantly associated with anxiety, as well as a range of other psychiatric disorders such as depression and substance abuse (e.g., Baler and Volkow, 2006; Hirsch and Mathews, 2012; Zainal and Newman, 2018). Cognitive models of generalized anxiety disorder have converged on cognitive control as a potential mechanism of psychopathology (Joormann, 2006; Joorman et al., 2009; Hirsch and Mathews, 2012). For example, the Attentional Control Theory (Eysenck and Derakshan, 2011) and the Processing Efficiency Theory (Eysenck and Calvo, 1992) were put forth to explain the reallocation of cognitive resources when processes such as inhibition, stress, and negative thoughts co-occur. These theories postulate that compromised cognitive control is linked to excessive and uncontrollable worry, a core symptom of anxiety. Indeed, cross-sectional studies have found an association between a range of cognitive control functions and anxiety disorders (e.g., Toren et al., 2000; Muris and Ollendick, 2005; Fujii et al., 2013), as well as the degree of cognitive control impairment being commensurate with the severity of anxiety among patients with generalized anxiety disorder (Hallion et al., 2017). The few studies examining longitudinal associations have found that executive function is related to anxiety problems in an adolescent population two years later (Han et al., 2016) and in adults nine years later (Zainal and Newman, 2018). The scarcity of studies examining longitudinal associations between of cognitive control and anxiety begs the question of directionality and whether cognitive control is an underlying mechanism that might mediate the effect of stress exposure on the development of anxiety.

Stress and cognitive control are processed by closely related neural systems (e.g., Herman et al., 2005), leading some researchers to speculate that stress exposure during childhood and adolescence, sensitive periods of neurocognitive development, can compromise the development of the neural regions that underlie the development of cognitive control (Shonkoff and Phillips, 2000; Lupien et al., 2009). For example, a longitudinal study of infants raised in a predominantly low-income environment found that the chronic physical and psychosocial stress exposure associated with poverty predicted later executive function in pre-kindergarten (Berry et al., 2012). In their longitudinal study examining childhood poverty (age 9) and later adult emotion regulation (age 24), Kim et al. (2013) found that cumulative chronic stress mediated the relationship, mimicking findings highlighting the mediating role of stress between childhood poverty and later cognitive control (e.g., Evans and Schamberg, 2009; Blair et al., 2011; Evans and Fuller-Rowell, 2013; Kim et al., 2018). These findings underscore the link between early stress exposure to later diminished executive function abilities (Gunnar et al., 2009; Blair, 2010; Ursache et al., 2013), but whether these relationships together explain anxiety outcomes remains unclear.

Although the aforementioned links all strongly suggest a mechanism by which early experiences of stress contribute to anxiety outcomes, few published studies to date have explicitly examined the relationship between stress exposure, cognitive control, and anxiety together. In a recent study, Huh et al. (2017) found mediating effects of emotion regulation (i.e., cognitive control in emotionally salient contexts) on the relationship between acute childhood stressors and adult anxiety symptoms in a clinical population using a cross-sectional design. Similarly, Affrunti and Woodruff-Borden (2015) found that executive functions mediated the relationship between fear perception and anxiety in 7- to 10-year-old children. With a short-term longitudinal design, Gulley et al. (2016) examined the interaction of effortful control and stressors on the development of anxiety over a 3-month period finding that, at low levels of stress, high level of effortful control protected against the development of anxious symptoms. With little to almost no prospective studies to draw from, some have speculated that adolescents with more effective cognitive control abilities are better able to process negative emotional information, which in turn lowers their risk for psychopathology (Martel et al., 2007; Micco et al., 2009). Similarly, Nigg (2006) theorizes that anxiety arises from experiences of both negative affect and impaired cognitive control. That is, greater exposure to stressors paired with lower levels of cognitive control may contribute to increased anxiety and depression (Anthony et al., 2002; Eisenberg et al., 2005). However, no studies to date have tested these theories by examining the longitudinal relations between early environmental stress exposure, cognitive control, and later anxiety, and thus, the directionality of these relationships remains unclear and beckons the need for further research.

In the present study, we conducted a prospective mediation analysis to evaluate the effect of environmental stress exposure during early adolescence on late adolescent anxiety and examine the possible mediating mechanism of cognitive control. Given previous findings, we hypothesize that:

(1) Increased stress exposure is associated with higher levels of anxiety.
(2) This relation between stress exposure and anxiety is partially mediated by cognitive control, with increased stress exposure leading to impaired cognitive control, whereas cognitive control in turn buffers against the development of anxiety.

Previous research examining the association between environmental stress exposure and anxiety has often operationalized environmental stress as poverty, leaving a vast range of other possible environmental stressors overlooked and/or under examined. Thus, the present study uses data from a sample of Mexican-origin youth in the United States who face unique challenges and may experience greater exposure to adversity ranging from fewer material and emotional resources to increased exposure to discrimination and neighborhood violence, and more chaotic and less stable home environments (Evans and Kantrowitz, 2002; Evans and Kim, 2010), experiences that can cause chronic stress beyond those of financial origins. Moreover, data from this sample of youth provide an opportunity to examine changes in cognition and anxiety in the context of

adolescence – a unique developmental time period marked by notable neurocognitive changes and heightened prevalence of stress-related psychological disorders (Merikangas et al., 2010; Romeo, 2017). Thus, it is critical for research to elucidate the potential risk factors that lead to the development of these disorders during this period of enhanced vulnerability.

MATERIALS AND METHODS

Participants

Participants were 674 Mexican-origin adolescents ($mean_{age}$ = 10.8 years, 50% male) enrolled in the California Families Project, an ongoing 12-year longitudinal study of Mexican-origin families (for additional details about the study, see Martin et al., 2019; Atherton et al., 2020). Of the 674 participants, 551 participants had longitudinal data for all our variables of interest at ages 14 (Time 1), 16 years (Time 2), and 18 years (Time 3) and were included in the analysis. Potential participants were drawn at random from rosters of students from the Sacramento and Woodland, CA, school districts. To be eligible for participation in this study, the focal child had to be in the fifth grade, of Mexican origin, and living with his/her biological mother; 72.6% of the eligible families consented to participate in the study, which was granted approval by the Institutional Review Board of University of California, Davis.

Measures

Environmental Stressors

We measured environmental stress exposure using a composite of three separate scales that were all administered at age 14: neighborhood criminal events, neighborhood quality dissatisfaction, and adolescent reports of discrimination experiences. Similar to other composite measures such as socioeconomic status, which is often defined as a composite of occupation, education, and income, our measure of environmental stress exposure is a formative construct: the events are largely independent of each other but collectively contribute to the construct (see Edwards and Bagozzi, 2000). Therefore, environmental stress exposure was calculated by summing the average scores of all three risk factors. Additive indices of cumulative stress exposure are robust and consistently predict mental health outcomes better than indices of singular stress exposure or alternative multiple stress exposure metrics (Evans et al., 2013; Kim et al., 2013; Evans and Cassells, 2014) and have been established as a reasonable method in capturing the confluence of physical and psychosocial challenges associated with adolescent adversity (Evans and English, 2002).

Neighborhood Criminal Events Scale

The adolescent reported on neighborhood-level violence using the Neighborhood Criminal Events Scale, which consists of 10 items. These items assess the extent to which there is violence and disorder in the neighborhood (Aneshensel and Sucoff, 1996; Bowen and Chapman, 1996; Sampson et al., 1997; Cutrona et al., 2000; Ross and Jang, 2000). The scale includes items, such as "How often did [violent crimes including stabbings, shootings, and violent assaults] happen in your neighborhood in the past year?" and "How often did [kids sell illegal drugs] in your neighborhood in the past year?" Ratings were made on a four-point scale ranging from 1 (almost never or never) to 4 (almost always to always). Higher scores indicated greater exposure to crime. The scale demonstrated good internal reliability ($\alpha = 0.88$).

Neighborhood Quality Dissatisfaction

The adolescent reported on his/her personal evaluation of attractiveness of the neighborhood using an abbreviated version of Neighborhood Quality Evaluation Scale (Roosa et al., 2005), which consists of six items. A typical item is "Your neighborhood is clean and attractive" and "Overall, you are satisfied with your neighborhood." Ratings were made on a four-point scale ranging from 1 (not at all true) to 4 (very true). Higher scores indicated higher perceptions of neighborhood quality. The average score was then reversed to reflect negative neighborhood quality, with higher scores indicating poorer perceptions of neighborhood quality, which was then used as part of the cumulative stressor score. This scale demonstrated excellent internal reliability ($\alpha = 0.93$).

Perceived Ethnic Discrimination

The adolescent reported his/her perceived personal experiences with ethnic discrimination using four items, which were adapted for use in the La Familia Project (Johnston and Delgado, 2004) from questions on the Racism in the Workplace Scale (Hughes and Dodge, 1997) and Schedule of Sexist Events (Klonoff and Landrine, 1995). Sample items include "You have heard your teachers at school making jokes or saying bad things about [Mexicans/Mexican–Americans]" and "Teachers think kids who speak Spanish don't do as well at school." Ratings were made on a four-point Likert scale, ranging from 1 (almost never or never) to 4 (almost always or always). Higher scores indicated greater experiences of discrimination. The scale demonstrated adequate internal reliability ($\alpha = 0.68$).

Cognitive Control

Adolescents completed the effortful control scale (16 items) from the short form of the Early Adolescent Temperament Questionnaire – Revised when the adolescent was 16 years old (EATQ-R; Ellis and Rothbart, 2001). The 16-item EATQ-R scale assesses various aspects of cognitive control including the capacity to perform an action when there is a strong tendency to avoid it, the capacity to focus and shift attention when desired, and the capacity to suppress and regulate dominant impulses. This scale includes items such as "When someone tells you to stop doing something, it is easy for you to stop." and "You pay close attention when someone tells you how to do something." Ratings were made on a four-point scale ranging from 1 (not at all true of you) to 4 (very true of you). Higher scores indicated greater cognitive control. The full scale demonstrated adequate reliability ($\alpha = 0.65$). Cognitive control assessed at age 16 (Time 2) was included as our mediator of interest.

Anxiety

Anxiety was assessed using the Mini-Mood and Anxiety Symptom Questionnaire (Casillas and Clark, 2000). For our

measure of anxiety, we composited the anxiety (three items; "How much have you felt keyed up or on edge") and anxious arousal (10 items; "Have you had trouble swallowing") items into an overall anxiety scale. Participants rated how much they "felt or experienced" each symptom "during the past week" using a four-point scale ranging from 1 (not at all) to 4 (very much). Higher scores indicated more anxiety. The scale demonstrated good reliability ($\alpha = 0.87$). Anxiety assessed at age 16 (Time 2) was included as a covariate given that our outcome of interest was anxiety at age 18 (Time 3).

Analytical Approach

Our prospective mediation analysis was framed around three time points (Time 1, 2, 3) in order to capture a full prospective mediation model. Several considerations informed the development of our analytical model: (1) the temporal sequence of variables required in a mediation model; (2) the need to account for the stability of anxiety over time, to ensure that the effects of environmental stress and cognitive control are, in fact, prospectively predicting anxiety (and not just due to the fact that anxiety symptoms are stable across adolescence); and (3) the equivalent distance of time between measurements. Our final model was determined by these constraints and captures the development of these constructs during the peak of adolescence. Thus, we examined self-reports of environmental stressors at age 14 (Time 1), cognitive control at age 16 (Time 2), and anxiety at age 18 (Time 3), while including anxiety at age 16 as a covariate[1].

To address our research questions, we conducted a prospective mediation analysis using SEM in Stata Version 13 (StataCorp, 2013). Bootstrapping procedures in SEM were used to test the significance of the mediation effects of cognitive control. In this study, 200 bootstrapping samples were generated from the original data set by random sampling to determine indirect effects of mediating variables and analyze the corresponding confidence intervals. This statistical approach is considered to be a robust method of analyzing indirect effects (Hayes, 2009).

RESULTS

Descriptive statistics, correlations, and α reliability estimates for all study variables were calculated prior to addressing our research questions and are displayed in **Table 1**. The hypothesized structural model comprised three observed variables: environmental stressors at age 14 (Time 1), cognitive control at age 16 (Time 2), and anxiety at age 18 (Time 3). In addition, we included anxiety at age 16 (Time 2) as a predictor of anxiety at age 18 (Time 3) in order to account for the fact that anxiety symptoms are likely stable over time and allow us to draw stronger inferences about prospective effects.

We hypothesized that individuals with higher levels of environmental stress exposure would later report higher levels of anxiety, as compared with peers with lower levels of environmental stress exposure (Hypothesis 1). Furthermore, we predicted that this effect would be mediated by cognitive control (Hypothesis 2). Indeed, structural equation modeling revealed that cumulative environmental stressors at age 14 had both direct (path c′, **Figure 1B**) and indirect (paths a and b, **Figure 1B**) effects on later anxiety at age 18 through their effects on cognitive control at age 16 even when previously reported anxiety at age 16 was included as a covariate. **Figure 1** shows the results of a test of the full model, including the total (**Figure 1A**) and indirect effects (**Figure 1B**) among cumulative environmental stressors, cognitive control, and anxiety.

Consistent with Hypothesis 1, our results show that adolescents who report higher levels of cumulative environmental stressors at age 14 later reported greater anxiety at age 18 (c; $\beta = 0.11$, $B = 0.06$, $z = 2.68$, $p = 0.02$). Consistent with Hypothesis 2, which predicts that cognitive control would mediate the relation between cumulative environmental stressors and early adulthood anxiety, our results demonstrate a significant effect of environmental stressors on cognitive control (a; $\beta = -0.20$, $B = -0.17$, $z = -4.52$, $p < 0.001$), of cognitive control on anxiety (b; $\beta = -0.10$, $B = -0.07$, $z = -2.91$, $p = 0.004$), and of environmental stressors on anxiety (c′; $\beta = 0.09$, $B = 0.05$, $z = 2.00$, $p = 0.05$). These effects remained statistically significant even while controlling for anxiety at age 16, which suggests that cognitive control as a mediator is prospectively predicting anxiety at age 18 over and above prior levels of anxiety. That is, those reporting higher levels of environmental stressors tended to have lower cognitive control. Higher cognitive control, in turn, was associated with lower levels of late adolescent anxiety. The bootstrapped unstandardized indirect effect was $B = 0.012$, confidence interval [0.002, 0.02], and thus, the indirect effect was statistically significant. As a partial mediator, cognitive control accounted for 18% of the association between

[1]Sex was also examined as a second covariate but did not change any of the findings (i.e., all significant effects remained significant), and thus was omitted from the final model presented here.

TABLE 1 | Mean, Standard Deviations (SD), and pairwise correlations among study measures.

Measure	Time at measurement	Age at measurement	*Mean*	*SD*	1	2	3
1. Environmental stressors	T1	14	1.67	0.44			
2. Cognitive control	T2	16	2.93	0.37	−0.19**		
3. Anxiety at Age 16	T2	16	1.3	0.3	0.18**	−0.33**	
4. Anxiety at age 18	T3	18	1.22	0.26	0.17**	−0.21**	0.35**

*The presentation of the pairwise correlations focus on the measures at timepoints relevant to the analysis. Correlation is significant at **$p < 0.001$.*

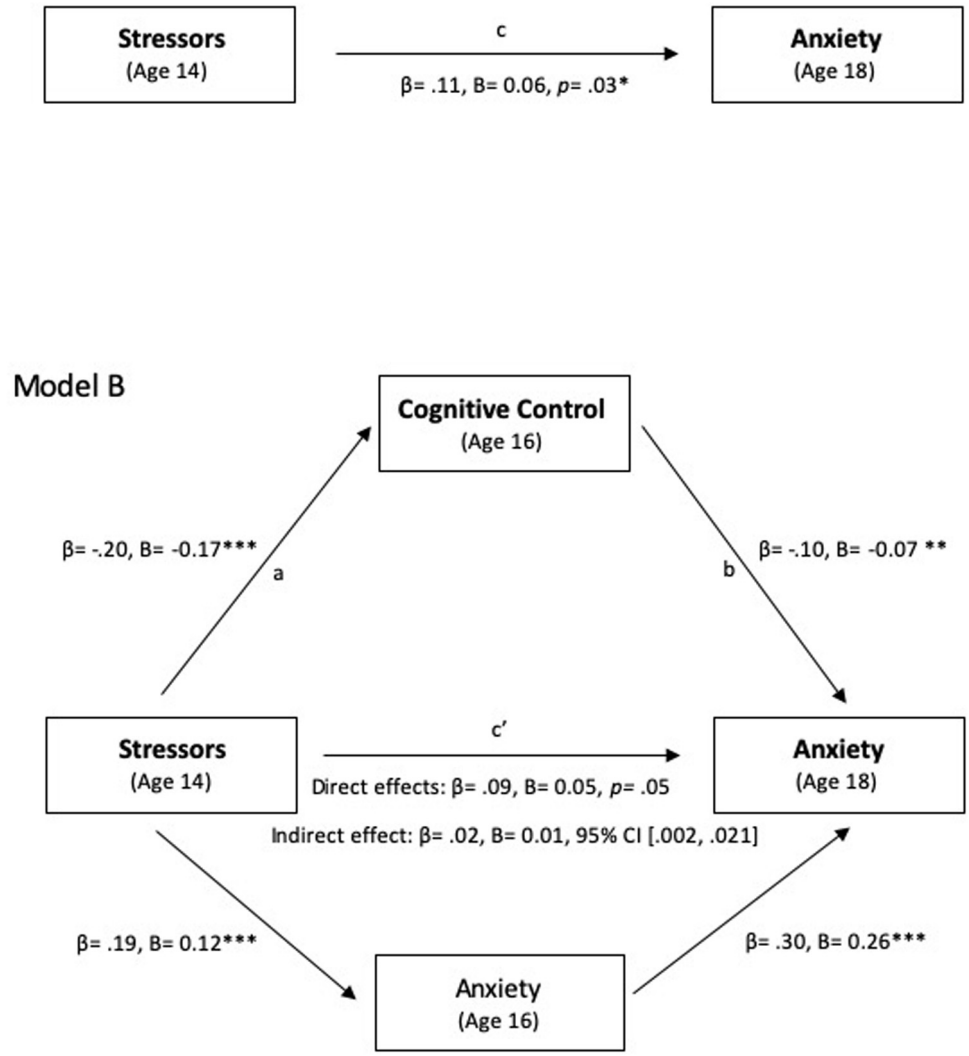

FIGURE 1 | Path model showing the effect of cumulative environmental stressors on anxiety mediated by cognitive control. Total effects model **(A)** and indirect effects model **(B)** demonstrate the cognitive control at age 16 partially mediated the relation between environmental stressors at age 14 and anxiety at age 18. Anxiety at age 16 is included as a covariate. Residual variances of cognitive control and anxiety at age 16 are correlated to account for association due to unmeasured common causes ($r = -0.03$). Both standardized and unstandardized coefficients are shown. $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

environmental cumulative stressors and adolescent anxiety (indirect effect/total effect): individuals reporting higher levels of cumulative environmental stress exposure tended to have decreased cognitive control ($\beta = -0.20$, $B = -0.17$, $p < 0.001$), cognitive control in turn was associated with decreased anxiety ($\beta = -0.10$, $B = -0.07$, $p = 0.004$). Taken together, these findings are consistent with the hypothesis that cumulative environmental stress exposure is associated with later anxiety at least in part because stress exposure impairs cognitive control, a critical factor in buffering against the development of anxiety.

DISCUSSION

The purpose of the current study was to investigate the potential meditational role of cognitive control in the longitudinal relation between cumulative environmental stress exposure and the development of late adolescent anxiety. Given previous research, we tested the hypotheses that (1) increased stress exposure would be associated with higher levels of anxiety, and (2) this association would be partially mediated by cognitive control, with increased stress exposure being associated with impaired cognitive control, which in turn is linked to increased anxiety.

In line with our first hypothesis, our findings revealed a statistically significant positive association between early adolescent cumulative environmental stress exposure and later adolescent anxiety, albeit with β = 0.11, the effect is considered small (small = 2%, medium = 15%, and large = 25%; Lachowicz et al., 2018). This is consistent with a large body of research demonstrating a link between early exposure to adverse experiences and a range of later physical and mental health outcomes (see Nusslock and Miller, 2016, for review). However, our findings point to the importance of examining stress exposure from different sources. Previous studies have examined child maltreatment, poverty, family instability, socioeconomic status, and trauma to operationalize stress and adversity. In our unique sample, we touched upon a small fraction of the breadth of stressors one may be exposed to during development. We included reports of discrimination, exposure to criminal activity, and neighborhood quality in our measure of cumulative environmental stress. Sources of stress are wide ranging – from health inequalities to experiences of racism and discrimination – therefore, we urge these diverse experiences of stress to be reflected in future research and to be considered for their potential cumulative effects.

In line with our second hypothesis, we found the aforementioned relationship was partially explained by adolescent cognitive control. Specifically, our findings demonstrated that cognitive control mediated the relation between cumulative environmental stress exposure at age 14 and anxiety at age 18: those with greater exposure to environmental stressors tended to then have lower cognitive control (medium effect; β = −0.20), but higher cognitive control, in turn, was associated with lower levels of late adolescent anxiety (small effect; β = −0.10). In fact, even after controlling for anxiety at age 16, our tested model demonstrates that cognitive control accounts for 18% of the total effect between environmental stress exposure at age 14 and anxiety at age 18, which indicates a medium proportion of explained variance (Lachowicz et al., 2018). As the first study to examine the three constructs in a prospective, longitudinal manner, our results converge with evidence from developmental psychology, public health, and neuroscience to chronicle the role of social systems in shaping the development of our mental and emotional health. More importantly, our findings uniquely identify cognitive control as an underlying mechanism, a protective factor that is both vulnerable to the influences of environmental stress yet potentially buffers against these deleterious effects on anxiety outcomes. Thus, efforts to mitigate mental health outcomes for youth ought to consider the role and malleability of cognitive control. Although results from cognitive control interventions are mixed (see Au et al., 2015 for meta-analysis), a growing number of interventions studies have shown some promise in improving mental health outcomes (Owens et al., 2013; Koster et al., 2017; Jopling et al., 2020). The prospect of optimizing this function is critical in promoting resilience, particularly during adolescence, a unique period of neurocognitive development and enhanced vulnerability.

It is important to note that despite the fact that the above relations were statistically significant, their β values ranged from small to medium. Specifically, the relation between cumulative environmental stress at age 14 and later anxiety at age 18 may be meaningful but smaller than expected given the findings from previous literature. It is important to note, however, that previous findings were either cross-sectional in nature and/or examined only two constructs, which may magnify the strength of the relationships. A longitudinal study examining poverty, chronic stress, and later cognitive control – as indexed by neural activity – reported similar β values for poverty and cognitive control ranging between 0.03 and 0.05, and for chronic stress and cognitive control ranging between −0.13 and −0.14 (Kim et al., 2013), which closely mirrors our findings for the direct effects of path a and c′ (**Figure 1**). As such, modest values may reflect the challenges in isolating causal mechanisms that are inherent to longitudinal work, where the dynamic relationship of variables gets diluted over time as other factors come into play. For example, our findings demonstrate that concurrent measurement of cognitive control and anxiety at age 16 leads to a stronger relationship ($r = -0.33$, $p < 0.001$) than cognitive control at age 16 and anxiety at age 18 ($r = -0.21$, $p < 0.001$). Note, however, that the indirect effect of cognitive control accounted for 18% of the total relationship, despite the weakened association over the 2 years and controlling for anxiety at age 16.

