NEUROBIOLOGICAL SYSTEMS UNDERLYING REWARD AND EMOTIONS IN SOCIAL SETTINGS

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NEUROBIOLOGICAL SYSTEMS UNDERLYING REWARD AND EMOTIONS IN SOCIAL SETTINGS

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EDITORIAL
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Editorial: Neurobiological Systems Underlying Reward and Emotions in Social Settings

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Editorial on the Research Topic

Neurobiological Systems Underlying Reward and Emotions in Social Settings

Emotions and reward are central to almost every aspect of human social life. The goal of this Research Topic was to collect new relevant research reports and theoretical frameworks on the neurobiological and psychological mechanisms underlying emotions and reward in different social settings, from the perspectives of neuroscience, biology, neurology, social medicine, philosophy, and psychology.

The human brain can be characterized as an inherently social organ; permanently adapting its function to the social context and constantly influenced by social interaction. In fact, it has been argued that the information processing capacity necessary for representing the complex social relationships in social groups was one of the driving factors in the evolution of the large primate and human cortex (1, 2). For an individual, being integrated in close social relationships has considerable consequences for physical and mental health and even for survival. This impact can even exceed the benefits of physical activity or absenteeism from alcohol (3). Further, most of the most frequent and debilitating mental disorders, like depression, anxiety disorders, or personality disorders, are characterized by profound deficits in social interactions, social cognition and emotion regulation as well as disturbances in social brain networks (4). The complementary use of new experimental paradigms and technologies in research (e.g., neuroimaging or virtual-reality) in the fields of psychiatry, neurology, neuroendocrinology, or phenomenology is necessary for a nuanced investigation of the mechanistic bases of social phenomena and might stimulate innovative multidisciplinary-based diagnostic and treatment strategies.

For a successful translation of basic science to implementation, research needs to integrate empirical experiments, clinical investigations, and theoretical models. We have covered all those three stages of research in our collection of 14 articles.

First, neural mechanisms of social cognition, emotions, and stress processing have been investigated in basic research with healthy subjects: Using functional magnetic resonance imaging (fMRI) and an empathic mirroring task, Ho et al. investigated an intervention designed for reducing parental stress. They found that the intervention's stress -reducing effect was mediated via selective neural responses and information trafficking patterns. Two other studies used

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electroencephalography (EEG) and emotional faces as stimuli; Yang et al. reported neural events underlying automatic and regulatory patterns of emotion appraisal, whereas Liu et al. found an interesting relationship between frontal EEG alpha asymmetry and individual differences in the processing of congruent and incongruent fearful faces. Similarly, but using diffusion tensor imaging (DTI) and fMRI, Jung and Kim looked at individual differences in the tendency to compare oneself with others, and found that these were predicted by different patterns of functional and structural brain connectivity. For the very relevant but understudied research field of olfaction, behavioral and fMRI evidence shows that social signals are transported with smells. Schäfer et al. demonstrate that mothers are able to detect the developmental state of children by smelling their body odors, especially when they have own children of similar age. Smelling odors of stressed persons leads to an increased activation of the Amygdala and related networks in healthy subjects that have a history of childhood trauma, as reported by Maier et al. This hypersensitivity to stress signals can be dampened by oxytocin.

Second, with a focus toward psychiatric patients, further clinical research is reported: An fMRI study on reward and affect by Soelch et al. found that increased reward-related neural activation during stress exposure was associated with positive affect in the daily life of young adults with a family history of depression. For females suffering from acute major depression, Warth et al., could show that an instructed positive interaction with their romantic partners results in higher stress levels, as assessed with cortisol on the one hand, but also improved relationship quality on the other hand. Therefore, adding to the evidence that the interaction of reward and stress is modulated in affective disorders. Likewise, in a single-subject study on a patient with acquired damage of bilateral amygdalae, Piretti et al. integrate the neural level with the subjective experience of emotions, thereby pointing out the interaction between this neural substrate and subjective shame during social norm violations. Kroczek et al. investigated interpersonal distance in social interaction using a novel paradigm in virtual reality to study social anxiety behavior of avoidance in real-life settings, and by integrating subjective experience, behavior, and physiology. For patients suffering from Borderline Personality Disorder, Schneider et al., could show a beneficial effect of applying the neuromodulator oxytocin for behavioral hypersensitivity/avoidance toward threatening facial stimuli. These findings nicely complement the above mentioned Maier et al.'s study of oxytocin's dampening effect to stress hypersensitivity in healthy controls with a history of childhood maltreatment.

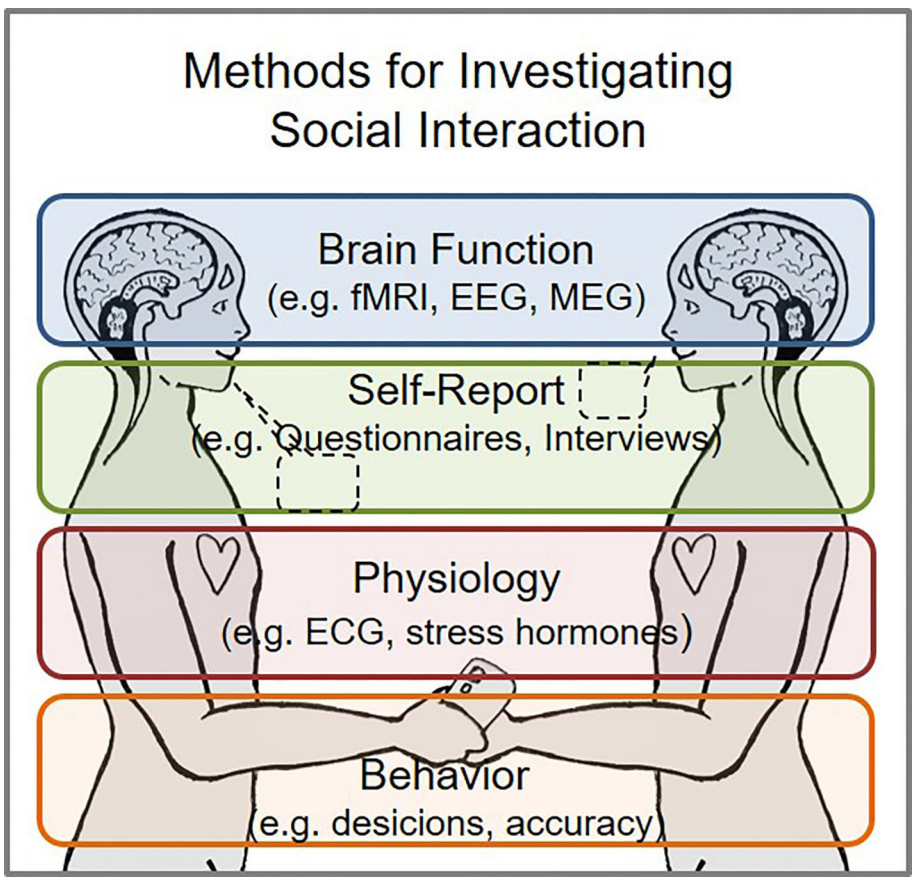

FIGURE 1 | Overview on multi-method perspectives for investigating social interaction.

At the third stage, in order to draw joint conclusions, review, and theoretical articles aimed to combine the heterogenous literature and integrate multiple perspectives; in these reviews, we particularly focused on integrating subjective and neurobiological proxies of emotions, stress and reward during contexts of social interaction. Eckstein et al. reviewed the current state of research on the role of social and non-social (robotic) touch for stress-relief from a medical as well as technical view, taking into account subjective experience and objective physiology. Matyjek et al. summarized multiple dimensions of social and non-social rewards, such as duration, familiarity, and source in a model in order to allow a differentiated description and recommendations for experimental comparisons. Levy and Bader follow on the empirical data above on subjective experience of emotions, empathy, and the integration of these experiences with neural data. They do so by providing a novel neuro-phenomenological framework (i.e., integrating neuroscience and subjective experience) on empathy, thereby extending dichotomous accounts and bringing forward an ecologically valid approach to real-life empathic encounters, while reporting empirical supporting evidence from magnetoencephalography (MEG) and other neuroimaging studies.

Taken together, the collection of studies in this research topic provides a multi-disciplinary outlook on emotions, reward, and social interactions by accumulating evidence from numerous neuroimaging techniques (MEG, EEG, fMRI, DTI), phenomenology, hormones, olfaction, virtual-reality, interventions, behavioral paradigms, and patient studies (**Figure 1**). The heterogeneity of these studies reflects the multiplicity of scientific approaches to study the complex processes and mechanisms involved in emotions and reward in social settings. This is particularly relevant at a time when (non-digital) social interaction is being reduced due to the Covid-19 pandemic, while providing an outlook on the involvement of multiple levels during social interactions. Thus, the research topic can motivate researchers to reproduce these findings and to test new hypotheses. For instance, what are the differences in mechanisms implicated during digital vs. non-digital social interaction? Does it influence interpersonal empathy? Does it implicate more stress and less reward? Finally, this topic can pave the road toward designing innovative interventions targeting the different levels of social interaction as outlined here (**Figure 1**).

AUTHOR CONTRIBUTIONS

ME and JL took the lead in writing this editorial while all authors contributed to finalizing it.

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Children's Body Odors: Hints to the Development Status

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Mothers can recognize their own children by body odor. Besides signaling familiarity, children's body odors may provide other information relevant to maternal caregiving behavior, such as the child's developmental status. Thus, we explored whether mothers are able to classify body odors on pre- vs. postpubertal status above chance levels. In total, 164 mothers were presented with body odor samples of their own and four unfamiliar, sex-matched children who varied in age (range 0–18 years). Pubertal status was measured by (a) determining the child's steroid hormone level and (b) parental assessment of the child's developmental stage using the Pubertal Development Scale. Mothers classified developmental status with an accuracy of about 64%. Maternal assessments were biased toward pre-puberty. Classification was predicted by perceptual evaluation of the body odor (i.e. intensity and pleasantness) and by the child's developmental stage, but not by hormones. In specific, mothers with pubertal-aged children classified body odors using the child's developmental status, whereas mothers with younger children only classified body odors using perceptual information (i.e. intensity and pleasantness). Our data suggests that body odors convey developmental cues, but how this developmental information is manifested in body odor remains unclear.

Keywords: olfaction, bonding, puberty, chemosignal, body odors, parent–child relationship, age

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INTRODUCTION

Body odors are a potent chemosignal in human social communication for two reasons. First, they allow recognition of the own relative among a number of individuals (Pause et al., 1998; Lundström et al., 2009). Second, both hedonic [i.e. pleasantness or attractiveness, (Kuukasjärvi et al., 2004; Croy et al., 2017)] ratings and neural activity (Cecchetto et al., 2019) support the idea that body odors communicate affective information to recipients. Both of these features of body odors are highly relevant in the context of mother–child bonding. In specific, kin recognition serves to facilitate a targeted investment of resources (Burnstein et al., 1994; Chapais et al., 2001), which is important for providing one's offspring with care. With regard to the affective value, in a previous study asking for parental perception of their children's body odors, we found that a baby's body odor was perceived as highly adorable and pleasant (Croy et al., 2017). In addition, mothers respond to infant's body odors with neural activation in reward-related processing areas [e.g. neostriate areas (Lundström et al., 2013)]. The authors concluded that the infantile odor may evoke a desire to bond in parents.

Kin recognition has been demonstrated in response to infants, preschool, and adolescent children (Porter et al., 1983; Weisfeld et al., 2003; Ferdenzi et al., 2010). Besides, recognition and a mother's preference for the body odor of her own child seem to affect each other.

For example, mothers who are not able to recognize their own child's body odor do not show a preference for their child's odor. Consistent with this, Croy et al. (2019) showed that mothers with postpartum bonding disorders had a lower preference for their own child's body odor, compared to healthy controls. Further, in a recent study conducted in our lab, we presented 164 healthy mothers to body odor probes of their own and sex-matched unfamiliar children in different age groups, from infancy to adulthood (Schäfer et al., in press). Interestingly, the relationship between source of the body odor (i.e. child vs. other) and odor preference in mothers, varied across the child's development – i.e. mothers preferred their own child's odor when the child was pre- or postpubertal, but not when the child was in early puberty. In that stage, the decrement in maternal pleasantness ratings of their son's body odor was associated with increasing testosterone levels in their sons. In addition, mothers were not able to identify their own child's body odor around puberty but were able to do so in pre- and late pubertal stages. Such findings, led to two suppositions; (1) that the loss of kin recognition with initial hormonal release around puberty is causal for a mother's lack of preference to her child's body odor and (2) that kin recognition and preference of the odor recover over time, because mothers get used to (i.e. are able to identify) the odor again.

In general, developmental cues are necessary for signaling a certain stage of maturity, which affects the amount and the manner of caregiving exerted by parents on their children. Several infantile facial characteristics facilitate a perception of cuteness, and thus elicit approach and attachment behavior (Kringelbach et al., 2016). Those features are lost with increasing development status and in the same time willingness for parental investment declines (Volk et al., 2007). In the domain of olfaction, similar mechanisms may be present.

In order to serve as a developmental cue, it is a prerequisite that body odors change during development. These changes are presumably due to developmental hormones. We base this assumption on the observation that female body odors smell different across the menstrual cycle. In specific, men rate female body odors as more pleasant during ovulation (Havlíček et al., 2017), and this preference is disturbed by women's hormonal contraceptive use (Kuukasjärvi et al., 2004). The particular hormones that mediate this alteration in odor preference across the menstrual cycle are yet to be identified but steroid hormones may be a likely candidate. Steroid hormones seem to affect body odor perception – for example, higher estradiol concentration is associated with higher attractiveness of female body odor (Lobmaier et al., 2018), whereas male body odor contains more androgen-derived steroids and is perceived as more intense (Sergeant, 2010). The relation to actual testosterone levels has however been unclear (Rantala et al., 2006).

As short-term hormonal fluctuations, such as those present during the menstrual cycle, are perceivable via body odor, we also assume that slow, long-term changes of hormonal and pubertal development from infancy (prepubertal stage) to adulthood (postpubertal stage) is reflected in body odor perception. Support for this supposition comes from a questionnaire study asking for parent's evaluation of their children's body odors across development (Croy et al., 2017). Parents reported less pleasantness of odors from their pubertal compared to younger children, which might mirror the increase of steroid hormones during that period.

Puberty is characterized by two main stages of development – the first stage, adrenarche, occurs between the age of 5 and 9 years and is characterized by arise of androgens without leading to visible changes. Children in that phase are still referred to as prepubertal. The second stage, gonadarche, begins between 9 and 11 years and is marked by testosterone and estradiol increase. During that phase, primary and secondary sexual features develop, peaking with transition to adulthood (Dorn et al., 2006).

The present study aimed to address whether body odors function as an indicator for development and explored the ability of mothers to identify a child's developmental stage, using body odor. We hypothesized that mothers are able to accurately distinguish pre- from postpubertal odors (H1). Further, we assumed that this ability depends on developmental familiarity of the mothers: a mother of a prepubertal child might be particularly good at accurately detecting prepubertal status in body odor, whereas a mother of a postpubertal child might be better able to classify postpubertal body odors (H2). Finally, we explored potential mechanisms (maternal perceptual ratings, hormonal and developmental status of the child) contributing to developmental classification of body odor (H3).

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the University of Dresden (Code: EK 104032015), and all participants provided written, informed consent in accordance with the Declaration of Helsinki. The study was part of a broader project assessing maternal kin recognition and hedonic evaluation of children's body odors (including the dimensions sweetness, wanting, and attraction) in relation to genetic analysis of the human leukocyte antigen complex. In order to facilitate readability, we omit from presenting the whole study here and focus on presentation of parts relevant for the current research question. For all further information, please compare (Schäfer et al., in press).

Participants

The sample consisted of $N = 164$ mothers ($M = 37.5$, $SD = 7.8$) with $N = 226$ children ($M = 7.6$, $SD = 5.9$ years, $n = 124$ girls, $n = 102$ boys), of whom 226 BO probes were sampled. Inclusion criteria was being the biological mother of a child between 0 and 18 years of age. Current pregnancy, insufficient knowledge of German language and anosmia or hyposmia were exclusion criteria. Olfactory performance was assessed prior to study inclusion with a short version of the standardized Sniffin Stick's Step II® screening for olfactory identification ability (Lötsch et al., 2016). In addition, prior to the experiment mothers were asked if they had acute rhino-sinonasal disorders (which could impair olfactory abilities), and were postponed to a later date if they reported having so.

Study Procedure

Participants came to an initial meeting in the lab of the Department of Psychosomatics at the University Hospital Dresden, in which the study procedure was explained and inclusion and exclusion criteria were tested. After meeting those criteria, participants were equipped with a study kit for sampling the body odors and hormonal status of their children at home.

The study kit included odorless shower gel, odorless detergent, a salivette (Salivette®, code blue, SARSTEDT AG & Co. KG, Nümbrecht, Germany), an unworn 100% cotton t-shirt or onesie in the respective size of the child, a re-closeable plastic zip bag, and a study protocol. In order to minimize potential sources of smell, the garment had been washed by the experimenter with an odorless detergent. The protocol contained detailed instructions for body odor and hormonal sampling, and also screened for potential confounders of the body odor sample – i.e. the presence of contamination of the sample (e.g. urine or feces), the medical condition of the child (use of drug and current illness), and the situation at home (smoking, pets, and number of persons who sleep in the children's room).

BO Sampling

The children slept for one night in the garment. Prior to that, parents were instructed to wash sheets and clothes additionally worn to the garment with odorless detergent (Denkmit Vollwaschmittel Ultra Sensitive, dm-drogerie markt GmbH & Co. KG, Karlsruhe, Germany[1]) and the children were asked to shower with the odorless shower gel (both EUBOS flüssig wasch+dusch, Dr. Hobein GmbH, Meckenheim, Germany[2]), as well as to refrain from usage of any perfumed hygiene products. After wearing the garment for one night, the sample was stored in a re-closeable plastic zip bag and brought back to the lab by the parents the next morning, which was where the sample was cut in half and then frozen (−25°C) until the experiment was carried out.

Hormonal Sampling and Assessment of Development Status

For all children aged between 5 and 18 years, hormonal sampling and maternal assessment of the pubertal status using the Pubertal Development Scale [PDS, (Watzlawik, 2009)] was performed. Hormonal sampling was carried out in the evening before the experimental night in order to measure hormonal status in direct relation to the body odor sample. Mothers were instructed to explain their children to chew for 60 s on the salivette until it contained sufficient saliva. Overnight, the salivette was stored in the fridge and the next morning, saliva and body odor sample were taken to the lab where they were frozen at −25°C until analyses. Hormonal analysis was carried out by the Dresden LabService GmbH. For each sample, testosterone and estradiol concentration was determined via immune-assay analyses as follows (Rohleder et al., 2006).

Concentration of alpha-amylase in saliva was measured by an enzyme kinetic method: saliva was processed on a Genesis RSP8/150 liquid handling system (Tecan, Crailsheim, Germany). First, saliva was diluted 1:625 with double-distilled water by the liquid handling system. Twenty microliters of diluted saliva and standard were then transferred into standard transparent 96-well microplates (Roth, Karlsruhe, Germany). Standard was prepared from "Calibrator f.a.s." solution (Roche Diagnostics, Mannheim, Germany) with concentrations of 326, 163, 81.5, 40.75, 20.38, 10.19, and 5.01 U/l alpha-amylase, respectively, and bidest water as zero standard. After that, 80 ml of substrate reagent (α-amylase EPS Sys; Roche Diagnostics, Mannheim, Germany) were pipetted into each well using a multichannel pipette. The microplate containing sample and substrate was then warmed to 37°C by incubation in a water bath for 90 s. Immediately afterward, a first interference measurement was obtained at a wavelength of 405 nm using a standard ELISA reader (Anthos Labtech HT2, Anthos, Krefeld, Germany). The plate was then incubated for another 5 min at 37°C in the water bath, before a second measurement at 405 nm was taken. Increases in absorbance were calculated for unknowns and standards. Increases of absorbance of diluted samples were transformed to alpha-amylase concentrations using a linear regression calculated for each microplate (GraphPad Prism 4.0c for MacOSX, GraphPad Software, San Diego, CA). The intra- and interassay coefficients for amylase were below 9 and 9%,respectively. The detection threshold for the analyzed samples was at 0.3 pg/ml for estradiol and at 1.8 pg/ml for testosterone.

Mothers completed the PDS (Watzlawik, 2009) which is a standardized assessment of pubertal status with sufficient reliability (r = 0.64–0.69) and validity (self- vs. external assessment, r = 0.39 and 0.83) (Watzlawik, 2009). The PDS comprises three questions for each boys and girls (development of body hair, growth of breast/beard, menarche, and voice break) which are summed up to a score indicating pubertal status (ranging from 3 = puberty has not begun) to 12 (development completed). According to the manual (Crockett and Petersen, 1987; Crockett, 1988; Carskadon and Acebo, 1993), the following categories were defined as indicators for the pubertal status of boys: prepubertal (3 points), early pubertal (4 or 5 points), midpubertal (6, 7, or 8 points), late pubertal (9–11 points), and postpubertal (12 points) status. For girls the classification was: prepubertal (2 and no menarche), early pubertal (3 and no menarche), midpubertal (>3 and no menarche), late pubertal (<7 and menarche), and postpubertal (8 and menarche) status.

Experimental Procedure

One and half hours before the experimental session, body odor samples were thawed. Subjects were asked to refrain from eating, drinking coffee, and smoking 1 h prior to the testing, as well as from usage of perfume on the study day. The experimenter refrained from usage of perfume and wore rubber gloves in order to not confound the odor of the samples.

In total, the mothers assessed six body odor samples including the body odor of the own child and four body odor probes of unfamiliar children, as well as an unworn blank probe (previously washed with the odorless detergent) to control for intensity of the body odor samples. The unfamiliar children were matched to the same sex as the own child and two different age groups (two children of the same age group as the own child, two children of a

[1] www.dm.de

[2] www.eubos.de

different developmental group; i.e. a prepubertal age group when the own child was postpubertal, and vice versa).

For body odor presentation, the experimenter instructed the subject to close the eyes during 6 s of smelling in order to focus on the smell and to not be biased by seeing if the sample belonged to a t-shirt or to a onesie. The sample was placed by the experimenter directly under the nose of the participants, with the armpit pad upward. After 6 s, the probe was placed back and the subject had to open her eyes and to rate the body odor.

Prior to the rating procedure, body odors were presented in a test trial without assessment of the probes. This was done in order to anchor the probes for intensity. The six samples were then rated on pleasantness and intensity using visual analogue scale (VAS), ranging from 0 ("not at all") to 100 ("very"). Afterward, mothers rated the age group of the body odor donor. Therefore, the subjects were instructed to choose one of the following categories for each sample: "<1 year," "1–3 years," "4–8 years," "9–13 years," "14–18 years," and ">18 years."

Statistical Analyses

All statistical analyses were performed with IBM SPSS Statistics 25 (IBM Corp, 2017).

For analyses, three age categories [based off Dorn et al. (2006)] were created to indicate the child's developmental status. These were as follow – prepubertal (0–8 years), midpubertal (9–13 years), and postpubertal (≥14 years). This grouping was confirmed by the prior assessed PDS categories. Almost all (126 out of 128, 98.4%) children aged 0–8 years had a PDS score which indicated prepuberty and 50 out of 55 (90.9%) of the children aged 14–18 years had a PDS score which indicated a late or postpubertal stage. We decided to exclude body odor probes of those seven children whose age groups did not align with the PDS for statistical analysis of H1 and H2. We also decided to exclude body odor probes of the $n = 42$ midpubertal children (9–13 years), as this group comprised children of heterogeneous developmental status at the transition between pre- to postpubertal status, and therefore was not suitable to be classified in one consistent stage (see **Table 1**).

This procedure led to a final sample size of 177 body odor probes for analysis of H1 and H2. As each mother rated multiple body odor samples, this resulted in 890 maternal assessments of developmental stage. For analyzing H3, we used the total sample of 226 body odor probes (=1127 assessments).

All analyses were carried out (a) for all children and (b) only for unfamiliar children excluding the own child's body odor sample from analyses. This additional analysis was done in order to not bias performance due to recognition of the own child's odor and thus assuming to know the age. For reasons of clearness, only analyses for all children are presented here. Results regarding the unfamiliar children are listed in the **Supplementary Material** (see **Supplementary Figures 3–5** and **Supplementary Tables 1–3**).