The present results should be considered in light of a few limitations. First, our measure of environmental stressors aimed to encapsulate the cumulative effects of stress through measures of environmental adversity. The range of measures included – from perceived discrimination to neighborhood quality – resulted in modest correlation between measures. However, this modest correlation may reflect the methodological issues of assessing environmental stress. Measurement has taken on a variety of forms in attempt to capture the broad range of physical to psychosocial sources (see Evans and English, 2002 for review). One promising approach indexes environmental stress exposure as a cumulative construct in attempt to capture the confluence of multiple external demands that may lead to suboptimal outcomes for youth. Literature on chronic stress shows that the *quantity* of risk factors encountered, as captured by a cumulative index, and not the particular *type* that seems to better predict outcomes (Kraemer et al., 2005; Sameroff, 2006; Evans and Cassells, 2014). With our cumulative score from three questionnaires, the self-reported levels of chronic stress were low in our sample (mean = 1.67, range = 0–4), which could reflect measurement issues and/or the possibility that our sample was not exposed to high levels of environmental stress. Future work would benefit from including a greater breadth of measures for a more robust index.

Second, our measure of cognitive control relied on self-report. In a meta-analysis of 282 studies of self-control, correlations within and across types of self-control measures were weak (Duckworth and Kern, 2011). Future work including some combination of behavioral, observational, and self-report may improve measurement validity. Lastly, the direction of the relationship between cognitive control and anxiety is arguable. That is, there is literature indicating impaired cognitive control *causes* anxiety (Abravanel and Sinha, 2015), anxiety *causes*

impaired cognitive control (Edwards et al., 2016), or that cognitive control moderates the relationship between stress and adversity on poor mental health outcomes (Extremera and Rey, 2015). Although correlational in nature, our novel findings hint at the first causal effect – that is, greater cognitive control is associated with later decreased anxiety – but all three effects have not been adequately examined together (as competing or complementary processes) in a longitudinal context.

The current study set out to synthesize findings from stress, cognition, and mental health literature and test previously untested theories on the directionality of these relationships during adolescence. As the first prospective longitudinal study in this area, our results deepen our understanding of the mechanism underlying early stress exposure and the development of anxiety during a developmentally sensitive period. More importantly, our findings underscore the importance of preserving cognitive control as a means of combating mental health disorders and as a possible protective factor in promoting resilience.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available due to confidentiality reasons. Data is available upon application through administrators of the California Families Project.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of University of California, Davis. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NT, SJ, JE, and RR contributed to the theoretical development of the study. OA supplied resources needed for study analysis. NT performed the data analysis and interpretation under the supervision of SJ, JE, and RR. NT drafted the manuscript. SJ, JE, RR, and OA provided revisions. All authors approved the final version of the manuscript for submission.

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Single-Dose of Testosterone and the *MAOA* VNTR Polymorphism Influence Emotional and Behavioral Responses in Men During a Non-social Frustration Task

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Previous studies suggest that testosterone and several neurotransmitters might interactively influence human aggression. The current study aimed to test potential interactions of a genetic variation linked to the catabolism of serotonin, dopamine, and norepinephrine and exogenous testosterone on the reaction towards non-social provocation. In total, 146 male participants were genotyped for a prominent polymorphism of the monoamine oxidase A (*MAOA*) gene resulting in a short and long variant. Participants completed a non-social frustration task after receiving either testosterone or a placebo gel in a double-blind set-up. Participants performed a non-social frustration task, where they had to direct a virtually moving ball into a barrel by pulling a joystick (neutral block). During a frustration block, the joystick repeatedly did not respond to participants' reactions thereby causing failed trials to which participants reacted with increased anger and stronger pulling of the joystick. We analyzed the effect of testosterone administration on emotion and behavior in individuals who either carried a low (L) or high (H) activity *MAOA* variant. Testosterone administration increased provocation-related self-reported anger and abolished the association between trait aggression and joystick deflection in the frustration block. In *MAOA*-H carriers endogenous testosterone levels at baseline were associated with increased joystick deflection in both blocks. There was, however, no interaction of testosterone administration and genotype. Although preliminary, the results rather indicate independent influences of exogenous testosterone administration and *MAOA*, but support an interaction of endogenous testosterone levels and *MAOA* genetics in a frustration task. The administration of testosterone seems to act on the subjective emotional experience in a provoking situation, while endogenous testosterone levels increased pulling impulses only in carriers of the *MAOA*-H variant.

Keywords: hormone application, monoamine oxidase A polymorphism, anger, testosterone, provocation

INTRODUCTION

The neurocognitive system "*frustrative nonreward*" is one of the subdomains defined by the research domain criteria (RDoC) that contribute to aggression. Externalizing behaviors, for example, seem to be characterized by deficits in processing the omission of a predicted reward (Gatzke-Kopp et al., 2009). As one of five subdomains of the negative valence system, the concept of frustrative non-reward describes the situation in which an individual is impeded from obtaining a previously available award. This becomes especially relevant if frustration appears after repeated or sustained effort, which stays unrequited. Typical effective response within such a frustrating situation is anger (Novaco, 2016), which ultimately can lead to aggression (Berkowitz, 1989). Other important concepts in the negative valence system, which may activate a defensive aggressive response, are an acute or sustained threat, and—more ambiguous, distant, or uncertain—potential harm (Kozak and Cuthbert, 2016). Each of these conceptual domains may be defined by specific neurobiological substrates including genetic or hormonal modulators and reflect the full range of human behavior from normal to abnormal. The current study aims to characterize the influence of a genetic polymorphism and the steroid hormone testosterone and their potential interaction on affective and behavioral responses to sustained frustration in healthy young males.

While aggression is typically associated with social threat or provocation, frustration can appear in social and non-social contexts. The RDoC framework declares the point subtraction aggression paradigm (PSAP) as an experimental task to assess aggression in the framework of frustrative non-reward (Del Pozzo et al., 2019). This task has a clear social component, as an ostensible opponent subtracts points or money from the participant who thereby loses an already achieved reward. Other paradigms that were more recently developed, however, do not present a social component (e.g., Panagiotidis et al., 2017; Tseng et al., 2017; Angus and Harmon-Jones, 2019; Seymour et al., 2020). In these tasks, participants try to achieve a reward, but either receive rigged feedback about their performance and the consequential loss of the reward or are impeded to fulfill the task due to technical manipulations. Across all paradigms, these manipulations lead to increased anger or irritability (Seymour et al., 2020).

Testosterone, similarly to findings in other species, is assumed to enhance human aggression especially in the presence of a social challenge (Eisenegger et al., 2011; Wingfield, 2016). However, research findings are heterogeneous and do not always support the enhancement of aggression *via* testosterone. Depending on the context and individual characteristics, testosterone seems to promote either prosocial or antisocial behaviors (Zilioli and Bird, 2017; Carré and Archer, 2018). To name just a few research findings, testosterone affected punishment behavior depending on the preceding fairness of an ostensible opponent (Dreher et al., 2016; Wagels et al., 2018); it increased reciprocity when participants were trusted with high investments in a trust game (Boksem et al., 2013) and cooperation with in-group members during the intergroup competition (Reimers and Diekhof, 2015); and finally, it promotes utilitarian choices (Carney and Mason, 2010; Arnocky et al., 2017) or behaviors that ensure a high social status (Eisenegger et al., 2010; Dreher et al., 2016). In a previously reported experiment on testosterone administration in healthy men, our group could show that males in the testosterone group compared to the placebo group adapted their behavior strategically to that of the opponent: they selected higher punishments if their ostensible opponent stole high amounts of money from their account, whereas they responded less aggressively when provocation was low or zero (Wagels et al., 2018). In a similar social provocation experiment, testosterone administration increased aggressive responses to provocation especially in individuals with low regulatory abilities, such as high impulsive men, but did not affect men scoring low on dominant or impulsive traits (Carré et al., 2017). Thus, context and personality seem to moderate the effects of testosterone administration.

However, despite the extensive research in the field of social endocrinology and the association of testosterone with a threat, provocation and aggression, a surprisingly small number of studies investigated its effects in a frustration context. Findings in our group suggest that testosterone administration increases angry responses to sustained frustration, which was induced through a technical manipulation prompting the participant to repeatedly fail the task (Panagiotidis et al., 2017). In this task, participants pulled a joystick to direct a moving ball into a virtual bottle, but a manipulation disrupted the joystick function. Thus, participants lost the trial and the associated monetary reward. While participants were found to pull the joystick stronger in the frustration block, testosterone administration did not increase this behavioral response. Interestingly data of Tseng et al. (2019), measuring neural responses in a frustration task, suggest that different neurocognitive circuits underlie the direct response to frustrating feedback and the behavioral reaction afterward. They conclude that especially the latter response is affected by re-orientation and top-down control. Hence, testosterone administration may primarily affect the emotional rather than the behavioral response following continuous frustration.

The X-chromosome-linked *MAOA* gene codes for the monoamine oxidase A, an enzyme that degrades serotonin, norepinephrine, and dopamine. The promoter region of the gene is characterized by a variable number of 30 base pair tandem repeats, usually comprising 2-, 3-, 3a-, 4-, 5-repeat alleles (Sabol et al., 1998; Deckert et al., 1999) which affect the expression of the gene. While the role of the 5-repeat allele is not yet entirely understood (Kim-Cohen et al., 2006), the shorter alleles (2 or 3 repeats) are associated with reduced transcriptional efficiency compared to the long alleles (3a or 4 alleles; Sabol et al., 1998; Deckert et al., 1999). Several studies show that this transcriptional efficiency influences proxies of aggression and anti-social behavior (Buckholtz and Meyer-Lindenberg, 2008; Godar et al., 2016). Instead of referring to the allele length, we will thus refer to the transcription characteristics using the abbreviation *MAOA*-L for the low transcriptional variants and *MAOA*-H for the high transcriptional variants. This classification is commonly used in the scientific community.

Interestingly, empirical evidence points to a sexually-dimorphic role of the *MAOA* VNTR (Reif et al., 2012; Perry et al., 2017). In particular, males, as opposed to females, have an increased tendency to show impulsive aggression if they carry a variant linked to lower *MAOA* activity (Godar et al., 2016). While not supported in all studies (Schlüter et al., 2016), in males these low activity variants are mostly related to increased aggression after provocation (McDermott et al., 2009; Kuepper et al., 2013) or social exclusion (Gallardo-Pujol et al., 2013). Findings on another *MAOA* variant (single nucleotide polymorphism, rs1465108) suggest that reduced control abilities could be an underlying mechanism since researchers found increased impulses to negative affect in these individuals (Chester et al., 2015). Neuroimaging studies suggest that the *MAOA* polymorphism might affect anger control (Denson et al., 2014) and anger reactivity (Alia-Klein et al., 2009).

The different effects of the *MAOA* VNTR observed in males and females may be influenced by sex-specific hormones such as testosterone. The concentration of the steroid hormone testosterone is much higher in males. Consequently, it could be assumed that high testosterone levels are the basis for the aggression enhancing effect observed in *MAOA*-L carriers. A previous study indicated that in individuals carrying a genetic variant associated with lower enzyme activity, higher levels of CSF testosterone levels were associated with increased Brown–Goodwin scores measuring lifetime aggression levels (Sjöberg et al., 2008). This may suggest an interaction of both factors motivating the current research question. To test, if such an interaction can explain sex differences, a mixed sample of males and females would be required. However, since the administration of Testim (testosterone gel) in females is currently not allowed in Germany and may have distinct effects in males and females *per se*, the current study focused on males only. Besides the notification of sex differences, other findings motivate to investigate a potential interaction of testosterone and *MAOA* activity. Testosterone and serotonin, which is degraded by *MAOA*, seem to have a close relationship (Perfalk et al., 2017). *MAOA* expression might influence aggression in interaction with testosterone more indirectly *via* serotonin (Birger et al., 2003; Montoya et al., 2012). Recently, it has also been shown that the effects of exogenous testosterone are moderated by variations in the dopaminergic system (Losecaat Vermeer et al., 2020). As suggested by the authors, testosterone might act *via* androgen-dependent actions on striatal dopamine to influence status-seeking motivation. Similar mechanisms might modulate reactions that emerge when an individual is impeded from obtaining a previously available reward. Finally, we observed that individuals who received a single dose of testosterone showed increased risk-taking if they were carriers of a *MAOA* variant associated with low activity (Wagels et al., 2017b). In a social provocation task, those individuals showed higher anger paralleled by reduced brain activity in the cuneus during a social provocation task if they did not receive testosterone (Wagels et al., 2019b). Here testosterone administration increased aggressive behavior independent of the *MAOA* variant in response to high provocation compared to low provocation (Wagels et al., 2018). Thus, instead of a biological interaction, that depicts a risk factor for aggression, *MAOA* and testosterone may have similar effects as distinct entities that nevertheless partially overlap and activate similar brain regions. If both factors have similar effects but do not directly interact, we might expect different patterns depending on the measured variable or the context: For instance, testosterone might affect the emotional reactivity to provocation, while the *MAOA* VNTR influences behavior in response to provocation.

In the current study, we aim to test for a possible interaction of testosterone administration with the *MAOA* VNTR during a non-social frustration task in which we previously found that testosterone increased the affective response anger. Concerning previous findings on the task (Panagiotidis et al., 2017; Wagels et al., 2019b), we assume an increase of anger and increased joystick amplitudes during the frustration block across participants. We reanalyzed the data since we specifically wanted to test if the *MAOA* VNTR interacts with the exogenously modulated or endogenous testosterone levels in a non-social frustration context, which has not been tested before. Merging two parallel data sets, we analyzed a larger sample than used in the previous study (Panagiotidis et al., 2017). Concerning the administration of testosterone and the influence of the *MAOA* VNTR, we suggest two opposing hypotheses (1 and 2) concerning the exogenous testosterone administration.

(1) *Interaction effect hypothesis*: in case of biological interactions that are influenced by exogenous testosterone manipulation, we assume an effect of testosterone administration on anger and increased behavioral impulses during the frustration task in carriers of the low activity *MAOA* variant (*MAOA*-L).
(2) *Separate mechanisms hypothesis*: testosterone and *MAOA* independently influence anger and behavior in the frustration task. We assume that testosterone administration will increase anger and that *MAOA*-L carriers will show increased behavioral reactions in the frustration task. We do not expect an interaction of testosterone administration and the MAOA variant.
(3) Additionally, we test, if endogenous testosterone levels (baseline levels before administration) interact with the MAOA variant, influencing anger and behavior in the frustration task.
(4) Since personality traits have been shown to influence the effects of testosterone administration on behavior, we test the influence of trait aggression, assuming that increased trait aggression enhanced anger and frustration related behavioral impulses more after testosterone administration.

MATERIALS AND METHODS

Sample

Participants were recruited by postings, advertisements in lectures, and online platforms of the university. General inclusion criteria were age above 18, fluent German language, and being male. In total, 146 male participants (origin: 95% Caucasian, 5% other) gave oral and written informed consent to take

part in the study. Exclusion criteria for study participation included current or previous psychiatric diagnosis assessed by the structured clinical interview (SCID I) for DSM IV (Wittchen et al., 1997). Further exclusion criteria were neurological problems, contraindications against magnetic resonance imaging (MRI; additional functional MRI measures were performed following the here reported experiment), left-handedness, high blood pressure, current nicotine consumption, and known allergic reactions to the testosterone gel. Participants were asked to refrain from alcohol consumption 24 h before participating in our study. One participant was excluded due to additional MR contraindications. One outlier had to be excluded because this participant did not perform the task adequately (no response in more than half of the trials). The results are therefore presented for 144 male participants. Of these 144 participants, 75 received testosterone (T), and 69 received placebo (PL). Both groups (T, PL) did not differ in age (M_T = 24.34, M_{PL} = 24.12; $t_{(142)} = -0.35$, $p = 0.727$). Regarding the *MAOA* VNTR polymorphism participants were grouped as *MAOA*-L (low activity variants) and *MAOA*-H (high activity variants).

Ethics Approval

Participants gave oral and written informed consent to participate in the study. All study procedures were compliant with the latest version of the Code of Ethics of the World Medical Association (Declaration of Helsinki). Additionally, the Medical Ethics Committee of the Medical Faculty, RWTH Aachen University approved of the described study procedures.

Procedure

Data analyses presented here are based on two merged data sets in which participants received transdermal testosterone application before performing the behavioral task reported here. Both studies included two parts, which were separated by a 1.5 h break. The first part of both studies was identical, while after the break, participants of one study additionally received arginine vasopressin before performing several tasks in the MRI scanner. In the other study, participants performed the same tasks in the MRI scanner but did not receive arginine vasopressin before the measurement. Since this administration of arginine vasopressin was not related to the reported data, which were assessed in the first part of the experiment, both data sets are merged for the current analyses.

In both studies, participants arrived in the early afternoon because of a reduced individual variability of testosterone levels at this time (Dabbs et al., 1990). A first blood sample was collected to measure hormonal baseline levels. Subsequently, either a placebo gel (hydrogel conventionally used for ultrasound) or a testosterone gel [5 g Testim^{TM}, containing 50 mg of the active agent (17-β hydroxyandrost-4-en-3-one)] was applied on the skin of the upper back and shoulders of the participant. Due to a neutral packaging experimenter and participants were blinded to group allocation (double-blind setup). Approximately half of the participants then provided a buccal swap for genotyping; all other participants gave a buccal swap at a prior screening. DNA from buccal mucosa cell samples was analyzed in a collaborate laboratory (to analyze the *MAOA* VNTR and polymorphic elements of the serotonin transporter gene (SLC6A4; Molecular Psychology, Ulm, Germany; for further descriptions see Wagels et al., 2017b and **Supplementary Material**). Variation in the SLC6A4 was not further considered for the analysis as this would have resulted in small groups with unequal group sizes.

The experimental task started after approximately 200–220 min post testosterone/placebo application. This time delay was chosen because the first peak of serum testosterone increase was detected here in a study that tested the effects of Testim^{TM} in hypogonadal males (Marbury et al., 2003). Previously, we could ensure a significant increase in plasma testosterone levels of the T compared to the PL group after 3 and a half hours up to approximately 6 h (Wagels et al., 2017a,b). After the experimental task reported here, a second blood sample was taken to measure hormonal levels (T1). Subsequently, participants in both studies underwent an MRI scan while performing a modified Taylor Aggression Paradigm and a scanner compatible version of the Balloon Analogue Risk Task.

Additionally, participants completed several questionnaires related to personality traits. In both studies, trait aggression was assessed with the Buss Perry Aggression Questionnaire (BPAQ; Buss and Perry, 1992).

Technical Provocation Task

In the Technical Provocation Paradigm (TPP; Panagiotidis et al., 2017; Wagels et al., 2019a), individuals are instructed to direct a horizontally moving ball into a barrel by pulling a joystick to win virtual gold coins. Participants are informed that each virtual coin will equal 20 real Euro Cents. The paradigm consists of two blocks each lasting 7 min including 40 trials. Unknown to the participant, the joystick does not respond to the participants' actions in 12 trials (frustration block). Since the moving ball does not drop down (vertically), the ball cannot be successfully placed in the barrel and a potential reward is missed. Also, a provoking message is given ("Please move the joystick!") following these manipulated trials before the next trial starts. Participants rate their emotions [emotional state rating, ESR (Schneider et al., 1994)] after each block. In this standardized emotion measure participants rate their happiness (How happy do you feel right now?), their anger (How angry do you feel right now?), their sadness (How sad do you feel right now?), their surprise (How surprised do you feel right now?) and their anxiety (How anxious do you feel right now?) on a five-point Likert-like scale from 1 "not at all" to 5 "extremely". Also, the joystick movement, measuring the pulling (maximal pulling equaled 200 mm) of the participant, is assessed during the complete experiment.

Statistical Procedures

Regarding the distribution of genetic variants and the treatment allocations, Chi-square tests of homogeneity were conducted. Hormonal levels were log-transformed (due to a skewed distribution) and subsequently analyzed using a repeated-measures ANOVA including time (t0, before gel application; T1, after the task) as within-subject factors and treatment (T, PL) and

TABLE 1 | Number of participants per group and genotype.

	PL	T
MAOA-L	27	31
MAOA-H	42	44

genotype (*MAOA*-L, *MAOA*-H) as between-subject factors. For validation of the testosterone manipulation, plasma testosterone levels should differ between T and PL at T1 (but not at baseline).

Further analyses were performed in R[1]. We calculated two general linear mixed models using the package lme4 including a random intercept (ID) and the following fixed factors: group (PL, T), genotype (*MAOA*-L, *MAOA*-H), condition (neutral, frustration), log-transformed baseline testosterone (t0) and trait aggression (BPAQ). In addition to the main effects, we specified interactions (condition*t0, genotype*t0, condition*group, condition*genotype, BPAQ*group, BPAQ*genotype, condition*BPAQ, genotype*group, genotype*group*BPAQ). In the first model, the dependent variable was subjective anger as assessed *via* the ESR during the paradigm presentation at the end of each block. In the second model, the dependent variable was the peak amplitude (maximal deflection) of the joystick within a trial which was calculated as an absolute value and averaged across each block.

RESULTS

There was no significant difference in the distribution of *MAOA*-L and *MAOA*-H carriers concerning the treatment allocation (**Table 1**), (1) = 0.31, $p = 0.738$.

Hormonal Levels

Blood serum testosterone levels were higher in the T group compared to the PL group, $F_{(1,133)} = 10.78$, $p = 0.001$, = 0.08 and at time point T1 compared to time point t0, $F_{(1,133)} = 6.46$, $p = 0.012$, = 0.05. There was an interaction of hormonal treatment and time, $F_{(2,132)} = 56.63$, $p < 0.001$, = 0.30. *Post hoc* comparisons demonstrated that treatment groups did not significantly differ from each other at t0 ($p = 0.730$), but at T1, $F_{(1,132)} = 33.71$, $p < 0.001$, = 0.20, with higher testosterone blood serum levels in the T group (see **Figure 1**). There were no main effects or interactions of the genetic variant (all $p > 0.05$).

Task

The general linear mixed model on anger showed significant effects for condition, trait aggression (BPAQ), and the interaction of condition by group (see **Table 2** for an overview on the fixed effects on the anger model). Anger was increased in the frustration block compared to the neutral block. *Post hoc* tests on the group by condition interaction showed an increase of anger after the frustration block both in the PL and in the T group. Groups did not differ in the neutral or frustration block, but the increase of anger was higher in the T group (see **Figure 2A**). Trait aggression was positively related to subjective anger (see **Figure 2B**).

[1]https://CRAN.R-project.org/

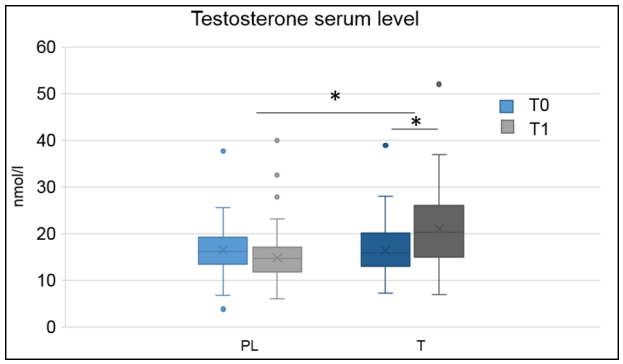

FIGURE 1 | Boxplots, depicting minimum, maximum, median, first quartile and third quartile of hormonal serum levels at baseline (t0) and directly after the applied paradigm (T1) for the placebo (PL) and testosterone (T) group, $^*p < 0.05$.

Regarding the joystick amplitude, the general linear mixed model showed significant effects for condition, trait aggression, baseline testosterone (t0), the interaction of BPAQ and condition, the interaction of genotype and t0 and the three-way-interaction of the group, condition, and BPAQ (see **Table 3** for an overview on the fixed effects of the joystick amplitude model). The amplitude was higher in the frustration block compared to the neutral block (see **Figure 3C**). The BPAQ and t0 were positively related to the joystick amplitude. To further disentangle the interaction of the BPAQ and condition, the slope of the BPAQ was tested separately for each condition, revealing a significant association in the neutral condition (Estimate = 13.21, SE = 3.52, $t = 3.76$, $p < 0.001$) but not in the frustration condition (Estimate = 6.27, SE = 3.52, $t = 1.78$, $p = 0.080$). However, this was further influenced by the treatment group: In the PL group, there was a significant positive relationship in the neutral (Estimate = 12.28, SE = 4.82, $t = 2.55$, $p = 0.01$) and frustration condition (Estimate = 10.23, SE = 4.82, $t = 2.12$, $p = 0.03$), while in the T group there was only a significant positive relationship in the neutral block (Estimate = 15.95, SE = 5.07, $t = 3.15$, $p < 0.001$), but no significant relationship in the frustration block (Estimate = 0.73, SE = 5.07, $t = 0.14$, $p = 0.89$; see **Figure 3A**).

The interaction of genotype by baseline testosterone showed that testosterone was not related to the joystick amplitude in *MAOA*-L carriers (Estimate = −0.96, SE = 4.79, $t = -0.20$, $p = 0.84$), but it was positively related to the joystick in *MAOA*-H carriers (Estimate = 16.00, SE = 4.41, $t = 3.62$, $p < 0.001$; see **Figure 3B**).

DISCUSSION

The current study aimed to investigate whether testosterone administration and the *MAOA* VNTR have interactive effects on emotion and behavior during a frustration task. Alternatively, they might exert separate effects on emotion and behavior in the frustration task. Indeed, the testosterone administration effect on anger reported previously (Panagiotidis et al., 2017) was present in the analysis of this merged and larger data

TABLE 2 | Effects on subjective anger during the frustration task.

	df (num)	*df* (den)	*F*	*p*	lower CI	upper CI
Condition	1	139	39.03**	<0.001	0.23	0.44
Group	1	134	0.72	0.347	−0.20	0.08
BPAQ	1	134	14.93**	<0.001	0.15	0.43
Genotype	1	134	0.02	0.900	−0.13	0.15
t0	1	134	0.38	0.539	−0.19	0.10
condition*t0	1	139	1.28	0.247	−0.16	0.04
t0*genotype	1	134	<0.001	0.987	−0.14	0.14
Condition*group	1	139	4.02*	0.047	−0.21	−0.003
Condition*genotype	1	139	0.49	0.485	−0.07	0.14
Group*genotype	1	134	1.15	0.234	−0.11	0.17
Group*BPAQ	1	134	0.22	0.640	−0.06	0.22
Genotype*BPAQ	1	134	1.28	0.260	−0.08	0.12
Condition*BPAQ	1	139	0.15	0.700	−0.23	0.05
Group*genotype*BPAQ	1	134	0.04	0.840	−0.16	0.13

*t0, log-transformed baseline testosterone levels; BPAQ, trait aggression score. *p < 0.05; **p < 0.001.*

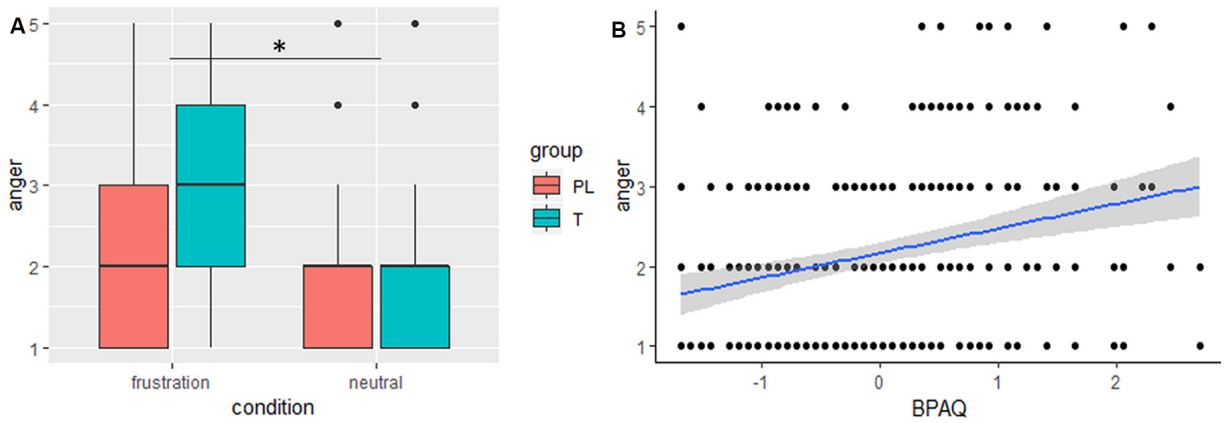

FIGURE 2 | **(A)** Boxplots, depicting minimum, maximum, median, first quartile, and the third quartile of subjective anger ratings after the frustration and after the neutral block are indicated separately for the placebo (PL) and testosterone (T) group. **(B)** The slope (blue) and confidence interval (gray) of trait aggression (BPAQ) is depicted predicting subjective anger, *$p < 0.05$.

TABLE 3 | Effects on the joystick deflection (peaks) during the frustration task.

	df (num)	*df* (den)	*F*	*p*	lower CI	upper CI
Condition	1	139	67.61**	< 0.001	9.40	15.19
Group	1	134	1.08	0.301	−2.74	9.31
Genotype	1	134	0.07	0.785	−5.19	6.92
BPAQ	1	134	8.29*	0.005	3.16	15.51
t0	1	134	5.28*	0.023	1.25	13.36
Condition*group	1	139	1.51	0.221	−4.64	1.04
Condition*genotype	1	139	3.21	0.075	−5.61	0.22
Condition*BPAQ	1	139	5.01*	0.027	−6.15	−0.44
Group*BPAQ	1	134	0.21	0.645	−4.56	7.48
Genotype*BPAQ	1	134	0.56	0.456	−3.70	8.47
Genotype*t0	1	134	6.52*	0.012	2.16	14.80
Group*t0	1	134	2.27	0.134	−11.38	1.32
Group*genotype	1	134	0.08	0.773	−6.98	5.14
Group*genotype*BPAQ	1	139	8.58*	0.004	1.46	7.18

*t0, log-transformed baseline testosterone levels; BPAQ, trait aggression scores, *p < 0.05; **p < 0.001.*

set, and this was not modulated by the *MAOA* VNTR. In contrast, the *MAOA* VNTR modulated the relationship of endogenous testosterone levels and behavior in the task, namely the joystick deflection. Individuals with high baseline T levels and the high active (*MAOA*-H) variant pulled the joystick stronger, than those with lower baseline testosterone

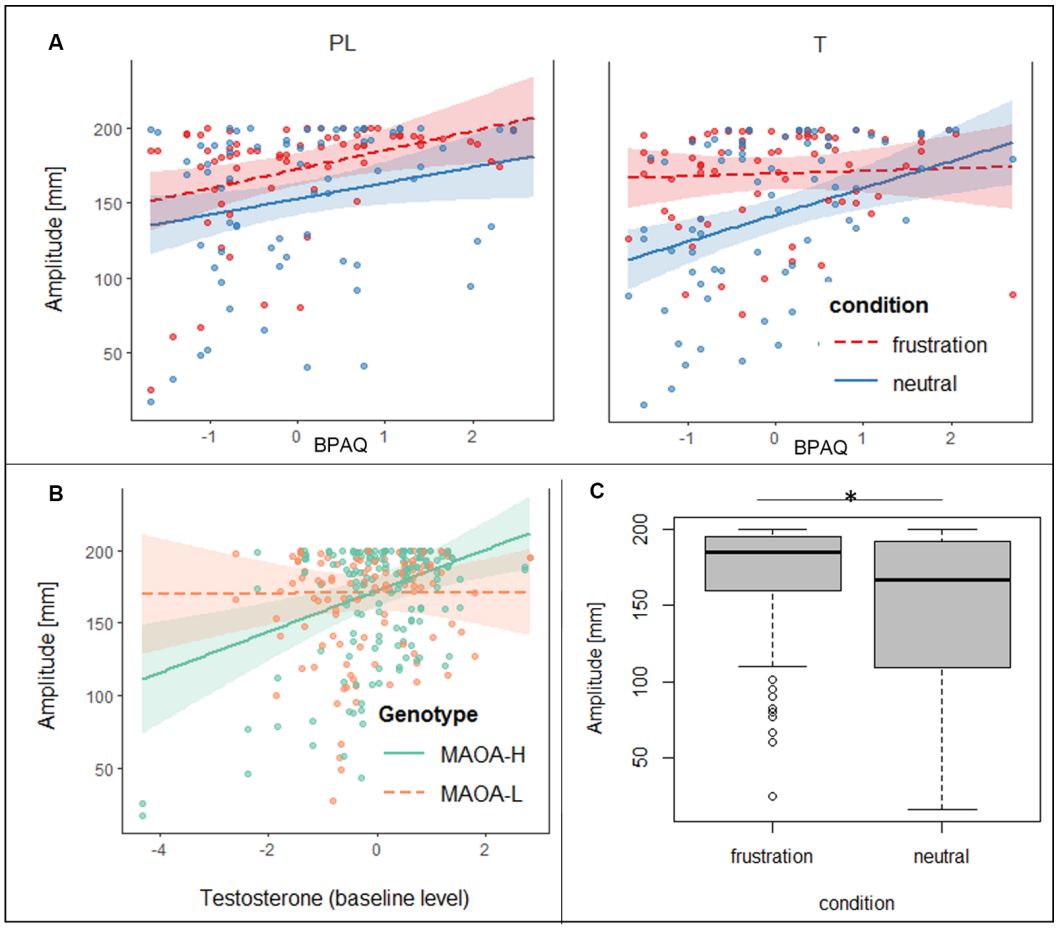

FIGURE 3 | (A) Slopes and confidence intervals of trait aggression (BPAQ) are indicated separately for the placebo (PL) and testosterone (T) group in the frustration block (red) and the neutral block (blue) predicting peak amplitudes of the joystick movement. **(B)** Slopes and confidence intervals of baseline testosterone levels (log-transformed, in t0) are depicted for *MAOA*-H (green) and *MAOA*-L (orange) predicting peak amplitudes of the joystick movement. **(C)** Boxplots, depicting minimum, maximum, median, first quartile, and the third quartile of the averaged peak amplitudes of the joystick movement is depicted for the neutral and frustration block, $*p < 0.05$.

levels. While our findings support previous studies that demonstrated genetic and hormonal effects in the context of anger provocation, the current results do not support that exogenous testosterone administration affects anger depending on the *MAOA* VNTR variant. While the administration of testosterone seems to influence the emotional reaction to frustration, anger, the *MAOA* VNTR seems to moderate the effect endogenous baseline testosterone levels have on behavior in the frustration task. Moreover, this behavioral response is altered not as a specific response to experimentally manipulated frustration but the effect appears across the task. This may point to the *hypothesis of separate mechanisms* regarding exogenous testosterone and the *MAOA* VNTR, but a potential interactive mechanism of endogenous testosterone and the *MAOA* VNTR.

On the one hand, the current findings underline the modulatory role of testosterone on anger outside of a social context as already shown in a previous analysis of a subsample (study 1, using testosterone application only; Panagiotidis et al., 2017). The findings in this merged and much larger data set substantiate the influence of testosterone during sustained frustration in a non-social context on anger development. The non-social element is particularly interesting since the effects of testosterone are frequently described in contexts such as social provocation or competition (Carré and Archer, 2018). That is likely because two popular hypotheses are usually applied to predict the effect of testosterone, both grounded in the social context: First, the challenge hypothesis (Wingfield et al., 1990) states that testosterone levels rise towards a social challenge thereby promoting aggressive responses towards a social challenger. Second, the status hypothesis refers to face-to-face groups arguing that high levels of endogenous testosterone may encourage behavior intended to dominate—to enhance one's status over other people (Mazur and Booth, 1998). These hypotheses can explain various behavioral effects including aggressive as well as prosocial behavior (Boksem et al., 2013; Dreher et al., 2016) but they cannot be allied to non-social contexts and they

rather neglect the influence of testosterone on the emotional system *per se*.

The current findings indicate that testosterone affects the emotional response to provocation independent of a social opponent that may challenge their promised reward, aim, status, or territory. Certainly, it is possible and even probable that participants felt challenged, when they did not receive a reward or when their joystick did not work. The behavioral differences, measured by the deflection of the joystick amplitude, may thus reflect the reaction to an acute challenge. However, the emotional rating was assessed after the completed block and thereby very likely represents the effect of the sustained frustration, not the acute challenge. Nevertheless, a competitive context was present, which might catalyze the testosterone effect as well. Our results furthermore show that this effect on the emotional component may not be limited to anger, since we also observe a reduction in happiness, with a stronger reduction in the group that received testosterone (see **Supplementary Material**).

Both, the competition induced challenge, and the acute loss of reward, which over time results in sustained frustration may require frustration tolerance or emotion regulation, which, if reduced, may lead to increased anger or conversely inhibit a reduction (Hawkins et al., 2013). Findings of an early study on circulating testosterone in adolescents suggest that high testosterone may actually lower frustration tolerance (Olweus et al., 1988). Emotion regulation might have been affected by testosterone administration in the current study as well. However, the absence of behavioral effects on the joystick pulling suggests that, even in the light of higher anger and reduced positive effect, testosterone administration did not increase aggressive behavioral tendencies, i.e., the joystick pulling. This might be an indication of high behavioral control despite increased frustration related to anger. Alternatively, the absence of a direct opponent or target for an aggressive retaliation may contribute to the missing behavioral effect. In terms of the social status hypothesis (Eisenegger et al., 2011) it is relevant to mention that there was no possibility to increase or restore the social status by aggressing against an opponent, which might be the motivating factor for an actual aggressive response.

Moreover, it is unclear if other emotions may influence the behavior in the non-social frustration task as well. For instance, lower fear in the T compared to the PL group during the neutral block may be an indication of more self-confidence in this task, which might also influence other emotional responses and behavior. While this was not included in the hypotheses, testosterone administration might influence other emotions, such as fear or anxiety, as indicated by observations of behavioral changes in fear-related constructs in previous studies (Aikey et al., 2002; Enter et al., 2016a,b; Wagels et al., 2017a). Also, trait aggression influences behavior in the frustration task. Individuals with high aggression traits are angrier and pull stronger at the joystick when frustrated. Most interestingly, this effect is not enhanced after testosterone administration, but reduced. Testosterone administration may "overrule" the influence of aggressive traits since even individuals with lower aggression traits pull more strongly at the joystick when they are in the frustration block. This is in contrast with previous findings that suggest, that testosterone administration primarily affects individuals who show a tendency to impulsive/ dominant responding (Carré et al., 2017).

The administered dosage of testosterone applied in the current study elevated testosterone levels within the normal range of human males. While we did not test the effects of testosterone administration on the neural system during the frustration task, succeeding tasks suggest that the administration influences neural activity as well (Wagels et al., 2017b, 2019b). Moreover, the effect of acute testosterone increase on the neural system was shown previously *via* a two-step method in which the authors first reduced circulating concentrations of testosterone by applying a gonadotropin-releasing hormone antagonism and then applied 100 mg of a testosterone gel, thereby rapidly increasing testosterone levels within the normal range (Goetz et al., 2014). In their study, the authors show that this acute testosterone increase elevated activity in the subcortical regions including the hypothalamus and corticomedial amygdala when participants saw angry facial expressions.

In the current study, we did not observe an influence of the *MAOA* VNTR on anger related to the frustration task. The *MAOA* polymorphism did not affect the joystick deflections as measured by the size of the peak amplitudes directly, either. However, in *MAOA*-H carriers, a greater deflection was observed in individuals with higher endogenous testosterone levels at baseline. This may seem to be a discrepancy to, the study by Sjöberg et al. (2008), which noticed that increased CSF testosterone levels were associated with lifetime aggression scores in *MAOA*-L carriers, not in *MAOA*-H carriers. Certainly, the current study methodologically differed largely from the study of Sjöberg et al. (2008). First, behavior during a frustration task was measured instead of life-time aggression and testosterone levels were assessed by blood serum samples. Most importantly, although *MAOA* and endogenous testosterone interacted at baseline, testosterone levels were later manipulated in half of the sample. Additionally, the task could have affected endogenous testosterone levels. Thus, the contrasting findings of both studies cannot be directly compared.

Nevertheless, potential biological mechanisms need to be discussed. On the molecular level, evidence that testosterone may directly interact with *MAOA* expression or its substrates is lacking so far in humans. Both genetic variants are thought to affect serotonin regulation (Risch and Nemeroff, 1992; Sabol et al., 1998; Deckert et al., 1999) and serotonin and testosterone seem to have an inverse relationship (Perfalk et al., 2017). Testosterone and serotonin thus might mutually influence aggressive behavior (Birger et al., 2003; Montoya et al., 2012). For a better understanding of the relationship between testosterone and serotonin or testosterone and *MAOA* levels, more studies are needed that investigate such a relationship and investigate how this influences anger and aggression. In addition to suggested molecular relationships, testosterone and serotonin

could both influence aggressive behavior *via* different pathways. The serotonergic system may modulate impulsive reactions or behavioral regulation and testosterone may influence emotional reactivity and motivations. An early finding may be interesting in this context: Here, researchers observed that high endogenous testosterone was associated with competitive aggression, but at the same time low CSF concentrations of a serotonin metabolite, reflecting low serotonin turnover, were associated with high rates of aggression such as threats, chases or assaults (Higley et al., 1996). In the current study, high endogenous testosterone levels were associated with increased behavioral responses in the frustration paradigm in *MAOA*-H carriers who are assumed to have a higher serotonin turnover as the transcription rate of *MAOA* is high. This contradictory finding may indicate that the observed effects are not primarily driven by serotonin.

Another *MAOA* metabolite is dopamine, which might be relevant in the context of aggression as well. The *MAOA* polymorphism previously modulated dopamine release in humans while viewing a movie of neutral or violent content (Schlüter et al., 2016). The authors reported an inversed relationship of aggressive behavior and dopamine release as only the *MAOA*-H group showed higher dopamine release and increased aggression after the violent movie while the *MAOA*-L group showed decreased aggressive behavior and no consistent dopamine release. Since in the current study, increased pulling behavior is observed when testosterone levels were higher in *MAOA*-H carriers, this could be an indication for interaction with dopamine release. While both, interactions with serotonin, as well as dopamine and testosterone would be possible, the context could be decisive for observing behavioral effects. Indeed, both in the study of Schlüter et al. (2016), who measured aggression using the PSAP, a well as in the current study, the paradigms had a clear reward (and frustrative non-reward) component which might involve the dopamine system. Frustrative non-reward can also be described as the state that occurs in response to negative prediction errors, which again is known to induce decreases in dopamine neuron firing (Eshel and Leibenluft, 2020). Changes in dopamine firing neurons might be differentially influenced by the *MAOA* variant and might further interact with testosterone levels. The question that remains here would be why the exogenous manipulation could influence emotions but not behavioral responses. If testosterone administration indeed affects the neural system, which can be assumed based on our previous work (e.g., Wagels et al., 2019b), it is unlikely that this would not affect the dopamine system if endogenous testosterone does. Moreover, endogenous testosterone levels would have changed at the time of the experiment. For a better understanding of the relationship between endogenous and exogenous testosterone and its relationship to *MAOA*, it would be advantageous to investigate processes underlying aggressive behavior in a within-subject design, thus being able to compare natural circulating testosterone levels and manipulated testosterone levels within an individual.

Importantly, an assumption of linear or inverse associations might be too simple. Non-linear effects and relationships are possible. Furthermore, other candidate genes are important risk factors of aggression and might certainly contribute to the findings (Beaver et al., 2007; Tielbeek et al., 2012). Nevertheless, it might be important to investigate different types of aggression concerning testosterone and candidate genes for aggression. A better understanding of biological factors underlying the reaction to frustration may also contribute to the understanding of pathological symptoms such as irritability or aggression in psychiatric groups.

LIMITATIONS

The current results have to be interpreted as preliminary results only. Subgroups in the current sample are small to moderate. The power of statistical tests on the interaction may thus have been reduced. Moreover, the current study only includes young healthy young males with no known history of traumatic experiences, which are often discussed in the context of *MAOA* VNTR effects. Previous findings suggest that environmental adversities might influence the effect of the *MAOA* VNTR on aggression (Byrd and Manuck, 2014; Nilsson et al., 2018). Future studies might therefore additionally assess stressful life-events. Also, the *MAOA* gene is X-chromosome linked and thus more complex effects in females can be expected which cannot be investigated in this study, due to a male-only sample. Another limitation of the study is the between-subject design, which does not allow a direct comparison of endogenous testosterone effects with the *MAOA* variant compared to the effects of exogenous testosterone levels with the *MAOA* variant.

CONCLUSION

The current study corroborates the influence of testosterone administration on angry emotions in non-social frustration contexts. As a reaction to frustration, testosterone increases anger and overrules the positive effect of trait aggression on joystick pulling behavior increasing impulsive movements also in low aggressive individuals. While not interacting with testosterone administration, the *MAOA* polymorphism modulated the relationship of endogenous testosterone levels at baseline and pulling behavior. *MAOA*-H carriers showed reduced pulling if testosterone levels were low and increased pulling if testosterone levels were high. We thus suggest that in the context of non-social frustration, testosterone administration and *MAOA* operate *via* separate mechanisms, while the *MAOA* polymorphism might influence how endogenous hormones influence behavior.

DATA AVAILABILITY STATEMENT

The anonymized data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee, Medical Faculty RWTH Aachen. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

UH, MV and LW designed the study and wrote the protocol. LW managed the literature searches and analyses. PH and LW drafted the manuscript. CM and SJ were responsible for the genotyping analysis. All authors contributed to and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.00093/full#supplementary-material.

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Sex-Specific Relationships Between Interoceptive Accuracy and Emotion Regulation

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Over the last years, there has been a resurge in the interest to study the relationship between interoception and emotion. By now, it is well established that interoception contributes to the *experience* of emotions. However, it may also be possible that interoception contributes to the *regulation* of emotions. To test this possibility, we studied the relationship between interoception and emotion regulation in a sample of healthy individuals (n = 84). We used a similar heartbeat detection task and a similar self-report questionnaire for the assessment of interoceptive accuracy and emotion regulation as in previous studies. In contrast to previous studies, we differentiated between male and female individuals in our analyses and controlled our analyses for individual characteristics that may affect the relationship between interoceptive accuracy and emotion regulation. We found sex-differences in interoceptive accuracy and emotion regulation that amounted to a sex-specific relationship between interoceptive accuracy and emotion regulation: Whereas interoceptive accuracy was related to reappraisal but not to suppression in male individuals, interoceptive accuracy was unrelated to reappraisal and suppression in female individuals. These findings indicate that the relationship between interoception and emotion regulation is far more complex than has been suggested by previous findings. However, these findings nonetheless support the view that interoception is essential for both, the *regulation* and *experience* of emotions.