Mothers are able to accurately distinguish pre- from post-pubertal odors (H1); classification ability depends on developmental familiarity of the mothers (H2)

We first assessed whether there was a significant difference of maternal classification in children of prepubertal vs. postpubertal stage using χ^2 test. Subsequently, we tested the sensitivity, specificity and accuracy of classification. Therefore, all maternal answers were categorized in one 4-field matrix for each developmental status, and this was based on their accuracy. The four categories are as follow – (1) a true positive (tp) or hit was assigned in case of correct detection of the developmental status, (2) a true negative (tn) was assigned when a mother correctly rejected the developmental status (e.g. not choosing prepubertal for a postpubertal body odor), (3) a false positive (fp) was assigned when a postpubertal sample was rated as prepubertal (or vice versa), and (4) a false negative (fn) was assigned, when a body odor sample was not detected as pre- or postpubertal even though it was pre-/postpubertal. We calculated sensitivity, specificity, and accuracy of the maternal classification for each developmental status. Additionally, we calculated the RATZ-index indicating how much the maternal hit rate increases compared to the chance level [relative increase of the hit rate compared to the random hit rate (Marx and Lenhard, 2010)]. The index can take values between 0 and 1, with values from 0.3 being seen as an improvement to the random rate.

In order to explore the impact of maternal developmental familiarity, we compared for each mother the classification of those body odor samples which had the same developmental status as the own child (developmental familiar classification) to the classification of those body odor samples which had a different developmental status as the own child (developmental unfamiliar classification). Classification performance across the groups was compared using a 4×2 χ^2 test calculator[3].

We tested the influence of hormonal contraceptive use on maternal classification performance, as this has been previously reported to influence olfactory perception (Derntl et al., 2013). On the day of testing, 38.5% of the mothers stated to use hormonal contraception, 54% stated not to use hormonal contraception, and 7.5% did not reply to this question. Comparison between the groups revealed no significant differences between the groups [χ^2 (1) = 5.70, $p = 0.127$], which is why we did not include this in further analyses. We also compared maternal classification performance for boys and girls within each developmental status, and found no significant differences [prepubertal classification: χ^2 (1) = 3.65, $p = 0.057$; postpubertal classification: χ^2 (1) = 0.10, $p = 0.757$]. Therefore, we did not perform any further sex-specific analyses.

Predictors of pre- vs. postpubertal body odor classification (H3)

For H3, logistic regression analyses including bootstrapping ($n = 1000$) were performed with the binary outcome of pre- vs. postpubertal maternal classification as dependent variable.

As predictors we modeled perceptual evaluation of the body odor (pleasantness and intensity) in order to assess the influence of affective perception on the classification. For exploring the influence of developmental cues on body odor classification, the PDS score and hormonal status (comprising the testosterone status for boys and the estradiol status for girls in pg/ml) were

[3]https://www.socscistatistics.com/tests/chisquare2/default2.aspx

TABLE 1 | Frequencies of all presented body odor samples classified by PDS category and age group.

	Age group					
PDS category	**Prepubertal (0–8 years)**	***n* (%) girls**	**Midpubertal (9–13 years)**	***n* (%) girls**	**Postpubertal (14–18 years)**	***n* (%) girls**
Prepubertal	126 (98.4%)	67 (53.2%)	15 (35.7%)	4 (26.7%)	0	0
Early pubertal	2 (1.6%)	2 (100%)	10 (23.8%)	2 (20.0%)	0	0
Midpubertal	0	0	10 (23.8%)	9 (90.0%)	5 (9.4%)	0 (0.0%)
Postpubertal	0	0	7 (16.7%)	4 (57.1%)	50 (90.9%)	35 (70%)

N = 226 children, n = 124 girls, n = 102 boys, n (%) girls = number and percentage of girls within the respective category.

included as further predictors. All predictors were tested in one model using enter method.

All analyses were performed across all children and all mothers and then for developmental familiar samples and developmental unfamiliar samples separately.

RESULTS

Mothers Are Able to Accurately Distinguish Pre- From Post-pubertal Odors (H1)

When presented to body odors of prepubertal children, mothers stated in 71.6% of the cases that those odors were from a prepubertal donor and in 28.17% that these odors were from a postpubertal donor. When presented to body odors of postpubertal children, mothers stated in 58.6% of the cases that those odors were from a prepubertal donor and in turn, mothers stated in 41.4% of the cases that the odors were from a postpubertal donor (see **Figure 1**). The classification of an odor as postpubertal was significantly higher when mothers were presented to postpubertal odors than when they were presented to prepubertal odors [χ^2 (1) = 10.82, $p = 0.001$]. Furthermore, this result reveals that BOs are more frequently rated as originating from a prepubertal than from a postpubertal donor.

The detection of prepubertal odors was performed with an accuracy of 63%. This value exceeds the 50% chance level. However, the RATZ-index of 0.11 is rather low and suggests that mothers do not perform substantially better than chance. Maternal assessments of prepubertal odors had a sensitivity of 72.0% and a specificity of only 38.7%, indicating that maternal assessments tended to accept the classification of a sample as prepubertal [χ^2 (1) = 472.63, $p < 0.001$].

A similar effect was found for postpubertal body odors, which were detected with an accuracy of 64.0% at an RATZ-index of 0.14. Maternal assessments of postpubertal odors had a sensitivity of only 41.4% and a specificity of 71.2%, indicating that maternal assessments tended to reject the classification of a sample as postpubertal.

Classification Ability Depends on Developmental Familiarity of the Mothers (H2)

Separate analyses of developmental familiar samples and developmental unfamiliar samples revealed that mothers were more accurate in classifying body odors of donors at the same developmental status as their own child (see **Supplementary Figures 1**, **2**).

Hence, mothers of prepubertal children could identify prepubertal odors with a higher accuracy of 65.2% (RATZ-index = 0.19; sensitivity = 74.4%; specificity = 43.8%) compared to the 60.6% accuracy of mothers having postpubertal children (RATZ-index: 0.04%; sensitivity = 67.7%; specificity = 35.7%). The difference between maternal classification of developmental familiar samples and developmental unfamiliar samples was significant [χ^2 (1) = 9.84, $p = 0.020$].

Similarly, mothers of postpubertal children were more accurate in classification of postpubertal body odors (developmental familiar samples: accuracy = 65.2%; RATZ-index: 0.19; sensitivity = 43.2%; specificity = 73.6%; developmental unfamiliar samples: accuracy = 62.2%; RATZ-index: 0.07%; sensitivity = 37.7%; specificity = 68.1%) and maternal classification differed significantly between both groups [developmental familiar samples vs. developmental unfamiliar samples: χ^2 (1) = 8.95, $p = 0.029$].

Predictors of Pre- vs. Postpubertal BO Classification (H3)

The overall regression model across all mothers was significant [χ^2 (4) = 79.98, $p < 0.001$], revealing that pleasantness ($p < 0.001$), intensity ($p < 0.001$), and pubertal status (PDS score, $p = 0.007$) predicted developmental classification, while hormones did not relate to maternal decision ($p = 0.952$, see **Table 2**). In particular, higher pleasantness predicted prepubertal classification, whereas higher intensity and higher pubertal status were associated with postpubertal classification (see **Figure 1**).

The further regression models testing the respective groups were significant for developmental familiar samples [χ^2 (4) = 38.62, $p < 0.001$] and for developmental unfamiliar samples [χ^2 (4) = 50.29, $p < 0.001$]. For classification of developmental familiar samples, pleasantness, ($p = 0.001$), intensity ($p = 0.001$), and pubertal status ($p = 0.001$) but not hormonal status ($p = 0.706$) predicted developmental classification (see **Table 3**). Higher pleasantness related to prepubertal classification, whereas higher intensity and higher pubertal status were associated with postpubertal classification. For classification of developmental unfamiliar samples, only the perceptual ratings, pleasantness ($p < 0.001$) and intensity ($p = 0.001$), emerged as significant predictors with higher pleasantness predicting pre-, and higher intensity predicting postpubertal classification (see **Table 4** and **Supplementary Figures 1**, **2**).

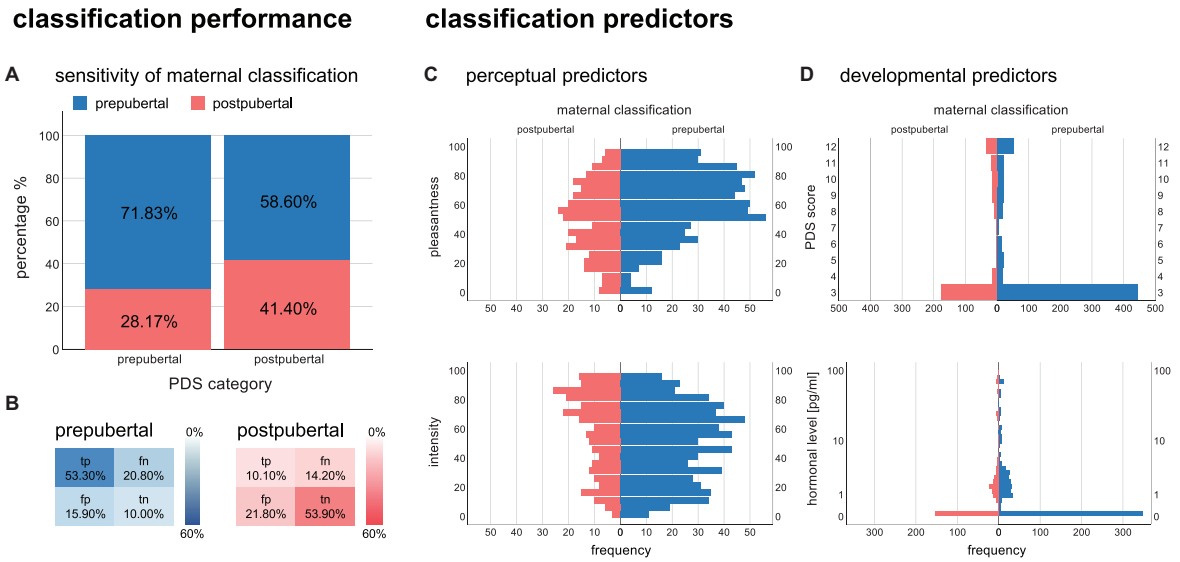

FIGURE 1 | Left panel: classification performance: **(A)** percentage of the sensitivity of maternal classification plotted by PDS categories; **(B)** percentage of frequency of true positives (tp), false positives (fp), false negatives (fn), and true negatives (tn) plotted in blue for prepubertal and in read for postpubertal body odors. Color intensity indicates frequency of choice. Right panel: classification predictors: **(C)** perceptual predictors (above: pleasantness, below: intensity); **(D)** developmental predictors [above: pubertal development scale (PDS), below: hormonal concentration in pg/ml, estradiol for girls, testosterone for boys]. Assessment of developmental predictors was carried out for all children from the age of 5 years on and therefore children under the age of 5 exhibit a value of 3 for the PDS (prepubertal) and a value of 0 for the hormonal concentration.

TABLE 2 | Results of logistic regression model predicting age classification; β, SE, Wald, df, *p*, e^{β}, 95% CI (e^{β}) of each predictor: all samples.

Predictor	β	SE β	Wald's χ^2	df	*p*	e^{β}	95% CI (e^{β})	
Pleasantness	−0.018	0.003	34.685	1	0.000	0.982	0.976	0.988
Intensity	0.013	0.003	23.358	1	0.000	1.014	1.008	1.019
Pds	0.062	0.023	7.212	1	0.007	1.064	1.017	1.114
Hormones	0.000	0.005	0.004	1	0.952	1.000	0.989	1.01
Constant	−0.848	0.284	8.928	1	0.003	0.428		

R^2 = 0.08 (Cox and Snell) and 0.12 (Nagelkerke). Model χ^2 (4) = 79.98, $p < 0.001$.

TABLE 3 | Results of logistic regression model predicting age classification; β, SE, Wald, df, *p*, e^{β}, 95% CI (e^{β}) of each predictor: developmental familiar samples.

Predictors	β	SE β	Wald's χ^2	df	*p*	Exp (*B*)	95% CI (e^{β})	
Pleasantness	−0.013	0.004	11.251	1	0.001	0.987	0.979	0.994
Intensity	0.012	0.004	11.426	1	0.001	1.013	1.01	1.02
Pds	0.092	0.028	10.519	1	0.001	1.096	1.04	1.16
Hormones	0.003	0.007	0.142	1	0.706	1.003	0.990	1.02
Constant	−1.240	0.373	11.075	1	0.001	0.289		

R^2 = 0.07 (Cox and Snell) and 0.10 (Nagelkerke). Model χ^2 (4) = 38.62, $p < 0.001$.

DISCUSSION

The present findings highlight that maternal classification of the body odor changes depending on the pubertal stage of the child. Further, accuracy of maternal classification was moderately low (i.e. around 64%). In detail, we observed a high sensitivity and low specificity in detection of prepubertal status and vice versa – i.e. postpubertal classification corresponded to low sensitivity and a high specificity. Hence, mothers were more prone to identify the presented body odors as prepubertal rather than postpubertal.

Mothers performed better when assessing developmental familiar samples than when assessing developmentally unfamiliar samples. This finding may indicate that mothers being exposed to a certain developmental stage are able to incorporate developmental knowledge better. This is illustrated by analysis of the classification's determinants – i.e. perceptual evaluation of the body odor, as well as the assessed pubertal status

TABLE 4 | Results of logistic regression model predicting age classification; β, SE, Wald, df, *p*, e^{β}, 95% CI (e^{β}) of each predictor: developmental unfamiliar samples.

Predictors	β	SE β	Wald's χ^2	df	*p*	Exp (*B*)	95% CI (e^{β})	
Pleasantness	−0.026	0.005	26.491	1	0.000	0.974	0.964	0.994
Intensity	0.014	0.004	10.826	1	0.001	1.014	1.006	1.023
Pds	0.001	0.042	0.000	1	0.990	1.001	0.922	1.086
Hormones	−0.004	0.010	0.182	1	0.670	0.996	0.977	1.015
Constant	−0.160	0.454	0.124	1	0.725	0.852		

R^2 = 0.12 (Cox and Snell) and 0.17 (Nagelkerke). Model χ^2 (4) = 50.29, $p < 0.001$.

predicted the maternal choice. In particular, the developmental familiar classification was guided by perceptual ratings and developmental information, whereas mothers based their decision on perceptual assessment only when rating developmentally unfamiliar samples.

The overall accuracy of developmental classification was low, although exceeding chance level. Body odors consist of various components including rather stable factors, such as the genetic profile (Milinski et al., 2013), but also highly variable influences, such as food, culture (Havlíček et al., 2017), or disease (Olsson et al., 2014). It is unclear how much variance each of these factors explain in odor perception. Typically, odors are difficult to identify in an unaided identification task and susceptible to label effects (Cuevas et al., 2009; Herz, 2003), which explains why odor perception is often ambiguous. Considering those facts, the low odor-identification accuracy found in this study is not surprising. Nonetheless, our data suggest that body odors at least carry the potential to signal developmental stage, which is explained in the following paragraphs.

The maternal susceptibility of detecting prepubertal status suggests that body odors serve as an important signal in human chemical communication. This appears especially true in infancy, when children are dependent on parental care. Parenting in the early childhood is characterized by formation of attachment, enabling the child to survive safely and to develop healthily in the world (Bowlby, 1958). Infantile positive signals, such as a cute baby face or babbling, trigger brain correlates of reward and approach behavior (Kringelbach et al., 2016). This is assumed to apply for body odors as well, and indeed, a baby's body odor elicits reward on a neural level, especially to mothers (Lundström et al., 2013). In our data, prepubertal status was detectable above chance by all mothers, independent from their expert status, which suggests that an infantile body odor may also serve as a universal cue for cuteness, similar to the "Kindchenschema." If this effect were to exist, it might have contributed to the maternal tendency to classify a body odor as prepubertal (rather than postpubertal), observed in this study. Further from an evolutionary perspective, our results may reflect a primacy to interpret children's body odors first as a general "cuteness." We assume that body odor perception leads to neural and behavioral responses similar to those observed for the "Kindchenschema" – i.e. a set of responses targeted to ensure the child's survival by formatting a bond that is prioritized over detachment (Glocker et al., 2009). Preliminary fMRI data from our lab indeed indicate that babies' body odors elicit neural correlates in the maternal brain similar to those reported for facial cuteness (Schäfer et al., 2019). However, further studies investigating the perception of infantile body odors across parents (including fathers) and non-parents still need to clarify the universality of such a stimulus.

Besides cuteness, odors may also communicate a certain degree of maturity. While maternal sensitivity for detecting postpubertal status was lower than for prepubertal status, postpubertal recognition was characterized by a higher specificity. These findings suggest that body odors change with increasing development, – however, which particular features determine this change and drive olfactory perception remains unclear. We did not observe any influence of steroid hormones on age classification. We know from our previous data that steroid hormones can affect maternal evaluation of pleasantness, however this finding is only apparent for male children in the transition from pre-to post-pubertal status [9–13 years (Schäfer et al., in press)].

We did not observe sex-related differences in maternal classification for postpubertal children. However, an important limitation is that we did not assess the menstrual cycle phase of postpubertal girls, which is known to affect body odor assessment (Havlíček et al., 2017). This should be regarded in further studies.

Salivary steroid hormones were measured in this study. These hormones fluctuate across the day (Landman et al., 1976) and do not always relate to secondary sexual features (Shirtcliff et al., 2009). Nevertheless, it is assumed that steroid hormones indicate maturity in the transition phase when the external development is not yet complete (Dorn et al., 2006). Based on our study we cannot exclude that steroid hormones are perceivable in body odor, further studies using different sampling methods may lead to different effects. Here, the external manifestation of pubertal development affected body odor classification, as children of higher pubertal status were more often classified as postpubertal. Further, this effect was driven by the mothers having experience with postpubertal children. As the onset of puberty is complex and characterized by various endocrinological cascades (Grumbach, 2002), we do not know if hormones other than steroids change body odor composition and further promote postpubertal recognition. The need of chemosensory body odor profiling is hence obvious in order to determine volatile odorants, which constitute body odor and affect hedonic evaluation.

As our study points out, perceptual assessment was a strong predictor for age classification across all mothers. Pleasantness was related to prepubertal classification, which is in line with previous findings on positive evaluation of infant's body odor (Fleming et al., 1993; Okamoto et al., 2016; Croy et al., 2017, 2019). Moreover, pleasantness perception of an

infant's odor is an important cue mediating parental care as it facilitates affectionate love (Okamoto et al., 2016). This affective component of body odor declines with age (Okamoto et al., 2016; Croy et al., 2017), which is supported by our results demonstrating that pleasantness drives pre- but not postpubertal classification. The latter was predicted by higher body odor intensity, which has been associated with less positive perception (Doty et al., 1978). In the sense of the mother-child relationship, this leads us to speculate that the intensity drives an avoidant reaction to postpubertal body odors. Hence, this could be interpreted as a mechanism for detachment, when the child becomes more independent and separates itself from parental care (Beyers et al., 2003).

CONCLUSION

In summary, this study demonstrates that developmental information is transcribed in body odor across childhood. While prepubertal status is generally transmitted and characterized by pleasant perception, postpubertal status is rather detected by mothers having expertise with children in that stage, and accompanied by higher intensity ratings. Mothers are further able to encode developmental information for classification when assessing body odors with similar developmental status to their own child. As the composition of body odor is still poorly understood, it remains to be determined how chemicals manifest body odor and how they actually influence olfactory perception.

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 Ethikkommission TU Dresden. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

IC, AS, and LS contributed to the conception and design of the study. LS acquired the data and wrote the first draft of the manuscript. LS and IC performed the statistical analysis. IC wrote the sections of the manuscript. AS and KW critically revised the manuscript. All authors contributed to the 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.2020.00320/full#supplementary-material

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Oxytocin Normalizes Approach–Avoidance Behavior in Women With Borderline Personality Disorder

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Background: Interpersonal deficits are a core symptom of borderline personality disorder (BPD), which could be related to increased social threat sensitivity and a tendency to approach rather than avoid interpersonal threats. The neuropeptide oxytocin has been shown to reduce threat sensitivity in patients with BPD and to modify approach–avoidance behavior in healthy volunteers.

Methods: In a randomized, double-blind placebo-controlled between-subject design, 53 unmedicated women with BPD and 61 healthy women participated in an approach–avoidance task 75 min after intranasal substance administration (24 IU of oxytocin or placebo). The task assesses automatic approach–avoidance tendencies in reaction to facial expressions of happiness and anger.

Results: While healthy participants responded faster to happy than angry faces, the opposite response pattern, that is, faster reactions to angry than happy faces, was found in patients with BPD. In the oxytocin condition, the "congruency effect" (i.e., faster avoidance of facial anger and approach of facial happiness vice versa) was increased in both groups. Notably, patients with BPD exhibited a congruency effect toward angry faces in the oxytocin but not in the placebo condition.

Conclusions: This is the second report of deficient fast, automatic avoidance responses in terms of approach behavior toward interpersonal threat cues in patients with BPD. Intranasally administered oxytocin was found to strengthen avoidance behavior to social threat cues and, thus, to normalize fast action tendencies in BPD. Together with the previously reported oxytocinergic reduction of social threat hypersensitivity, these results suggest beneficial effects of oxytocin on interpersonal dysfunctioning in BPD.

Keywords: placebo, reaction time, angry, happy, congruency effect

INTRODUCTION

Interpersonal dysregulation is a prominent and lasting symptom of patients with borderline personality disorder (BPD). Patients with BPD report more often about frequent negative interactions, less social integration, and poorer social support than do healthy individuals (1). Factors influencing such experiences could be symptoms such as fear of abandonment and impulsive behavior and also deficits in social cognition (e.g., empathy, cooperation, emotion recognition, and regulation) (2, 3). A related aspect is hypersensitivity to threatening information when processing emotional states of others (4). Patients with BPD tend to detect subtle signals of threat and to focus their attention on threatening interpersonal cues (4–6). Furthermore, faster initial saccades into the eyes—the most threatening part—of angry faces in patients with BPD suggest approach rather than avoidance behavior to interpersonal threat cues (7). In an experimental approach–avoidance task (AAT), anger-prone women with BPD reacted faster in approaching than avoiding angry—potentially threatening—faces than healthy women did (8). In such tasks, appetitive stimuli, such as happy faces, usually trigger approach behavior in healthy participants, while aversive or threatening stimuli, such as angry faces, trigger avoidance (9). Hence, healthy participants are faster when instructed to approach happy faces and to avoid angry faces than vice versa. This has been referred to as the "congruency effect": affect-congruent behaviors (approach happy/avoid angry) can be performed faster than affect-incongruent (approach angry/avoid happy) behaviors, which require the individuals to override fast affect-congruent tendencies (10–12). Taken together, there is increasing evidence that interpersonal dysfunctioning is associated with threat hypersensitivity and deficient avoidance of interpersonal threat in BPD, which may be a major factor underlying the high prevalence of reactive aggression in BPD (13).

Interestingly, the neuropeptide oxytocin has been found to modulate interpersonal processes, such as threat sensitivity and avoidance in healthy individuals (14). There is some evidence from healthy samples, which suggests that oxytocin may influence social threat approach (15). For instance, increased approach behavior was found toward angry faces after intranasal oxytocin administration in healthy male participants with low levels of social anxiety (11). Approach behavior also increased toward pleasant social stimuli (e.g., pictures of attractive men) in the oxytocin condition compared with the placebo condition in healthy women (16). However, there is inconsistency in data since a study by Theodoridou et al. (17) did not find any effects of intranasal oxytocin on behavioral tendencies to facial and non-facial stimuli depicting one of five emotions, except for a general prolongation of reaction times, in a large sample of healthy men and women.

Recently, oxytocin has become a rising topic in BPD research and is currently tested as an adjuvant in the treatment of BPD (18). Although the number of studies investigating the effects of oxytocin in BPD is still small and results remain heterogeneous, the first beneficial effects of oxytocin on threat processing have been reported: First, the intranasal administration of oxytocin reduced BPD patients' attention bias to angry faces in a dot probe task (19). Second, the above-mentioned tendency for faster and more saccades toward the eyes of angry faces was not found in patients with BPD following intranasal oxytocin administration, suggesting a decrease of social threat hypersensitivity (7). Until now, oxytocinergic modulation of approach–avoidance behavior has not been studied in BPD.

Given this background, we investigated the effects of oxytocin on approach–avoidance behavior using an AAT with angry and happy faces in 53 women with BPD and 61 healthy women. In a randomized, double-blind design, participants received either 24 IU of oxytocin or placebo intranasally. We expected a replication of the results by Bertsch et al. (8) with more approach behavior to angry faces in BPD in comparison to avoidance behavior. In the oxytocin condition, we expected reduced approach behavior toward potentially threatening angry stimuli in patients with BPD.