Keywords: heartbeat detection, interoception, reappraisal, suppression, sex differences

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INTRODUCTION

More than two centuries ago, William James challenged contemporary beliefs about emotions by claiming that the perception of autonomic changes is an essential part of an emotional experience (James, 1884). Although James has been heavily criticized for his claims (Cannon, 1927), the idea that emotional experiences involve the perception of autonomic changes persisted over the centuries. Nowadays, it is widely acknowledged that the perception of autonomic changes, in conjunction with a context-dependent interpretation of these changes, forms the basis of emotional experiences (Schachter and Singer, 1962). However, the perception and interpretation of autonomic changes may not only be relevant for the *experience* of emotions but also the *regulation* of emotions (Critchley and Garfinkel, 2017).

An accurate perception and interpretation of autonomic changes may lead to emotional experiences that are easy to understand and to regulate, whereas an inaccurate perception and interpretation of autonomic changes may lead to emotional experiences that are difficult to understand and to regulate. Accumulating evidence suggests that this is indeed the case (Critchley and Garfinkel, 2017). Most of the evidence has been gathered in studies that used objective measures of interoceptive accuracy and subjective measures of emotion regulation to investigate the relationship between the perception and interpretation of autonomic changes and the regulation of emotional experiences (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). These studies revealed a positive relationship between interoceptive accuracy and emotion regulation, implying that individuals who were more accurate in interoception were also more efficient in the regulation of their emotional experiences. Interestingly, the positive relationship between interoceptive accuracy and emotion regulation was unaffected by the type of strategy that was employed to regulate the emotional experiences (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). Individuals who were more accurate in interoception were generally more efficient in the regulation of their emotional experiences (Füstös et al., 2013; Kever et al., 2015), regardless whether they re-interpreted the emotional experience *via* reappraisal strategies (Gross and John, 2003) or inhibited the emotional experience *via* suppression strategies (Gross and John, 2003). However, it remained unclear whether this was similarly true for male and female individuals because sex differences were not explored (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). As other studies revealed differences in interoceptive accuracy between male and female individuals (Bornemann and Singer, 2017; Grabauskaitė et al., 2017), it may be possible that interoceptive accuracy was differentially related to emotion regulation in male and female individuals (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015).

In the present study, we investigated whether the relationship between interoceptive accuracy and emotion regulation differed between male and female individuals. We assessed individuals' interoceptive accuracy with the same heartbeat detection task that has been used in previous studies (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). Individuals' emotion regulation was determined on basis of a widely used self-report questionnaire that assessed similar aspects of emotion regulation as in previous studies (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015), namely reappraisal and suppression. As previous studies employed a correlation-based approach to data analysis (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015), we also used correlation-based methods to compare the relationship of interoceptive accuracy and emotion regulation between male and female individuals. Individual characteristics that are known to affect the relationship between interoceptive accuracy and emotion regulation were under statistical control during data analysis, which has not been done in previous studies (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). Of particular interest were individual characteristics such as age (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in older than younger individuals; Khalsa et al., 2009b; Shiota and Levenson, 2009), body mass index (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in non-lean than lean individuals; Rouse et al., 1988; Andrei et al., 2018), psychopathology (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in mentally disordered than healthy individuals; Pollatos et al., 2009; Aldao and Nolen-Hoeksema, 2010), autism (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in autistic than non-autistic individuals; Samson et al., 2012; Garfinkel et al., 2016), empathy (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in non-empathetic than empathetic individuals; Lebowitz and Dovidio, 2015; Shah et al., 2017) and alexithymia (i.e., suppression use is more pronounced and interoceptive accuracy is more compromised in alexithymic than non-alexithymic individuals; Herbert et al., 2011; Laloyaux et al., 2015). These individual characteristics were assessed with self-report questionnaires. Our study design, thus, allowed us to investigate the relationship between interoceptive accuracy and emotion regulation in male and female individuals with more methodological rigor than in previous studies (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). We expected this relationship to be more pronounced in male than female individuals because interoceptive accuracy has previously been reported to be higher in male than female individuals (Bornemann and Singer, 2017; Grabauskaitė et al., 2017).

MATERIALS AND METHODS

Participants

Eighty-four individuals participated in the study which was part of a larger project investigating the interplay between interoceptive accuracy and emotion processing (Lischke et al., 2020). A screening questionnaire indicated that these individuals were aged between 18–35 years, native speakers and free of mental health problems that required psychotherapeutic treatment at the time of the study. Two individuals did not provide valid data, limiting the number of individuals that could be considered in the statistical analysis to 82 individuals. However, a power analysis (G*Power; Faul et al., 2009) indicated that a sample size of 34 male and 34 female individuals would be large enough to guarantee that meaningful relationships between interoceptive accuracy and emotion regulation could be detected in the statistical analysis ($\alpha = 0.05$, $1\text{-}\beta = 0.80$, $r = 0.40$, one-sided correlation analysis). All individuals provided written informed consent to the study procedures that were approved by the local ethics committee and carried out following the Declaration of Helsinki.

Procedure

Following a debriefing about the study procedure, individuals were seated in a chair and prepared for the heartbeat detection task (Schandry, 1981). After completion of the heartbeat detection task, self-report questionnaires were administered. The questionnaires assessed psychopathology (BSI-18; Franke et al., 2017), alexithymia (Toronto Alexithymia Scale, TAS-20; Franz

et al., 2008), autism (Autism Quotient, AQ-10; Allison et al., 2012), empathy (Emotional Contagion Scale, ECS; Doherty, 1997) and emotion regulation in terms of reappraisal and suppression (Affective Style Questionnaire, ASQ; Hofmann and Kashdan, 2010).

Heartbeat Detection Task

As outlined elsewhere in more detail (Schandry, 1981), individuals were asked to count their heartbeats during three different time intervals (25, 35, 45 s) while their heart rate was recorded with a portable heart rate monitor (Polar Electro Oy, Kempele, Finland). They were not informed about the length of the time intervals and they were not allowed to use any measure that facilitated their task performance. An established algorithm[1] was used to derive individuals' interoceptive accuracy from their task performance (Schandry, 1981).

Statistical Analyses

To account for deviations from normality, non-parametric analyses were performed. Sex-differences in individuals' demographical (age), anthropometric (body mass index) and psychological (psychopathology, alexithymia, autism, empathy, emotion regulation, and interoception) characteristics were investigated with Mann–Whitney tests (Monte Carlo Simulations with 10,000 samples). Sex-specific correlations between individuals' interoceptive accuracy and emotion regulation were investigated with Spearman correlations. To obtain unbiased correlation coefficients, partial correlations[2] were computed that controlled for differences in individuals' demographical (age), anthropometric (body mass index) and psychological (psychopathology, alexithymia, autism, and empathy) characteristics. The resulting correlation coefficients were compared with one another to confirm possible differences between the respective correlations (Steiger, 1980). The significance level for all analyses was set at $p \leq 0.05$, two-sided for Mann–Whitney tests and one-sided for Spearman correlations. In addition to the significance values (p), effect size measures (d, r, q) were determined to facilitate the interpretation of the analyses (Cohen, 1992). All analyses were performed with SPSS 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant Characteristics

Male and female individuals did not differ in demographical (age: $U = 736.50$, $p = 0.340$, $d = 0.21$; see **Table 1**) but anthropometric (body mass index: $U = 258.000$, $p \leq 0.001$, $d = 1.49$; see **Table 1**) characteristics: Male individuals were as old as female individuals but had a greater body mass index than female individuals. Male and female individuals also differed on certain psychological characteristics: psychopathology (BSI-18-GSI: $U = 817.50$, $p = 0.833$, $d = 0.05$; see **Table 1**) and autism (AQ-10: $U = 780.00$, $p = 0.557$, $d = 0.12$; see **Table 1**) was similarly pronounced among male and female individuals but alexithymia was more pronounced among male than female individuals (TAS-20: $U = 568.00$, $p = 0.012$, $d = 0.58$; see **Table 1**) and empathy was less pronounced among male than female individuals (ECS: $U = 336.50$, $p < 0.001$, $d = 1.21$; see **Table 1**). Emotion regulation was more pronounced among male than female individuals, with male individuals showing more reappraisal and, at least on a trend level, more suppression than female individuals (ASQ-REA: $U = 608.00$, $p = 0.029$, $d = 0.49$; ASQ-SUP: $U = 640.50$, $p = 0.058$, $d = 0.42$; see **Table 1**). Interoceptive accuracy was also more pronounced among male than female individuals (IAc: $U = 593.00$, $p = 0.024$, $d = 0.52$; see **Table 1**).

Relationship Between Interoceptive Accuracy and Emotion Regulation

Among female individuals, interoceptive accuracy was uncorrelated with emotion regulation: interoceptive accuracy neither correlated with reappraisal (ASQ-REA: $r_{(33)} = 0.04$, $p = 0.400$; see **Figure 1**) nor with suppression (ASQ-SUP: $r_{(33)} = -0.03$, $p = 0.423$; see **Figure 1**). Among male individuals', on the contrary, interoceptive accuracy correlated with emotion regulation: interoceptive accuracy correlated with suppression (ASQ-SUP: $r_{(33)} = 0.35$, $p = 0.02$; see **Figure 1**) but not with reappraisal (ASQ-REA: $r_{(33)} = -0.19$, $p = 0.141$; see **Figure 1**). A comparison of the correlation coefficients confirmed that interoceptive accuracy correlated with emotion regulation among male but not female individuals (ASQ-SUP: $z = 1.72$, $p = 0.043$, $q = 0.39$; ASQ-REA: $z = 0.07$, $p = 0.472$, $q = 0.02$) and that the correlation between interoception and emotion regulation among male individuals was true for suppression but not for reappraisal ($z = 1.61$, $p = 0.054$, $q = 0.30$).

DISCUSSION

In the present study, we investigated whether interoceptive accuracy was differentially related to emotion regulation in male and female individuals. Interoceptive accuracy was assessed with a well-established heartbeat detection task and emotion regulation was assessed with a widely used self-report questionnaire that differentiated between reappraisal and suppression. The relationship between interoceptive accuracy and the different emotion regulation strategies was investigated with correlation-based analyses. These analyses revealed sex- and strategy-specific correlations between interoceptive accuracy and emotion regulation. In male individuals, interoceptive accuracy correlated with suppression but not with reappraisal. In female individuals, on the contrary, interoceptive neither correlated with suppression nor with reappraisal. This pattern of correlations emerged in a series of well-powered and hypothesis-driven analyses, which involved a formal comparison of the respective correlation coefficients. The resulting test statistics corresponded to medium effect sizes, implying that we found a robust and meaningful relationship between interoceptive

[1]
$$\mathrm{IAc} = \frac{1}{3}\sum\left(1 - \frac{|n\,\mathrm{heartbeats}_{\mathrm{real}} - n\,\mathrm{heartbeats}_{\mathrm{counted}}|}{n\,\mathrm{heartbeats}_{\mathrm{real}}}\right)$$

[2] For the sake of completeness, full correlations were also computed. As can be seen in the **Supplementary Material**, similar results were obtained when full instead of partial correlations were used in the analyses.

TABLE 1 | Individual characteristics.

	Female individuals (n = 41)			Male individuals (n = 41)			Test statistic
	M	*SD*	Range	*M*	*SD*	Range	*p*
Age (years)	26.00	3.53	20.00–34.00	26.73	4.64	17.00–35.00	0.340
Body mass index (kg/m^2)	20.85	1.91	18.13–27.24	24.13	2.87	17.59–31.56	0.001***
Autism (AQ-10)	2.39	1.05	0.00–4.00	2.29	1.45	0.00–6.00	0.557
Empathy (ECS)	54.80	5.88	40.00–72.00	49.15	4.79	37.00–59.00	0.001***
Alexithymia (TAS-20)	39.85	10.13	20.00–65.00	44.63	10.38	25.00–67.00	0.012**
Psychopathology (BSI-18-GSI)	0.45	0.40	0.00–1.44	0.38	0.27	0.00–0.94	0.833
Emotion regulation (ASQ)							
Suppression (ASQ-SUP)	2.65	0.71	1.00–4.11	2.92	0.61	1.78–4.00	0.058†
Reappraisal (ASQ-REA)	3.43	0.66	2.20–5.00	3.73	0.57	2.60–4.80	0.029*
Interoceptive accuracy (IAc)	0.61	0.18	0.31–0.94	0.70	0.16	0.42–0.98	0.024*

*Note. ECS, Emotional Contagion Scale (Doherty, 1997); AQ-10, Autism Quotient 10 (Allison et al., 2012); TAS-20, Toronto Alexithymia Scale 20 (Franz et al., 2008); BSI-18-GSI, Brief Symptom Inventory 18–Global Severity Index (Franke et al., 2017); ASQ, Affective Style Questionnaire (Hofmann and Kashdan, 2010); ASQ-SUP, Affective Style Questionnaire—Suppression (Hofmann and Kashdan, 2010); ASQ-REA, Affective Style Questionnaire—Reappraisal (Hofmann and Kashdan, 2010); IAc, Interoceptive accuracy (Schandry, 1981). ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$, $^{\dagger}p \leq 0.10$.*

accuracy and emotion regulation in terms of suppression but not reappraisal in male as compared to female individuals. The positive nature of this relationship suggests that male individuals with high interoceptive accuracy were more likely to use suppression for emotion regulation than male individuals with low interoceptive accuracy.

Previous studies also reported a positive relationship between interoceptive accuracy and emotion regulation (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). However, not all of these studies differentiated between reappraisal and suppression in their analyses, which complicates a comparison of the respective findings. The findings of the present study are, nonetheless, broadly consistent with the findings of those studies that performed similar analyses (Füstös et al., 2013; Kever et al., 2015). These studies found a relationship between interoceptive accuracy and suppression that was similar to the one that was found in the present study (Kever et al., 2015). However, these studies also found a relationship between interoceptive accuracy and reappraisal (Füstös et al., 2013; Kever et al., 2015), which was not found in the present study. There are several methodological differences between these studies that may account for the divergence of findings (e.g., differences in the size and composition of the samples, differences in the assessment of interoceptive accuracy and emotion regulation, differences in the analysis of the relationship between interoceptive accuracy and emotion regulation). One of the most striking differences is the differentiation between male and female individuals in the analyses (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015), which has only been done in the present study. Sex-differences in interoceptive accuracy and emotion regulation have already been shown in previous studies (Graser et al., 2012; Bornemann and Singer, 2017; Erreygers and Spooren, 2017; Grabauskaitė et al., 2017): Male individuals were more accurate in interoceptive accuracy (Bornemann and Singer, 2017; Grabauskaitė et al., 2017) and more engaged in suppression and reappraisal for emotion regulation (Graser et al., 2012; Erreygers and Spooren, 2017) than female individuals. We found similar sex-differences in interoceptive accuracy and emotion regulation in the present study, indicating the need to consider sex-differences when analyzing the

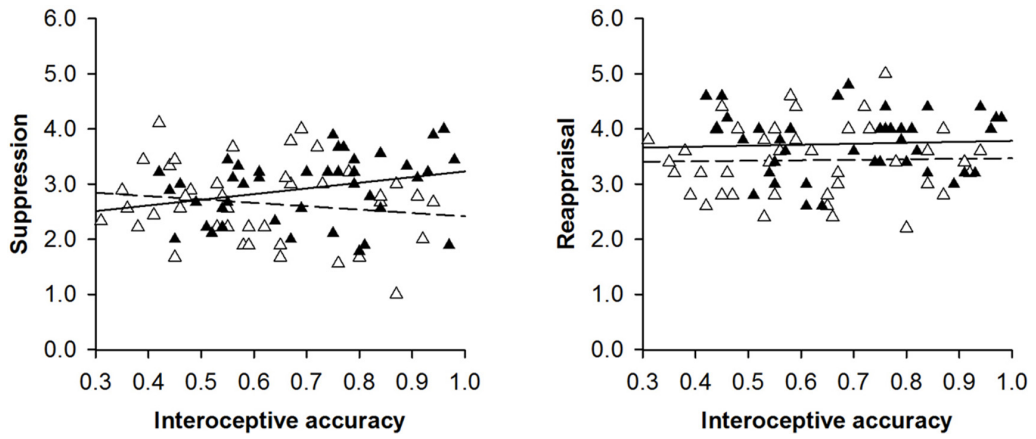

FIGURE 1 | Scatterplots with lines of best fit demonstrating the relationship between interoceptive accuracy and reappraisal or suppression among female (white triangles and dashed lines) and male (black triangles and solid lines) individuals. For visualization purposes, raw data was used.

relationship between interoceptive accuracy and emotion regulation. However, male and female individuals may also differ in other characteristics that affect the relationship between interoceptive accuracy and emotion regulation, like, for example, empathy (Doherty, 1997), alexithymia (Franz et al., 2008), autism (Baron-Cohen et al., 2001) or psychopathology (Franke et al., 2017). Consequently, we not only considered individuals' sex in our analyses but also controlled our analyses for differences in individuals' sociodemographic (age), anthropometric (body mass index) and psychological (psychopathology, autism, alexithymia, and alexithymia) characteristics. As could be expected on basis of other studies showing more interoceptive accuracy and more suppression in male as compared to female individuals (Abler and Kessler, 2009; Graser et al., 2012; Bornemann and Singer, 2017; Grabauskaitė et al., 2017), we found interoceptive accuracy to be related to suppression but not reappraisal in male as compared to female individuals. Considering the methodological rigor that we applied to these analyses, it seems reasonable to assume that the divergent findings of the present and previous studies are due to methodological differences in data analysis (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). It should be noted, however, that the present and previous studies used correlation-based methods for data analysis. As a consequence, we cannot make causal inferences about the relationship between interoceptive accuracy and suppression or reappraisal in male and female individuals. We, thus, recommend the use of other methods in future studies. Future studies that employ experimental methods, like, for example, the use of pharmacological agents for the manipulation of interoceptive and emotional processes (Khalsa et al., 2009a) or the use of emotion regulation tasks for the manipulation of interoceptive and emotional processes (Füstös et al., 2013), may help to gain more insights into the sex- and the strategy-specific relationship between interoceptive accuracy and emotion regulation.

Notwithstanding these methodological considerations, the findings of the present study can also be explained on basis of theoretical considerations that pertain to the definition of the different emotion regulation strategies (Gross and John, 2003): Reappraisal involves a re-interpretation of emotional experiences that takes place at the cognitive level, whereas suppression involves an inhibition of emotional experiences that takes place on the autonomic and behavioral level. Based on this definition, it could be expected that reappraisal and suppression engage different but overlapping brain regions for the regulation of emotional experiences. Studies investigating the neural correlates of suppression and reappraisal identified a network of brain regions that comprised prefrontal brain regions like the ventral and dorsal prefrontal cortex or the dorsal anterior cingulate cortex (Goldin et al., 2008; Hayes et al., 2010; Giuliani et al., 2011a) and (para-)limbic brain regions like the amygdala or insula (Goldin et al., 2008; Hayes et al., 2010; Giuliani et al., 2011b). Although most of these brain regions were engaged during both emotion regulation strategies (Goldin et al., 2008; Hayes et al., 2010; Giuliani et al., 2011a,b), the insula was more engaged during suppression than reappraisal in these studies (Goldin et al., 2008; Hayes et al., 2010; Giuliani et al., 2011b). However, the insula has also been shown to be engaged during interoception (Critchley et al., 2004; Pollatos et al., 2007a,b; Zaki et al., 2012; Ronchi et al., 2015), in particular in studies that investigated the relationship between interoceptive and emotional experiences (Critchley et al., 2004; Zaki et al., 2012). Due to the aforementioned differences in insula engagement during suppression and reappraisal (Goldin et al., 2008; Hayes et al., 2010; Giuliani et al., 2011b), it could be expected that interoception, which also involved insula engagement (Critchley et al., 2004; Zaki et al., 2012), would be more related to suppression than to reappraisal. Moreover, it could even be expected that this relationship would be more pronounced for male than female individuals because male individuals have been reported to show more insula engagement than female individuals (Lee et al., 2005; Biswal et al., 2010). These expectations were confirmed in the present study where we found interoceptive accuracy to be related to suppression but not to reappraisal in male as compared to female individuals, presumably due to sex- and strategy-specific differences in insula engagement during the integration of interoceptive and emotional experiences. It should be noted, however, that studies investigating sex- and strategy-specific differences in insula engagement during interoception and emotion regulation are scarce. As a consequence, it remains to be determined in future studies whether sex- and strategy-specific differences in insula engagement in fact account for sex- and strategy-specific relationships between interoception and emotion regulation. Considering the complexity of the processes involved in the regulation and experience of interoceptive and emotional phenomena (Pace-Schott et al., 2019), it may be possible that the interplay between interoception and emotion regulation is far more complex than can be assumed on basis of the present study. To address this issue, future studies are warranted that combine subjective measures (e.g., emotion regulation questionnaires) and objective measures (e.g., recordings of neural and autonomic changes during emotion regulation tasks) of interoception and emotion regulation in their investigations.

Given that we found a relationship between interoception and suppression but not reappraisal in male as compared to female individuals, we asked ourselves whether this relationship would be adaptive or maladaptive for these individuals. As previous studies revealed more mental health problems in individuals who used suppression than reappraisal for emotion regulation (Gross, 1998; Moore et al., 2008; Hofmann et al., 2009; Aldao and Nolen-Hoeksema, 2010; Brans et al., 2013), it may be possible that we found a maladaptive rather than adaptive relationship between interoceptive accuracy and emotion regulation. However, the findings of the aforementioned studies have been challenged by the findings of studies that used a more sophisticated methodology to investigate the effects of different emotion regulation strategies on mental health (Bonanno et al., 2004; Troy et al., 2010; Westphal et al., 2010; Meyer et al., 2012; Kalokerinos et al., 2015). These studies suggest that it may depend on the person- and/or context-related factors whether the use of a particular emotion strategy leads to more or less mental health problems (Kashdan and Rottenberg, 2010; Bonanno and Burton, 2013; Sheppes et al.,

2015). Consequently, it may be premature to assume that the relationship between interoceptive accuracy and suppression was maladaptive for the individuals of the present study. As none of these individuals reported mental health problems that required psychotherapeutic treatment, it may even be more likely that this relationship was adaptive rather than maladaptive for these individuals. It should be noted, however, that we relied on self-report measures to determine the presence of mental health problems and the utilization of the mental health system. Future studies should use observer-based measures, like, for example, structured interviews and expert ratings (Lischke et al., 2017), to determine mental health problems and mental health system utilization. These types of studies may help to determine whether the sex- and strategy-specific relationship between interoception and emotion regulation is adaptive or maladaptive for individuals.

Coming to an end, we would like to point out that the findings of the present study replicate and extend the findings of previous studies that also investigated the relationship between interoceptive accuracy and emotion regulation (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). In contrast to previous studies (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015), we differentiated between male and female individuals in our analyses and controlled our analyses for individual characteristics that may affect this relationship. As could be expected on basis of previous studies reporting differences in interoception and emotion regulation between male and female individuals (Abler and Kessler, 2009; Graser et al., 2012; Bornemann and Singer, 2017; Grabauskaitė et al., 2017), we found interoceptive accuracy to be related to suppression but not reappraisal in male as compared to female individuals. We, thus, believe that future studies investigating the relationship between interoceptive accuracy and emotion regulation may benefit from employing a similar methodological approach as the one that we employed in the present study. These types of studies may help to further refine the findings of previous studies that suggested a less complex relationship between interoceptive accuracy and emotion regulation than the findings of the present study (Füstös et al., 2013; Weiss et al., 2014; Kever et al., 2015). Nonetheless, the extant findings already support historic and contemporary views that the perception and interpretation of autonomic changes are relevant for the *experience* and *regulation* of emotions (James, 1884; Critchley and Garfinkel, 2017).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on reasonable request to the corresponding author.

ETHICS STATEMENT

The study was reviewed and approved by the Ethics committee of the University of Rostock. The participants provided their written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

AL, RP, and MW designed the study. AM-M and RJ collected the data. AL, MW, and RP analyzed the data. AL and RP wrote the manuscript. AM-M, MW, and RJ contributed to writing, reviewing and editing of the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.00067/full#supplementary-material.

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Humor Improves Women's but Impairs Men's Iowa Gambling Task Performance

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The Iowa Gambling Task (IGT) is a popular method for examining real-life decision-making. Research has shown gender related differences in performance, in that men consistently outperform women. It has been suggested that these performance differences are related to decreased emotional control in women compared to men. Given the likely role of emotion in these gender differences, in the present study, we examine the effect of a humor induction on IGT performance and whether the effect of humor is moderated by gender. IGT performance and parameters from the Expectancy Valence Model (EVM) were measured in 68 university students (34 men; mean age 22.02, SD = 4.3 and 34 women; mean age 22.3, SD = 4.1) during a 100 trial-IGT task. Participants were exposed to a brief video before each of the IGT decisions available; one half of the samples (17 men and 17 women) was exposed to 100 humor videos, while the other half was exposed to 100 non-humor videos during the task. We observed a significant interaction between gender and humor, such that under humor, women's performance during the last block (trials 80–100) improved (compared to women under non-humor), whereas men's performance during the last block was worse (compared to men under non-humor). Consistent with previous work, under non-humor, men outperformed women in the last block. Lastly, our EVM results show that humor impacts the learning mechanisms of decision-making differently in men and women. Humor impaired men's ability to acquire knowledge about the payoff structure of the decks, and as a consequence, they were stuck in suboptimal performance. On the other hand, humor facilitated women's ability to explore and to learn from experience, improving performance. These findings deepen our understanding of the mechanisms underlying IGT decision-making and differential effects of humor in men and women.

Keywords: decision-making, humor, gender differences, Iowa gambling task, cognitive control

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INTRODUCTION

In addition to performing other computations, the brain can be considered a decision-making device, such that perceptual, mnemonic, and motor capabilities evolved to support the decisions that lead to adaptive actions (Gazzaniga, 2014). One of the most popular tasks to measure decision-making is the Iowa Gambling Task (IGT; Bechara et al., 1994; Hooper et al., 2004),

which mimics real-life decision-making in several ways. During the IGT, participants choose from four decks of cards. Each deck yields a fixed, predetermined proportion of monetary punishments and rewards. Participants learn, through exploration, which deck (or decks) will allow them to maximize their earnings as they play, based on their experience receiving feedback from the decks on each trial. Good total performance results from discriminating between "advantageous" (low risk decks) and "disadvantageous" (high risk decks). While total performance is informative, the Expectancy Valence Model (EVM) allows for the separate characterization of three different candidate mechanisms that each influence performance. Namely, three parameters ("*w*", "*a*", and "*c*") can be computed (Busemeyer and Stout, 2002). The parameter "*w*" indicates the extent to which participants are more motivated by rewards or by punishments. The parameter "*a*" indicates the extent to which participants learn by updating their expected valences (the expected monetary net profit for each deck) with experience, or whether the initial expected valences remain influential. Finally, the parameter "*c*" indicates the extent to which participants use the expected valences to guide their decisions, or whether their choices are random. Therefore, by computing these parameters, we have a more nuanced understanding of individual and group differences in task performance.

The idea that emotions are relevant during IGT learning is well-established (van den Bos et al., 2013). According to the Somatic Marker Hypothesis (Bechara et al., 1996), emotions signal how likely it is to obtain punishment or reward, guiding decision-making in situations of complexity and uncertainty (Bechara and Damasio, 2005). According to this theoretical framework, decision-making depends on two neural systems: emotional and cognitive (Bechara, 2005). The emotional system encompasses the orbitofrontal cortex (OFC), the amygdala, and the ventral striatum/nucleus accumbens (Bechara, 2005). The cognitive system encompasses the dorsolateral prefrontal cortex (dlPFC), the anterior cingulate cortex (ACC), and the dorsal striatum (Bechara, 2005; van den Bos et al., 2013). The emotional system signals the actual or anticipated pain or pleasure of feedback, while the cognitive system allows for control of decisional behavior, often by suppressing the activity of the emotional system during the last blocks of the task (Bechara, 2005; van den Bos et al., 2013).

There is consistent evidence that there are gender differences in IGT performance (Reavis and Overman, 2001; Bolla et al., 2004; Overman et al., 2006; Weller et al., 2010). Research shows that, compared to men, during the IGT, women usually obtain less money and need more trials to consistently choose the advantageous decks (Bolla et al., 2004; Weller et al., 2010). Additionally, neurobiological evidence indicates that compared to men, women show hypoactivation of several brain structures (i.e., OFC, dlPFC, and nucleus accumbens) while solving the IGT (see van den Bos et al., 2013). For instance, women exhibit less activation of right lateral orbitofrontal cortex (l-OFC), instead engaging the left medial orbitofrontal (mOFC); by contrast, men exhibit extensive activation of both the right and the left l-OFC (Bolla et al., 2004). The m-OFC seems to be implicated in processing regular patterns, comparing options which are close in reward value, with a focus on more immediate rewards. In contrast, the l-OFC has been implicated in processing with irregular patterns, valuing, and adjusting choice behavior as contingencies change with a focus on long-term rewards (Byrnes et al., 1999; Hooper et al., 2004; Frank and Claus, 2006). Therefore, gender differences in OFC activation may indicate that, women would focus more on immediate and regular patterns of choices than on irregular ones; by contrast, men would focus on irregular patterns of choices. This could help explain why women may need more trials than men before they adjust their choice behavior (Overman et al., 2011). Additionally, gender differences in the activation of the ventral striatum/nucleus accumbens during the IGT have also been reported (van den Bos et al., 2012; Van Hasselt et al., 2012). Namely, women show hypoactivation of ventral striatum/nucleus accumbens than men during IGT. The ventral striatum/nucleus accumbens is involved in reward learning, especially during the initial blocks of the task (Bechara, 2005). However, as the task progresses, activation of brain structures sensitive to short-term reward decreases, and brain structures associated to long-term advantageous choices control the task (Bechara, 2005).

There is evidence suggesting that brain structures hypoactivated by women during the IGT are functionally connected (see Azim et al., 2005; van den Bos et al., 2013) and involved in the transition from emotional to cognitive control during the IGT (Gray et al., 2002; Ueda et al., 2003; Tanaka et al., 2007, 2016; Doya, 2008; Homberg et al., 2008). Therefore, women's IGT performance could benefit from any intervention that increases the activation of these key brain structures and, as a result, strengthens the transition from emotional to cognitive control. We suggest that humor could be a good candidate.

Humor is a pleasurable and enjoyable experience associated with reward activity (Mobbs et al., 2003) that most scientists consider an extension of social play (Martin, 2007). The difference between humor and other types of social play is that, when we are experiencing humor, we are not playing with physical objects but with concepts and ideas that resolve seeming contradictions (Gervais and Wilson, 2005). Humorous "resolutions" often do not actually make sense in the real world, and they are a way of playing creatively with the cognitive mechanisms that we normally use in more serious contexts (Forabosco, 1992).

Women seem to hyperactivate some humor-related brain structures compared to men (Weinberger, 1993; Diekamp et al., 2002; Gray et al., 2002; Ueda et al., 2003; Azim et al., 2005). Moreover, some of the brain structures than women activate more than men when processing humor are the same structures that seem to be hypoactivated when women perform the IGT. For instance, there is evidence that under humorous conditions, women show greater activation of nucleus accumbens and recruit left prefrontal cortex more strongly than men, suggesting a larger reward network response (Azim et al., 2005). As such, it has been suggested that humor may increase women's cognitive control through a dopaminergic pathway (Weinberger, 1993; Gray et al., 2002; Ueda et al., 2003; Azim et al., 2005). Generally, reward-related dopamine is likely to exert a multi-faceted influence upon decision-making, through the activity of its forward afferents along the mesolimbic, striatal, and cortical

pathways, with the nucleus accumbens playing a pivotal role in action selection (Everitt and Robbins, 2005). According to psychopharmacology research, dopamine activity can influence decision-making by modulating what is learned about the value of an outcome (Lidow et al., 1991; Goldman-Rakic et al., 1992; Frank et al., 2007; Schwartenbeck et al., 2014). If so, humor may facilitate reward learning in women, but not necessarily in men. However, this hypothesis remains to be tested.

The main objective of the present study was to examine the effect of humor on IGT performance and whether the effect of humor is moderated by gender. Humor was induced by asking participants in an experimental condition to watch humorous videos interspersed with the IGT. Participants under a control condition watched non-humor videos instead. Informed by previous research, we hypothesized that humor would increase women's IGT performance. Therefore, we predicted that women in the humor condition would choose more cards from advantageous decks than women in the non-humor condition, specifically toward the end of the task (namely during blocks three, four, and five), because we hypothesize that humor will facilitate the transition from emotional control to cognitive control (Bechara, 2005). By contrast, humor should not affect men's IGT performance. Therefore, we did not expect to find statistically significant differences between men in the humor and non-humor conditions in the number of cards chosen from advantageous decks. As mentioned above, in previous studies, men have achieved higher IGT performance than women (Bolla et al., 2004; Weller et al., 2010). These gender differences occur only during the last blocks of the task (namely during blocks three, four, and five; Reavis and Overman, 2001; Overman et al., 2006; Weller et al., 2010). Therefore, we expect to find that the women in the non-humor condition will choose less advantageous deck cards than the men in the non-humor condition, specifically, at blocks three, four, and five. Finally, the effect of humor on the processes underlying IGT decision-making will also be explored from the EVM perspective, which, to our knowledge, has not been previously done and could potentially help us understand gender differences in performance.

METHOD

Participants

Inclusion criteria for participation were (1) being an undergraduate student at the Pontificia Universidad Católica de Chile, (2) being older than 18 years old, (2) speaking Spanish, and (3) having normal or corrected-to-normal vision[1]. Exclusion criteria were (1) reporting severe depressive symptomatology according to the Self-Report Questionnaire (SRQ) (Harding et al., 1980; Vielma et al., 1994), (2) reporting the presence a neurological disorder, (3) reporting a history of drug abuse, and (4) reporting having consumed alcohol, caffeine or drugs 24 h before participating in the experimental task.

In order to estimate the sample size, we used the software G* Power 3.1 with parameters for large effect size *F*s (0.40), a probability error α (0.05), and a statistical power of (0.80), which leads to a minimum of 52 participants (26 women and 26 men). Nonetheless, when we reached the sample size of 26 women, there were not still enough men enrolled, so we decided to continue the recruitment till we get an equivalent number of men and women. As such, 72 participants (37 women and 35 men) completed the study. Data from four of these participants (one man and three women) were excluded from the analyses because they did not fulfill all participation criteria. Namely, one of these participants reported having consumed drugs before the experiments and three reported severe depressive symptomatology according to the SRQ. Therefore, we finally analyzed the data of 68 participants (34 men; mean age 22.02, SD = 4.3 and 34 women; mean age 22.3, SD = 4.1).

Questionnaires

The Self-Report Questionnaire (Harding et al., 1980) was used to assess depressive symptomatology. It consists of 25 yes/no questions. The SRQ has been validated for the Chilean population (Vielma et al., 1994). Subjects scoring higher than 11 points or answering affirmatively questions 21–25 (elevated probability of depressive symptomatology) were not included in the study sample, as depression has shown to affect decision-making (Dalgleish et al., 2004; Battersby et al., 2006).

The State-Trait Anxiety Inventory (STAI) (Spielberger, 1970) was used to assess anxiety symptoms. It consists of 40 questions divided into two subscales: state anxiety (SA) and trait anxiety (TA). The STAI has been validated for Chilean population (Vera-Villarroel et al., 2007). We assessed this variable because higher trait anxiety scores are related to impairments in decision-making and could potentially affect our results (Miu et al., 2008).

Humorous and Non-humorous Videos

To induce humor, we selected 200 videos (100 humorous and 100 non-humorous) from 240 public access videos (120 humorous and 120 non-humorous) available at www.youtube.com. Selection criteria were the presence or absence of humor in ecological situations [i.e., humorous videos depicted situations with non-sensical or with incongruity resolution structure while non-humor videos depicted mundane situations in which nothing of any emotional impact occurred (e.g., mowing the lawn, walking down the street)], and an adequate duration of stimuli to present a video before each decision (raw video mean duration = 12.84 s; video SD = 5.81 s). The total 240 videos were presented in a randomized order to 50 subjects (25 men and 25 women) who were not part of the present sample. We asked them to rate the videos using a humor scale ranging from 0 to 10 points (0 "not humorous at all"; 10 "the most humorous thing ever"). We eliminated all the videos that showed significant differences in ratings between men and women, as well as those less than three standard

[1]In the present study we did not measure separately Sex and Gender. We will assume participants responses about their sexual identity refer to gender (i.e., men and women) instead of sex (male and female). Data regarding the participants specific gender identities were not collected.

deviations away from the mean of the opposite condition, which resulted in the elimination of 40 videos (20 humorous and 20 non-humorous). The final video selection consisted of 100 humorous and 100 non-humorous videos. Men (*humor*: mean = 4.18, SD = 0.51; *non-humor*: mean = 1.50, SD = 0.25). Women (*humor*: mean = 4.24, SD = 0.46; *non-humor*: mean = 1.51, SD = 0.23). To examine whether there were statistically significant differences in the video ratings, we conducted a two-way factorial ANOVA (Gender × Video type [humor/non-humor]). Results showed a main effect of video type ($F_{1,198}$ = 220, $p < 0.001$, η^2 = 0.917), indicating that humorous videos were rated as significantly more humorous than non-humorous videos. Neither the main effect of Gender nor the interaction (Gender × Video type) was statistically significant. Humorous videos were assigned to the experimental group and non-humorous videos to the control group. The mean duration of the final selection of the videos was 12.91 (SD = 5.89) and 10.41 s (SD = 5.03) for the humorous and the non-humorous videos, respectively[2].

The Iowa Gambling Task

The IGT was designed as a realistic decision-making task (Bechara et al., 1994; Hooper et al., 2004). On each trial, participants choose a card from one of four card decks (A, B, C, and D). After each choice, participants are rewarded with virtual money (reward) or punished with a loss of virtual money (punishment). Participants must learn as they play which are the advantageous and disadvantageous decks to solve the task and maximize earnings. Participants can change decks at will; however, they are warned that some decks are worse than others in terms of total payment, and that the win/loss proportions and amounts stay fixed within each deck. Likewise, they are informed that the goal is to win as much money as they can, or to avoid losing money as much as possible.

Card decks A and B are monetarily risky/disadvantageous, and C and D are monetarily safe/advantageous. Card decks A and B are associated with large, immediate rewards (e.g., $100) but continuing to select from these decks results in accumulating less profit, or loss, because of occasional, large monetary punishments. Choosing from card decks A and B leads to a net loss of $250 during the first 10 trials. By contrast, card decks C and D are associated with small immediate rewards (e.g., $50) but with small monetary punishments. Continuing to select from these decks results in accumulating more profit, and choosing from decks C and D leads to a net gain of $250 during the first 10 trials.

An outcome score was calculated by subtracting the total number of cards selected from the disadvantageous decks (A + B) from the total number of cards selected. The remaining cards are from the advantageous decks (C + D) for each of the 5 sets of 20 choices, called blocks (Bolla et al., 2004; Overman et al., 2006; Weller et al., 2010).

[2]All videos used in the current study are available at the following link: https://www.dropbox.com/sh/qc8n4f2j6v594xs/AABcN7cnh_W-QY3s9KCdpiRHa?dl=0

Procedure

The Ethics Committee of the Pontificia Universidad Católica de Chile (PUC) approved the study. All experiments were performed at the Neuro-dynamic Laboratory of the School of Psychology of the PUC. We recruited participants for the study through an advertisement published in the PUC student website. Those interested in participation were informed about the inclusion and exclusion criteria and provided with more study details *via* email. If they reported that they met the inclusion criteria, we finally invited them to come to the lab.

In-lab session, first, we provided participants with more details about the study and completed the informed consent process. Next, participants completed a battery of questionnaires comprised of the SRQ and STAI-t. Then, they sat down in a comfortable chair in front of a computer screen and completed the IGT. Task instructions were presented in writing on the computer screen. The distance from participant's eyes to computer screen was 60 cm, visual angle 4.7°. Study duration was approximately 1 h. Participants received one movie ticket in compensation for participation.

Each trial began with the word "*video*," which appeared on the screen for 1,500 ms. Then the video itself appeared, followed by a decision-making trial. During these trials, participants saw four deck options (labeled A, B, C, and D) and chose one by clicking on the deck with a USB mouse. When participants selected a deck, its perimeter lit up in red. After that, the screen changed to black for 200 ms, after which, the feedback appeared for 2,000 ms. Feedback could be a win (e.g., you won +100) or a win and a loss (e.g., you won 100, but lost −50). Each card's feedback depended on the probabilities according to IGT manual (Bechara, 2007). During the screen showing the four deck options, on the central superior area of the screen, two bars appeared. A green bar showed cumulative wins and losses and a red bar represented the amount of money they owed (all participants started the task with $2,000 CLP virtual money). After feedback, these bars automatically updated according to the feedback on that trial. We emphasized to participants that positions and deck contingencies were fixed during the whole task, that they could change decks at will, and that there was no association whatsoever between the videos and the decks. Participants had no specific information about how to solve the task, nor did they know how long it would take. Participants completed 100 videos and 100 trials (divided into 5 blocks of 20 trials each).

Calculation of Expectancy Valence Model Parameter

The EVM is a reinforced learning model. It produces three cognitive processes parameters, "*w*", "*a*", and "*c*". According to Wetzels et al., 2010, the model assumes that, after selecting a card from deck *k*, $k \in \{1, 2, 3, 4\}$ on trial *t*, participants calculate the resulting net profit or valence. This valence v_k is a combination of the experienced reward W(*t*) and the experienced loss L(*t*):

$$v_k(t) = (1-w)W(t) + \mathrm{w} \cdot L(t) \quad (1)$$

This equation uses the EVM parameter "*w*," which provides information about whether participants pay more attention to, or are more motivated by, rewards compared to punishments. Values of "*w*" range between 0 and 1. Values lower than 0.50 are indicative of being relatively more motivated by rewards than by punishments, whereas values higher than 0.50 are indicative of being relatively more motivated by punishments than by rewards, and values equal to 0.50 are indicative of being equally motivated by rewards and punishments (Wetzels et al., 2010).

Based on the sequence of valences v_k experienced previously, the participants form an expectation Ev_k of the valence for deck *k*. Learning occurs when new feedback changes the value of the expected valence Ev_k. In a given time *t*, if the experienced valence differs from the expected one, then the value Ev_k needs to be adjusted. The way the value is adjusted is given by the following equation:

$$Ev_k(t+1) = Ev_k(t) + \alpha \cdot \left(v_k(t) - Ev_k(t)\right) \quad (2)$$

In this equation, the updating rate $\alpha \in [0, 1]$ determines the impact of recently experienced valences. Opting for the deck with the highest expected valence is a "greedy" strategy that in the long run can lead to a suboptimal solution, given it involves little exploration. To ensure initial deck exploration from the participants, an additional equation is added to the model. The equation is a standard reinforcement learning method called softmax selection or Boltzman exploration:

$$\Pr\left[S_k(t+1)\right] = \frac{\exp\left(\theta(t)Ev_k\right)}{\sum_{j=1}^{4}\exp\left(\theta(t)Ev_j\right)} \quad (3)$$

In this equation, $\frac{1}{\theta(t)}$ is the "temperature" at the trial *t*, and $\Pr(S_k)$ is the probability of selecting a card from deck *k*. Higher temperatures mean more random decisions, which means a higher level of exploration, while lower temperatures mean less exploration, and more exploitation of the decks with higher expected valences. A temperature of zero indicates the participant decides only based on expected valence, choosing the deck with the highest expected valence.

In the EV model, the temperature changes, given the number of observations, according to the following formula:

$$\theta(t) = \left(\frac{t}{10}\right)^{c} \quad (4)$$

where "*c*" is the response consistency or sensitivity parameter (also called the exploration parameter). When fitting to data, the parameter is constrained to the interval [−5, 5]. Positive values of "*c*" make response consistency θ values increase with the number of observations, which means $1/\theta$ values will decrease. This leads to lower "temperatures," meaning choices are guided more by expected valences. Negative values of "*c*" mean choices will become more and more random as the number of cards selected increases.

Being "*i*" a given participant, the current IGT study calculated participant's specific parameters "w_i," "a_i," and "c_i" by minimizing the sum of the one-step-ahead prediction errors:

$$\sum_{t=1}^{T} -\ln p\left(y_t | y^{t-1}, w_i, a_i, c_i\right) \quad (5)$$

DATA ANALYSIS

Trait anxiety has been shown to affect IGT performance, and women report more trait anxiety than men (Miu et al., 2008); therefore, to examine whether there were differences between the groups in this variable, we first conducted a two-way factorial ANOVA [Gender × Condition (Humor/Non-humor)] in which the dependent variable was trait anxiety. The main effect of Gender, the main effect of Condition, and the interaction were not statistically significant, indicating that there were no significant differences in trait anxiety among groups. Therefore, this variable was not considered in further analyses.

In order to examine the effect of humor on IGT performance and whether the effect of humor differed by Gender, we conducted a three-way ANOVA (Gender × Condition × Blocks) considering as the dependent variable the number of advantageous deck cards chosen (C + D). In addition, in order to explore the effect of humor in the three cognitive latent processes ("*w*," "*a*," and "*c*") underling decision-making, we performed a two-way (Gender × Condition) MANOVA. Prior to conducting these analyses,

TABLE 1 | Descriptive statistics for IGT performance.

		Experimental (*n* = 34)	Control (*n* = 34)
		***M* (SD)**	***M* (SD)**
Men (*n* = 34)	B1	8.12 (2.29)	9.12 (1.93)
	B2	8.41 (2.57)	9.71 (3.33)
	B3	10.06 (1.95)	10.59 (2.40)
	B4	10.71 (2.93)	7.71 (3.74)
	B5	9.47 (1.59)	11.71 (3.90)
Women (*n* = 34)	B1	9.94 (1.68)	10.29 (1.49)
	B2	12.18 (3.97)	10.06 (2.11)
	B3	11.65 (3.77)	9.82 (1.63)
	B4	11.00 (3.55)	11.00 (2.52)
	B5	11.65 (4.43)	9.06 (2.56)

TABLE 2 | Descriptive statistics for Expectancy Valence Model.

		Experimental (*n* = 34)	Control (*n* = 34)
		***M* (SD)**	***M* (SD)**
Men (*n* = 34)	Parameter "*w*"	0.44 (0.41)	0.48 (0.40)
	Parameter "*a*"	0.0003 (0.00039)	0.003 (0.003)
	Parameter "*c*"	−1.4 (1.19)	−0.97 (0.64)
Women (*n* = 34)	Parameter "*w*"	0.08 (0.09)	0.17 (0.21)
	Parameter "*a*"	0.0016 (0.0018)	0.0004 (0.00048)
	Parameter "*c*"	−0.41 (1.21)	−0.39 (1.35)

we checked normality, linearity, and sphericity assumptions. When needed, outliers were replaced using the mean plus two standard deviations method recommended by Field (2013). In case the sphericity assumption was violated, we used the parameter ε Greenhouse-Geisser to correct for such violations. We applied a Bonferroni correction to *post-hoc* comparisons. **Table 1** shows descriptive statistics for IGT performance and **Table 2** shows descriptive statistics for Expectancy Valence Model.