MATERIALS AND METHODS

Participants

Fifty-three unmedicated women with a current *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), diagnosis of BPD (BPD; $M_{\text{number of IPDE symptoms}} = 6.43$, $SD = 1.17$, range: 5–9; $M_{\text{age}} = 30.19$, $SD = 7.51$ years, range: 19–49 years; 26 oxytocin/27 placebo) and 61 healthy female controls (HC; $M_{\text{age}} = 28.36$, $SD = 7.65$ years, range: 18–52 years; 30 oxytocin/31 placebo) with no lifetime psychiatric diagnosis took part in the study (**Table 1**). Originally, 60 patients and 62 HCs were assessed; however, six patients had to be excluded because they had <50% valid trials (correct joystick movement in accordance to task of condition) in one or more conditions of the paradigm, and one patient and one HC had to be excluded because of technical difficulties in the recording.

Exclusion criteria were a current and lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, and alcohol or drug (nicotine excluded) dependence over the last 12 months (assessed via urine toxicology screenings and interviews), pregnancy, severe medical illness, severe visual handicap, neurological disorders, and organic brain damage. The number of comorbidities can be seen in **Table 2**. Participants were recruited through a central unit for diagnostics, which is part of the Clinical Research Unit funded by the German Research Foundation (DFG; KFO 256) (20). Additionally, participants had to be free of psychotropic medication for at least 2 weeks before participation.

Diagnostic Assessment

Axis I and II disorders were assessed by the Structured Clinical Interview (SCID-I) (21) and the International Personality Disorder Examination (IPDE) (22), respectively. Diagnoses were given by trained and qualified diagnosticians in accordance with DSM-IV (23). Intelligence (IQ) was estimated by the use of Raven's progressive matrices (24). Self-rating questionnaires assessed borderline symptom severity (Borderline Symptom List, BSL) (25), depressiveness (Beck Depression Inventory, BDI) (26), childhood traumatization (Childhood Trauma Questionnaire,

TABLE 1 | Demographic, hormonal, and clinical characteristics.

	BPD		HC				
	M	SD	M	SD	T/F_{df}	*p*	η_p^2
Age (in years)	30.19	7.51	28.36	7.65	1.28_{112}	0.202	
IQ	108.71	10.89	115.66	11.15	-3.34_{111}	0.001*	
Progesterone (ng/ml)	2.80	3.84	1.25	2.14	2.70_{112}	0.008	
Estradiol (pg/ml)	65.69	51.64	65.80	66.37	-0.10_{112}	0.992	
BSL	1.50	0.86	0.11	0.14	$122.39_{1,104}$	<0.001*	0.54
BDI	21.23	11.22	1.76	2.43	$142.04_{1,104}$	<0.001*	0.58
ECR-R anxiety	5.12	1.11	2.06	0.85	$253.22_{1,110}$	<0.001*	0.70
ECR-R avoidance	4.01	1.13	2.79	0.64	$152.74_{1,110}$	<0.001*	0.58
DERS	132.43	19.68	65.30	12.49	$417.17_{1,105}$	<0.001*	0.80
BIS	89.33	13.28	59.18	10.18	$151.62_{1,106}$	<0.001*	0.59
STAXI: trait anger	27.67	6.13	17.23	3.93	$92.92_{1,105}$	<0.001*	0.47
CTQ	60.72	23.39	30.63	7.85	$64.50_{1,105}$	<0.001	0.39

M, means; SD, standard deviation. Significant p-values marked with an asterisk. Bonferroni corrected for multiple testing. Factor "IQ" included as a covariate for questionnaire data. BSL, Borderline Symptom List; BDI, Beck Depression Inventory; ECR-R, Experiences in Close Relationships-Revised; DERS, Difficulties in Emotion Regulation Scale; BIS, Barratt Impulsiveness Scale; STAXI, State–Trait Anger Inventory; CTQ, Childhood Trauma Questionnaire.

CTQ) (27), attachment (Experiences in Close Relationships-Revised, ECR-R) (28), emotion dysregulation (Difficulties in Emotion Regulation Scale, DERS) (29), impulsivity (Barratt Impulsiveness Scale, BIS) (30), and trait anger (State–Trait Expression Inventory, STAXI) (31).

Hormonal Assessment

A blood sample was taken in 5-ml heparin-plasma Vacutainer tubes in order to analyze progesterone and estradiol to control for menstrual cycle. Samples were analyzed at the Central Laboratory of the University of Heidelberg, Germany, using chemiluminescence immunoassays (ACS:180® Estradiol-6 II test from Bayer Diagnostics, Germany). The assay detection limits were 0.2 ng/ml for progesterone and 11.8 pg/ml for estradiol. There was a minimal cross-reactivity with other related compounds. For progesterone, the coefficient for intra-assay precision was <3%, and the coefficients of variation for inter-assay and intra-assay precision were <6%. For estradiol, the coefficient for intra-assay precision was <6%, and the coefficients of variation for inter-assay and intra-assay precision were <7%.

Approach–Avoidance Task

The AAT (32) consisted of 192 trials in four blocks with 16 training trials and 32 main trials per block. The intertrial interval was 2–4 s, and between blocks laid 21–24 s. Blocks were counterbalanced across participants. Happy and angry faces with direct gaze from eight actors [four male and four female; selected from (33)] were presented as stimuli in a pseudorandomized order. Each stimulus was presented twice per block during the main trials and 12 times in total. Before each block, participants received either the instruction to push angry faces away from them and pull happy faces toward them (congruent condition) or the opposite instruction (incongruent condition) using a joystick (Attack 3, Logitech, Apples, Switzerland). Pushing or pulling the joystick resulted in shrinking or enlarging of the face ("zooming effect") (32). Then participants had to move the joystick back to the starting position. Participants were instructed to react as fast as possible. All participants underwent both conditions. The number of correct trials and reaction times, that is, the time from stimulus presentation until completion of the movement of the joystick, were recorded.

TABLE 2 | Current and lifetime comorbidities in BPD.

Comorbidity	Current (*n*)	Lifetime (*n*)
Mood disorder	15	45
Anxiety disorder	20	23
Obsessive–compulsive disorder	3	4
Posttraumatic stress disorder	9	21
Eating disorder	8	24
Substance dependence	0	9
ASPD	1	2
APD	19	20

ASPD, antisocial personality disorder; APD, avoidant personality disorder.

Experimental Protocol

The study was conducted with a double-blind, placebo-controlled design. Participants were screened via telephone and participated in a face-to-face diagnostic interview prior to the experiment. Experiments took place in the afternoon between 12 and 5 p.m. in order to control for diurnal hormonal patterns at the University Hospital of Heidelberg. Participants were asked to abstain from caffeine intake and smoking on the experimental day and from food intake 2 h before the experiment. Each participant was informed about the study protocol, gave written informed consent, and provided a urine sample for drug screening and pregnancy test as well as a blood sample for hormonal assessments. Then participants filled out

questionnaires. Following a protocol of our previous studies (7, 34–36), oxytocin (24 IU, Syntocinon Spray, Novartis, Basel, Switzerland) or placebo (spray with the same inactive ingredients but oxytocin) was intranasally applied by the participant with six puffs of 2 IU in each nostril. After administration, participants were asked to lie back in a 45° angle for 10 min. The drugs were prepared by an independent pharmacist according to an externally computerized randomization list (simple randomization). Electrodes for EEG measurements in another experiment were applied, and participants performed an emotion classification paradigm prior to the here reported experiment (results will be published elsewhere). Seventy-five minutes after application, participants were seated in front of a laptop with an attached joystick in a dimly lit, sound-attenuated room. Participants were instructed and completed a short training session. The duration of the AAT was ∼12 min.

Ethical Standards

The study was conducted according to the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. It was approved by the Ethics Committee of the Medical Faculty at Heidelberg University, Germany. All participants gave written informed consent and received equal monetary compensation for their participation.

DATA ANALYSIS

Data processing was performed in R (37) and data analyses in IBM SPSS statistics 25 (IBM, Armonk, NY). Independent *t*-tests were used to analyze differences in age, intelligence, and hormonal data between patients and HCs. Analyses of covariance (ANCOVAs) were performed for questionnaire data controlling for IQ due to a significant group difference. Bonferroni correction was used to control for multiple comparisons.

For AAT data, trials with reaction times of <150 or >1,500 ms were excluded from further analysis (included trials in analysis: 95.5%) (32). Participants with <50% valid trials (correct joystick movement in accordance to task of condition) in one or more conditions were excluded ($n = 6$) (38). Initial reaction time, that is, time from stimulus presentation until movement onset, was used for analysis. To analyze behavioral data, 2 × 2 × 2 × 2 repeated-measure analyses of covariance (rm-ANCOVA) with group (BPD and HC) and substance (oxytocin and placebo) as between-subjects factors and emotion (angry and happy) and congruency (congruent and incongruent) as within-subjects factors were used. IQ and estradiol and progesterone levels in order to control for hormonal levels and menstrual cycle were included as covariates. Dunn's multiple comparisons with Bonferroni correction for multiple testing were calculated as *post hoc* tests. Results were considered to be significant at $p < 0.05$. Partial eta squared (η_p^2) was used as a measure of effect sizes for rm-ANCOVAs and Cohen's *d* as a measure of effect sizes for *post-hoc* tests.

In an exploratory approach, correlations were calculated to test for possible associations between the congruency effect in angry faces (incongruent–congruent) and borderline symptom severity (IPDE criteria), attachment (ECR-R), impulsivity (BIS), trait anger (STAXI), or emotion dysregulation (DERS) separately in the oxytocin and placebo conditions in patients with BPD. Pearson's correlations were used for normally distributed data, and Spearman's correlation was used for skewed data (IPDE criteria only).

RESULTS

Demographics and Clinical Scores

The groups did not differ with regard to age, but a significant difference was found in the IQ; that is, patients with BPD had a lower—but still in the normal range—IQ than did HC. Groups differed significantly in all questionnaire data (see **Table 1** for detailed information).

Approach–Avoidance Behavior

There was a significant group-by-emotion interaction [$F_{(1,106)} = 6.24$, $p = 0.014$, $\eta_p^2 = 0.06$; **Table 3**] with faster reaction times in patients with BPD for angry than happy faces ($p < 0.05$, $d = -0.09$) and faster reaction times in HC for happy than angry faces ($p < 0.05$, $d = 0.09$). Furthermore, the analysis also revealed a significant group-by-emotion-by-congruency interaction [$F_{(1,106)} = 5.36$, $p = 0.022$, $\eta_p^2 = 0.05$; **Figure 1**]. *Post-hoc* tests showed that, in patients with BPD, reaction times for angry faces did not differ between congruent (avoid) and incongruent (approach) conditions ($p > 0.05$, $d = -0.11$), while HC responded significantly slower in the incongruent (approach angry) than congruent (avoid angry) condition ($p < 0.01$, $d = -0.26$), which is consistent with the congruency effect. For happy faces, both groups showed slower reactions in the incongruent (approach happy) than congruent (avoid happy) condition (BPD: $p < 0.01$, $d = -0.68$; HC: $p < 0.01$, $d = -0.52$).

We found a significant substance-by-congruency interaction [$F_{(1,106)} = 4.18$, $p = 0.043$, $\eta_p^2 = 0.04$; **Figure 1**]. *Post-hoc* tests revealed slower reaction times for incongruent trials in the oxytocin than in the placebo condition ($p < 0.01$, $d = 0.27$), while no substance effect emerged for congruent trials ($p > 0.05$, $d = 0.52$).

There were no further significant main or interaction effects (all $F \leq 0.02$, $p \geq 0.05$, $\eta_p^2 \leq 0.01$; **Figure 2**), and the correlation analyses did not reveal any significant associations with borderline symptom severity or self-report data in the oxytocin (IPDE: $r_s = 0.29$, $p_s = 0.152$; ECR-R anxiety: $r = 0.10$, $p = 0.631$; ECR-R: avoidance: $r = -0.10$, $p = 0.630$; BIS: $r = -0.05$,

TABLE 3 | Mean reaction times (M) in ms and standard error (SE) to angry and happy faces in patients with borderline personality disorder (BPD) and healthy controls.

	BPD		HC	
	M	SE	M	SE
Angry	715.73	14.24	702.29	13.06
Happy	725.07	15.73	692.89	14.43

Factor "IQ" and estradiol and progesterone levels included as covariates.

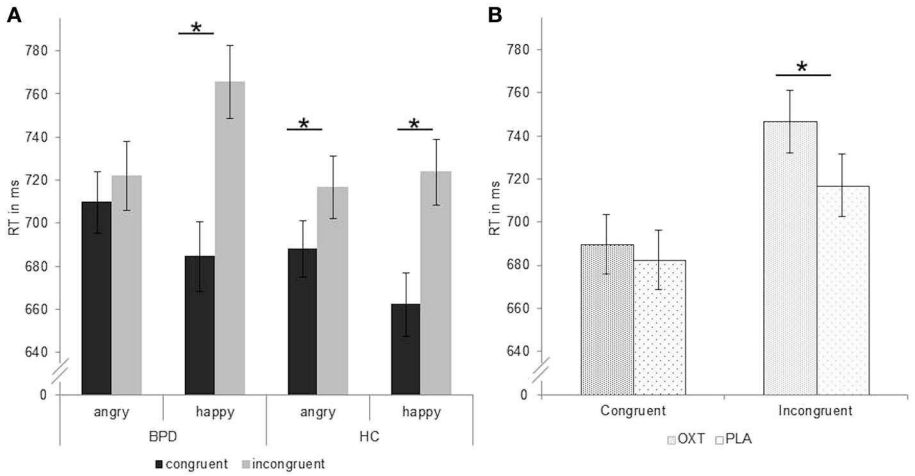

FIGURE 1 | Reaction times in ms (mean ± standard error) during performance of the approach–avoidance task. **(A)** Significant group-by-emotion-by-congruency interaction with missing congruency effect for angry faces in patients with borderline personality disorder (BPD). **(B)** Significant substance by congruency interaction with longer reaction times after application of oxytocin than placebo in the incongruent condition over all participants. Factor "IQ" and estradiol and progesterone levels included as covariates. Significant comparisons are marked with an asterisk indicating $p < 0.05$ at the *post-hoc* test. OXT, oxytocin; PLA, placebo.

$p = 0.795$; STAXI: $r = 0.19$, $p = 0.363$; DERS: $r = 0.05$, $p = 0.826$) or placebo (IPDE: $r_s = 0.02$, $p_s = 0.935$; ECR-R anxiety: $r = 0.13$, $p = 0.519$; ECR-R: avoidance: $r = -0.14$, $p = 0.489$; BIS: $r = 0.02$, $p = 0.920$; STAXI: $r = -0.23$, $p = 0.245$; DERS: $r = -0.27$, $p = 0.170$) condition in patients with BPD.

DISCUSSION

The study revealed three major findings: First, patients with BPD responded faster to angry than happy faces, while healthy participants showed the opposite pattern, that is, faster responses to happy than to angry faces. Second, patients with BPD were as fast in approaching as in avoiding angry faces and did not show the typical congruency effect for angry faces. Third, reaction times in incongruent conditions (approach angry and avoid happy faces) were slower in the oxytocin condition across both groups, leading to a more pronounced congruency effect under oxytocin (**Figure 2**); in the case of patients with BPD, this prolongation resulted in a normalization of behavioral tendencies in response to angry faces in comparison to previous results (8); that is, they were faster in avoiding than in approaching angry faces.

Our first finding of faster reaction times to angry compared with happy faces is in line with the theory that patients with BPD show a bias toward threatening information (4). For example, patients with BPD show faster initial saccades into the eyes of angry faces, (7) are more likely to recognize even subtle signals of anger in facial stimuli (5), and misconstrue happy, fearful, or neutral faces more often as angry (6). In the healthy participants though, positive stimuli triggered faster emotional reactions than negative stimuli, replicating previous findings (39).

In line with our *a priori* hypothesis, our second finding replicated a missing congruency effect for angry faces in an independent sample of BPD patients (8). Patients with BPD were as fast in approaching as in avoiding angry faces, suggesting a deficit in fast avoidance tendencies for interpersonal threat cues. Notably, patients in the current sample were not faster in approaching than avoiding angry faces as reported by Bertsch et al. (8) who, however, only included anger-prone patients with BPD. Such anger-prone patients might feel particularly provoked by interpersonal threats and have more pronounced avoidance deficits compared to an "average" BPD sample as included in this study, increasing the risk of aggressive behavior.

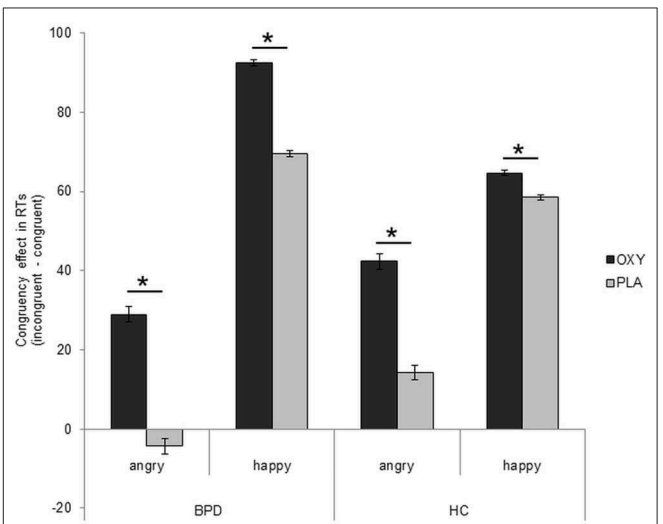

FIGURE 2 | Presentation of congruency effect after application of oxytocin in patients with borderline personality disorder (BPD). Difference scores (incongruent–congruent conditions) of reaction times in ms (mean ± standard error). Factor "IQ" and estradiol and progesterone levels included as covariates. Significant comparisons are marked with an asterisk indicating $p < 0.05$. OXT, oxytocin; PLA, placebo.

Since we did not find any significant correlations with anger or other trait measures in the current study and the heterogeneity among patients with BPD is large, further studies with larger groups are needed to further elucidate the circumstances under which deficient threat avoidance, that is, increased approach behavior toward threat stimuli, is related to anger outburst and aggressive behavior.

Finally, our third and most important finding confirms our hypothesis of an oxytocinergic modulation of approach–avoidance behavior in BPD. Across both groups, participants in the oxytocin condition responded generally slower than those in the placebo condition. This is consistent with previous reports of prolonged reaction times in the AAT after oxytocin administration (17, 39). Furthermore, according to a substance-by-congruency interaction, oxytocin particularly increased reaction times in affect-incongruent (approach angry and avoid happy faces), but not affect-congruent (avoid angry and approach happy faces) conditions. Most interestingly, with oxytocin administration, patients with BPD were faster in avoiding than approaching angry faces, thus showing the "normal" congruency effect. This oxytocin-induced normalization of approach–avoidance behavior in comparison to previous results (8) might be related to more cognitively controlled action tendencies to social threat cues as suggested by data indicating reduced prefrontal–amygdala communication during deficient emotional action control in terms of increased approach behavior toward angry faces in BPD in a functional neuroimaging study using the AAT (8). Oxytocin might also affect amygdala activation, a region involved in the processing of fast emotional behavioral tendencies since a previous neuroimaging study in healthy men has revealed decreased amygdala activation after oxytocin vs. placebo administration during threat approach, but not avoidance (39). Oxytocin effects on the amygdala were also observed in patients with BPD who showed not only less fast and less frequent saccades but also lower amygdala activity toward angry eyes compared to patients in the placebo group (7). Although we can only speculate about the neural underpinnings of the current effects, an oxytocinergic modulation of amygdala activation and/or prefrontal–amygdala coupling affecting cognitive control seems likely.

It needs to be noted that oxytocin had similar behavioral effects in patients and HCs and that no significant interaction with group was found. Our results also partly differ from those of previous studies where oxytocin had a reinforcing effect on approach behavior toward threatening stimuli in healthy volunteers (11, 15). The heterogeneity of oxytocinergic effects on behavioral tendencies in healthy individuals needs to be addressed in further studies and could be related to differences in sex or other sample characteristics (anxiety level and attachment style) as well as methodological issues, such as paradigm, design (within vs. between subject), or context (neuroimaging vs. behavioral lab) (15).

When the current findings are interpreted, several limitations need to be considered, such as the limited sample size, the between-subject design, and the comorbid mental disorders in the BPD group. Additionally, we specifically focused on a female sample in order to avoid potential bias induced by sex. However, we do not have reliable data on hormonal contraception of the participants, which could be a possible confounding factor. The AAT was conducted ∼75 min after substance application, which is still in the range of elevated peripheral and presumably also central oxytocin levels (40, 41) but might be past its peak levels (30–60 min after application) in the cerebral spinal fluid (42). Therefore, a replication in a larger sample including male and female participants and a clinical control group, as well as including imaging techniques in order to understand more about underlying mechanisms, are necessary next steps. Additionally, dose-dependent effects of oxytocin need to be investigated in future studies, preferably in a pre–post design. If replication studies prove our results as reliable, future study designs need to extend to more naturalistic environments in order to examine oxytocin as a potential drug for BPD treatment.

Despite these potential shortcomings, this study revealed an oxytocin-induced normalization of threat avoidance behavior in patients with BPD by prolonging reaction times in affect-incongruent (approach angry and avoid happy faces) conditions. Together with previous results and consistent with a recently published review (3), the current findings suggest beneficial effects of oxytocin for patients with threat hypersensitivity and deficient threat avoidance, as found in BPD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available Requests will need to be reviewed and agreed upon with the Clinical Research Unit (KFO 256) as the data was collected as part of it.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty at Heidelberg University, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IS: acquisition of data, analysis and interpretation of data, and drafting and finalizing of the manuscript. SB: acquisition of data, analysis and interpretation of data, and critical revision. IV and KR: study conception and design and critical revision. AS: acquisition of data and critical revision. SH: study conception and design, drafting of the manuscript, and critical revision. KB: study conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision.

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Interpersonal Distance During Real-Time Social Interaction: Insights From Subjective Experience, Behavior, and Physiology

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Physical distance is a prominent feature in face-to-face social interactions and allows regulating social encounters. Close interpersonal distance (IPD) increases emotional responses during interaction and has been related to avoidance behavior in social anxiety. However, a systematic investigation of the effects of IPD on subjective experience combined with measures of physiological arousal and behavioral responses during real-time social interaction has been missing. Virtual Reality allows for a controlled manipulation of IPD while maintaining naturalistic social encounters. The present study investigates IPD in social interaction using a novel paradigm in Virtual Reality. Thirty-six participants approached virtual agents and engaged in short interactions. IPD was varied between 3.5 and 1 m by manipulating the distance at which agents reacted to the participant's approach. Closer distances were rated as more arousing, less pleasant, and less natural than longer distances and this effect was significantly modulated by social anxiety scores. Skin conductance responses were also increased at short distances compared to longer distances. Finally, an interaction of IPD and social anxiety was observed for avoidance behavior, measured as participants' backward motion during interaction, with stronger avoidance related to close distances and high values of social anxiety. These results highlight the influence of IPD on experience, physiological response, and behavior during social interaction. The interaction of social anxiety and IPD suggests including the manipulation of IPD in behavioral tests in Virtual Reality as a promising tool for the treatment of social anxiety disorder.

Keywords: Virtual Reality, psychophysiology, social anxiety, approach, avoidance

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INTRODUCTION

Interpersonal distance (IPD), the physical space between persons, sets the ground for social interactions. As a part of non-verbal communication, IPD allows to coordinate social behavior in face-to-face encounters (1). IPD reflects the feeling of comfort in social situations and is largely dependent on relational and cultural factors as well as positive or negative attitudes (2, 3). Different

zones of spatial distances have been related to different social functions (4): Intimate space (0–45 cm), personal space (45–120 cm), social space (129–365 cm), and public space (365–762 cm). Following Hayduk (5), personal space is defined as the area that individuals maintain around themselves where intrusion through others causes discomfort. Intrusions in personal or even intimate space have been related to an increased feeling of threat and increased physiological arousal (6, 7). This is in line with findings that show increased activation of the amygdala for close IPD (8). IPD is therefore a salient feature of social interaction [(9) for an overview]. Importantly, IPDs reflect both avoidance-related and approach-related behavior. A recent study investigated the influence of a fairness manipulation on distance and gaze behavior in Virtual Reality (10). While participants generally avoided unfair agents, the reversed pattern, i.e., approach toward unfair agents, was observed for participants who actively punished unfair agents. This demonstrates the sensitivity of distance measures to different motivational behaviors. Furthermore, IPD is of great interest for the investigation of mental disorders where processing of social information may be affected, like social anxiety disorders and autism spectrum disorders (11, 12).