RESULTS

Differences in Iowa Gambling Task Performance

The result of the three-way ANOVA (Condition × Gender × Block) revealed a significant main effect of Gender ($F_{1, 64} = 4.35$, $p = 0.04$, *partial* $\eta^2 = 0.06$) indicating that men chose fewer cards from advantageous decks than women overall. There was a significant main effect of Block ($F_{3.39, 217.07} = 3.42$, $p = 0.014$, *partial* $\eta^2 = 0.05$), indicating that participants improved their performance across the task. Neither the main effect of Condition ($F_{1, 64} = 0.60$, $p = 0.44$, *partial* $\eta^2 = 0.00$) nor the interaction of Gender × Condition ($F_{1, 64} = 2.41$, $p = 0.13$, *partial* $\eta^2 = 0.04$) were statistically significant. However, the interaction of Gender × Block was statistically significant ($F_{3.39, 217.07} = 9.05$, $p < 0.001$, *partial* $\eta^2 = 0.12$), indicating that men chose fewer cards from advantageous decks than women at block four ($t = -2.98$, $p < 0.01$, *partial* $\eta^2 = 0.12$) but more from advantageous decks at block five ($t = 2.33$, $p = 0.02$, *partial* $\eta^2 = 0.08$) collapsing across condition. Critically, the Block × Condition × Gender interaction was statistically significant ($F_{3.39, 217.07} = 9.05$, $p < 0.001$, *partial* $\eta^2 = 0.12$) indicating that women in the experimental (humor) condition selected more cards from the advantageous decks than women in the control (non-humor) condition by block five ($t = 2.09$, $p = 0.04$, *partial* $\eta^2 = 0.06$). See **Figure 1A**. The situation for the men was very different. Men in the humor condition chose more cards from advantageous decks than those in the non-humor condition during block four ($t = 2.60$, $p = 0.01$, *partial* $\eta^2 = 0.18$), but during block five, the situation reversed completely, and men in the non-humor condition chose more advantageous deck cards than those in the humor condition ($t = -2.19$, $p = 0.04$, *partial* $\eta^2 = 0.13$) (see **Figure 1B**). Directly comparing men and women, in the non-humor condition, men chose fewer cards from the advantageous decks than women at block four ($t = -3.01$, $p < 0.01$, *partial* $\eta^2 = 0.22$), but at block five, men in the non-humor condition chose more cards from advantageous decks than women in the non-humor condition ($t = 2.34$, $p = 0.03$, *partial* $\eta^2 = 0.15$) (see **Figure 2A**). Furthermore, women in the humor condition chose more cards from advantageous decks than men in the humor condition at block one ($t = -2.65$, $p < 0.01$, *partial* $\eta^2 = 0.18$) and block two ($t = -3.28$, $p < 0.01$, *partial* $\eta^2 = 0.25$). See **Figure 2B**.

Differences in Expectancy Valence Model Parameters

The result of the two-way (Gender × Condition) MANOVA indicated that the multivariate main effect of Gender was statistically significant, Pillai's Trace $V = 0.264$, $F(3,62) = 7.43$, $p = 0.001$, *partial* $\eta^2 = 0.264$. Univariate analyses showed that collapsing across condition, compared to women, men had higher "*w*" scores $F(1,64) = 19.89$, $p < 0.001$, $\eta^2 = 0.237$, $M_{men} = 0.458$, $SD_{men} = 0.399$; $M_{women} = 0.123$, $SD_{women} = 0.167$, and lower "*c*" scores, $F(1,64) = 8.15$, $p < 0.006$, *partial* $\eta^2 = 0.113$, $M_{men} = -1.18$, $SD_{men} = 0.96$; $M_{women} = -0.4$, $SD_{women} = 1.2$. The multivariate main effect of condition was not statistically significant, Pillai's Trace $V = 0.072$, $F(3,62) = 0.161$, $p = 0.196$, *partial* $\eta^2 = 0.072$. Finally, the multivariate interaction of Gender × Condition was statistically significant, Pillai's Trace $V = 0.224$, $F(3,62) = 5.98$, $p = 0.001$, *partial* $\eta^2 = 0.224$. The results of the univariate ANOVAs showed that the interaction effect was statistically significant only for the parameter "*a*," $F(1,64) = 16.95$, $p < 0.001$, *partial* $\eta^2 = 0.21$ (see **Figure 3**). Namely, men in the humor condition had significantly lower parameter "*a*" scores than women in the humor condition ($t = -2.86$; $p < 0.01$; *partial* $\eta^2 = 0.20$; $M_{men\ humor} = 0.0003$, $SD_{men\ humor} = 0.0004$; $M_{women\ humor} = 0.0016$, $SD_{women\ humor} = 0.0017$). Conversely, men in the non-humor condition had higher parameter "*a*" scores than women in the non-humor condition ($t = 3.15$; $p < 0.01$; *partial* $\eta^2 = 0.24$; $M_{men\ non\text{-}humor} = 0.003$, $SD_{men\ non\text{-}humors} = 0.003$; $M_{women\ non\text{-}humor} = 0.0004$, SD_{women}

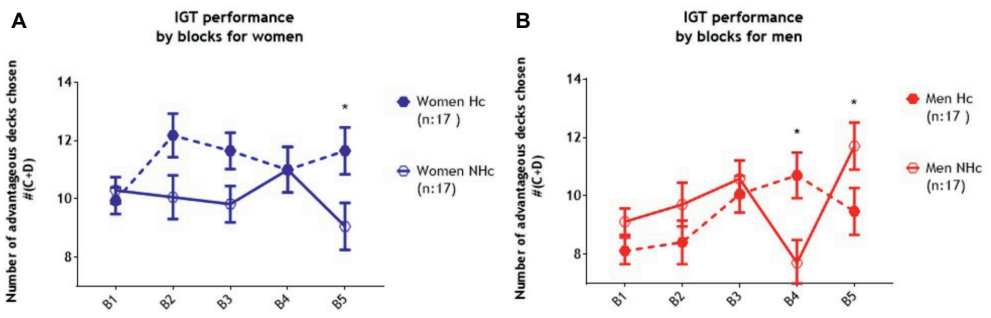

FIGURE 1 | Results for IGT performance under the non-humor condition (NHc: 17 men and 17 women) and the humor condition (Hc: 17 men and 17 women) with standard error of the mean (SEM). The 100 trial-task was divided into 5 blocks of 20 trials each. **(A)** Analysis for Blocks × Condition in women revealed significant differences for Block 5 benefiting Hc over NHc. **(B)** Analysis for Blocks × Condition in men revealed significant differences for Block 4 benefiting Hc over NHc, and during Block 5 inverting the relationship, benefiting NHc over Hc.

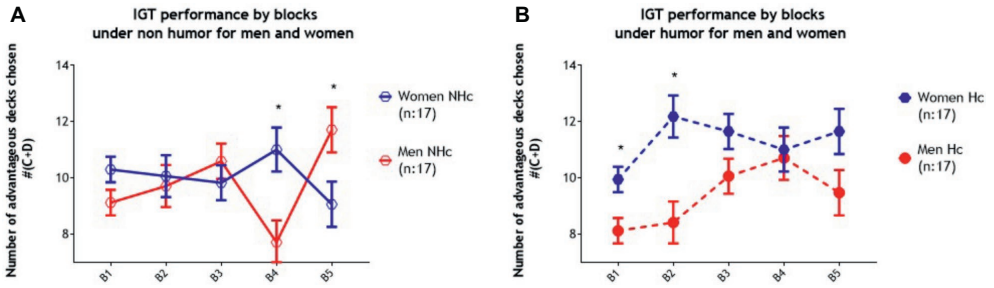

FIGURE 2 | Results for IGT performance under the non-humor condition (NHc: 17 men and 17 women) and the humor condition (Hc: 17 men and 17 women) with standard error of the mean (SEM). The 100 trial-task was divided into 5 blocks of 20 trials each. **(A)** Analysis for Blocks × Condition under NHc revealed significant differences during Block 4, benefiting women over men, and Block 5, benefiting men over women. **(B)** Analysis for Blocks × Condition under Hc revealed significant differences during Block 1 and 2, benefiting women over men.

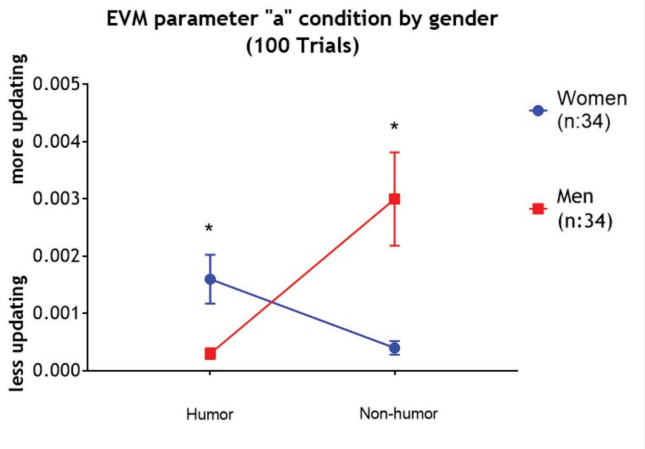

FIGURE 3 | Results for the EVM analysis on parameter "*a*" (updating rate score) with standard error of the mean (SEM). Analyses revealed a significant interaction of Gender × Condition, indicating that women in the humor condition had higher scores than men in the humor condition, and men in the control condition had higher scores than women in the control condition. We also observed that women in the humor condition had higher scores than women in the control condition. Finally, men in the humor condition had lower scores than men in the control condition.

$_{\text{non-humor}}$ = 0.0004). In addition, women in the humor condition had higher parameter "*a*" scores than women in the non-humor condition, (t = 2.59; $p < 0.05$; *partial* η^2 = 0.17). For men, the situation was reversed: men in the humor condition had lower parameter "*a*" scores than the men under the non-humor condition (t = −3.29; $p < 0.01$; *partial* η^2 = 0.25).

DISCUSSION

The main purpose of the present study was to examine the effect of humor on IGT performance, and whether the effect of humor on IGT was moderated by gender. We expected that humor would increase women's, but not men's IGT performance, specifically during the last blocks of the task. In line with our hypothesis, we found that women exposed to humorous videos outperformed women exposed to non-humorous videos at the end of the task (block five). The effect size of humor was medium to large (d = 0.72). Consistent with this, we found that women in the humor condition had higher parameter "*a*" scores than women in the control condition (reflecting an increase in memory/learning processes). The effect size of humor on parameter "*a*" was large (d = 0.91).

Contrary to our hypothesis, we did find an effect of humor on men's IGT performance at the end of the task (block five), unlike women, men in the humor condition underperformed on the task compared with men in the control condition. The effect size of humor on men's IGT performance was medium to large (d = 0.75). We found it striking that humor improved women's IGT performance at block five, but impaired men's performance at this very same block. We also found significant differences between men in the humor condition and men in the control condition at block four, with men in the humor performing better than men in the non-humor condition. The effect size was large (d = 0.89). Consistent with this, men in the humor condition had lower parameter "*a*" scores than men in the control condition (reflecting a decrease in memory/learning processes). The effect of humor on men's parameter "*a*" was large (d = 1.26).

Our results strongly imply that humor is beneficial for decision-making, but only in women. IGT research has shown that during the last blocks of the task, performance depends on a cognitive brain system, which allows cognitive control of long-term decisional behavior and suppresses the activity of an emotional system that triggers impulsive short-sighted decisions (Bechara, 2005; van den Bos et al., 2012, 2013). In order to successfully solve the task, participants need to exert top-down control to stop focusing on regular and immediate rewards, and pay attention to more irregular and long-term rewards (Bechara, 2005; van den Bos et al., 2013). We suggest that humor may influence women's decision-making by facilitating cognitive control during the last block of the IGT, helping women to choose cards from decks that provide long-term rewards. According to neurobiological evidence, changing to long-term decisions requires an increase in dlPFC activity (Knoch et al., 2006; Fecteau et al., 2007), which is usually hypoactivated in women during the IGT, and may be related to their difficulty exerting consistent cognitive control as the task unfolds (van den Bos et al., 2013). Consistent with our results, humor has been shown to indirectly increase dlPFC activity among

women, *via* nucleus accumbens activity (Gray et al., 2002; Ueda et al., 2003; Azim et al., 2005; Tanaka et al., 2007; Doya, 2008; Homberg et al., 2008; Tanaka et al., 2016). Thus, it is possible that humor enhances cognitive control by increasing the activity of these areas during the IGT. Nevertheless, our behavioral study cannot directly measure brain activity, so further research is needed to support this hypothesized neural mechanism by which humor improves IGT performance in women.

Another possibility is that humor may have influenced decision-making by modulating the value of the expected valences, or "updating rate," during the task (parameter "*a*"). In terms of memory/learning, parameter "*a*" reflects the impact of recently experienced valences. Small values of parameter "*a*" are indicative of slow changes, weak recency effects, long associative memories, and slow forgetting during the task (Wetzels et al., 2010). We found that women in the experimental condition had higher parameter "*a*" scores than women in the control condition. This indicates that they demonstrated more efficient memory/learning processes, showing more deck exploration and integrating feedback information as a possible expected value to a greater extent. They explored different decks other than A and B more frequently than women in the control condition, which therefore may have helped them form a better representation of the long-term advantages of decks C and D. In fact, women in the control group showed a mean value of parameter "*a*" of 0.0004, indicating they seem to explore almost never, which reflects a state of no knowledge about the payoff structure of the decks (Humphries et al., 2015).

It is difficult to explain why we did not observe a significant effect of humor on IGT performance in women during blocks three and four. One possibility is that the strength of the humor manipulation grows over time. In our study, participants had a total of 12 min of humor induction and approximately 8 min of IGT decisions, adding to 20 min total. One study showed that after 30–40 min, humor seems to have stronger physiological effects (Weisenberg et al., 1998). Therefore, we presume that, if the number of IGT trials were increased, differences in performance between women in the humor and control conditions would be systematically found from block 5 onwards. Future studies using more trials and/or longer periods of emotional induction are needed.

Contrary to our hypothesis, we found statistically significant differences in the performance of men in the humor and control conditions. Men in the humor condition performed better than men in the control condition during block four, but during block five the situation reversed, and men in the control condition performed better than men in the humor condition. Additionally, men in the humor condition had lower parameter "*a*" (updating rate) scores than men in the control condition.

A closer inspection of the data reveals that during blocks 1–3, men in both groups show slow learning from choosing very few C and D deck cards (mean of 8 out of 20) in block 1 and 2, and a mean close to 10 in block 3, decisions that were nearly random. As such, among men generally, the knowledge of the task was likely extremely low during the first three blocks. According to Damasio (2003) participants need to acquire implicit knowledge of the value structure of the decks in order to later on ensure advantageous behavior. Near random choices indicate a failure in learning the differential value structure of the decks. Additionally, research on IGT supports the notion that beyond an emotional hunch, a minimum level of explicit knowledge about the value of the decks is necessary to generate a hypothesis about which deck/s are necessary to maximize performance (Maia and McClelland, 2004). In order to reverse our bad choices, we at least need to have the notion that we are doing it badly (explicit knowledge, Maia and McClelland, 2004), so "taking a risk" is a good option when we already know that doing the same is equal to or worse than doing something different. Under these circumstances, prospect theory (Kahneman and Tversky, 1979) predicts that we will risk when we know that losing is very probable. The pronounced decrease in the number of cards chosen from advantageous decks from block three to block four among men in the control condition, and the abrupt increase we observed from block four to block five can be interpreted in the light of this theoretical framework.

A completely different scenario is observed in men in the humor condition. Men in the humor condition show very little risk-taking, and very low explicit knowledge, as evidenced by near-chance deck selection in blocks 4 and 5. The EVM results support our interpretation, as men in the humor condition had extremely low parameter "*a*" scores, indicating zero knowledge about the value structure of the decks, while those under the non-humor control condition had significantly higher parameter "*a*" scores, indicating more learning about the value structure of the decks over time.

The detrimental effect of humor on IGT decision-making performance in men, to our knowledge, has not been previously reported. As we formerly stated, we suggest that the men under humor could not form the body of knowledge of the decks' value, which is necessary to explicitly form hypotheses and strategize to maximize earnings. One could possibly think that this decisional behavior reflects the emotional system predominance over the task. Nevertheless, if the emotional system were "in control" of the decisional behavior of men in the humor condition, we would expect that choices with the highest expected valence were chosen (choices that provide highest reward value), leading to a focus mostly on immediate rewards (A + B deck choices). But as we previously mentioned, their choices were instead mostly random, indicating a state of no knowledge. Using the somatic marker hypothesis as an explanatory framework, it is expected that non-conscious autonomic responses or emotion-based biasing signals, precede explicit insight on the IGT decisions (Damasio, 2003). According to this, what probably happened is that humor interfered with the emotional signals necessary to form "hunches," or implicit knowledge of the value structure of the decks, so as the task progresses, they never really form explicit knowledge about the decks, producing as a result random choice through the whole task. Regrettably, our behavioral study does not provide data about the neural correlates of attention while participants solve the task. Thus, more research about the differential neural mechanisms by which emotion impacts decision-making in men and women is needed.

Previous studies have found that, compared to men, women usually make poorer IGT choices, and need more trials to

solve the task (Bolla et al., 2004; Weller et al., 2010). In line with our hypothesis, at the end of the task, men in the non-humor condition chose more advantageous deck cards than women in the non-humor condition. However, contrary to our hypothesis, at block four women chose more advantageous deck cards than men (in the non-humor condition). No differences were found among men and women at block three. Differences found between women and men at block four and five may be due to the abovementioned implementation of risk by men, which possibly help them to perform better by the end of the task.

Finally, we expected humor would cancel out typical gender differences in IGT performance during the last blocks. In line with this hypothesis, we found no statistical differences between men and women in the humor condition during blocks three, four and five. Therefore, the gender differences observed in the non-humor condition during block five were not present in the humor condition. This was the combined result of two effects: men in the humor condition showed decreased performance in block five, and women in the humor condition showed improved performance in the same block.

Our study differed from previous studies in the use of videos that interspersed each decision (100 videos for 100 choices). Therefore, our participants needed to split their attention between the videos and the decisions while performing the task. A previous study (Preston et al., 2007) found that men had poorer IGT performance than women when their attention was divided between the IGT and another task. So, the exposure of our participants to a dual-task like paradigm may have had a more negative impact on men than on women. We propose that decreased attention could be the mechanism by which humor impairs men's performance, which would lead to almost no exploration, slower learning, and poor total choice behavior. Alternatively, humor may have been detrimental to men's decision-making performance because the funny videos may have decreased their motivation to complete the task in a serious way, by shifting their mindset from a serious (bona-fide performance) to a playful (non-bona-fide mode), devaluing the goal of performing well. In future studies, measures of humor-related states (e.g., the State-Trait-Cheerfulness Inventory, Ruch, 1997) would allow for more complete characterization of the psychological mechanisms at work here.

The present study has some limitations. First, it is an experiment and therefore, its results may not generalize to real-life situations. Additional studies with higher ecological validity in which the effect of humor over real-life decision-making is examined are still needed. Second, we did not assess whether the effect of humor on decision-making was affected by the characteristics (content or structure) of the videos used. Studies exploring whether the type of humor moderates the relationship between humor on decision-making need to be conducted. Third, research has shown that reactions to humorous stimuli may cover two orthogonal dimensions, funniness, and aversiveness (see Ruch and Deckers, 1992; Ruch and Rath, 1993; Heintz, 2019). In our study, we controlled for gender differences in the subjective funniness of the videos, but we did not control for potential gender differences in the subjective aversiveness of the videos. Therefore, our results may have been affected by this extraneous, unmeasured variable. Fourth, it has been previously reported that men prefer sexual (Thorne et al., 1983), aggressive (Brodzinsky et al., 1981; Crawford, 1989; Herzog and Hager, 1995) or dark humor (Aillaud and Piolat, 2012; Martin and Ford, 2018) more than women, therefore, we did not include videos with these types of humor. Our results cannot be generalized to dark humor or to stimuli that are sexual or violent. Fifth, all participants were university students, and the results may not generalize to other samples. Sixth, it may have been interesting to include measurements of positive and negative emotions or attention allocation during the task to examine potential emotional and cognitive mechanisms underlying the effects of humor on IGT performance. Future studies including other behavioral and neurophysiological variables (e.g., ERPs, the PANAS, etc.) are recommended. Seventh, unfortunately, we did not collect information regarding specific emotions (other than humor) evoked by the non-humorous videos. Therefore, we cannot be completely sure that they did not evoke in the participant some type of emotion that could affect our results (e.g., boredom). As such, the results of the present study should be taken with caution and replicated in future studies in which the specific emotions elicited by the videos are collected during the task. Eighth, some preliminary evidence suggests that IGT performance may be affected by stress, especially among women (Preston et al., 2007; van den Bos et al., 2009). It is possible that women experience higher stress during the IGT than men, and that this could explain gender differences in performance. Unfortunately, we did not assess stress during the task. Replication studies in which the influence of stress and other positive and negative feelings are controlled during the task should be conducted in the future. It may be also interesting to know whether similar effects can be produced by inducing other positive emotions and by using methods other than videos. In spite of this, our study has several important strengths. First, this is the first study evaluating the effect of humor on the IGT, and whether that effect is moderated by gender. Additionally, to our knowledge, this is also the first study that uses both IGT decision-making performance evaluation and EVM together to interpret results. Our findings contribute to better understanding the cognitive mechanisms underlying decision-making in men and women. Furthermore, unlike previous studies measuring emotional effects on the IGT, it takes simultaneously gender and humor into account, providing a more complete picture of decision-making, and showing differences that may remain hidden when the moderator of gender is not considered. Also, previous studies involving induction of positive and negative emotions during the IGT have used a single stimulus, of short duration (i.e., a happy or sad video of 2.5 min before the task), without taking into account that this period of time may not be enough to induce a lasting emotional effect across the whole task. We presented the stimulus throughout the task and for longer periods of time, allowing for slow emotional changes in participants as the task progressed.

In conclusion, humor impaired men's and improved women's decision-making performance. These differences may be due to gender differences in humor processing and in how men and women efficiently allocate attentional resources in complex

scenarios; however, the neural mechanisms underlying these differences remain unclear. Future studies exploring differential brain mechanisms of the effect of humor on decision-making in men and women by means of brain exploration techniques such as electroencephalography and/or fMRI are needed.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the Pontificia Universidad Católica de Chile (PUC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF-T contributed in the design, implementation, data analysis and data interpretation of the study. LG-P and IR contributed to the analysis of the data. LG-P, KM, VL, and ER contributed to the interpretation of the data, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript. JF wrote the first draft. LG-P and KM modified the final draft of the article.