Social anxiety is characterized by the fear of negative evaluation through others (13). This fear is typically related to social situations, like eating in public, giving a talk, or informal conversations. Highly social-anxious individuals perceive social stimuli as more threatening and this also relates to IPD, where close distances are perceived more threatening than longer distances (11, 14–16). Furthermore, in Virtual Reality paradigms, social anxiety has been related to avoidance behavior such as backward head motion, aversion of eye contact, slow approach and increased distance to virtual agents (14–16). These studies highlight the role of IPD in social interaction and suggest IPD as a target for the investigation of social anxiety. However, so far no studies have investigated the influence of social anxiety for a range of IPDs while measuring subjective experience, physiology, and behavior.

Besides the important role of IPD in social interaction only a small number of studies have systematically investigated the influence of IPD on experience, physiology, and behavior (17). Typically, the stop-distance paradigm has been employed to study IPD and personal space [see (5)]. In this paradigm, the participant approaches an experimenter/confederate and stops as soon as the closeness feels uncomfortable (active stop task). Alternatively, the experimenter/confederate approaches the participant and is stopped by the participant (passive stop task). The stop-distance technique shows high reliability (17) and possesses moderate ecological validity. Furthermore, the stop-distance technique has been successfully applied both in real and in virtual settings (18). However, while the paradigm may be useful to measure personal space itself, there are some limitations when it comes to the study of IPD during social interaction. First, it might be difficult to reach full control over other non-verbal cues, such as eye-gaze and body posture. These cues have been shown to influence social interaction (19) and are directly related to IPD (15). Secondly, even when non-verbal cues are carefully controlled, for example, in a virtual reality paradigm, the absence of other social cues might render the interaction unrealistic. Social interaction is a dynamic process between two or more interaction partners, where all partners respond to social cues elicited by each other (20). Lastly, using the stop-distance technique, it is difficult to sample measures at various distances [but see (17)]. Therefore, data on the effects of IPD is limited to a few sample points and a systematic investigation of the effects of IPD on subjective experience, physiology and behavior has been missing.

The goal of the current study was to address these issues by systematically investigating the influence of IPD on experience, physiology, and behavior in real-time social interaction and to further relate these measures to social anxiety. For that reason, a novel experimental paradigm was implemented in Virtual Reality where participants had to approach virtual agents and engage in minimal social interactions. Crucially, IPD was varied by manipulating the reaction distance (1 to 3.5 m) at which the virtual agents responded to the participants' approach by changing from a passive to a responsive mode, i.e., looking up. This allowed varying IPD in a controlled manner while presenting real-time social interactions, where virtual agents directly responded to participants' approach. Subjective experience of these interactions was assessed *via* ratings of arousal, valence, and realism. Autonomic activity (ECG, EDA) was continuously measured during approach and interaction to test the influence of IPD on physiological arousal. Finally, we evaluated participants' movements once the reaction distance had been reached in order to characterize avoidance behavior.

We hypothesized that participants would rate close IPD in social interaction as more arousing, less pleasant, and less realistic compared to intermediate and remote distances. Furthermore, close distances should elicit increased autonomic activity in terms of skin conductance response (SCR) and changes in heart rate (HR). We also expected to find increased avoidance and reduced approach behavior at close distances. Finally, it was hypothesized that these effects should be modulated as a function of social anxiety, with high social-anxious individuals showing increased sensitivity to close distances compared to low social-anxious individuals.

METHODS

Participants

Forty healthy adults participated in the present study. Four participants had to be excluded due to technical problems during data acquisition. The remaining 36 participants were healthy students who did not report any mental or neurological disease (mean age = 21.75, sd = 3.03, range 18–34, 18 female). Participants received credit points as compensation. For two participants, distance measures were not recorded and these participants were excluded from the analysis of avoidance behavior. Experimental procedures were in line with the Declaration of Helsinki and the study was approved by the ethics board of the German Society for Psychology (DGPs).

Questionnaires

Questionnaires were used to assess social anxiety [SPIN (21, 22)], presence [IPQ (23)], state and trait anxiety [STAI (24)], as well as demographic information. Using the median split of the Social Phobia Inventory score (median = 16.5), participants were assigned into two groups: Low social-anxious participants (LSA, SPIN mean = 11.78, sd = 3.95) and high social-anxious participants (HSA, SPIN mean = 24.89, sd = 5.95). **Table 1** depicts comparisons of groups with respect to assessed questionnaires: SPIN, State Trait Anxiety Inventory and the iGroup Presence Questionnaire (Subscales: Spatial Presence, Involvement, Experiences Realism and General item). With respect to the STAI, the trait version was assessed only before the start of the experiment and the state version was assessed before and after the experiment. There was a significant difference in the trait anxiety score as well as in the post experiment state anxiety score, with higher anxiety in the HSA group compared to the LSA group.

Apparatus

The virtual environment was presented *via* head mounted display (HMD, HTC Vive) and participants wore headphones for auditory stimuli. The Virtual environment was created using the Unreal Engine (Version 4.21, Epic Games). The virtual environment was controlled by a scripted experiment paradigm as well as simulation data acquisition established using the VR experiment control software CyberSession (Version 5.8, VTplus, Würzburg, Germany). During the experiment, participants were located in a virtual room with three tables arranged in a triangular pattern in the center of the room (see **Figure 1**). Size of the participants' avatars was always set to 170 cm, so that participants were about the same height as the virtual agents. The body of the avatar of the participants was not displayed. Distance between tables was always six meters. Participants navigated freely through the virtual room by using a gamepad held in the right hand. There were three virtual agents (all male) each with a fixed location at one of the three tables. Agents were either in a passive mode in which they looked at their mobile phone or in a responsive mode in which they looked up from the mobile phone and directed their eye-gaze toward the participant. The transition from passive to responsive mode was triggered when participants reached a specific distance to the agent. These distances were the main experimental manipulation and varied between 1 and 3.5 m in steps of 0.5 m (6 distances in total). For each agent, a pre-recorded audio segment of "*Hello*" was available.

TABLE 1 | Mean and standard deviations for all obtained questionnaires separately for the HSA and LSA group.

Measure	HSA Mean (sd)	LSA Mean (sd)	t-test p-value
SPIN	24.89 (5.95)	11.78 (3.95)	<.001
Age	21.78 (2.41)	21.72 (3.61)	.957
STAI Trait	43.03 (7.00)	34.73 (6.68)	<.001
STAI State Pre	39.83 (10.19)	34.61 (7.29)	.087
STAI State Post	38.67 (8.38)	32.77 (5.82)	.020
IPQ-G	4.17 (1.65)	4.39 (1.09)	.639
IPQ-SP	2.68 (1.03)	2.58 (0.46)	.711
IPQ-INV	3.88 (0.90)	3.90 (0.90)	.926
IPQ-ER	2.79 (0.84)	2.57 (0.70)	.393

Comparison between groups was done using Welch two sample t-tests. SPIN, Social Phobia Inventory; STAI, State Trait Anxiety Inventory; IPQ, iGroup Presence Questionnaire with subscales; G, General; SP, Spatial Presence; INV, Involvement; ER, Experienced Realism.

Measures

Physiological measurements included ECG, EDA, and EMG. For ECG recordings two electrodes were attached to the chest, one at the sternum and one at the left, lower coastal arch. With respect to EMG recordings, each two Ag/AgCl electrodes were positioned on the neck above the left and right *Musculus trapezius*. Reference and ground electrodes were located on the left and right mastoid, respectively. Skin conductance was assessed *via* two electrodes located on the palmar surface of the left hand. All physiological data was recorded using a V-Amp amplifier (BrainProducts, Gilching, Germany) with a sample rate of 1000 Hz. Data analysis of physiological measures was only conducted for ECG and EDA. EMG data was not further analyzed. In order to allow for free movements, participant wore the amplifier in a bag attached to a belt.

As a behavioral measurement, we recorded the distance between participant and each of the agents as a continuous measurement with a sample rate of 90 Hz. The distance was calculated from head of the participant to the heads of the virtual agents.

In order to synchronize data collection from different sources (i.e., physiology and distances) we used Lab Streaming Layer and recorded data with the Lab Streaming Recorder (25).

Furthermore, ratings were assessed in every trial following the interaction with the agent. Ratings were obtained for arousal ("*How high is your emotional arousal?*"), valence ("*How pleasant do you feel?"),* and realism ("*How natural was the interaction?").* All ratings were given on a scale from 0 to 100.

Procedure

After electrode preparations, participants were introduced into the virtual environment. Initially, there was an exploration phase of 2 min, where participants navigated freely through the virtual room with no agents present. This initial exploration phase was conducted to accustom participants to the virtual environment.

After completion of the exploration phase, the actual experiment was started. There were 36 trials. At the beginning of a trial participants were located at one of the three tables, with two virtual agents standing at the two other tables in front of them (left and right side, see **Figure 1**). Virtual agents were in a passive mode, each staring at a smart phone. There was no agent at the table where the participants were located. After a delay of 1 s, an audio instruction was presented *via* headphones which asked the participant to approach and greet one of the agents (left or right side was balanced across trials). There were 12 trials per agent and the order of agents was pseudorandomized. Initially, navigation was disabled to prevent participants from leaving the starting position before or during the instruction. After the audio instruction, navigation was enabled and participants moved

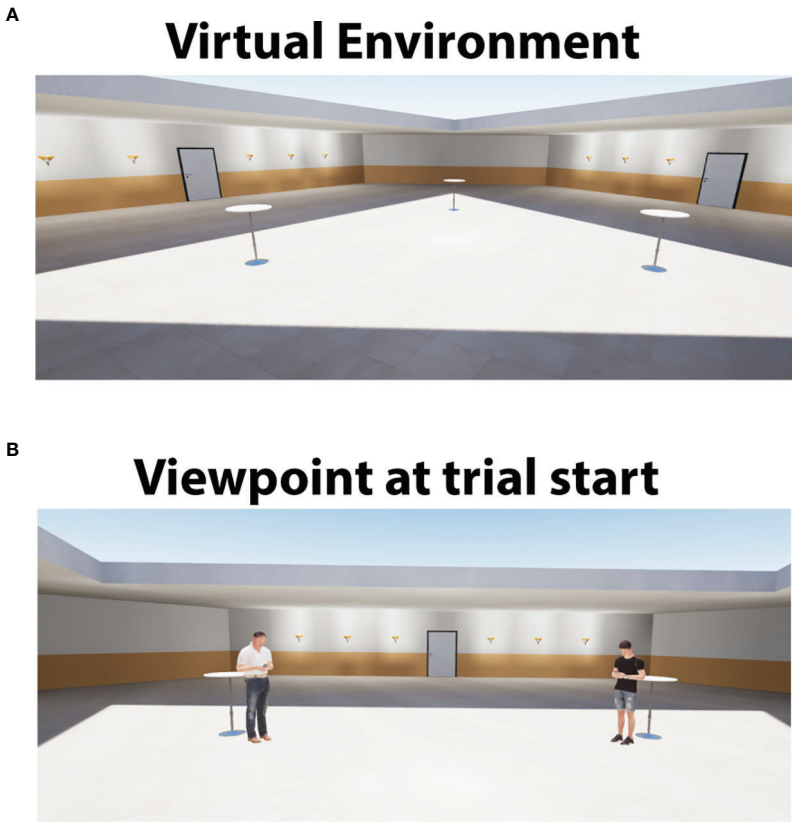

FIGURE 1 | (A) Virtual Environment with no virtual agents present. **(B)** Virtual environment at the beginning of a trial with two agents in passive mode. Participants were equidistant from both agents (always 6 m).

toward one of the agents. At a specific pre-defined distance agents changed from the passive mode to the responsive mode by looking up and fixating the participant (reaction distance). The order of reaction distances over trials was pseudorandomized. In total, there were six trials per reaction distance with two trials per reaction distance per agent. Participants were instructed to greet the agent, as soon as the agent responded to their approach by looking up. The agents then responded by saying "*Hello*" (the agent's response was controlled by the experimenter). Following this interaction, participants were asked to rate arousal, valence, and realism on a scale from 0 to 100 (a score of 100 was indexed as highly arousing, pleasant or realistic). After the ratings, the next trial started. The starting position of the new trial was always the table which had been approached in the previous trial. A trial lasted for about 40 s. There was a break of self-determined length after 18 trials. The total duration of the experiment was about 30 min.

Data Processing

Data analysis was conducted in Matlab (Mathworks, USA). Preprocessing pipelines were adapted to requirements of the individual measures.

Preprocessing of the ECG data included referencing of the ECG channels, filtering (highpass: 5 Hz, lowpass: 30 Hz, notch: 50 Hz). For HR analysis, R waves were identified using a Matlab implementation of the Pan-Tompkin algorithm (26). Data was segmented into epochs of 6 s following the initial reaction of the agent (i.e., the onset of the agent's change into the responsive mode). HR was calculated for all segments and then exported for statistical analysis.

With respect to EDA data, a lowpass filter with a cut-off of 1 Hz was applied. In analogy to HR processing, EDA data was segmented into epochs related to the initial reaction of the agent (1 s baseline pre onset and 6 s post onset of the change into the responsive mode). Epochs were baseline corrected using the pre onset interval and peak amplitude was identified between 2 and 6 s post onset and exported for statistical analysis.

For behavioral data analysis, the distance between participant and agent was processed in order to extract two measures, approach distance and avoidance distance. With respect to the approach distance, the minimum distance was extracted that participants set to the virtual agents after the agent had changed into the responsive mode. The avoidance distance was then calculated as the maximum distance which participants would establish between themselves and the agent after the final approach distance had been adjusted with the gamepad, which served as a baseline. Importantly, these two distances measured different aspects of movement and distance: the approach

distance was mainly determined by participants' movement *via* the gamepad and served as a manipulation check as it allowed to ensure that participants stopped at the reaction distance without restricting movement. **Figure 2** displays the distribution of distances at which participants stopped for each reaction distance. In contrast, the avoidance distance was analyzed as a dependent measure as it is more related to changes in body posture after the general distance had been set with the gamepad.

Finally, ratings (arousal, valence, realism) were averaged across trials for each distance (six trials per distance).

Statistical Analysis

Statistical analysis was performed using R (27). In order to standardize data for inter-individual differences, the maximal reaction distance of 3.5 m was taken as a reference distance and measures at all other distances were computed in relation to the individual reference. All measures were then analyzed using ANOVAs with *Reaction Distance* as within-subject factor (five levels: 1, 1.5, 2, 2.5, 3 m; all in relation to the reference at 3.5 m) and *Social anxiety* as between-subject factor (two levels: HSA and LSA). Violations of sphericity were corrected using the Greenhouse-Geisser method (28). Significant effects were followed-up with *post hoc* t-tests with a correction for multiple comparisons according to Holm (29). As we hypothesized to find increased effects in the HSA group compared to the LSA group, one-sided t-tests were used when the assessing group differences for particular distances. Significance tests were conducted with $\alpha = 0.05$.

RESULTS

Ratings

Arousal

A mixed ANOVA with *Reaction distance* as a within-subject factor and *Social Anxiety* as between-subject factor revealed a main effect of *Social Anxiety,* $F(1,34) = 5.25$, $p = .028$, $\eta_p^2 = 0.134$, and a main effect of *Reaction Distance,* $F(4,136) = 11.86$, $p < .001$, $\eta_p^2 = 0.259$ ($\varepsilon = 0.49$), as well as a trend for the interaction between *Social Anxiety* and *Reaction Distance,* $F(4,136) = 2.82$, $p = .068$, $\eta_p^2 = 0.077$ ($\varepsilon = 0.49$). Arousal ratings were increased in the HSA group compared to the LSA group. Social interactions at a distance of 1 and 1.5 m were rated as more arousing than longer distances greater 2 m. The interaction effect, although only trending, suggested increased Arousal at short distances in the HSA group compared to the LSA group [1 m: $t(24.54) = 2.38$, $p = .051$, $d = 0.793$; 1.5 m: $t(22.87) = 2.59$, $p = .041$, $d = 0.862$; other distances $p > .10$]. In summary, ratings of arousal differed as a function of both social anxiety and reaction distance (**Figure 3A**).

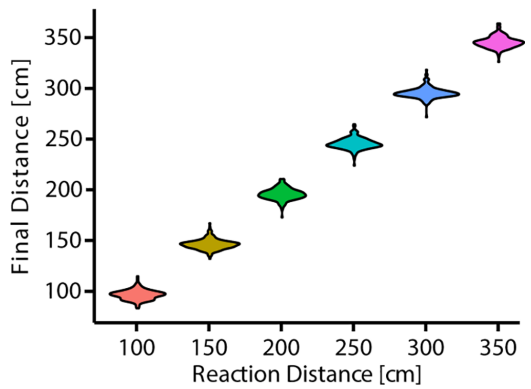

FIGURE 2 | Violin plot depicting the distribution of final distances which were set by the participants after the virtual agents changed from a passive to an active mode.

Valence

Valence ratings revealed a main effect of effect of *Social Anxiety,* $F(1,34) = 4.63$, $p = .039$, $\eta_p^2 = 0.12$, and a main effect of *Reaction Distance* $F(4,136) = 11.79$, $p < .001$, $\eta_p^2 = 0.258$ ($\varepsilon = 0.58$). There was no interaction of both factors, $F(4,136) = 2.18$, $p = .115$. Participants in the HSA group rated the interactions as less pleasant compared to the LSA group and interactions at 1 m distance were rated as less pleasant compared to longer distances [1 m vs. 1.5 m: $t(35) = -4.67$, $p < .001$, $d = 0.777$; 1 m vs. 2 m: $t(35) = -4.23$, $p = .001$, $d = 0.705$; 1 m vs. 2.5 m: $t(35) = -4.30$, $p = .001$, $d = 0.694$; 1 m vs. 3 m: $t(35) = -4.67$, $p = .001$, $d = 0.716$]. These data demonstrate that pleasantness of social interaction in VR was affected both by distance and social anxiety (**Figure 3B**).

Realism

With respect to the ratings of the realism of an interaction, there was a main effect of *Reaction Distance,* $F(4,136) = 6.13$, $p = .001$, $\eta_p^2 = 0.153$ ($\varepsilon = 0.62$), and an interaction effect between *Social Anxiety* and *Reaction Distance,* $F(4,136) = 4.56$, $p = .008$, $\eta_p^2 = 0.118$ ($\varepsilon = 0.62$). *Post hoc* t-test revealed that the interactions at a short distance were rated as less realistic compared to longer distances in the HSA group (1m vs. 1.5m: $t(17) = -3.19$, $p = .036$, $d = 0.751$; 1 m vs. 2 m: $t(17) = -3.24$, $p = .036$, $d = 0.764$; 1 m vs. 2.5 m: $t(35) = -3.27$, $p = .036$, $d = 0.771$; 1 m vs. 3 m: $t(35) = -2.96$, $p = .044$, $d = 0.697$) but not in the LSA group (all $p > .5$). Therefore, social interactions at a short distance were rated as less realistic compared to longer distances but this effect was only present in high social-anxious participants (**Figure 3C**).

Physiological Parameters

As physiological variables, HR (in the six seconds following the agents initial reaction) and SCR (elicited by the initial reaction of the agent) was analyzed. With respect to HR there was no significant main effect or interaction (all $F < 1$, see **Figure 4A**). With respect to SCR, the ANOVA revealed a significant main effect of *Reaction Distance,* $F(4,136) = 9.54$, $p < .001$, $\eta_p^2 = 0.219$ ($\varepsilon = 0.55$). There was no main effect of *Social Anxiety* and no interaction effect (all $F < 1$). *Post hoc* t-test revealed that an agent's reaction at a short distance of 1 m elicited an increased SCR compared to longer distances [1 m vs. 1.5 m: $t(35) = 4.26$, $p = .001$, $d = 0.711$; 1 m vs. 2.5 m: $t(35) = 3.86$, $p = .004$, $d = 0.645$; 1 m vs. 3 m: $t(35) = 273.86$, $p = .059$, $d = 0.456$; all other distances: $p > .1$]. These data show that physiological arousal,

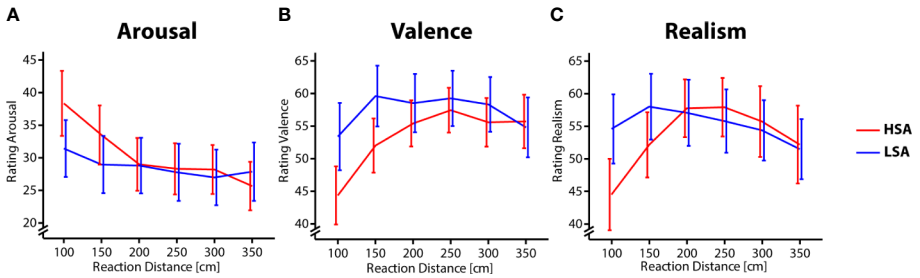

FIGURE 3 | Ratings for different Reaction Distances and Social Anxiety. High social-anxious participants are shown in red and low social-anxious participants are shown in blue. Error bars reflect the standard error of the mean. **(A)** Arousal ratings, **(B)** Valence ratings, and **(C)** Realism ratings.

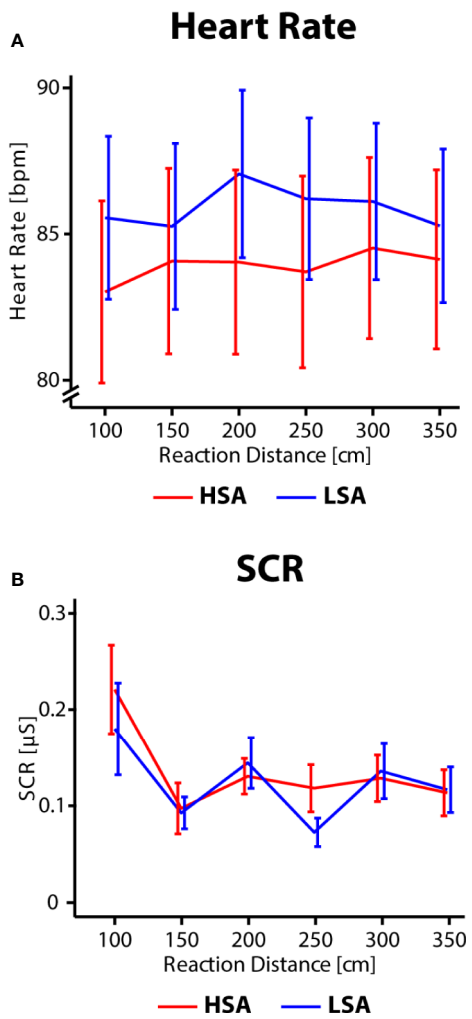

FIGURE 4 | (A) Heart rate in beats per minute (bpm). **(B)** SCR in microSiemens [µS]. Data are shown for different Reaction Distances and Social Anxiety. High social-anxious participants are shown in red and low social-anxious participants are shown in blue. Error bars reflect the standard error of the mean.

as indexed by SCR, was sensitive to reaction distance in social interactions (**Figure 4B**).

Behavior

The distance by which participants retracted from a virtual agent was analyzed as a behavioral measure of avoidance. The ANOVA revealed a main effect of *Social Anxiety*, $F(1,32) = 4.91$, $p = .034$, $\eta_p^2 = 0.154$, a main effect of *Reaction Distance,* $F(4,128) = 13.97$, $p = .001$, $\eta_p^2 = 0.331$ ($\varepsilon = 0.35$), and an interaction effect between *Social Anxiety* and *Reaction Distance,* $F(4,136) = 3.84$, $p = .044$, $\eta_p^2 = 0.13$ ($\varepsilon = 0.35$). *Post hoc* t-tests revealed that there was a trend toward increase of avoidance in the HSA compared to the LSA group at a distance of 1 m, $t(19.65) = 2.48$, $p = .056$, $d = 0.787$, other distances $p > .4$. In summary, there was increased retraction away from the virtual agent at a short interaction distance in the HSA group compared to the LSA group (see **Figure 5**).

DISCUSSION

The present study varied the distance at which participants engage in social interaction with virtual agents. This was achieved by manipulating the distance at which the virtual agents reacted to the participants' approach by switching from a passive to an active mode, i.e., by looking up and focusing on the participant. The results show that physical distance during social interaction affects subjective experience as well as physiological parameters and behavioral avoidance. Social interactions at a close physical distance of one meter were rated as more arousing, less pleasant, and less realistic compared to distances above two meters and elicited an increased physiological response as reflected in the SCR. Finally, participants also showed increased avoidance at a close distance compared to longer distances. Importantly, the subjective experience with respect to arousal and realism as well as the behavioral avoidance also differed as a function of social anxiety. In detail, high social-anxious participants rated interactions at close distances as less realistic and more arousing compared to low social-anxious participants. Furthermore, high

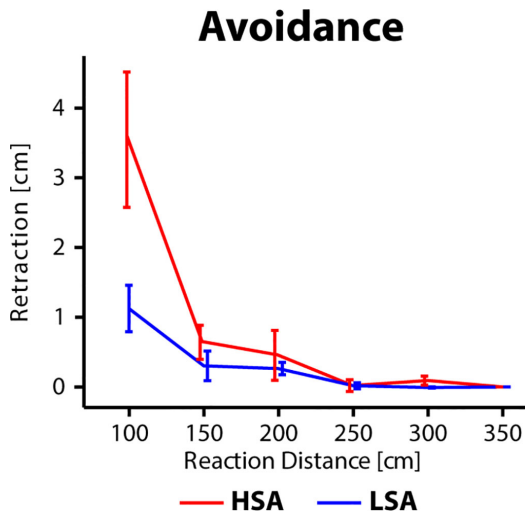

FIGURE 5 | Distance in cm by which participants retracted from the virtual agent after the final position was set with the gamepad. Data shown for different Reaction Distances and Social Anxiety. High social-anxious participants are shown in red and low social-anxious participants are shown in blue. Error bars reflect the standard error of the mean.

social-anxious participants displayed more avoidance behavior at the closest distance compared to low social-anxious participants.

The increased arousal ratings and reduced pleasantness ratings are in line with the existing literature that show increased threat perception elicited by close IPDs within the personal space (6, 7). The effect of IPD on arousal was further modulated by social anxiety suggesting that social cues and especially close distances are perceived as even more threatening for persons with high social anxiety (11, 14–16). However, this interaction between distance and social anxiety was not reflected in the physiological parameters. While there was a general effect of IPD on physiological arousal, as indexed by SCR [see Ref. (6) for an evaluation of IPD using startle probes], this effect was similar for high and low social-anxious participants. This was unexpected, as one might predict that the increased perception of threat might also lead to an increased physiological response. Previous studies, however, have shown that physiological responses are often similar between high and low social-anxious participants (15, 30). These and our findings suggests that emotion processing in social anxiety might be related to the interpretation of physiological states rather than actual physiological responding (30).

Importantly, we found an effect of IPD not only for arousal and valence but also for realism. To our knowledge, the present study is the first to assess realism ratings with respect to IPD in VR. Crucially, realism of social interactions was rated differently between persons with high and low social anxiety scores. LSA participants did not differentiate between IPDs with respect to realism, HSA participants, however, rated social interactions at close distances as less realistic. This suggests that high social-anxious persons differ in their beliefs about "normal" social interaction from low social-anxious persons. One could speculate that this might be the case because HSA persons are more likely to evaluate social interactions on the basis of their own subjective experience and not on the basis of social cues provided by their interaction partners (13).

The rating data should also be discussed with respect to the Uncanny Valley Hypothesis [UVH (31)]. The UVH states that humanlike characters who are close to real humans but do not completely resemble them will induce a negative affective state. It is possible that the relation between distance and pleasantness was modulated by the uncanny valley effect, as anthropomorphic features may be more prominent at closer distances. Note, however, that results with respect to the UVH are mixed and even contradictory results, i.e., increased pleasantness related to increasing human likeness, have been reported (32). Furthermore, the present study showed not only reduced pleasantness but also reduced realism ratings for close distances (at least in HSA participants). Therefore, it is unlikely that the present effects were solely driven by the Uncanny Valley effect. However, this should be further investigated in future studies where human likeness is explicitly manipulated.

Finally, we observed increased avoidance in HSA participants related to IPD that was reflected in retraction from the virtual agents. This finding is in line with previous measures of avoidance behavior such as reduced eye-contact, backward head movements or speed of approach (10, 14, 15, 33). In a previous study by Wieser et al. (15), avoidance behavior was related to social anxiety, but there was no modulation of avoidance with respect to IPD. Note, however, that in the study by Wieser et al., the agent moved toward the participant while the participant remained stationary. Therefore, one explanation might be that in the active approach toward the agent might increase the salience of distance and thereby result in increased avoidance behavior with respect to IPD. This should be addressed in future experiments. Furthermore, these studies should include measurements of eye gaze as previous studies have highlighted the relation of distance and gaze direction (3, 10, 34).

The present experiment highlights Virtual Reality as a technique for the study of social interaction. High experimental control while maintaining naturalistic settings are key advantages of VR. This is especially relevant for the investigation of IPD because of the limitations of presenting controlled social interactions. Our results as well as previous work show that real and virtual social stimuli elicit similar responses (35, 36). Here, we demonstrate that a paradigm in Virtual Reality is sensitive to even small manipulations of distance as well as to inter-individual variation in social anxiety. These advantages of social interactions in VR may also be of interest for therapeutic use. It has been demonstrated that VR exposure therapy can be successfully used with patients suffering from social anxiety (37). On the basis of our results, we suggest to implement distance manipulations as a tool in virtual exposure therapy.

It has to be acknowledged, however, that it is quite challenging to provide highly realistic social interactions in VR.

In the present experiment, social interactions were defined as a short greeting between participant and virtual agent, where the response of the virtual agent was controlled by the experimenter. Technological advances might help in future studies to test more elaborate interactions including dialogues with a virtual agent. Another limitation of the present experiment is that the individually preferred IPD was not assessed. Again, this should be addressed in future studies by adding a session with the stop-distance technique to the experiment and relating the assessed distances to the preferred distance. This should increase the sensitivity to effects of IPD.

The analysis of social anxiety on the basis of a median split combined with a relatively small sample size brings some limitations with respect to statistical power. It should be noted, however, that the median in the present sample (16.5) was only 2.5 point below a cut-off score of 19 that has been suggested to distinguish between social phobia subjects and controls (38). Therefore, the present group analysis might be useful for evaluating the role of physical distance with respect to clinical applications. Nevertheless, the present study should be seen as a starting point for future investigations with increased sample size.

Summarizing, we measured effects of IPD and social anxiety on subjective experience, physiology, and behavior during real-time social interaction in Virtual Reality. Our results show increased arousal, reduced valence and, for the first time, reduced realism for close IPDs. The effects on arousal and realism appear to be amplified in high social-anxious participants in comparison to low social-anxious participants. IPD also affected SCR in both groups. Finally, we observed increased avoidance behavior for close distances in high social-anxious participants. In total, these results suggest Virtual Reality is able to induce relevant verbal and nonverbal emotional responses in virtual social settings and thus is a useful tool in studying social interaction and developing interventions for social training purposes or psychotherapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by Ethics Committee of the Deutsche Gesellschaft für Psychologie (DGPs). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LK, MP, and AM designed research. LK programmed the experiment, supervised data acquisition, and analyzed data. BL and MM supervised the virtual environment creation and experiment paradigm programming. LK, MP, and AM wrote the paper. BL and MM commented the paper.

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Conflict of Interest: AM and MM are shareholders of a commercial company (VTplus GmbH) that develops virtual environment research systems for empirical studies in the field of psychology, psychiatry, and psychotherapy. MM is an executive officer and BL is an employee of the same company.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Processing Facial Expressions That Conflict With Their Meanings to an Observer: An Event Related Potential Study

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As social signals, identical facial expressions can be perceived differently, even oppositely, depending on the circumstances. Fast and accurate understanding of the information conveyed by others' facial expressions is crucial for successful social interaction. In the current study, we used electroencephalographic analysis of several event-related potentials (ERPs) to investigate how the brain processes the facial expressions of others when they indicate different self-outcomes. In half of the trial blocks, a happy face indicated "Win" and an angry face indicated "Lose." In the other half of the blocks, the rule was reversed. The results showed that the N170 could distinguish expression valence and the N300 could distinguish outcome valence. The valence of the expression (happy or angry) and the valence of the outcome (Win or Loss) interacted with each other in the early, automatic perceptual processing stage (N1) as well as in the later, cognitive evaluation stage (P300). Standardized Low-Resolution Electromagnetic Tomography (sLORETA) results indicated that the N1 modulation only occurred for happy faces, which may relate to automatic emotion regulation, while the interaction on P300 was significant only for angry faces, which might be associated with the regulation of negative emotions.

Keywords: facial expression, outcome evaluation, event-related potential, N1, P3

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INTRODUCTION

The facial expressions of others convey information that is important for social communication. The processing of facial expression has been found to be strongly modulated by situational context such as the emotional valence of background images (Carroll and Russell, 1996), the meaning conveyed by stories accompanying facial expressions (Righart and de Gelder, 2006), and the race (Herzmann et al., 2013), attractiveness (Liang et al., 2010), and trustworthiness (Ruz et al., 2013) of people whose faces are being viewed.

As a social signal, the same facial expression can be perceived differently depending on these influencing factors. This phenomenon could be assumed in two ways. First, how much does the expression on a perceived face influence the attentional resources that it can attract? For example, when someone is in a singing competition, even though the audience includes hundreds of faces, the judges' faces are the center of one's attention because their facial expressions are valid predictors of one's score. Second, what is the relationship between the

valence of the expression itself and the valence of the meaning it conveys? A happy face of a partner indicates one's team is winning. In this case, both the valence of the facial expression and the valence of its outcome to him/her are positive. However, when the face of one's opponent is frustrated, its outcome is also positive for him/her, despite the negative valence of the expression itself. In order to integrate a facial expression in a particular outcome, we must check whether its outcome valence and its specific emotional valence are contextually appropriate. According to previous studies, the processing and decoding of facial expressions of emotion involves a double check of valence and specific emotional information for the perceiver (Aguado et al., 2013, 2019). However, how the valence of a perceived emotion and the valence of the self-outcome it conveys are processed in the brain has not yet been explored.

The main goal of the present study is to investigate how the brain processes the facial expressions of others when they indicate different self-outcomes with electrophysiological recording. In the current study, different valences of facial expressions (happy and angry) were used to indicate the outcomes in a monetary gambling game. A participant was presented with two rectangles on the screen, one associated with a positive outcome (Win) and the other associated with a negative outcome (Loss). After they selected a rectangle, a picture of facial expression would appear to reveal the outcome. In half of the trial blocks, a happy face indicated "Win" and an angry face indicated "Lose." In the other half of the blocks, the rule was reversed. Four conditions were created: (matched conditions) valence of the face and valence of the outcome were both positive or both negative (Happy face indicated Win; Angry face indicated Loss); (mismatched conditions) valences were opposite (Happy face indicated Loss; Angry face indicated Win). Before each block, participants were instructed as to which pairing would be used. The even-related potentials (ERPs) obtained during these different conditions were then compared.

Based on the abundant evidence from affective priming studies (Fazio et al., 1986; Moors and De Houwer, 2001; Klauer and Musch, 2003), we assume that the valence of perceived emotion checking is automatic, taking place at early processing stages. According to previous studies about outcome evaluation (Wu and Zhou, 2009; Yang et al., 2018), we assume that the valence of outcome checking is intentional, taking place at later processing stages. A general prediction that directly follows this account is that the valence matching between facial expressions (happy/angry) and outcome (win/lose) should have differential effects on the processing of positive and negative expressions.

Numerous ERP studies have investigated the time course of facial expression processing (Werheid et al., 2005; Trautmann et al., 2009; Vlamings et al., 2009; Lassalle and Itier, 2013; Zhang et al., 2013; Recio et al., 2014; Yuan et al., 2014). Several ERP components have been consistently observed. N100 (the fronto-central distributed negative component) and P100 (the parietal positive component) reflect very fast, automatic early perceptual processing of faces. N170 (the negative parietal-occipital component) is specifically elicited by faces and is sensitive to affective valence. The fronto-central vertex-positive potential (VPP), N300, and P300 are components that reflect the differentiation and evaluation of various facial expressions (Luo et al., 2010). The present study hypothesized that among the ERP components usually elicited by facial expressions, P300 would be selectively modulated by the outcome (Win or Lose). P300 is often modulated by the emotional or arousing content of stimuli. Studies have shown that compared with neutral stimuli, emotional stimuli enhanced the P300 component, and this modulation was stronger for highly arousing stimuli (Carretie et al., 1997; Cramer, 1998). Additionally, this component is thought to reflect evaluative processing, such that its amplitude increases when more cognitive resources are allocated (Friedman et al., 2001; Wu and Zhou, 2009; Asaumi et al., 2014; Roca et al., 2015). We assume that in the conditions for which the two valences are inconsistent, increased cognitive resources would be demanded, which would contribute to a larger P300 than when the two valences were consistent. We also hypothesize that ERP discrimination of the expressions would be earlier than that of the outcomes because the participants need to recognize the expression before they can know the outcome. Further, a recent ERP study found that early perceptual components such as P100 were also sensitive to social-emotional regulation, supporting the flexibility and modifiability of early ERP components (Beckes et al., 2013). Therefore, we hypothesize that an interaction between the two valences also occur between the early components such as N1 and P1.

MATERIALS AND METHODS

Participants

Twenty right-handed participants with no history of neurological disorders, brain injury, or developmental disabilities participated in the experiment. All had normal or corrected-to-normal vision. The study was approved by the Medical Ethical Committee of Shenzhen University. All participants provided their written informed consent. Data from two participants were excluded because the percentage of bad electroencephalographic (EEG) epochs was too high (35%). Thus, 18 participants were included in the final analysis (10 men; age: 24.95 ± 0.65 years).

Stimuli

The stimuli used comprised 120 photos of faces from the native Chinese Facial Affective Picture System (CFAPS), including 60 happy faces and 60 angry faces. The recognition consistency was 86.64 ± 8.38% for happy expressions and 83.77 ± 6.56% for angry expressions. The intensity of happy and angry expressions was 6.43 ± 0.86 and 6.78 ± 0.69, respectively. No significant differences of recognition accuracy or intensity were found between the two categories of faces ($p > 0.5$). Faces of men and women were represented equally. Happy and angry faces were identical to each other in size, background, contrast grade, brightness, and other physical properties. All faces were gray-scale and were presented on a black background (3.0° × 3.5° visual angle).

Experimental Procedures

Stimulus presentation and behavioral data acquisition were performed using E-Prime software (Version 1.0, Psychology Software Tools, Inc.). During the task, participants sat comfortably in an electrically-shielded room approximately 100 cm from a 15-inch color computer monitor. Each trial began with the individual presentation of two gray rectangles (2.3° × 3.2° of visual angle), which indicated two alternative options on the left and right sides of a fixation point. The participant was informed that one rectangle corresponded to a "Win" and the other to a "Loss." The participant was asked to gamble by pressing the "F" or "J" key on a keyboard with their index fingers to choose one rectangle. The rectangles remained on the screen until the participant chose a side. Next, a blank interval lasting 400–700 ms (randomly) was presented, followed by the presentation of a face at the chosen location that represented the outcome. The photo remained on the monitor for 800 ms. The inter-trial interval varied from 1,500 to 2,500 ms (see **Figure 1**).

Trials were presented in four blocks of 120 trials (total 480 trials). Before two of the four blocks, participants were informed that a happy face indicated a "Win" and an angry face indicated a "Loss." In the other two blocks, they were told the reverse. Block order was counterbalanced across participants. Participants were informed that each trial was worth 10 renminbi (RMB) (i.e., they could win or lose 10 RMB on each trial).

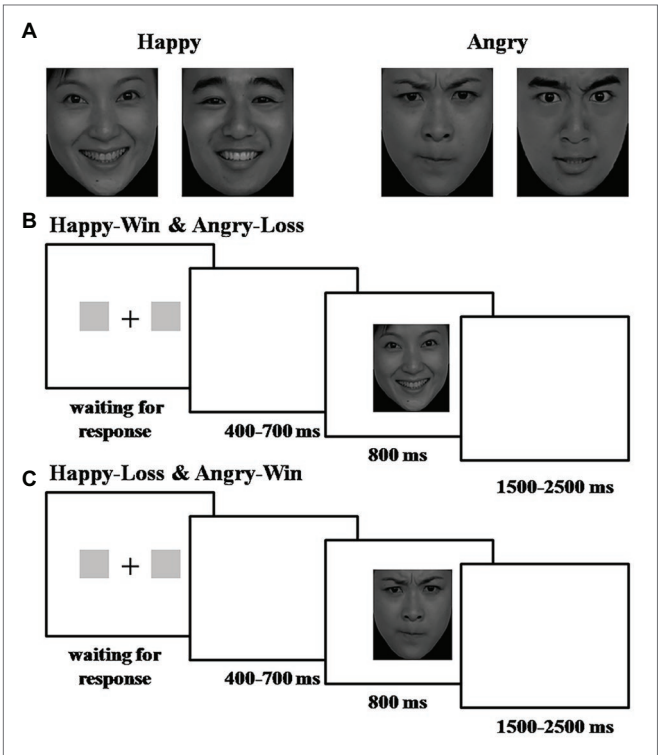

FIGURE 1 | Experimental procedure and stimuli. **(A)** Examples of the photos used: (left) happy male/female faces; (right) angry male/female faces. The faces were selected from the revised version of the Chinese Facial Affective Picture System (CFAPS). **(B)** Experimental procedure for Happy-Win and Angry-Loss blocks. **(C)** Experimental procedure for Happy-Loss and Angry-Win blocks.

We used a 2 × 2 within subject experimental design. The first factor was the valence of the facial expressions: Happy or Angry. The second factor was the valence of the outcome indicated by the face: Win or Loss. There were four conditions: Happy-Win, Happy-Loss, Angry-Win, and Angry-Loss.

Before the experiment, the task, its rules, and meaning of the faces were explained to the participants. Additionally, they were told that the higher the points they earned, the more bonus money they would receive at the end of the experiment. However, after the task, they were briefed that their total gains and losses were balanced.

Electroencephalography Acquisition and Analysis

Electroencephalographic data were recorded from a 64-electrode scalp cap using the 10–20 system (Brain Products, Munich, Germany) with the reference on the left and right mastoids. A vertical electrooculogram (EOG) was recorded with electrodes placed above and below the left eye. EEG and EOG data were amplified, band-pass filtered (0.01–100 Hz), and sampled at 500 Hz. All electrode impedances were maintained below 5 kΩ.

EEG data were pre-processed and analyzed using MATLAB R2011b (Math Works, US) and EEGLAB toolbox (Delorme and Makeig, 2004). EEG data at each electrode were down-sampled to 250 Hz, re-referenced to the grand average, and band-pass filtered (0.01–30 Hz). EEG data from 200 ms before until 800 ms after the onset of the facial stimuli were extracted. In order to discard data that was contaminated by EOG artifacts, the data were decomposed by extended infomax ICA using binica, as implemented in EEGLAB (Jung et al., 2001). Epochs with amplitude values exceeding ± 50 μV at any electrode were excluded from the average.

Data Measurement and Analysis

We mainly analyzed the ERP elicited by happy and angry faces. The averaged epoch was 1,000 ms, including a 200 ms pre-stimulus baseline. In this study, the amplitudes of N1, P1, VPP, N170, N300, and P300 components were measured and analyzed. Based on the topographical distribution of the grand-averaged ERP activity and previous studies (Righart and de Gelder, 2006; Williams et al., 2006; Luo et al., 2010), different sets of electrodes for each component were chosen. Fz, F3, F4, FCz, FC3, and FC4 electrode sites were selected for the analysis of N1 (90–140 ms) and VPP (140–220 ms); Pz, P3, P4, POz, PO3, and PO4 were selected for the analysis of P1 component (100–160 ms); N170 component (140–200 ms) was analyzed at the P7, P8, PO7, and PO8 electrode sites; N300 component (250–400 ms) was analyzed at the T7, T8, FT7, and FT8 electrode sites; and 10 electrode sites (Cz, C3, C4, CPz, CP3, CP4, Pz, P3, P4, and POz) were selected for the statistical analysis of P300 component (300–500 ms). A three-way repeated measure analysis of variance (ANOVA) on the amplitude of each component was conducted with Face pictures (two levels: Happy, Angry), Outcome (two levels: Win, Loss), and Electrode site as within-subject factors. Degrees of freedom for F-ratios were corrected according to the Greenhouse-Geisser method.

Statistical differences were considered significant at $p < 0.05$; *posthoc* comparisons were Bonferroni-corrected at $p < 0.05$.

sLORETA Analysis

We used Standardized Low-Resolution Electromagnetic Tomography (sLORETA) to determine the sources of the differences that we found in the N100 and P300 components. sLORETA is a functional imaging method based on certain EEG and neuroanatomical constraints (Pascual-Marqui et al., 1994). It computes images of electrical activity from the EEG data in a realistic head model using the MNI152 template and estimates the three-dimensional distribution of the current density within 6,239 voxels at a spatial resolution of 5 mm. This method has been established as useful for determining deep structures such as the ACC and others within the temporal lobe (Pizzagalli et al., 2004; Zumsteg et al., 2006).

For the current dataset, in order to localize the brain structures responsible for the effects we observed on N100 and P300, a *t*-test was performed for the current densities on different conditions for N100 and P300 in their respective time windows (N100: 90–140 ms; P300: 300–500 ms), employing a LOT-F-ratio statistics for paired groups (Happy-Loss > Happy-Win for N100 and Angry-Win > Angry-Loss for P300, separately), with 5,000 bootstrapping and a level of significance of $p < 0.05$.

RESULTS

N100

The Face (Happy vs. Angry) × Outcome (Win vs. Loss) interaction was significant for N100 amplitude [$F_{(1, 17)} = 5.433$, $\eta_p^2 = 0.242$, and $p = 0.032$]. The pairwise comparisons revealed that when the facial expression was Happy, Losses elicited significantly greater negative amplitude than Wins (−2.781 μV for Happy-Loss and −2.336 μV for Happy-Win, $p = 0.005$). The difference between Win and Loss was not significant for angry faces (−2.518 μV for Angry-Loss and −2.525 μV for Angry-Win, $p = 0.0968$; see **Figure 2**).

N170

We found a significant main effect of face on N170 amplitude such that angry faces elicited significant larger amplitudes than happy faces. [Happy: −5.922 μV; Angry: −6.258 μV; $F_{(1, 17)} = 7.457$, $\eta_p^2 = 0.305$, and $p = 0.014$]. We did not find a main effect of outcome or an interaction between Face and Outcome (see **Figure 3A**).

N300

We found a significant main effect of Outcome for N300 amplitude such that Wins elicited significantly greater negative amplitudes than Losses [Wins: −4.177 μV; Losses: −3.710 μV; $F_{(1, 17)} = 10.848$, $\eta_p^2 = 0.390$, and $p = 0.004$; see **Figure 3B**].

P300

We found a significant main effect of Outcome on P300 amplitude. Wins elicited significant larger amplitudes than Losses [Wins: 4.257 μV; Losses: 3.950 μV; $F_{(1, 17)} = 11.004$, $\eta_p^2 = 0.393$, and $p = 0.004$]. We also found a significant main effect of Electrode [$F_{(9, 153)} = 6.618$, $p < 0.001$]. Specifically, FCz, FC3, FC4, Cz, C3, C4, and Pz electrodes elicited larger amplitudes than the others ($p < 0.05$). Additionally, we found that the three-way interaction of Face × Outcome × Channel was significant [$F_{(9, 153)} = 3.283$, $\eta_p^2 = 0.162$, and $p = 0.016$]. Pairwise comparison revealed that significantly larger amplitudes occurred for angry faces on Wins

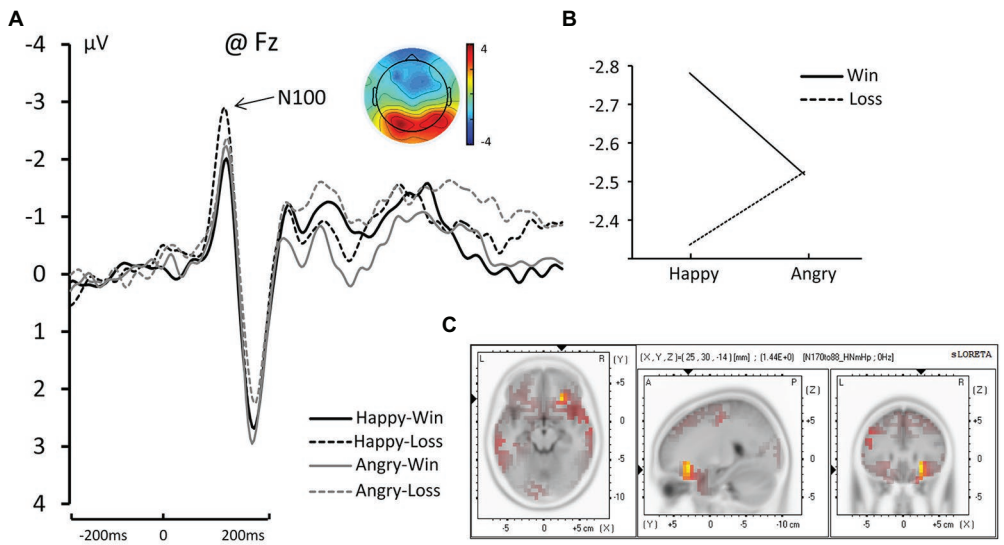

FIGURE 2 | (A) The grand average and scalp topography of N100 component at Fz site for four conditions [Happy-Win (black lines); Happy-Loss (black dotted line); Angry-Win (gray line); Angry-Loss (gray dotted line)]. **(B)** The interaction of Face × Outcome on N100. **(C)** Standardized Low-Resolution Electromagnetic Tomography (sLORETA) results of "Happy-Loss" > "Happy-Win" in time windows of N1.