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The Association Between Vulnerable/Grandiose Narcissism and Emotion Regulation

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Narcissism has been widely discussed in the context of career success and leadership. Besides several adaptive traits, narcissism has been characterized by difficulties in emotion regulation. However, despite its essential role in mental health, there is little research on emotion regulation processes in narcissism. Specifically, the investigation of not only the habitual use of specific regulation strategies but also the actual ability to regulate is needed due to diverging implications for treatment approaches. Thereby it is important to differentiate between vulnerable and grandiose narcissism as these two phenotypes might be related differently to regulation deficits. The aim of this study was to examine the association between grandiose and vulnerable narcissism and emotion regulation in healthy individuals (30f/30m) focusing on the strategy reappraisal. Additionally, potential sex effects have been explored. Narcissism was assessed using self-report measures and emotion regulation with self-report questionnaires as well as an experimental regulation task. During this task, participants were presented with pictures of sad/happy faces with the instruction to indicate their subjective emotions via button press. Depending on the condition, participants either indicated their natural response or applied cognitive control strategies to regulate their own subjective emotions. Results indicate no relationship between grandiose and vulnerable narcissism and emotion regulation ability, irrespective of sex. Individuals high on vulnerable narcissism use the maladaptive regulation strategy suppression more frequently than individuals with low expressions. Individuals high on grandiose narcissism, in contrast, seem to avoid the suppression of positive emotions and do not express negative emotions in an uncontrolled manner. Interestingly, while grandiose narcissism was not associated with depressive symptoms, vulnerable narcissism correlated positively with depressive symptoms and anhedonia. Findings of this study underline the need to differentiate between grandiose and vulnerable manifestations of narcissism. Against our expectation, narcissism was not related to emotion regulation performance. In line with previous research, grandiose narcissism seems less harmful for mental health, while

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vulnerable narcissism is associated with psychological problems and the use of rather maladaptive emotion regulation strategies, i.e., suppression. Future research should investigate the relationship between pathological narcissism and emotion regulation also by extending the scope to other relevant regulation strategies.

Keywords: vulnerable narcissism, grandiose narcissism, emotion regulation, reappraisal, suppression, depression, anhedonia, sex

INTRODUCTION

The concept of narcissism has gained increasing attention, for instance, in the context of leadership, and has been linked to positive factors such as high achievement, innovation, and charisma as well as to negative factors such as lack of concern for others, risk to company's reputation (e.g., fraud), and arrogance (for review see Grijalva et al., 2015; Fatfouta, 2019). Usually, a narcissistic person is described by an inflated self-view, dominance, and exploitive and self-serving behavior. Such definition, however, neglects important aspects of narcissism such as vulnerability, interpersonal hypersensitivity, depressiveness, and social withdrawal (Pincus and Lukowitsky, 2010). Research indeed revealed two manifestations of narcissism, namely grandiosity and vulnerability, which seem to have divergent implications for regulatory styles and mental health (Kealy et al., 2012; Marčinko et al., 2014; Krizan and Herlache, 2018; Kaufman et al., 2020). How these two manifestations relate to the ability to regulate emotions, which is essential for well-being, has only been scarcely investigated.

Krizan and Herlache (2018) suggested a unified conceptual framework, the narcissism spectrum model, describing narcissism in terms of dimensions of individual tendencies that vary in severity and their presentation (grandiosity vs vulnerability). In more detail, the model suggests entitled self-importance as common core of grandiose and vulnerable narcissism with grandiosity and vulnerability reflecting excesses in approach- and avoidance-orientations, respectively. Accordingly, individuals high in grandiose narcissism tend to seek and satisfy self-aggrandizing and rewarding goals. They use self-regulatory styles focusing on self-enhancement rather than on costs, which is manifested in assertive, arrogant and exhibitionist social behavior (Krizan and Herlache, 2018). In line, research revealed a link between grandiosity and high extraversion, dominance, overconfidence, and positive affect (Rhodewalt et al., 1998; Cain et al., 2008; Fulford et al., 2008; Miller et al., 2011; Krizan and Herlache, 2018; Kaufman et al., 2020). Individuals high in vulnerable narcissism, in contrast, tend to detect and combat threats to the self-image (i.e., fight-flight responses). They use self-regulatory styles which excessively focus on self-protection revealed through dismissive, shy, but ultimately volatile social behavior (Krizan and Herlache, 2018). Vulnerable narcissism is further related to low self-esteem and feelings of self-worth, anxieties, neuroticism, and depressiveness (Marčinko et al., 2014; Krizan and Herlache, 2018; Kaufman et al., 2020). The inhibited temperament of individuals high in vulnerable narcissism often leads to a frustration of narcissistic needs for admiration and success (Krizan and Herlache, 2018). Vulnerable narcissism has been even linked to homicidal ideation, parasuicidal behavior, and suicide attempts (for review see Pincus and Lukowitsky, 2010) which underlines the importance to differentiate between grandiose and vulnerable themes in research and also clinical care.

The relationship between narcissism and mental health has been widely discussed. In order to stay psychologically healthy, adequate emotion regulation is crucial (Gross, 1998; Eftekhari et al., 2009; Aldao et al., 2010; Werner and Gross, 2010). The most frequently investigated emotion regulation strategy is reappraisal, an essential component of cognitive behavioral therapy (Beck et al., 1979). Reappraisal refers to the ability to change how a person thinks about a situation in order to alter the emotional response (Gross, 1998; Gross and Thompson, 2007). It is considered a very effective emotion regulation strategy (Webb et al., 2012), as it intervenes early in the process of emotion generation (Gross, 1998; Gross and Thompson, 2007). Research indeed demonstrated numerous positive effects of reappraisal such as increased positive and decreased negative emotions (Troy et al., 2018; Webb et al., 2012) and better psychological health (e.g., Kraaij et al., 2002). Furthermore, experimental studies revealed that individuals high in habitual reappraisal show less physiological reactivity in response to anger induction (Mauss et al., 2007). When it comes to narcissism, little is known about reappraisal or emotion regulation in general. Distinguishing between grandiose and vulnerable narcissism, the latter in particular appears to be associated with regulatory difficulties (e.g., Zhang et al., 2015). Zhang et al. (2015) examined the association between overt and covert narcissism (often used interchangeable with "grandiose" and "vulnerable" narcissism, Pincus and Lukowitsky, 2010) and emotion regulation difficulties. The authors additionally examined respiratory sinus arrhythmia as index of an individual's physiological regulation and related it to difficulties in habitual emotion regulation. The study revealed that covert/vulnerable narcissism was related to overall emotion regulation difficulties, non-acceptance of emotional responses, impulse control difficulties, limited access to emotion regulation strategies, and a lack of emotional clarity, while individuals high in overt/grandiose narcissism had more emotional awareness and clarity. Respiratory sinus arrhythmia reactivity in response to stress induction moderated the association between covert/vulnerable narcissism and emotion regulation difficulties. In line, Given-Wilson and colleagues revealed that vulnerable but not grandiose narcissism is related to affect dysregulation (Given-Wilson et al., 2011).

Further research showed altered physiological arousal in response to stress in individuals scoring high on narcissism (Kelsey et al., 2001) and differentiated psychophysiological reactivity during coping between overt/grandiose and covert/vulnerable narcissists (Kelsey et al., 2002). Previous research investigated predominantly habitual emotion regulation by means of self-report questionnaires. However, the frequency of how often a person applies specific emotion regulation strategies does not imply how successful a person can regulate emotions. For this reason, it is important to include measures of the actual emotion regulation ability in order to interpret emotion regulation difficulties. The current study therefore aims to examine the association between grandiose and vulnerable narcissism and emotion regulation, particularly focusing on the emotion regulation strategy reappraisal. We differentiate between the use of reappraisal in everyday life (i.e., habitual reappraisal) and the ability to regulate emotions by means of reappraisal when instructed to do so (i.e., reappraisal ability). Furthermore, we aim to assess the relationship between grandiose and vulnerable narcissism and depressive symptoms. Based on findings of Zhang et al. (2015) and Given-Wilson et al. (2011), we expect that vulnerable narcissism is linked to emotion regulation difficulties as reflected in decreased use of reappraisal in daily life, a reduced emotion regulation ability, and increased depressive symptoms. Grandiose narcissism, in turn, is expected to be not related to emotion regulation difficulties and depressive symptoms.

MATERIALS AND METHODS

Participants

The sample comprised 60 healthy participants (30 females, 30 males; see **Table 1** for more details) with no previous/current mental disorder assessed with the structured clinical interview according to the DSM-IV (Wittchen et al., 1997). Participants were recruited via flyers and announcements in online portals (e.g., University's blackboard) and were Caucasians since the emotion regulation task included only Caucasian stimuli.

All participants gave written informed consent and received financial compensation (10 Euro). The study was approved by the local ethics committee of the Medical Faculty of the RWTH Aachen University and conducted according to the Declaration of Helsinki.

Questionnaires

Participants completed measures assessing verbal intelligence (Wortschatztest, WST; Schmidt and Metzler, 1992), depressive symptoms (Beck Depression Inventory II, BDI-II; Hautzinger et al., 2006) and anhedonia (Mood and Anxiety Symptom Scale, MASQ; Watson and Clark, 1991). In order to investigate emotion regulation strategies applied in daily life (i.e., habitual emotion regulation), the emotion regulation questionnaire (ERQ; Gross and John, 2003; Abler and Kessler, 2009) and the emotion regulation inventory (ERI; König, 2011) were used.

To quantify grandiose narcissism, participants completed the 15 item version of the narcissistic personality inventory (NPI-15; Raskin and Hall, 1979; Raskin and Terry, 1988; Schütz et al., 2004). Items have a forced-choice format each consisting of a narcissistic and a non-narcissistic option. The total score ranges from 0 to 15 with higher scores indicating increased grandiose narcissism. The NPI-15 has frequently been used in research and is sufficiently consistent and stable over time (Schütz et al., 2004; Bertl et al., 2017; Ozimek et al., 2018). In our study, participants reached a mean total score of 7.93 (SD = 1.77) which is relatively high compared to other studies examining students and the general population (Schütz et al., 2004; Ozimek et al., 2018). Ackerman et al. (2011) revealed a three factor structure of the NPI consisting of the subscales Leadership/Authority, Grandiose Exhibitionism, and Entitlement/Exploitiveness. Applying structural equation modeling analysis to several narcissism measures, including the NPI, Ackerman et al. (2011) further suggested that the NPI subscales Leadership/Authority (e.g., "I like to have authority over others") and Grandiose Exhibitionism (e.g., "I prefer to be the center of attention") are linked to grandiose narcissism whereas the scale Entitlement/Exploitiveness (e.g., "I find it easy to manipulate people") represents the key "ingredient" of narcissism (common to grandiose and vulnerable narcissism), reflecting a broader tendency toward antagonism (Ackerman et al., 2011; Krizan and Herlache, 2018). For this reason, we considered the subscales Leadership/Authority and Grandiose Exhibitionism as measures of grandiose narcissism. To provide a full picture of narcissism, we additionally report results for the NPI-15 total score and for the NPI-15 Entitlement/Exploitiveness scale in **Tables 1–5**.

Vulnerable narcissism has been assessed using a shortened and revised version of the original narcissism inventory (NI-R; Deneke and Hilgenstock, 1998; Neumann and Bierhoff, 2004). The NI-R comprises 42 items examining the classic narcissistic self and idealistic self. Items are rated on a 5-point Likert scale ranging from 1 = "not at all true" to 5 = "completely true." The total score ranges from 42 to 210 with higher scores indicating increased vulnerable narcissism. Participants in our study reached an average total score of 115.10 and SD = 22.02 (Mean item score = 2.72, SD = 0.51), which is in line with previous studies (Ozimek et al., 2018). The NI-R shows a good internal consistency and validity (Neumann and Bierhoff, 2004; Ozimek et al., 2018). It has been used in several previous studies (e.g., Neumann and Bierhoff, 2004; Ozimek et al., 2018; Rohmann et al., 2012) and has been recommended as a valid measure of vulnerable narcissim (Bierhoff et al., 2019). Recently, Altmann (2017) revealed a three-factor structure of a brief (17-item) version of the NI-R consisting of the subscales Admiration (e.g., "I think others envy my good looks"), Pretension ("I set high moral standards for myself – many others are less strict with themselves"), and Mistrust ("Never show your weakness to others, because they will only take advantage of it"). In accordance with the author's recommendation, we consider the subscales Pretension and Mistrust as measures of

TABLE 1 | Sociodemographic and clinical characteristics, emotion regulation, and narcissism for the total sample as well as for females and males separately [presented as mean; *n* = 60 (30 females, 30 males)].

	Mean females (SD)	Mean males (SD)	*p*	Mean total (SD)	Range total (min–max)
Age (in years)	34.30 (10.31)	35.10 (10.08)	0.778	34.70 (10.12)	22–54
Education (in years)	14.17 (2.47)	14.80 (3.04)	0.389	14.48 (2.77)	10–21
Verbal Intelligence (WST)	32.87 (3.28)	34.37 (2.68)	0.056	110.08 (10.08)	92–139
Depression (BDI-II)	3.23 (2.86)	3.13 (3.36)	0.560	3.18 (3.10)	0 – 11 (0 – 63)
Anhedonia (MASQ)	44.97 (11.42)	48.77 (12.59)	0.145	46.87 (12.07)	24 – 78 (22 – 110)
Reappraisal (ERQ)	28.17 (5.68)	41.87 (9.95)	0.911	27.95 (5.98)	12 – 37 (6 – 42)
Suppression (ERQ)	12.07 (4.43)	14.13 (5.35)	0.159	13.10 (4.98)	4 – 24 (4 – 28)
Uncontrolled expression NEG (ERI)	7.40 (3.71)	5.87 (4.07)	0.070	6.63 (3.94)	0 – 15 (0 – 20)
Controlled expression NEG (ERI)	14.70 (3.67)	11.57 (3.84)	0.003**	13.13 (4.04)	5 – 20 (0 – 20)
Empathic suppression NEG (ERI)	7.67 (2.68)	8.13 (3.57)	0.817	7.90 (3.14)	0 – 16 (0 – 16)
Distraction NEG (ERI)	10.72 (1.74)	9.70 (2.51)	0.653	9.88 (2.15)	4 – 14 (0 – 16)
Reappraisal NEG (ERI)	9.73 (3.08)	9.50 (2.98)	0.655	9.62 (3.01)	3 – 15 (0 – 16)
Uncontrolled expression POS (ERI)	10.60 (2.27)	8.50 (3.05)	0.006**	9.55 (2.87)	1 – 14 (0 – 16)
Controlled expression POS (ERI)	12.23 (2.73)	10.33 (2.71)	0.018*	11.28 (2.86)	5 – 16 (0 – 16)
Empathic suppression POS (ERI)	5.77 (2.81)	5.77 (3.42)	0.929	5.77 (3.11)	0 – 16 (0 – 16)
Distraction POS (ERI)	1.90 (1.71)	2.07 (2.86)	0.494	1.98 (2.34)	0 – 12 (0 – 16)
Grandiose Narcissism					
NPI-15 Total	7.77 (1.19)	8.10 (1.77)	0.665	7.93 (1.51)	5 – 12 (0 – 15)
NPI-15 Leadership/Authority	3.37 (1.27)	4.33 (1.45)	0.012*	3.85 (1.44)	1 – 7 (0 – 9)
NPI-15 Grandiose Exhibitionism	2.60 (0.72)	2.10 (0.92)	0.020*	2.35 (0.86)	0 – 3 (0 – 3)
NPI-15 Entitlement/Exploitiveness	0.73 (0.45)	0.53 (0.51)	0.111	0.63 (0.49)	0 – 1 (0 – 1)
Vulnerable Narcissism					
NI-R Total	112.27 (24.14)	117.93 (19.68)	0.264	115.10 (22.02)	63 – 162 (42 – 210)
NI-R Admiration	39.50 (10.87)	43.70 (11.72)	0.203	41.60 (11.40)	19 – 80 (17 – 85)
NI-R Pretension	27.27 (6.05)	28.50 (4.46)	0.419	27.88 (5.30)	13 – 38 (18 – 90)
NI-R Mistrust	37.97 (11.27)	40.67 (9.60)	0.254	39.32 (11.47)	20 – 59 (15 – 75)

*BDI-II, Beck Depression Inventory II; ERI, Emotion Regulation Inventory; ERQ, Emotion Regulation Questionnaire; IQ, intelligence quotient; MASQ, Mood and Anxiety Symptom Scale; NEG, Negative emotions; NI-R, Narcissism Inventory Revised; NPI-15, Narcisstic Personality Inventory, 15 items; POS, positive emotions; SD, standard deviation; WST, Wortschatztest. P-values indicate sex differences, *p ≤ 0.05, **p ≤ 0.01.*

vulnerable narcissism. To provide a full picture of narcissism, we additionally report results for the NI-R total scale and for NI-R Admiration in **Tables 1–5**.

Table 2 shows correlations between grandiose and vulnerable narcissism as assessed with the NPI-15 and NI-R, respectively.

Experimental Emotion Regulation Task – Emotion Regulation Ability

In contrast to emotion regulation questionnaires (i.e., ERQ and ERI), which capture self-reported use of specific emotion regulation strategies in everyday life, the actual emotion regulation ability can be measured by means of an experimental task. For this reason, participants performed an emotion regulation task which was successfully implemented in a previous study (Loeffler et al., 2018; Loeffler et al., 2019). Emotion regulation difficulties occur in particular in social interactions. Since facial emotions convey important information in social communication, they offer an ideal possibility to examine social emotion regulation. Therefore, 45 sad and 45 happy Caucasian faces of the FACES database (Ebner et al., 2010) were presented for 4 s on a computer screen. Subsequently, participants indicated via button press how sad (regarding sad faces) or happy (regarding happy faces) they felt on a scale ranging from 1 (not at all) to 8 (very). Faces of the same emotions were grouped into mini-blocks of five trials. The inter-stimulus interval amounted to 2–4 s.

The task consisted of three counterbalanced conditions, implemented in three separate blocks (each condition containing 15 sad and 15 happy faces). In the *view* condition, no regulation was applied and participants should imagine that they encounter the person depicted on the picture on the street or somewhere else. In the two experimental conditions *up-regulation* and *down-regulation* they should imagine that the person on the picture was a close person in order to increase the personal relevance. In the *up-regulation* condition, participants were additionally instructed to imagine that the person on the picture was sad/happy because of them whereas in the *down-regulation* condition they should imagine they had nothing to do with the emotional state of the person on the picture. Stimuli were presented by Presentation Software (Neurobehavioral Systems, Albany, CA, United States) and viewed on a laptop screen.

Statistical Analysis

Habitual Emotion Regulation

The association between grandiose and vulnerable narcissism and the use of cognitive emotion regulation strategies in

TABLE 2 | Spearman correlation coefficients of the association between grandiose and vulnerable narcissism.

		Grandiose narcissism (NPI-15)			
		Total	**Leadership/authority**	**Grandiose exhibitionism**	**Entitlement/exploitiveness**
Vulnerable narcissism (NI-R)	Total	−0.016	−0.008	−0.086	−0.092
	Admiration	−0.022	0.063	−0.234	−0.099
	Pretension	0.010	−0.043	0.052	0.104
	Mistrust	−0.152	−0.193	0.111	−0.177

*There are no significant correlations. *p ≤ 0.05.*

TABLE 3 | Spearman correlation coefficients of the association between narcissism and habitual emotion regulation.

	Grandiose narcissism (NPI-15)				Vulnerable narcissism (NI-R)			
	Total	**Leadership/ Authority**	**Grandiose exhibitionism**	**Entitlement/ Exploitiveness**	**Total**	**Admiration**	**Pretension**	**Mistrust**
Reappraisal (ERQ)	−0.138	−0.025	−0.221	0.008	0.055	0.069	0.124	−0.053
Reappraisal NEG (ERI)	−0.032	0.037	0.010	−0.169	0.005	0.106	0.082	−0.053
Suppression (ERQ)	−0.010	−0.100	0.155	0.008	0.331**	0.331**	0.104	0.387**
Uncontrolled expression NEG (ERI)	−0.211	−0.317*	0.073	0.037	0.205	0.146	0.039	0.143
Controlled expression NEG (ERI)	−0.173	−0.198	0.099	0.136	−0.193	−0.187	0.066	−0.245
Empathic suppression NEG (ERI)	0.039	−0.023	0.159	0.020	0.147	−0.102	0.150	0.227
Distraction NEG (ERI)	0.271*	0.223	0.092	0.049	0.039	−0.037	0.163	0.014
Uncontrolled expression POS (ERI)	−0.061	−0.070	−0.139	0.014	0.167	0.183	0.255*	0.005
Controlled expression POS (ERI)	−0.163	−0.031	−0.169	−0.069	0.095	0.058	0.232	−0.012
Empathic suppression POS (ERI)	−0.213	−0.277*	0.150	−0.016	0.148	0.109	0.042	0.227
Distraction POS (ERI)	−0.046	−0.135	0.091	0.078	0.167	0.183	−0.044	0.091

*NEG, negative emotions; POS, positive emotions. Significant correlations indicated with *p ≤ 0.05, **p ≤ 0.01*

everyday life was examined by correlating scores (total score and subscale scores) of the NPI-15 (grandiose narcissism) and NI-R (vulnerable narcissism) with reappraisal scores (ERQ and ERI). Due to violations of normal distribution, Spearman correlations have been used. Moreover, we conducted uncorrected exploratory correlations between narcissism scores and strategies additionally assessed with the ERQ and ERI (e.g., suppression) using Spearman correlations. To test for sex differences in habitual emotion regulation, Mann-Whitney *U* tests have been conducted (see **Table 1** for details).

Emotion Regulation Ability

First, to investigate emotion regulation ability irrespective or narcissism, emotion ratings of the experimental task were averaged and analyzed with a repeated-measures ANOVA with condition (view, up-regulation, down-regulation) and emotion (sad and happy) as within-subject factors and sex (male and female) as between-subjects factor to account for potential sex effects. Next, analyses were repeated with total scores of the NPI-15 and NI-R as covariates. In a final step, analyses were conducted with subscale scores (instead of total scores) of the NPI-15 and NI-R as covariates. Significant effects were followed-up with Bonferroni-corrected pairwise comparisons or with Spearman correlations.

Depression/Anhedonia

Furthermore, to describe the relationship between narcissism (NPI-15 and NI-R), depressive symptoms (BDI-II and MASQ), and sex, Spearman correlations were calculated due to violations of normality.

RESULTS

Findings revealed a stronger expression of grandiose narcissism (but not vulnerable narcissism) in men compared to women (NPI-15 subscale Leadership/Authority and Grandiose Exhibitionism; see **Table 1**). The following sections describe the association between narcissism and habitual emotion regulation, emotion regulation ability, and depression symptoms.

Habitual Emotion Regulation

Grandiose Narcissism (NPI-15 Leadership/Authority, Grandiose Exhibitionism)

Grandiose narcissism did not significantly correlate with the emotion regulation strategy reappraisal ($p \geq 0.089$) Exploratory analyses revealed a significant negative correlation between grandiose narcissism (NPI-15 Leadership/Authority) and the empathic suppression of positive emotions (ERI; $r = -0.277$, $p = 0.032$) as well as with the uncontrolled expression

TABLE 4 | The association between narcissism and emotion regulation ability.