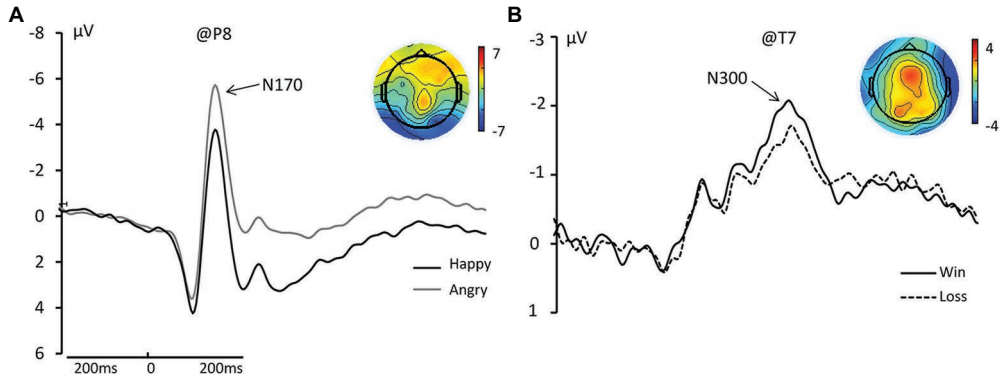

FIGURE 3 | (A) The grand average and scalp topography of N170 component at P8 site for two conditions [Happy (black lines); Angry (gray line)]. **(B)** The grand average and scalp topography of N300 component at T7 site for two conditions [Win (black lines); Loss (black dotted line)].

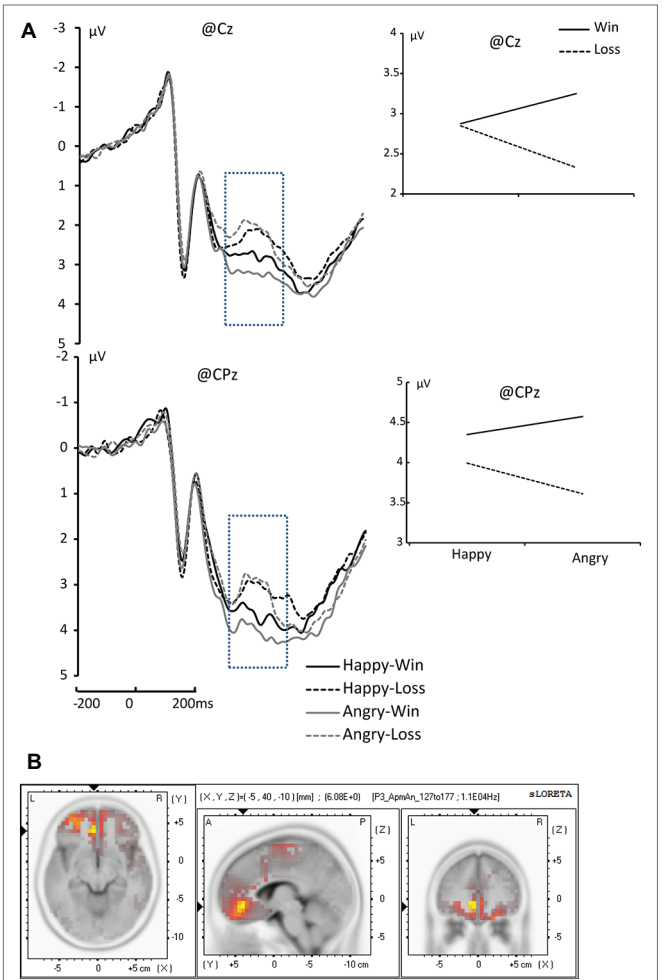

FIGURE 4 | (A) The grand average of P300 component at Cz and CPz, [Happy-Win (black lines); Happy-Lose (black dotted line); Angry-Win (gray line); Angry-Lose (gray dotted line)]. **(B)** sLORETA results of "Angry-Win" > "Angry-Lose" in time windows of P3 (marked with blue dotted rectangles in the waveforms).

than on Losses at Cz, C3, C4, CPz, and CP3 ($p = 0.001$, $p = 0.006$, $p = 0.031$, $p = 0.013$, and $p = 0.004$, respectively; see **Figure 4A**).

We did not find any significant main effects or interactions for other ERP components.

Standardized Low-Resolution Electromagnetic Tomography

The analyses revealed a difference in the inferior frontal gyrus and middle frontal gyrus (BA47/BA11) between Happy-Loss and Happy-Win conditions within the N1 time window such that the Happy-Loss condition resulted in significantly higher current density than the Happy-Win condition [Montreal Neurological Institute (MNI) coordinates = (25, 30, −14), $p = 0.017$; see **Figure 2C**]. The Angry-Win resulted in significantly higher activation in the anterior cingulate cortex (BA32) and orbitofrontal region (BA11) than did the Angry-Lose condition within the P300 time window (MNI = −5, 40, −10, $p = 0.018$; **Figure 4B**).

DISCUSSION

This study explored how the brain processes facial expressions that indicate monetary outcome for oneself. Our results show that the brain first distinguishes the valence of the expression (happy from angry in our case), as reflected in a significant main effect of the facial expression in the N170 component. The brain also distinguishes the outcome, as reflected in the observed significant main effect of outcome on N300. The processing of self-outcome interacted with the processing of facial expression in the early automatic stage and also in the later evaluative stage, as reflected by the observed significant interactions that affected N1 and P300 amplitude.

The Interaction in the Early Automatic Stage of Processing: N100

In the frontal N1, we found a significant interaction of Face × Outcome in which the difference in amplitude between Win and Loss was significant for a happy face, but not for an angry face. Specifically, the Happy-Loss condition elicited a significantly larger negativity than the Happy-Win condition. This result indicates that the outcome for the observer began

to interact with the perception of the facial expression at a very early, automatic stage. The enhancement during the Happy-Lose condition could be related to an initial amplification of relevant processing generated by top-down factors (Hillyard and Picton, 1987; Ruz et al., 2013). In the mismatched blocks, facial expressions were not tied to their natural meanings. Therefore, the recognition of the outcome from the facial expression was likely associated with higher processing demands, which requires the allocation of more cognitive resources (Williams et al., 2003). The sLORETA results revealed a significant difference between Happy-Loss and Happy-Win which was related to higher activation in the orbitofrontal cortex (BA11) in the Happy-Lose condition than in the Happy-Win condition. This brain region has been found to be specifically activated in automatic emotion regulation (ER) (Ochsner and Gross, 2005; Phillips et al., 2008; Etkin et al., 2011; Hallam et al., 2015). The automatic ER seems to underlie this processing. ER refers to the processes involved in the initiation, maintenance, and modification of the occurrence, intensity, and duration of feeling states (Gross and Levenson, 1993; Eisenberg et al., 2000). Automatic ER specifically means the ER with features of automaticity (i.e., immediacy, efficiency, and redundancy of conscious intent (Gollwitzer and Sheeran, 2006). The brain regions that support automatic ER include medial frontal areas such as the medial orbitofrontal cortex (mOFC). Based on the literature, the mOFC is a heteromodal association area that unites information from the sensory modalities, representations of past experiences, and the processing of contextually-relevant information (Hallam et al., 2015). It is thus suitable for handling the expressions of others that convey information with changing valences, which requires the integration of multiple types of information, such as those from sensory input, experience, and social contexts.

Why the Win/Loss difference was only significant for happy faces was not immediately clear. It might be related to the lower priority that happy faces have in social interactions. Studies suggest that angry expressions are initially prioritized by our cognitive system because we benefit from early detection of potential threats in the environment (Fox et al., 2000; Avero and Calvo, 2006). However, unlike detection tasks, happy expressions show clear advantages in recognition tasks. Happy faces were found to be recognized faster and more accurately (Leppanen and Hietanen, 2004). The same study also found that a smiling mouth became visually salient very early (~95 ms), which corresponds temporally with the N100 (Calvo et al., 2014). Another study showed that among all expressions, only recognition of happy expressions was unaffected by the intensity of the expressions—even low intensity happy faces were recognized with nearly 100% accuracy (Hess et al., 1997). In situations in which happy faces indicate a negative outcome, they would likely be quickly recognized and then modulated through automatic ER. Angry faces might not yet be recognized during this time window.

The Discrimination of the Two Valences: N170 and N300

N170 is a negative-going component detected at the occipito-temporal electrode sites that peaks around 170 ms post-stimulus. The component clearly distinguishes faces from non-face visual stimuli. However, evidence regarding whether N170 is responsive to emotional expression is conflicted; while some studies found that N170 did not discriminate emotional expressions (Luo et al., 2010; Nakajima et al., 2012), others found that it did (Batty and Taylor, 2003; Miyoshi et al., 2004; Lynn and Salisbury, 2008; Herbert et al., 2013). In particular, N170 amplitude has been reported to differ between happy and angry faces (Krombholz et al., 2007). In line with these latter studies, here we found a main effect of facial expression on N170 in which angry faces elicited significantly larger amplitudes than happy faces.

After decoding the facial expressions, the valence of the outcome could be distinguished *via* the N300 component; we found significantly larger negative amplitude for Wins than for Losses. The N300 largely reflects the dimensionality of the affective valence in higher-level phases of cognitive processing, such as stimulus evaluation and selection (Carretie et al., 2001a,b; Campanella et al., 2002; Luo et al., 2010). In the current study, the participants needed to mentally recognize and label the presented facial expressions, then deduce the monetary outcome. Thus, a main effect of facial expression (N170) before a main effect of outcome (N170) was a reasonable observation.

The Interaction in the Evaluation Stage: P300

Scientists believe that P300 is involved in a large number of cognitive and affective processes and it is traditionally associated with the allocation of mental resources (Olofsson et al., 2008). When a facial expression contains information that is important to an observer (e.g., monetary gain or loss), it usually draws more attention and requires more cognitive resources to analyze and evaluate. Interestingly, in the current study, we found that during the P300 time window, the positive and negative facial expressions were evaluated differently under different conditions. A three-way interaction of Face × Outcome × Channel was observed. The difference between Angry-Win and Angry-Loss was significant in the central regions. sLORETA results found that regions that were differentially activated between Angry-Win and Angry-Loss were localized in the ACC (BA32) and orbitofrontal region (BA11). These regions have been found to be responsible for the regulation of negative emotions (Levesque et al., 2003; Ochsner et al., 2004, 2012; Phan et al., 2005; Mak et al., 2009). In the current design, in the blocks where the angry face indicated a positive outcome, the participant may need to suppress the negative affect aroused by the naturally negative stimulus and re-identify the face as positive. Thus, recruiting neural circuits related to the regulation of negative affect is unsurprising for this condition.

Other studies have shown that valence can also affect later components, such as, P3 (Olofsson et al., 2008). Interestingly, we did not observe a significant effect of facial expression on the ERPs for which a main effect of expression has often been found (e.g., N300 and P300). We assume this was because the most important information for the participants was not the expressions themselves, but the monetary outcome. Therefore, after recognizing the expressions in the N200 time window, processing of the outcome likely

dominated and the effect of the expressions during the N300 and P300 time windows would be weakened.

Actually, ERP studies have produced ambiguous results on the time course of face and valence processing. Some research have found that the P1 and N1 can be modulated by emotional valence (Levesque et al., 2003; Ochsner et al., 2004, 2012; Phan et al., 2005; Mak et al., 2009). Rellecke and colleagues found that automatic enhanced encoding of angry faces were indicated by P1, N170, and EPN in the early processing stages. However, our results only found the main effect of emotional valence in N170 and the valence and outcome interactions with the processing of other's facial expression in an early automatic stage (Levesque et al., 2003; Ochsner et al., 2004, 2012; Phan et al., 2005; Mak et al., 2009). Let us note that this early P1 modulation by emotion is debated as many studies also failed to report modulations of the P1 by facial expressions of emotion (Levesque et al., 2003; Ochsner et al., 2004, 2012; Phan et al., 2005; Mak et al., 2009). We assumed that the reason is that these components are related to differentiation of certain expressions (Olofsson et al., 2008), which should occur after valence processing according to the dimensional model.

In conclusion, the current investigation explored how facial expression stimuli are processed when they indicate positive or negative outcomes for those observing them. The results suggest that early perceptual processing of facial expression is influenced by the valence of outcomes, as evidenced by an enhanced N100 component when happy faces indicate a financial loss. Subsequently, the valence of the face is decoded by the N170 component and the valence of the outcome is discriminated by the N300 component. At a later cognitive evaluation stage, the face and outcome valences interact again, as evidenced by the differences in the P300 component between financial gains and losses represented by angry faces. This interaction may reflect the regulation of emotional responses that are elicited by negative stimuli when the stimuli indicate positive outcomes.

The sample size (n = 18) was a limitation of the current study as it is relatively small for an ERP study. Our findings should therefore be validated using larger sample sizes.

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 Medical Ethical Committee of Shenzhen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: QY and YW. Performed the experiments: YZ and JW. Analyzed the data: JW. Wrote the manuscript: QY and YW.

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The Functional Role of Individual Alpha-Based Frontal Asymmetry in the Processing of Fearful Faces

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The ability to quickly identify fearful faces is important for the activation of defense mechanisms that allow an individual to deal with potential emergencies. This study examined the relationship between frontal electroencephalography (EEG) alpha asymmetry and the processing of congruent and incongruent fearful faces among female participants using event-related potentials (ERPs). Behavioral results showed that individuals with more left frontal EEG alpha asymmetry had shorter response times than individuals with more right frontal EEG alpha asymmetry during the cue-target task. ERP results indicated that, for individuals with more left frontal EEG alpha asymmetry, enhanced N1 reflected more rapid processing of emotional faces in the early stage, and enhanced P3 indicated that these individuals directed more attentional and motivational resources to the evaluation of emotional faces in the late stage. For individuals with more right frontal EEG alpha asymmetry, enhanced N2 indicated that these individuals experienced more conflict for incongruent fearful faces in the late stage. The present findings suggest that frontal EEG alpha asymmetry during resting conditions can reflect individual differences in the processing of congruent and incongruent fearful faces.

Keywords: frontal electroencephalography alpha asymmetry, facial expression, fearful face, event-related potential, ERP

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INTRODUCTION

Investigation of the factors that underlie individual differences in the evaluation of emotional stimuli continues to be a central focus in the field of affective neuroscience. Fear expression as the fundamental emotional face stimuli plays an important role in human survival and adaptation (Itier et al., 2006; Luo et al., 2010). The ability to quickly identify fearful faces is important in evaluating a dangerous situation and planning an appropriate psychological or behavioral response (Rossignol et al., 2005; Peng et al., 2012). The purpose of the current study was to examine how the processing of fearful faces is related to frontal electroencephalography (EEG) alpha asymmetry during resting conditions, which is a neurophysiological index of emotional processing (Jackson et al., 2003; Kline et al., 2007; Papousek et al., 2012, 2017).

Frontal EEG alpha asymmetry reflects differences in activation of the alpha frequency band (typically 8–13 Hz) of the left and right frontal cortices; there is an inverse relationship between activity within the alpha range and cortical processing (Davidson, 1995; Laufs et al., 2003). Research suggests that frontal EEG alpha asymmetry during resting conditions can moderate the response to emotional stimuli. For example, individuals with more left frontal EEG alpha asymmetry (ILA)

have less negative and more positive affect (Tomarken et al., 1992), superior emotional flexibility (Kline et al., 2007; Papousek et al., 2012), more effective emotion regulation (Jackson et al., 2003; Papousek et al., 2017), and lower stress-induced cortisol levels (Quaedflieg et al., 2015), compared to individuals with more right EEG alpha asymmetry (IRA). Recently, Suo et al. (2017) found that ILA had a larger P3 to negative pictures than to positive and neutral pictures, whereas there were no significant ERP differences to negative, positive, and neutral pictures for IRA, suggesting that left-active individuals direct more attentional resources to negative pictures. In addition, Harmon-Jones and Gable (2009) found that greater left frontal-central activation during dessert pictures predicted faster local-target response times after dessert pictures, indicating that greater left frontal-central activation caused narrowing of attention. These findings suggest that frontal EEG alpha asymmetry during resting conditions can reflect individual differences in emotional perception tendencies to emotional stimuli.

Event-related potentials (ERPs) have high temporal resolution and can be used to study the unfolding of emotional processing. A large number of studies have investigated the time course of neural activity underlying the processing of fearful faces using ERPs. Findings indicate that fearful faces elicit a larger P1 (Eimer and Holmes, 2002, 2007; Holmes et al., 2003; Pourtois et al., 2005; Vuilleumier and Pourtois, 2007), a larger P2 (Ashley et al., 2004), and a sustained positive amplitude (Eimer and Holmes, 2002, 2007). Furthermore, some studies have also examined the time course of neural activity underlying the processing of congruent and incongruent fearful faces using ERPs; these studies have examined several ERP components that measure early processing periods and late processing periods, respectively. For example, Peng et al. (2012) showed that for the expression effect (fearful vs. neutral faces), there were differences in early time periods (N1 and P2) between predictable and unpredictable trials, whereas there were no differences in the late time periods (N220–350 and P3). These results reveal that the processing of congruent and incongruent fearful faces differs mainly in the early stage of neural activity after face onset. However, Yang et al. (2012) showed that incongruent fearful faces had larger P2 and N200–300 amplitudes than incongruent neutral faces, whereas there were no differences between congruent fearful and neutral faces for these ERP components. In the early processing period, N1 is associated with early perceptual processing (Peng et al., 2012), and P2 is correlated with increased attention allocation to emotional stimuli (Peng et al., 2012; Yang et al., 2012; Jin et al., 2013). In the late processing period, N2 reflects the monitoring of cognitive interference (Dennis and Chen, 2007; Folstein and Van Petten, 2008; Peng et al., 2012), and P3 is considered to index the attentional and motivational resources allocated to the evaluation of fearful faces (Peng et al., 2012; Ran et al., 2014). The present study explored how frontal EEG alpha asymmetry during resting conditions relates to the processing of congruent and incongruent fearful faces using ERP markers.

In addition, emotional processing is different between women and men. Studies have shown that compared with men, women are more accurate and faster in identifying emotional stimuli (Thayer and Johnsen, 2000; Collignon et al., 2010), have more intense emotional experiences (Lang et al., 1993), and are better able to memorize emotional events (Ros and Latorre, 2010). Furthermore, there are differences in both early and late ERP components between women and men. For the early ERP components, women show larger P1 to subthreshold fearful faces (Lee et al., 2017) and enhanced P2 in response to incongruent negative stimuli (Jin et al., 2013), as compared to men. For the late ERP components, women show larger P3 responses and better memory retrieval for emotional stimuli (Gasbarri et al., 2006), as compared to men.

Given the above, the current study aimed to examine the relationship between frontal EEG alpha asymmetry and the processing of congruent and incongruent fearful faces among female participants using ERP markers. In this study, participants first completed a 2 min resting task and then completed a cue-target task. For the purposes of this study, we were interested in early processing components (e.g., N1 and P2) and late processing components (e.g., N2 and P3) as they relate to the processing of congruent and incongruent fearful faces. Previous studies have indicated that frontal EEG alpha asymmetry during resting conditions can be considered as a neural index of emotional regulation (Jackson et al., 2003; Kline et al., 2007; Papousek et al., 2012, 2017). Relative left lateralization is associated with flexible emotional responses, whereas relative right lateralization is associated with inflexible emotional responses. Thus, we expected ILA to direct more attentional and motivational resources to emotional faces, which would result in enhanced N1 and P3 amplitudes, while IRA were expected to experience more conflict for incongruent emotional faces, resulting in enhanced N2 amplitude. That is, it was expected that frontal EEG alpha asymmetry during resting conditions would reflect individual differences in the processing of congruent and incongruent fearful faces.

MATERIALS AND METHODS

Participants

G * Power software was used to calculate the sample size in order to achieve a power of 0.85 at an α level 0.05 with an effect size of 0.30. The output of G * Power software indicated that a sample size of 52 was required. As such, 56 healthy female undergraduate students (M = 21.91 years, SD = 2.37 years, age range = 19–28 years) were paid to participate in this study. All participants self-reported that they were right-handed with normal or corrected-to-normal vision and had no neurological or psychological disorders. All participants completed the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), and all participants were suitable for the experiment because their scores on the BDI and BAI were within the normal range. All participants gave their written informed consent, and the study was approved by the local ethics committee of Ningbo University.

Experimental Materials

Emotional Questionnaire Materials

The BDI is a 21-item self-report measure designed to assess depression (Beck et al., 1979). The Chinese BDI scale has a

split-half reliability coefficient of 0.88 and a Cronbach's alpha coefficient of 0.89 (Zhang et al., 1990). The BAI is a 21-item self-report measure designed to assess anxiety (Beck et al., 1988). The Chinese BAI has good reliability, with a Cronbach's alpha coefficient of 0.95 (Zheng et al., 2002).

Emotional Face Materials

In total, 60 emotional faces were selected from the Chinese Facial Affective Picture System Database (Wang and Luo, 2005); these included 15 fearful male and 15 fearful female faces (valence: M = 2.62, SD = 0.32; arousal: M = 6.71, SD = 0.99) as well as 15 neutral male and 15 neutral female faces (valence: M = 4.68, SD = 0.32; arousal: M = 4.22, SD = 0.28). There were significant differences between fear faces and neutral faces in terms of valence [$F(1,58) = 596.49$, $p < 0.001$] and arousal [$F(1,58) = 172.06$, $p < 0.001$] (please see Peng et al., 2012).

Procedure

After attending the lab, participants signed the informed consent form and completed the emotional questionnaires. Then, participants were seated in an acoustically and electrically shielded examination chamber, approximately 100 cm from a computer screen, and electrodes were attached. (1) Participants were asked to complete a 2 min resting task, in which recording of resting EEG was obtained; the 2 min resting task included 1 min eyes open (O) and 1 min eyes closed (C). Two sequences were used, O–C–C–O and C–O–O–C; the presentation of these sequences was balanced between the subjects. (2) Participants were asked to complete the cue-target task, which was a modified version of the task used by Peng et al. (2012) (see **Figure 1**). During the cue-target task, each trial started with a white cross for 100 ms. After a 500-ms black blank, the cue word (i.e., the word "fear" or "neutral") was presented for 150 ms. After another 200-ms black blank, the target face was presented for 200 ms, followed by a black blank whose longest duration was 1,500 ms. Half of the participants were instructed to use their left hand to press the "F" key if a fearful face was shown or to use their right hand to press the "J" key if a neutral face was shown, whereas the other half of the participants were instructed to use a reversed key arrangement. For incorrect or invalid responses, an exclamation mark was displayed for 200 ms; otherwise, the black blank remained for another 200 ms. Finally, a green blank was presented for a random duration of 2,100–2,300 ms, allowing the participant to relax for a while. In each trial, the chance of a consistent prime-face sequence was 50%; there were four conditions in the experiment: "fear" word-fear face, "fear" word-neutral face, "neutral" word-fear face, and "neutral" word-neutral face. The experiment consisted of 180 formal trials, divided over two blocks.

E-prime 2.0 software was used to present the 2 min resting task and the cue-target task. All stimuli were presented in the center of a 17-inch LCD screen (resolution 1024 × 768, refresh rate 60 Hz).

EEG Recording and Analysis

Electroencephalography data were recorded using a NeuroScan recorder with a NuAmps amplifier. The electrode cap contained 40 Ag/AgCl electrodes, which were positioned according to the International 10–20 system. EEG signals were acquired by a DC model with a sampling rate of 1,000 Hz and a bandwidth of 100 Hz. Vertical and horizontal electrooculograms (EOGs) were recorded; the left mastoid electrode served as the reference. The impedance of all electrodes was kept under 5 kΩ.

EEG Data Analysis

Electroencephalography asymmetry measures were taken from the 2-min resting task. Neuroscan 4.3 software was used to analyze the EEG data. According to previous studies (Feng et al., 2012; Papousek et al., 2012; Huang et al., 2015; Suo et al., 2017; Zhou and Liu, 2017), all data were inspected visually to eliminate intervals in which ocular or muscle artifacts occurred. Only participants who had at least 30 s of artifact-free data in the recording periods were included in the final sample

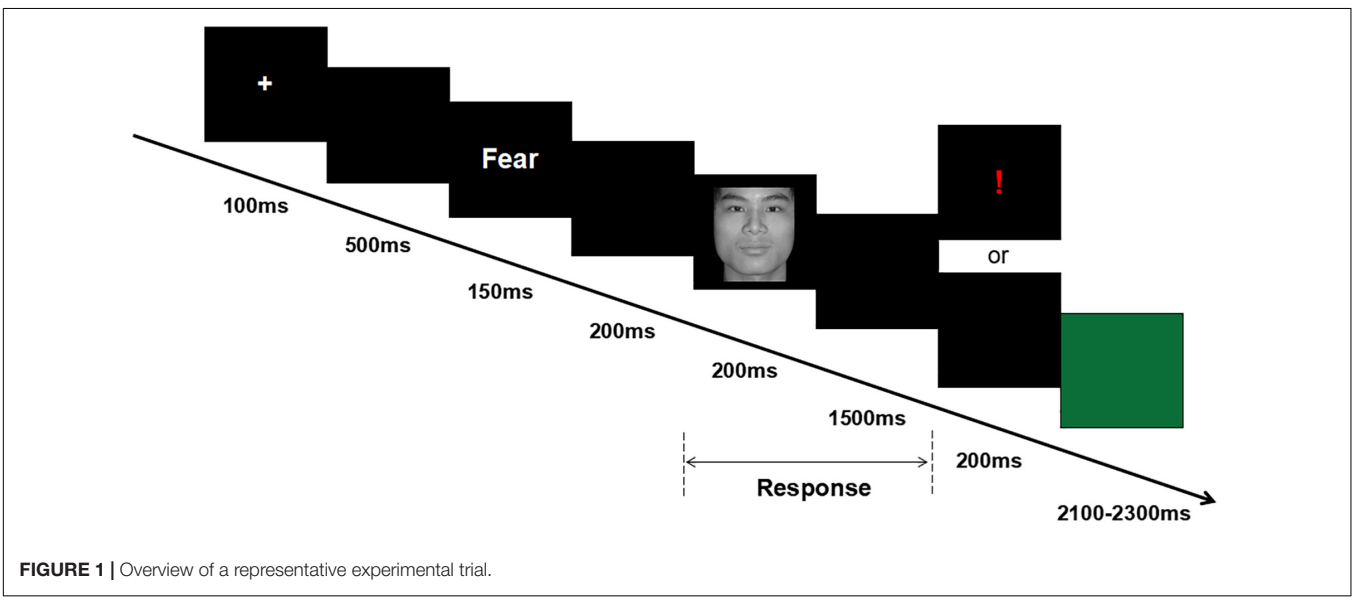

FIGURE 1 | Overview of a representative experimental trial.

(n = 56). Offline analysis of EEG signals was re-referenced to the Cz electrode[1] and was filtered using a 30 Hz bandwidth (24 dB/octave slope). Power spectra were derived by fast Fourier transform with a Hamming window (epoch length 1 s, 50% overlap) for the 2-min resting task. For consistency with previous research (Papousek et al., 2012; Suo et al., 2017), we focused on the alpha band (8–13 Hz) in the frontal electrodes F3 and F4. A laterality coefficient (LC) indexing relative left- versus right-sided activation was used. EEG LC values were computed as follows: LC = $[(L - R)/(L + R)] \times 100$. Positive values indicate higher alpha activity in the left compared to the right hemisphere.

ERP Data Analysis

The offline analysis of EEG signals was re-referenced to the mean of the left and right mastoids and was filtered using a 0.05- to 30-Hz bandwidth (24 dB/octave slope). Vertical and horizontal EOGs were filtered out according to the computation rule commonly used in ERP studies (Gratton et al., 1983). The artifact rejection criterion was an amplitude of $\pm 100\ \mu V$. **Table 1** shows the average trial number of four conditions for ILA and IRA. The EEG was averaged by channel and time window from 100 ms before prime cue to 1,400 ms after prime cue. The 100-ms interval before prime cue onset served as the baseline interval. According to previous studies (Folstein and Van Petten, 2008; Luo et al., 2010; Peng et al., 2012; Yang et al., 2012), for the grand-mean ERP waveforms, we measured the mean amplitudes of N1 (480–520 ms after prime onset or 130–170 ms after face onset) and P2 (540–600 ms after prime onset or 190–250 ms after face onset) over the anterior (Fz, FCz, and Cz) regions, and the mean amplitudes of N2 (630–730 ms after prime onset or 280–380 ms after face onset) and P3 (830–1,130 ms after prime onset or 480–780 ms after face onset) over the anterior (Fz, FCz, and Cz) and posterior (Pz and CPz) regions.

Statistics

According to a median split of frontal EEG alpha asymmetry scores during the 2-min resting task (Papousek et al., 2012; Suo et al., 2017), individuals were divided into two groups: ILA and IRA. The behavioral measures (the accuracy rates and the response times) were analyzed using a 2 (prime cue: "neutral" word vs. "fear" word) × 2 (expression type: neutral face vs. fear face) × 2 (group: ILA vs. IRA) mixed factor ANOVA, in which prime cue and expression type were the within-subject factors and group was the between-subjects factor. Then, for N1 and P2, a 2 (prime cue: "neutral" word vs. "fear" word) × 2 (expression type: neutral face vs. fear face) × 2 (group: ILA vs. IRA) fixed-measures ANOVA was performed, in which prime cue and expression type were the within-subjects factors and group was the between-subjects factor. For N2 and P3, a 2 (prime cue: "neutral" word vs. "fear" word) × 2 (expression type: neutral face vs. fear face) × 2 (electrode: anterior vs. posterior) × 2 (group: ILA vs. IRA) fixed-measures ANOVA was performed, in which prime cue, expression type, and electrode were the within-subjects factors and group was the between-subjects factor. The significance levels were set at 0.05.

[1]Cz reference has been utilized more often in the EEG asymmetry literature than other reference montages (see Coan and Allen, 2003; Coan and Allen, 2004; for review). Therefore, the present study used the Cz reference to analyze the EEG data. In addition, there was a significant correlation between frontal alpha asymmetry scores when using the Cz reference and frontal alpha asymmetry scores when using the mean reference of the left and right mastoids ($r = 0.695$, $p < 0.001$). This result suggests that frontal alpha asymmetry results did not change when using linked mastoids as a reference compared to when using Cz as a reference.

TABLE 1 | The average trial number of the four conditions for ILA and IRA, respectively.

	ILA(n = 28) M (Minimum, Maximum)	IRA(n = 28) M (Minimum, Maximum)
FC-FF	42 (27, 45)	40 (24, 45)
FC-NF	41 (31, 45)	40 (24, 45)
NC-FF	42 (30, 45)	39 (20, 45)
NC-NF	41 (27, 45)	39 (22, 45)

FC: fear cue; NC: neutral cue; FF: fearful face; NF: neutral face.

RESULTS

In this section, we first report the behavioral results. Then, the ERP results are reported. For the sake of brevity, the statistical effects that did not reach significance are omitted.

Behavioral Results

Before statistical analysis, the no-response trials were removed. Then, subjects were divided into two groups (IRA and ILA) based on a median split of baseline asymmetry. **Table 2** shows the mean ages, mean scores on the emotional questionnaires (BAI and BDI), and the LCs for the ILA and IRA groups.

Table 3 and **Figure 2** show the accuracy rates and the response times in the four conditions, for ILA and IRA, respectively. **Table 4** shows the statistical results for the behavioral data, for the ILA and IRA groups.

For the accuracy rates, the main effect of the prime cue was significant, $F(1,54) = 16.81$, $p < 0.001$, $\eta^2 = 0.237$, indicating that the accuracy rate for the word "fear" was higher than for the word "neutral." The main effect of expression type was significant, $F(1,54) = 55.19$, $p < 0.001$, $\eta^2 = 0.505$, indicating that the accuracy rate for fear faces was lower than for neutral faces. The interaction effect of prime cue × expression type was significant, $F(1,54) = 33.94$, $p < 0.001$, $\eta^2 = 0.386$. The simple effect analysis of prime cue × expression type showed that the accuracy rate for fear faces when the prime cue was the word "fear" was higher than that when the prime cue was the word "neutral" ($p < 0.001$), whereas there was no significant difference between neutral faces

TABLE 2 | The mean age, scores on the emotional questionnaires (BAI and BDI), and laterality coefficient (LC) for ILA and IRA, respectively.

	ILA(n = 28) M(SD)	IRA(n = 28) M(SD)	$t(p)$
Age	22.07 (2.07)	21.75 (2.66)	0.50 (0.616)
BAI	26.21 (5.32)	26.64 (6.17)	0.28 (0.782)
BDI	6.57 (6.31)	7.75 (7.03)	−0.66 (0.512)
LC	−16.07 (11.23)	11.14 (14.46)	−7.86 (0.000)

TABLE 3 | The means and standard deviations of the behavioral data (accuracy rate and response time) for ILA and IRA, respectively.

	ILA(n = 28) M(SD)	IRA(n = 28) M(SD)
ACC		
FC-FF	0.96 ± 0.04	0.95 ± 0.04
FC-NF	0.97 ± 0.03	0.96 ± 0.04
NC-FF	0.93 ± 0.04	0.90 ± 0.06
NC-NF	0.98 ± 0.02	0.97 ± 0.03
RT		
FC-FF	611.49 ± 87.25	676.63 ± 125.94
FC-NF	626.84 ± 84.90	675.16 ± 109.10
NC-FF	649.95 ± 93.17	717.69 ± 132.91
NC-NF	637.52 ± 81.76	683.33 ± 114.21

TABLE 4 | The statistical results for the behavioral data (accuracy rate and response time) for ILA and IRA, respectively.

	F	p	η^2
Accuracy rate			
PC	16.81	0.000	0.237
ET	55.19	0.000	0.505
G	2.96	0.091	0.052
PC × ET	33.94	0.000	0.386
G × PC	0.42	0.522	0.008
G × ET	1.67	0.202	0.030
G × PC × ET	3.194	0.080	0.056
Response time			
PC	54.50	0.000	0.502
ET	2.30	0.135	0.041
G	4.39	0.041	0.075
PC × ET	13.67	0.001	0.202
G × PC	0.00	0.995	0.000
G × ET	3.19	0.080	0.056
G × PC × ET	0.10	0.757	0.002

PC: Prime Cue; ET: Expression Type; G: Group.

when the prime cue was the word "fear" and when the prime cue was the word "neutral" (p = 0.068).

For response times, the main effect of the prime cue was significant, $F(1,54) = 54.50$, $p < 0.001$, $\eta^2 = 0.502$, indicating that reaction times to the word "fear" were shorter than to the word "neutral." The main effect of group was significant, $F(1,54) = 4.39$, $p = 0.041$, $\eta^2 = 0.075$, indicating that the reaction times of the ILA group were shorter than those of the IRA group. The interaction effect of prime cue × expression type was significant, $F(1,54) = 13.67$, $p = 0.001$, $\eta^2 = 0.202$. The simple effect analysis of prime cue × expression type showed that when the prime cue was the word "neutral," the reaction times for fear faces were longer than neutral faces (p = 0.003), whereas there was no significant difference between fear faces and neutral faces when the prime cue was the word "fear" (p = 0.256).

ERP Results

Figure 3 shows the average amplitudes in the four conditions at Fz, FCz, Cz, CPz, Pz electrodes for ILA and IRA, respectively. **Table 5** shows the means and standard deviations of ERP data for ILA and IRA, and **Table 6** shows the statistical results for the ERP data for ILA and IRA.

For N1, the main effect of group was significant, $F(1,54) = 4.85$, p = 0.032, η^2 = 0.082, indicating that ILA had larger N1 amplitudes than IRA.

For P2, the main effect of expression type was significant, $F(1,54) = 11.29$, $p = 0.001$, $\eta^2 = 0.173$, indicating that fear faces induced larger P2 amplitudes than neutral faces.

For N2, the main effect of expression type was significant, $F(1,54) = 25.55$, $p < 0.001$, $\eta^2 = 0.321$, indicating that fear faces induced smaller N2 amplitudes than neutral faces. The main effect of electrode was significant, $F(1,54) = 67.88$, $p < 0.001$, $\eta^2 = 0.557$, indicating that the anterior region induced greater N2 amplitudes than the posterior region. The interaction effect of prime cue × expression type was significant, $F(1,54) = 10.36$, $p = 0.002$, $\eta^2 = 0.161$. The interaction effect of prime cue × electrode was significant, $F(1,54) = 5.37$, $p = 0.024$, $\eta^2 = 0.090$. The interaction effect of prime cue × electrode × group was significant, $F(1,54) = 5.61$, $p = 0.021$, $\eta^2 = 0.094$. The interaction effect of prime cue × expression type × group × electrode was significant, $F(1,54) = 5.41$, $p = 0.024$, $\eta^2 = 0.091$. The simple effect analysis of prime cue × expression type × electrode × group showed that for IRA,

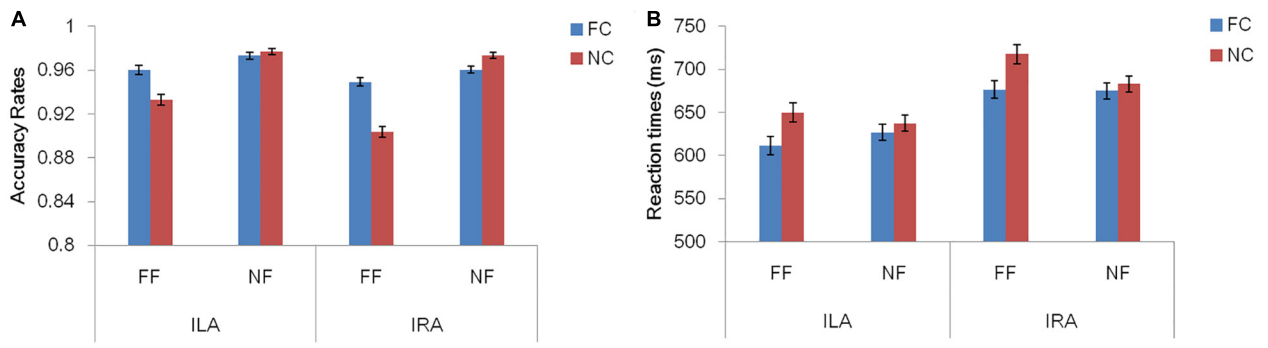

FIGURE 2 | The accuracy rates **(A)** and response times **(B)** for the four conditions, for ILA and IRA, respectively. FC: fear cue; NC: neutral cue; FF: fearful face; NF: neutral face.

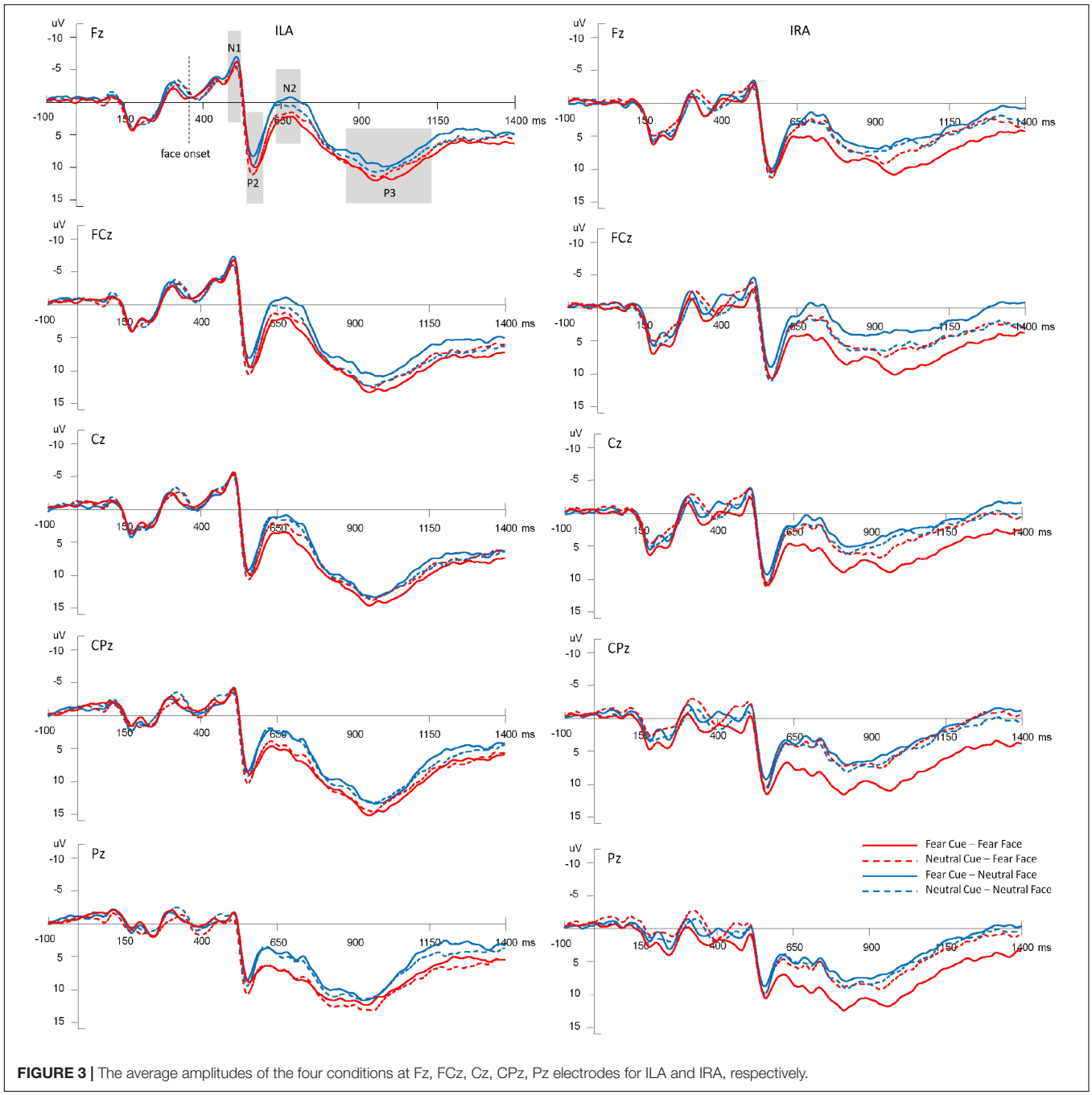

FIGURE 3 | The average amplitudes of the four conditions at Fz, FCz, Cz, CPz, Pz electrodes for ILA and IRA, respectively.

fear faces when the prime cue was the word "neutral" induced greater N2 amplitudes than when the prime cue was the word "fear" (p's < 0.05). However, there were no significant differences for ILA (p's > 0.05).

For P3, the main effect of expression type was significant, $F(1,54) = 12.69$, $p = 0.001$, $\eta^2 = 0.190$, indicating that fear faces induced greater P3 amplitudes than neutral faces. The main effect of group was significant, $F(1,54) = 4.68$, $p = 0.035$, $\eta^2 = 0.080$, indicating that ILA had greater P3 amplitudes than IRA. The interaction effect of prime cue × expression type was significant, $F(1,54) = 5.61$, $p = 0.021$, $\eta^2 = 0.094$. The interaction effect of prime cue × electrode × group was significant, $F(1,54) = 4.99$, $p = 0.030$, $\eta^2 = 0.085$. The interaction effect of prime cue × expression type × electrode × group was significant, $F(1,54) = 4.11$, $p = 0.048$, $\eta^2 = 0.071$. The simple effect analysis of prime cue × expression type × electrode × group showed that fear faces induced greater P3 amplitudes when the prime cue was the word "fear" than when the prime cue was the word "neutral" for the IRA group only (p's < 0.05). However, there were no significant differences in the ILA group (p's > 0.05). Another simple effect analysis method showed that the ILA group had a larger P3 than the IRA group for the word "neutral,"

TABLE 5 | The means and standard deviations of the ERP data (N1, P2, N2, and P3) for ILA and IRA, respectively.

	ILA(n = 28) M(SD)	IRA(n = 28) M(SD)
N1		
FC-FF	−5.00 ± 4.38	−1.47 ± 5.05
FC-NF	−5.23 ± 6.22	−2.89 ± 4.97
NC-FF	−4.19 ± 3.91	−2.82 ± 5.25
NC-NF	−4.36 ± 3.94	−1.74 ± 4.77
P2		
FC-FF	9.30 ± 5.46	9.63 ± 6.99
FC-NF	7.67 ± 5.96	8.02 ± 6.49
NC-FF	9.94 ± 5.29	9.54 ± 8.75
NC-NF	8.63 ± 4.79	9.38 ± 6.95
Anterior N2		
FC-FF	3.51 ± 5.83	4.84 ± 7.08
FC-NF	0.58 ± 6.05	1.35 ± 6.23
NC-FF	2.80 ± 5.57	2.55 ± 9.12
NC-NF	1.68 ± 4.83	2.45 ± 6.87
Posterior N2		
FC-FF	7.01 ± 4.69	8.47 ± 5.36
FC-NF	4.21 ± 5.19	4.34 ± 5.37
NC-FF	6.92 ± 5.03	5.03 ± 7.40
NC-NF	4.71 ± 4.33	4.83 ± 6.01
Anterior P3		
FC-FF	11.93 ± 6.06	8.67 ± 12.05
FC-NF	10.06 ± 5.66	4.55 ± 12.57
NC-FF	11.50 ± 5.85	6.30 ± 12.22
NC-NF	11.09 ± 6.19	5.78 ± 11.82
Posterior P3		
FC-FF	12.04 ± 4.95	9.97 ± 10.37
FC-NF	10.39 ± 5.43	5.70 ± 10.25
NC-FF	12.36 ± 5.71	6.47 ± 10.21
NC-NF	10.85 ± 6.06	6.37 ± 9.74

TABLE 6 | The statistical results for the ERP data (N1, P2, N2, and P3) for ILA and IRA, respectively.

	F	p	η^2
N1			
PC	0.71	0.404	0.013
ET	0.26	0.609	0.005
G	4.85	0.032	0.082
PC × ET	3.77	0.057	0.065
G × PC	1.13	0.293	0.020
G × ET	0.01	0.960	0.000
G × PC × ET	3.41	0.070	0.059
P2			
PC	2.92	0.093	0.051
ET	8.20	0.006	0.132
G	0.03	0.870	0.001
PC × ET	1.41	0.240	0.025
G × PC	0.04	0.848	0.001
G × ET	0.51	0.477	0.009
G × PC × ET	0.58	0.449	0.011
N2			
PC	0.87	0.355	0.016
ET	25.55	0.000	0.321
E	67.88	0.000	0.557
G	0.05	0.825	0.001
PC × ET	10.36	0.002	0.161
PC × E	5.37	0.024	0.090
G × PC	1.92	0.171	0.034
G × ET	0.11	0.739	0.002
G × E	0.80	0.376	0.015
ET × E	2.63	0.111	0.046
PC × ET × E	0.82	0.369	0.015
G × PC × ET	2.65	0.110	0.047
G × PC × E	5.61	0.021	0.094
G × ET × E	0.04	0.846	0.001
G × PC × ET × E	5.41	0.024	0.091
P3			
PC	0.39	0.535	0.007
ET	12.69	0.001	0.190
E	0.67	0.418	0.012
G	4.70	0.035	0.080
PC × ET	5.61	0.021	0.094
PC × E	3.32	0.074	0.058
G × PC	1.66	0.203	0.030
G × ET	0.78	0.381	0.014
G × E	0.17	0.684	0.003
ET × E	0.34	0.561	0.006
PC × ET × E	0.64	0.429	0.012
G × PC × ET	2.44	0.124	0.043
G × PC × E	5.00	0.030	0.085
G × ET × E	1.14	0.291	0.021
G × PC × ET × E	4.11	0.048	0.071

PC: Prime Cue; ET: Expression Type; G: Group; E: Electrode.

regardless of whether it was followed by fear faces or neutral faces, and for the word "fear" followed by neutral faces (p's < 0.05). However, there was no significant difference between ILA and IRA for the word "fear" followed by fear faces ($p > 0.05$).