Emotion regulation ability		
Condition	$F(1.625, 94.267) = 65.238$	$p < 0.001^{***}$
Emotion	$F(1, 58) = 42.072$	$p < 0.001^{***}$
Sex	$F(1, 58) = 0.235$	$p = 0.630$
Condition × Emotion	$F(1.868, 108.341) = 8.925$	$p < 0.001^{***}$
Condition × Sex	$F(1.625, 94.267) = 0.163$	$p = 0.850$
Emotion × Sex	$F(1, 58) = 0.359$	$p = 0.552$
Condition × Emotion × Sex	$F(1.868, 108.341) = 1.310$	$p = 0.273$
Grandiose narcissism (NPI-15)		
NPI-15 Total	$F(1, 56) = 0.144$	$p = 0.706$
NPI-15 Total × Condition	$F(1.626, 91.036) = 0.129$	$p = 0.837$
NPI-15 Total × Emotion	$F(1, 56) = 0.127$	$p = 0.722$
NPI-15 Total × Sex	$F(1, 56) = 0.021$	$p = 0.884$
NPI-15 Total × Condition × Emotion	$F(1.891, 105.874) = 0.216$	$p = 0.794$
NPI-15 Total × Condition × Sex	$F(1.626, 91.036) = 0.069$	$p = 0.900$
NPI-15 Total × Emotion × Sex	$F(1, 56) = 0.330$	$p = 0.568$
NPI-15 Total × Condition × Emotion × Sex	$F(1.891, 105.874) = 1.954$	$p = 0.149$
NPI-15 Leadership/Authority	$F(1, 52) = 0.753$	$p = 0.390$
NPI-15 Leadership/Authority × Condition	$F(1.612, 83.810) = 0.752$	$p = 0.448$
NPI-15 Leadership/Authority × Emotion	$F(1, 52) = 0.001$	$p = 0.999$
NPI-15 Leadership/Authority × Sex	$F(1, 52) = 0.403$	$p = 0.528$
NPI-15 Leadership/Authority × Condition × Emotion	$F(1.892, 98.377) = 0.017$	$p = 0.980$
NPI-15 Leadership/Authority × Condition × Sex	$F(1.612, 83.810) = 0.038$	$p = 0.936$
NPI-15 Leadership/Authority × Emotion × Sex	$F(1, 52) = 0.056$	$p = 0.814$
NPI-15 Leadership/Authority × Condition × Emotion × Sex	$F(1.892, 98.377) = .685$	$p = 0.499$
NPI-15 Grandiose Exhibitionism	$F(1, 52) = 0.028$	$p = 0.868$
NPI-15 Grandiose Exhibitionism × Condition	$F(1.612, 83.810) = 0.750$	$p = 0.449$
NPI-15 Grandiose Exhibitionism × Emotion	$F(1, 52) = 0.342$	$p = 0.561$
NPI-15 Grandiose Exhibitionism × Sex	$F(1, 52) = 0.524$	$p = 0.472$
NPI-15 Grandiose Exhibitionism × Condition × Emotion	$F(1.892, 98.377) = 0.290$	$p = 0.737$
NPI-15 Grandiose Exhibitionism × Condition × Sex	$F(1.612, 83.810) = 2.481$	$p = 0.101$
NPI-15 Grandiose Exhibitionism × Emotion × Sex	$F(1, 52) = 1.746$	$p = 0.192$
NPI-15 Grandiose Exhibitionism × Condition × Emotion × Sex	$F(1.892, 98.377) = 0.047$	$p = 0.948$
NPI-15 Entitlement/Exploitiveness	$F(1, 52) = 0.233$	$p = 0.631$
NPI-15 Entitlement/Exploitiveness × Condition	$F(1.612, 83.810) = 2.724$	$p = 0.083$
NPI-15 Entitlement/Exploitiveness × Emotion	$F(1, 52) = 0.190$	$p = 0.665$
NPI-15 Entitlement/Exploitiveness × Sex	$F(1, 52) = 1.453$	$p = 0.234$
NPI-15 Entitlement/Exploitiveness × Condition × Emotion	$F(1.892, 98.377) = 1.729$	$p = 0.185$
NPI-15 Entitlement/Exploitiveness × Condition × Sex	$F(1.612, 83.810) = 1.495$	$p = 0.231$
NPI-15 Entitlement/Exploitiveness × Emotion × Sex	$F(1, 52) = 1.213$	$p = 0.276$
NPI-15 Entitlement/Exploitiveness × Condition × Emotion × Sex	$F(1.892, 98.377) = 3.398$	$p = 0.037^{*}$
Vulnerable narcissism (NI-R)		
NI-R Total	$F(1, 56) = 5.362$	$p = 0.024$
NI-R Total × Condition	$F(1.553, 86.988) = 3.621$	$p = 0.042$
NI-R Total × Emotion	$F(1, 56) = 0.680$	$p = 0.413$
NI-R Total × Sex	$F(1, 56) = 0.519$	$p = 0.474$
NI-R Total × Condition × Emotion	$F(1.862, 104.289) = 0.095$	$p = 0.897$
NI-R Total × Condition × Sex	$F(1.553, 86.988) = 0.437$	$p = 0.597$
NI-R Total × Emotion × Sex	$F(1, 56) = 2.020$	$p = 0.161$
NI-R Total × Condition × Emotion × Sex	$F(1.862, 104.289) = 1.575$	$p = 0.212$
NI-R Admiration	$F(1, 52) = 2.623$	$p = 0.111$
NI-R Admiration × Condition	$F(1.548, 80.505) = 0.162$	$p = 0.795$
NI-R Admiration × Emotion	$F(1, 52) = 0.210$	$p = 0.649$
NI-R Admiration × Sex	$F(1, 52) = 1.390$	$p = 0.244$

(Continued)

TABLE 4 | Continued

Emotion regulation ability		
NI-R Admiration × Condition × Emotion	$F(1.876, 97.531) = 0.452$	$p = 0.625$
NI-R Admiration × Condition × Sex	$F(1.548, 80.505) = 0.398$	$p = 0.620$
NI-R Admiration × Emotion × Sex	$F(1, 52) = 0.069$	$p = 0.794$
NI-R Admiration × Condition × Emotion × Sex	$F(1.876, 97.531) = 0.919$	$p = 0.397$
NI-R Pretension	$F(1, 52) = 3.523$	$p = 0.066$
NI-R Pretension × Condition	$F(1.548, 80.505) = 0.243$	$p = 0.727$
NI-R Pretension × Emotion	$F(1, 52) = 0.643$	$p = 0.426$
NI-R Pretension × Sex	$F(1, 52) = 2.050$	$p = 0.158$
NI-R Pretension × Condition × Emotion	$F(1.876, 97.531) = 0.791$	$p = 0.449$
NI-R Pretension × Condition × Sex	$F(1.548, 80.505) = 0.259$	$p = 0.715$
NI-R Pretension × Emotion × Sex	$F(1, 52) = 9.115$	$p = 0.004^{**}$
NI-R Pretension × Condition × Emotion × Sex	$F(1.876, 97.531) = 0.181$	$p = 0.821$
NI-R Mistrust	$F(1, 52) = 0.350$	$p = 0.556$
NI-R Mistrust × Condition	$F(1.548, 80.505) = 2.086$	$p = 0.142$
NI-R Mistrust × Emotion	$F(1, 52) = 0.087$	$p = 0.769$
NI-R Mistrust × Sex	$F(1, 52) = 0.235$	$p = 0.630$
NI-R Mistrust × Condition × Emotion	$F(1.876, 97.531) = 0.004$	$p = 0.995$
NI-R Mistrust × Condition × Sex	$F(1.548, 80.505) = 1.034$	$p = 0.344$
NI-R Mistrust × Emotion × Sex	$F(1, 52) = 0.001$	$p = 0.972$
NI-R Mistrust × Condition × Emotion × Sex	$F(1.876, 97.531) = 0.429$	$p = 0.640$

*Findings indicate main effects and interactions of the repeated measures AN(C)OVAS. Follow-up Spearman correlations of the significant fourway-interaction between NPI-15 Entitlement/Exploitiveness, Condition, Emotion, and Sex revealed that only within females (not males), ratings in the view condition correlated negatively with narcissism scores. In more detail, females with higher Entitlement/Exploitiveness scores indicated lower subjective emotion ratings when instructed to indicate their natural response to sad and happy faces (i.e., they seem to be less emotionally affected by the emotional state of others). *p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001.*

TABLE 5 | Spearman correlation coefficients of the association between narcissism and depression / anhedonia symptoms.

	BDI-II	**MASQ-Anhedonia**
Grandiose Narcissism		
NPI-15 Total	0.062	0.020
NPI-15 Leadership/Authority	0.052	−0.150
NPI-15 Grandiose Exhibitionism	0.003	−0.162
NPI-15 Entitlement/Exploitiveness	−0.110	0.048
Vulnerable Narcissism		
NI-R Total	0.354**	0.248
NI-R Admiration	0.212	0.184
NI-R Pretension	0.038	−0.066
NI-R Mistrust	0.357*	0.319*

*Significant correlations indicated with *p ≤ 0.05, **p ≤ 0.01.*

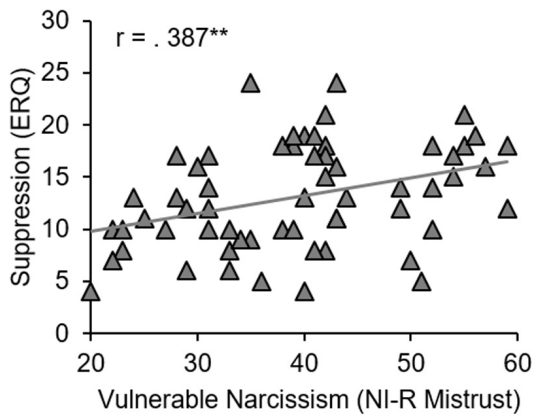

FIGURE 1 | Spearman correlation between the emotion regulation strategy suppression (ERQ) and vulnerable narcissism (NI-R-Mistrust). **p ≤ 0.01.

of negative emotions (ERI; $r = -0.317$, $p = 0.014$). No further significant correlations emerged (see **Table 3** for further details).

Vulnerable Narcissism (NI-R Pretension, Mistrust)

Similar to grandiose narcissism, vulnerable narcissism was not significantly related to reappraisal ($p \geq 0.347$). Exploratory analyses, however, revealed a significant positive association between vulnerable narcissism (NI-R Mistrust) and suppression (ERQ; $r = 0.387$, $p = 0.002$; see **Figure 1**). Moreover, the NI-R subscale Pretension correlated positively with the uncontrolled expression of positive emotions (ERI; $r = 0.255$, $p = 0.050$). No further significant correlations emerged (see **Table 3** for further details).

Sex

Females applied the emotion regulation strategies "controlled expression of negative emotions" (ERI; $p = 0.003$), "uncontrolled expression of positive emotions" (ERI; $p = 0.006$), and "controlled expression of positive emotions" (ERI; $p = 0.018$) more often

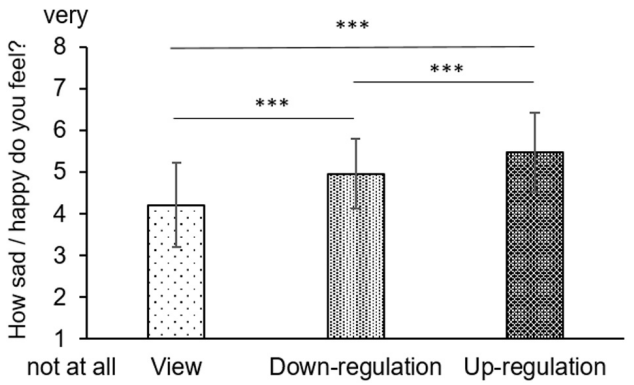

FIGURE 2 | Emotion ratings during the emotion regulation task (mean ratings with standard deviations). ***$p \leq 0.001$.

than males. No further significant sex differences emerged (all $p \geq 0.070$, see **Table 1** for details).

Emotion Regulation Ability

Emotion Regulation Ability

Bonferroni-corrected follow-up pairwise comparisons of a significant main effect of condition [$F(1.625, 94.267) = 65.238$, $p < 0.001$] revealed significant differences between all three conditions (view vs up-regulation: $p \leq 0.001$, view vs down-regulation: $p \leq 0.001$, up-regulation vs down-regulation: $p \leq 0.001$, see **Figure 2**), confirming successful emotion regulation. Furthermore, there was a significant main effect of emotion [$F(1, 58) = 42.072$, $p < 0.001$] with significantly higher happiness than sadness ratings. This difference between happiness and sadness ratings was particularly pronounced in the view condition as suggested by follow-up pairwise comparisons of a significant condition-by-emotion interaction [$F(1.868, 108.341) = 8.925$, $p < 0.001$]. There were no further significant main effects or interactions (see **Table 4** for details).

Grandiose Narcissism (NPI-15 Leadership/Authority, Grandiose Exhibitionism)

Repeated-measures ANCOVA revealed no significant main effect or interactions of grandiose narcissism (see **Table 4** for further details).

Vulnerable Narcissism (NI-R Pretension, Mistrust)

Repeated-measures ANCOVA showed a significant three-way interaction between NI-R Pretension, emotion, and sex [$F(1, 52) = 9.115$, $p = 0.004$]. Follow-up Spearman correlations unveiled that only within females [$r = 0.607$, $p < 0.001$], but not males ($r = -0.150$, $p = 0.430$), narcissism scores correlated positively with happiness ratings (Fisher's $z = 3.14$, $p = 0.001$). No further main effects or interactions of vulnerable narcissism were significant (see **Table 4** for further details).

Depression/Anhedonia

Grandiose Narcissism (NPI-15 Leadership/Authority, Grandiose Exhibitionism

There was no significant association between grandiose narcissism and depression (BDI-II) or anhedonia (MASQ) (see **Table 5** for details).

Vulnerable Narcissism (NI-R Pretension, Mistrust)

Vulnerable narcissism (NI-R Mistrust) was positively related to depressive symptoms (BDI-II; $r = 0.357$, $p = 0.005$) and anhedonia (MASQ; $r = 0.319$, $p = 0.013$) (**Figure 3**; see **Table 5** for details).

Sex Effects

There were no significant sex differences in depressive symptoms (BDI-II; $p = 0.560$) or anhedonia (MASQ; $p = 0.226$; see **Table 1** for details).

DISCUSSION

The current study investigated the association between two forms of narcissism, namely grandiose and vulnerable narcissism, and emotion regulation in a sample of healthy individuals. We differentiated between habitual reappraisal, i.e., how often a person self-reports to use reappraisal in daily life, and reappraisal ability, i.e., the ability to regulate emotions using reappraisal when instructed to do so. Results revealed no significant association between (grandiose and vulnerable) narcissism and emotion regulation ability as well as the habitual use of reappraisal. However, exploratory analyses showed that vulnerable narcissism was related to a greater use of the emotion regulation strategy suppression whereas individuals high on grandiose narcissism seem to refrain from using this strategy. Furthermore, only vulnerable narcissism was linked to depressive symptoms.

Against our expectation, there was no significant association between vulnerable narcissism and habitual reappraisal. On the one hand, this could be due to the fact that the sample consisted of healthy participants without any history of mental disorders. Perhaps the (reduced) use of specific emotion regulation strategies (i.e., reappraisal) only becomes apparent in (sub)clinical samples. Future research should therefore investigate emotion regulation in pathological narcissism. On the other hand, even healthy individuals with high narcissistic expressions may show a (dis)favor for specific emotion regulation strategies, though probably not regarding the regulation strategy investigated here. Supporting this assumption, the current study revealed that healthy individuals with higher scores in vulnerable narcissism use suppression more frequently in daily life than individuals with low scores. This strategy refers to the suppression of an emotional reaction (e.g., facial expressions) once a full emotion has already been elicited (Gross and Thompson, 2007). Due to its limited effects on subjective emotions and unwanted "side-effects" such as increased cardiovascular arousal (Gross and Levenson, 1997), suppression is often considered as rather maladaptive. In this

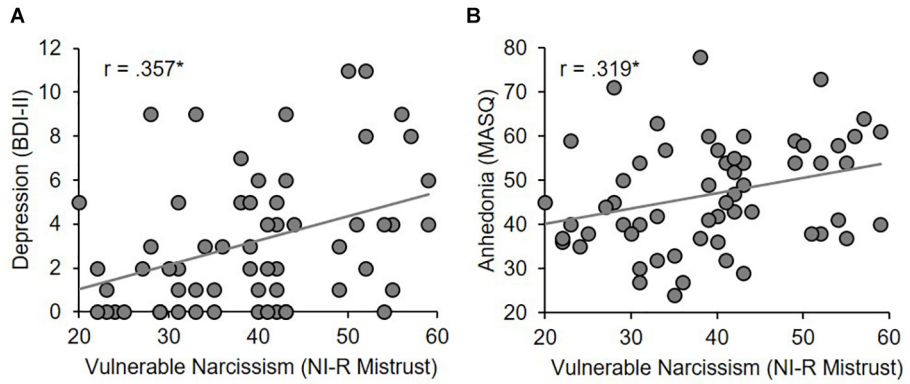

FIGURE 3 | Spearman correlations between depressive symptoms (**A**, BDI-II) and anhedonia (**B**, MASQ) and vulnerable narcissism (NI-R Mistrust). *$p \leq 0.05$.

sense, our findings support the notion that vulnerable narcissism appears to be associated with less adaptive emotion regulation. The finding that specifically the NI-R subscale Mistrust relates to a greater use of emotion suppression is in line with previous research (Altmann, 2017) and appears plausible as Mistrust is characterized by the expectation to be exploited by others (Altmann, 2017), which might require the deception of own emotions. Important to note, NI-R Mistrust does not cover the full range of vulnerable traits. Future studies should therefore extent findings to other aspects of vulnerable narcissism such as neuroticism, contingency and withdrawal. In line with our expectation of grandiose narcissism being related to less emotion regulation disturbances, our findings imply that individuals high in grandiose narcissism seem to avoid the suppression of positive emotions. Since grandiose narcissism is linked to an approach-orientation toward rewards it is not surprising that individuals with high expressions of grandiosity do not suppress positive feelings. The link between reduced use of this rather maladaptive strategy and grandiose narcissism was, however, only significant for the NPI-15 subscale Leadership/Authority, which has been claimed to reflect rather adaptive aspects of grandiosity (Ackerman et al., 2011). It comprises self-perceived leadership ability, social potency, and dominance and could be linked to the fearless dominance aspect of psychopathy as well as to self-esteem (Ackerman et al., 2011). It is important to mention that the mere use of certain (mal)adaptive strategies (e.g., suppression) does not necessarily indicate (dys)functional emotion regulation. In certain challenging contexts, suppression of the emotional response may be even desirable. Difficulties arise when emotion regulation strategies are inflexibly applied. Future research should therefore examine how individuals react to different situations to determine whether the strategies are applied flexibly and appropriate to the context. The emotional state of narcissists has been shown to be determined by their approach versus avoidance behavior (Czarna et al., 2018), which goes along with positive or negative emotionality, respectively (Elliot and Thrash, 2002). This is in line with the narcissism spectrum model (Krizan and Herlache, 2018) stating that vulnerable narcissists are rather avoidance-oriented and sensitive to threats, while grandiose narcissists are approach-oriented and sensitive to rewards. In support of this model, our findings related vulnerable narcissism to the avoidance-oriented emotion regulation strategy suppression whereas grandiose narcissism was linked to a reduced use of it.

In line with previous findings (Given-Wilson et al., 2011; Zhang et al., 2015), our results further revealed that vulnerable narcissism, but not grandiose narcissism, is associated with depressive symptoms. In more detail, higher expressions in NI-R Mistrust (vulnerable narcissism) were related to higher self-reported depressive symptoms and anhedonia. Mistrust refers to "competitive rivalry, devaluing others if they are not a source of admiration, and concealing one's needs and faults" and could be linked to a reduced life satisfaction (Altmann, 2017). It might therefore reflect maladaptive aspects of vulnerable narcissism. The NI-R Pretension, which relates to high moral standards and a desire to be admired for it (Altmann, 2017), was unrelated to depressive symptoms suggesting rather adaptive aspects of vulnerability. This interpretation is in line with previous findings of a positive, though small association with life satisfaction (Altmann, 2017). Importantly, only healthy participants with low depressive symptoms which have no clinical relevance have been included in this study. For this reason, future studies should examine the relationship between depression and narcissism in mild to moderately depressed individuals. In agreement with our results, previous research supports, however, an association between vulnerable narcissism and depression (Miller et al., 2011) as well as with characteristics predisposing to mental problems such as low self-esteem (Boldero et al., 2015). Furthermore, it has been shown that individuals at risk for depression tend to apply suppression rather than reappraisal (Ehring et al., 2010) suggesting an association between maladaptive emotion regulation use, which seems to be characteristic for vulnerable narcissism and mental health problems.

Important to note, we cannot necessarily deduce from our findings on habitual emotion regulation whether a person has emotion regulation difficulties, but only how often a certain (mal)adaptive regulation strategy is applied. We have therefore additionally examined the actual ability to regulate emotions by

means of an experimental task. Similarly to habitual reappraisal, grandiose narcissism was not related to reappraisal ability, which is in line with findings of Zhang et al. (2015). Surprisingly, neither was vulnerable narcissism significantly associated with reappraisal ability. A particular strength of our study was the assessment of both negative and positive emotion regulation but both without significant relations to narcissism, making valence-specific regulation deficits in narcissism unlikely. However, females with high expressions of vulnerable narcissism generally indicated higher happiness ratings during the emotion regulation task. Specifically, women high in NI-R Pretension reported high subjective happiness, which is in line with our suggestion that Pretension might reflect rather adaptive aspects of vulnerability. As mentioned earlier, our findings of a lacking association between narcissism and emotion regulation ability may be due to the inclusion of only healthy participants. Furthermore, non-significant results might be also the result of a relatively small sample and potentially lack of statistical power. Although it limits the number of participants included, our experimental assessment of regulation abilities is an important strength of our study, complementing previous studies on self-reported regulation. Likewise, the investigated regulation strategy, namely reappraisal, may account for the results. Since the "cognitive wave" in psychotherapy, there has been a strong focus on cognitive processes in emotion regulation and their significance for mental health. Nevertheless, other regulation strategies need to be considered as well. It has been suggested, for instance, that pathological narcissism might be specifically linked to externalizing regulation strategies such as substance use (Pincus and Lukowitsky, 2010).

The current study makes an important contribution to a better understanding of emotion regulation processes in vulnerable and grandiose narcissism. Our findings underline the need to examine both phenotypes since vulnerable narcissism (specifically Mistrust) seems to be related to rather maladaptive emotion regulation strategies and mental health problems while no such associations emerged for grandiose narcissism. However, it has been questioned whether these subtypes can really be separated or whether they are merely extremes of one narcissistic dimension between which narcissists can oscillate depending on environmental changes (e.g., experiences of insult or success; Lammers et al., 2013; Lammers and Doering, 2018). In line, Ronningstam (2009) highlights an oscillation between grandiose and vulnerable states and further proposes that narcissistic personality disorder is characterized by "a pervasive pattern of fluctuating and vulnerable self-esteem ranging from grandiosity and assertiveness to inferiority or insecurity, with self-enhancing and self-serving interpersonal behavior, and intense reactions to perceived threats" (p. 118). But even if vulnerable and grandiose narcissism represent two extremes of a narcissism dimension, it is mandatory to consider both phenotypes, both in research and health care. Otherwise, there is a risk of an underrepresentation of vulnerable narcissism, which may lead to a biased diagnosis of narcissism and in the worst case non-optimal treatment of individuals with predominantly vulnerable narcissistic traits.

DATA AVAILABILITY STATEMENT

The dataset for this study will not be made publicly available because we do not have an ethics votum for sharing the data.

ETHICS STATEMENT

The study involves human participants and was reviewed and approved by the local ethics committee of the Medical Faculty of the RWTH Aachen University. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the study. AH collected the data. LL and AH analyzed the data and drafted the manuscript. All authors contributed to the interpretation of the results. Furthermore, all authors critically revised the manuscript and approved the publication of its content.

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