DISCUSSION

The present study examined whether frontal EEG alpha asymmetry during resting conditions is related to the processing of congruent and incongruent fearful faces among female participants. Behaviorally, we found that the IRA group had longer reaction times than the ILA group during the cue-target task. The ERP results showed that there was a modulating effect of frontal EEG alpha asymmetry on congruent and incongruent fearful faces in N1, N2, and P3 time intervals.

The behavioral results showed that the accuracy of fearful faces when the prime cue word was "fear" was higher than when the prime cue word was "neutral." These results indicated that fearful faces processing was influenced by anticipation that congruent prime cue had higher accuracy than incongruent prime cue for fearful faces. Some studies have shown "negative bias" for the processing of emotional information, in which negative stimuli are often quicker to attract attention and priority in mental processing (Smith et al., 2006; Yang et al., 2010). In

the present study, the word "fear" was considered as a negative stimulus that would attract more attentional resources, thus helping participants to better judge subsequent fearful faces. Furthermore, the reaction time results showed that reactions times for fearful faces were longer than for neutral faces when the prime cue word was "neutral." When the prime cue word was "neutral," incongruent fearful faces produced more cognitive conflict than congruent neutral faces, leading to longer response times. Further, the behavioral results showed that the average reaction time of the IRA group was longer than that of the ILA group. Frontal EEG alpha asymmetry can be considered as an index of emotional regulation. Research has shown that IRA has less effective emotion regulation compared with ILA (Jackson et al., 2003; Papousek et al., 2017). Therefore, IRA must devote more time to evaluate threat cues or stimuli, resulting in longer reactions times in the cue-target task.

The ERP results indicated that ILA had larger N1 amplitudes than IRA. Previous studies have shown that N1 is associated with early perceptual processing (Pourtois et al., 2000; Peng et al., 2012). N1 serves as a rapid detector and predictor of potential information based on coarse aspects of input; this detection is valuable for recognizing and analyzing threatening information (Bar et al., 2006). The results of the present study suggest that ILA can detect emotional face stimuli faster than IRA in the early stage.

Further, fearful faces, when the prime cue word was "neutral," induced greater N2 amplitudes than when the prime cue word was "fear," among the IRA group only. Previous studies have shown that the N2 component is related to conflict monitoring. For example, N2 is sensitive to the degree of conflict between response alternatives in the flanker task (Kopp et al., 1996; Van Veen and Carter, 2002; Folstein and Van Petten, 2008). Therefore, we suggest that N2 may reflect the monitoring of cognitive interference. In the present study, there was more conflict for incongruent fearful faces than for congruent fearful faces, leading to larger N2 amplitudes for the IRA group. However, ILA exhibits superior emotional flexibility (Kline et al., 2007; Papousek et al., 2012) and more effective emotion regulation (Jackson et al., 2003; Papousek et al., 2017). For example, Jackson et al. (2003) found that ILA displayed attenuated startle magnitude after the offset of negative stimuli, reflecting an automatic emotion regulation process aimed at reducing negative affectivity. Recently, research showed that ILA prefers reappraisal over suppression to regulate negative events (Papousek et al., 2017). Thus, there was no significant difference in N2 amplitude between congruent and incongruent fearful faces for the ILA group.

In addition, the ILA group exhibited larger P3 amplitudes than the IRA group for the word "neutral," regardless of whether it was followed by fear faces or neutral faces, and for the word "fear" when followed by neutral faces. In studies using emotional stimuli, P3 has been summarized as reflecting the allocation of limited resources toward motivationally salient environment stimuli, in which motivationally relevant stimuli (e.g., emotional stimuli) naturally and automatically arouse and direct attentional and motivational resources (Hajcak et al., 2010; Eddy et al., 2015). According to this, ILA can automatically direct attention and motivation to emotional face stimuli, as compared with IRA. Furthermore, for ILA, there was no significant difference in P3 amplitude between fearful faces followed by the word "neutral" and those followed by the word "fear"; there was also no significant difference in P3 amplitude between neutral faces followed by the word "neutral" and those followed by the word "fear." Considering that emotional P300 effects reflect rapid attention to emotional stimuli, and are associated with improved processing efficiency (Öhman et al., 2001; Hajcak et al., 2010; Eddy et al., 2015), these results indicate that ILA directed more attentional and motivational resources to the evaluation of congruent and incongruent emotional face stimuli. However, for IRA, congruent fearful faces induced greater P3 amplitudes than incongruent fearful faces, whereas there was no significant difference between congruent and incongruent neutral faces. These results indicate that, for IRA, attentional and motivational resources were directed to the evaluation of fearful faces only when the prime cue word was "fear."

The present study suggests that frontal EEG alpha asymmetry during resting conditions is associated with the processing of congruent and incongruent fearful faces. The neuro-laterality models of affect and psychopathology assume that the left and right frontal cortical hemispheres are differentially involved in processes modulating affective responses to emotional challenges (Davidson, 1998; Eippert et al., 2007; Harmon-Jones et al., 2010). It has been proposed that greater left frontal EEG activity during resting conditions is associated with greater affective flexibility as compared to asymmetry in favor of the right hemisphere (Papousek et al., 2012). This is consistent with the present findings indicating that relative activation intensity of the left frontal cortex and right frontal cortex during resting conditions is sensitive to the processing of congruent and incongruent fearful faces. To our knowledge, this study is the first to demonstrate such a link between frontal EEG alpha asymmetry during resting conditions and the processing of fearful faces.

A potential limitation of the present study is that it is unclear how frontal EEG alpha asymmetry during resting conditions relates to the processing of congruent and incongruent fearful faces. A previous study found that fear emotion induced by fear stimuli increased activation of the frontal cortex. With the increased frontal cortical activity, there was a downward trend in amygdala activation (Goldstein et al., 2010). Future research should assess whether the frontal cortex affects activation of the amygdala, thereby modulating the processing of congruent and incongruent fearful faces. The second limitation is that this study aimed to examine whether frontal EEG alpha asymmetry during resting conditions is associated with the processing of congruent and incongruent fearful faces among female participants only. One gender was chosen given that emotional processing is reportedly different between women and men (Thayer and Johnsen, 2000; Collignon et al., 2010; Jin et al., 2013; Lee et al., 2017). Future research needs to investigate whether there is a gender difference in their connections. Finally, there were several methodological limitations of this study. First, based on previous studies (Papousek et al., 2012; Suo et al., 2017), the present study created two artificial groups based on a median split of frontal alpha asymmetry; this may decrease the statistical and explanatory power of the study. Second, the number of incorrect

responses was not very high in the current study, and the correct and incorrect trials were pooled for ERP analyses. This approach might not be optimal for assessment of amplitude variation in response to congruent and incongruent stimuli for the N2 component, which is usually investigated only for correct trials.

The present study suggests a relationship between frontal EEG alpha asymmetry and the processing of congruent and incongruent fearful faces. In this study, ILA quickly processed the emotional faces in the early stage and directed more attentional and motivational resources to the evaluation of the emotional faces in the late stage, while IRA experienced more conflict for incongruent fearful faces in the late stage and longer reaction times during the cue-target task. Therefore, frontal EEG alpha asymmetry during resting conditions can reflect individual differences in the processing of congruent and incongruent fearful faces.

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 Ethic Committee at the Department of Psychology, Ningbo University. 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

Both authors developed the ideas and wrote the manuscript.

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The Role of Amygdala in Self-Conscious Emotions in a Patient With Acquired Bilateral Damage

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Shame plays a fundamental role in the regulation of our social behavior. One intriguing question is whether amygdala might play a role in processing this emotion. In the present single-case study, we tested a patient with acquired damage of bilateral amygdalae and surrounding areas as well as healthy controls on shame processing and other social cognitive tasks. Results revealed that the patient's subjective experience of shame, but not of guilt, was more reduced than in controls, only when social standards were violated, while it was not different than controls in case of moral violations. The impairment in discriminating between normal social situations and violations also emerged. Taken together, these findings suggest that the role of the amygdala in processing shame might reflect its relevance in resolving ambiguity and uncertainty, in order to correctly detect social violations and to generate shame feelings.

Keywords: amygdala, moral emotions, shame, emotion recognition, Guilt

INTRODUCTION

The amygdala is a subcortical nucleus which has been related to a broad variety of functions including facial emotion recognition, social cognition, and reward learning (Adolphs, 2010; Janak and Tye, 2015). While early findings highlighted the amygdala's role in processing facial expressions, specifically fear expressions (Adolphs et al., 1994; Calder, 1996), and were initially interpreted by hypothesizing the amygdala involvement in processing stimuli signaling threat (Adolphs, 2010), more recent investigations highlighted that its role in processing faces might have something to do with the allocation of processing resources toward specific features to disambiguate facial expression meaning (Adolphs, 2010; Spezio et al., 2007). While patients with amygdala damage have been associated with reduced ability to recognize fearful faces (Adolphs et al., 1994; Calder, 1996), they, however, display spared abilities to recognize the same emotion by other body parts (i.e., gestures, Atkinson et al., 2007) or modalities (i.e., prosody, Adolphs and Tranel, 1999;

Bach et al., 2013). Moreover, they also show reduced tendency to fixate the eye region (Adolphs et al., 2005; Spezio et al., 2007), ignoring the facial features that are diagnostic when recognizing fearful expressions (Smith et al., 2005). Aside from disambiguation, the amygdala might play further roles in emotional processing. Indeed, several neuroimaging studies reported that amygdala activation is sensitive to a wide repertoire of emotional stimuli, including both negatively and positively valenced items (Costafreda et al., 2008; Sabatinelli et al., 2011) and leading to the hypothesis that the amygdala might be involved in arousal processing (Anderson et al., 2003). Indeed, amygdala activation is modulated by the arousal of the stimuli (Anderson et al., 2003; Ball et al., 2009; Bonnet et al., 2015) and is coupled with psychophysiological responses (Bonnet et al., 2015).

Neuroimaging studies revealed that amygdala activation was associated with shame induction (Finger et al., 2006; Pulcu et al., 2014) and that amygdala volume correlated with shame proneness (Whittle et al., 2016). In addition, deep-brain stimulation of the amygdala induced in a patient the emotional experience of shame (Inman et al., 2018). Specifically, a patient's emotional response was modulated by a stimulation intensity of 5 V associated with shame experience, and higher stimulations were associated with fear experience. In addition, these emotional responses were not evoked in other patients undergoing the same stimulation protocol (Inman et al., 2018). Together, these findings suggest that the amygdala might play a crucial role in generating shame experience.

However, other studies highlighted the amygdala's role in understanding social situations (Martin and Weisberg, 2003; Noack et al., 2015; Lymer et al., 2018) and in detecting social violations (Berthoz et al., 2006; Bas-Hoogendam et al., 2017). These latter functions are highly correlated with shameful experiences, since shame generation requires accurate social situation assessment and is usually triggered by social and moral violations (Tangney et al., 2007). Specifically, shame usually occurs when an individual perceives the self or the persona as inadequate with respect to the accepted social and moral standards (Tangney et al., 1992), especially when a specific aspect of the self-image is perceived as defective (Gausel and Leach, 2011). In addition, shame generation leads to behavioral inhibition (Tangney et al., 2007) and, together with guilt, which is often associated with shame, promotes changing in the self and the behavior against immorality (Gausel and Brown, 2012; Martinez et al., 2014).

The aim of the present study is to clarify how amygdala damage can affect shame processing at different levels. In order to achieve this aim, we tested a patient with acquired brain damage at the level of bilateral amygdalae and surrounding tissues with different tasks tapping social cognitive skills, emotion facial recognition, and subjective experience. Specifically, we tested the subjective emotional experience of a patient by asking him to rate his level of shame associated with specific social situations. These situations involved violations of social and moral standards. If the amygdala is involved in generated emotional responses, we expect reduced shame emotional ratings compared with that in control participants in any condition. Conversely, if no difference or differences only in some conditions on the ratings between controls and the patient are present, it might not be attributed to primary emotional deficit. Hence, in this latter outcome, the role of the amygdala in moral judgment might not be ascribed to shame or guilt generation. Aside from this experimental task, to control for other basic deficits that might influence the outcome of this experimental tasks, the patient's cognitive abilities and social cognitive skills were further investigated in a neuropsychological assessment. In addition, the patient was also evaluated on a set of emotion recognition tasks, following previous studies on patients with amygdala damage which reported deficits in recognizing fearful faces and spared ability to recognize emotion through body parts and prosody. Moreover, testing emotion recognition would allow us to ascertain whether shameful facial expression, which, different from other moral emotions, was also reported to be characterized by distinctive features (i.e., gaze movement downward and blushing) (Asendorpf, 1990; Keltner and Buswell, 1997), might also be impaired. Indeed, we hypothesized that shame experience deficit, if present, might also have impaired the patient's ability to recognize the same emotion in others.

MATERIALS AND METHODS

Case Description

FF is a right-handed middle-aged man, with 13 years of education, who was admitted to the rehabilitation ward with a diagnosis of Erdheim–Chester disease (non-Langerhans cells histiocytosis, see Diamond et al., 2014), with neurological and dermatological symptoms. About 2 years earlier, FF showed hyperprolactinemia and diabetes insipidus, and subsequently, he reported hyposthenia and hypoesthesia of the lower limbs, balance issues, emotional lability, and hypogeusia and received a diagnosis of gait ataxia and mild right hemiparesis. The MRI scan, acquired at the moment of the diagnosis, revealed bilateral cortical thickening mainly at the level of the amygdala. The lesion extended to the pituitary stalk, optic chiasm, and hypothalamus and involved also the lenticular nucleus, internal and external capsule in the left hemisphere, and the external capsule in the right hemisphere. Moreover, diffuse signal intensity alterations involved the cervical and thoracic spinal cord (mainly in the

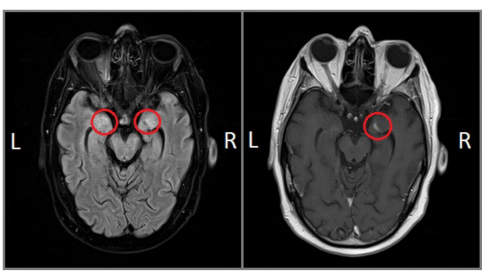

FIGURE 1 | FF's MRI scans: FLAIR **(left)** and T1-weighted gadolinium-enhanced **(right)** sequences.

posterior columns). At the time of testing, the neurological symptoms had regressed, with a marked reduction of the emotional lability, mild improvement of the motor abilities, and minimal impairments in the cerebellar tests. Likewise, the MRI pattern at 5 months after the diagnosis and 4 months before the neuropsychological testing (see **Figure 1**) revealed a marked reduction in intensity alteration at the level of the amygdala, hippocampus, and pituitary stalk. Signal alterations located within the bilateral internal and external capsule, as well as at the level of right lenticular nucleus, were no longer detectable.

Before taking part in the experiment, patient FF, as well as a sample of healthy controls, signed an informed consent, which was approved by the local ethical committee (CEUR – regional ethical committee of Friuli Venezia Giulia). Healthy control samples included 13 age- and education-matched healthy male individuals (age: 48.6 ± 9.3, education: 13.8 ± 3.2, MMSE: 29.5 ± 0.5) who were tested on all the experimental tasks, as well as on Positive and Negative Affect Schedule (PANAS) and TOSCA. The sample size of the healthy control group was chosen based on previous single-case studies in the field of emotion processing (Pishnamazi et al., 2016; Bennetts et al., 2017; Bach et al., 2019).

For technical reasons, three individuals from the sample of the healthy controls were not tested in the emotion recognition from the prosody task and the emotional gestures recognition task, while another participant was not tested on PANAS.

TABLE 1 | Neuropsychological battery and questionnaires.

Test	Range	Cutoffs	Raw score (corrected score)	*Z*-scores
Memory				
Digit span forward	0–9	< 4.26	6 (5.75)	
Corsi's span forward	0–9	< 3.46	5 (4.74)	
Digit span backward	0–9	< 2.65	4 (3.71)	
Corsi's span backwards	0–9	< 3.08	5 (4.77)	
Prose memory	0–28	< 7.5	14.5 (15)	
Executive functions and attention				
Trail making test				
-A	–	> 94	59 (56)	
-B	–	> 283	158 (152)	
Phonemic/semantic alternate fluency	–	< 12.7	26 (25.31)	
-Composite shifting index		< 0.38	1.15 (1.12)	
Similarities	0–28		**6***	
Raven's progressive matrices	0–36	≤ 18.96	34 (31.80)	
Tower of London test	0–36		32	-0.57¥
Wisconsin Card Sorting Test				
-Number of categories	0–6	≤ 2	**2***	
-Number of perseverations	0–36	≥ 6.41	–	
Verbal judgment test	0–50	–	46 (40.25)	
Cognitive estimation test	0–27	≤ 12	9 (9.62)	
Language				
Phonological fluency	–	< 17.35	**18 (13.3)***	
Semantic fluency	–	< 28.34	**27 (27.34)***	
Praxis				
Freehand copying of drawings task	0–12	≤ 7.18	9 (8.4)	
Clock drawing test	0–10	≤ 8	8.5	
Perception				
Facial recognition test	0–54	< 39	39	
Affective state				
PANAS				
-Positive	0–50		37	0.95§
-Negative	0–50		18	-0.05§

*The table shows the patient's performances on the neuropsychological battery including short-term (digit span forward and Corsi's span forward, Monaco et al., 2013) and long-term memory (prose memory, Novelli et al., 1986), working memory (digit span backward and Corsi's span backwards, Monaco et al., 2013), attention (trail making test – part A, Giovagnoli et al., 1996) and executive functions (trail making test – part B, Giovagnoli et al., 1996; phonemic/semantic alternate fluency, Costa et al., 2014; similarities subtest of WAIS, Wechsler, 2014; Tower of London test, Krikorian et al., 1994; Raven's progressive matrices, Carlesimo et al., 1996; Wisconsin card sorting test, Caffarra et al., 2004; verbal judgment test, Spinnler and Tognoni, 1987; and cognitive estimation test, Scarpina et al., 2015), fluency (phonological fluency, Carlesimo et al., 1996; semantic fluency, Costa et al., 2014), praxis (freehand copying of drawings task, Carlesimo et al., 1996; clock drawing test, Mondini et al., 2003), and perception (facial recognition test, Benton et al., 1994; Albonico et al., 2017). *Impaired performance. § Obtained with healthy controls mean and standard deviation scores. ¥ Obtained with normative data.*

Neuropsychological Assessment

FF underwent a neuropsychological battery to assess his cognitive abilities (see **Table 1**). The battery included short- and long-term memory (prose memory), working memory (digit span backward and Corsi's span backwards, attention (trail making test – part A) and executive functions (trail making test – part B, phonemic/semantic alternate fluency, WAIS similarities subtest, Tower of London test, Raven's progressive matrices, Wisconsin card sorting test, verbal judgment test, and cognitive estimation test), fluency (phonological fluency and semantic fluency), praxis (freehand copying of drawings task and clock drawing test), and perception (facial recognition test). Finally, the PANAS (Crawford and Henry, 2004) was administered in order to assess the current affectivity of the participants. PANAS, consisting of 10 items measuring both negative and positive affect, is a self-report questionnaire in which participants are asked to indicate their level of experienced affect in that moment in a 5-point Likert scale.

Social Cognition Battery

Social cognition battery (Prior et al., 2003) is a self-administered task with four different tests assessing different aspects of social cognition, namely, the emotion attribution, the theory of mind, the social situation, and the moral/conventional distinction. In each test, the participant is asked to read brief stories and to answer the related questions. In the emotion attribution test, brief stories describe one character in a specific situation (e.g., *Silvia wakes up and sees a poisonous spider in her bed*). The participant is asked to give a free answer to specific questions related to the feeling of the character (e.g., *How does Silvia feel in this situation?*). Stimuli include seven different emotions: sadness (N = 10), fear (N = 10), shame (N = 12), disgust (N = 3), happiness (N = 10), anger (N = 10), and envy (N = 3). In the theory-of-mind task, stories (N = 13) involved two or more characters interacting (e.g., *Katia and Emma are two children and are playing at home. Emma gets a banana and puts it close to her ear and says to Katia: Look, it's a phone*). The participant must answer specific questions related to the character's point of view (e.g., Is what Emma said true?). The social situation task includes stories in which two distinct social behaviors are highlighted (written in bold): one involves a normal social behavior and the other a social norm violation. The participant is asked to rate whether the behavior of the character can be considered normal, using the letters from "a" to "d" to indicate, respectively, a normal behavior to an extremely strange behavior. This test provides three scores: normal behavior identified, social violations identified, and the severity of the social violations. In the moral/conventional distinction test, stories related to children behaviors at school are presented. In half of the stories (N = 6), one character is a victim of harm or of an injustice by other characters (moral condition), while in the other half of the stories, one character is involved in a social rule violation, without provoking any injury to other individuals. Participants are asked to answer four questions: (1) whether the character is behaving in a proper way, (2) how serious is the behavior from a scale of 0 to 10, and (3) whether this behavior can be considered right in another country with different rules or (4) in case the teacher allows any children to behave as they want. Hence, for each condition of the moral/conventional distinction task, three different scores are provided: accuracy in detecting forbidden behavior (1), the severity of the violation (2), and the accuracy in detecting forbidden behavior without given rules (3 and 4).

Shame and Guilt Task (SGT)

To measure participants' subjective experience of shame and guilt, we developed the SGT. The SGT is a behavioral task that recreates several scenarios of social interaction between the participant and different partners. During this interaction, the participant is exposed to different social judgments concerning his person or behavior through verbal scripts. Such an interaction is recreated by proposing the partner's photo in addition to the evaluation expressed in text form. To maximize the interpersonal aspect during such interactions, we have employed the face as a salient social stimulus, in addition to the assessment (our target stimulus).

Participants were asked to imagine that the person in the picture (the "judge") expresses the judgment directed toward them, as in a real social interaction. In the test, stimuli included 18 pictures associated with 18 judgments. Judgments included two conditions: the "social standards" condition involved violations of social norms or social standards (e.g., "You have put on a lot of weight") and the "harming others" condition involves injuries or harm toward an individual, made by the participant (e.g., "You destroyed my life"). While the social "standards condition" should elicit higher shame ratings, the "harming others" condition should elicit higher ratings of both shame and guilt, as proposed in previous studies (Lewis et al., 1993; Tangney et al., 2007). Pictures were taken from the NimStim database (Tottenham et al., 2009) and included Caucasian individuals of both genders (50% females). Participants were asked to imagine that the person in the picture (the "judge") expresses the judgment directed toward them and to rate their subjective experience of shame and guilt on a Likert scale from 0 to 6.

Emotion Recognition Tasks

Emotional Facial Expressions Recognition Task

In this task, we included 120 grayscale facial pictures taken from the Montreal Set of Facial Displays of Emotion (MSFDE, Beaupré et al., 2000). A subset of this database includes pictures obtained by morphing neutral and emotional pictures at various degrees (20, 40, 60, and 80%). We selected for each emotion (anger, disgust, fear, happiness, sadness, and shame) morphed pictures from 20 to 80% and fully emotional pictures. For each condition (each emotion at any intensity of expression), we included four items (i.e., four different face identities) (e.g., four trials for anger expressed with the intensity of 20%). Participants were asked to label the emotion presented into different labels (anger, disgust, fear, happiness, sadness, shame, and neutral).

Emotional Prosody Recognition Task

Participants were auditorily exposed to 48 sentences with neutral content (e.g., "the book is on the table") and emotional prosody,

through the use of headphones. The emotions were anger, fear, disgust, happiness, sadness, and surprise. Stimuli included four items for each emotion and were presented in random order. Participants were asked first to identify the emotion conveyed by the prosody by choosing among different options (anger, fear, disgust, happiness, sadness, surprise, and neutral) and then to rate the intensity of the emotion on a Likert scale from 0 to 7.

Emotional Gestures Recognition Task

The set of 32 grayscale body photographs expressing emotional body gestures used in the current task is derived from BEAST[1] (De Gelder and Van den Stock, 2011; see also Cecchetto et al., 2014). The actors' faces were covered by a gray circle, so that her/his facial emotion was not visible. Emotions included anger, fear, happiness, and sadness. Participants were asked to identify the emotion expressed by body gestures by selecting between five options – anger, fear, happiness, sadness, and neutral – and to rate on a Likert scale ranging from 1 to 7 the intensity of the emotion expressed.

Statistical Analyses

The patient's scores on the neuropsychological and social cognition batteries were compared with the available normative data, while those on the other tests, including PANAS, emotion recognition tasks, and SGT, were compared with the controls' scores. Specifically, we used the software "SingleBayes_ES.exe[1]," implementing the method described by Crawford and Garthwaite (2007) and Crawford et al. (2010), which is widely used in case report studies and allows controlling for type I errors when comparing the patient's and controls' performance scores. This method estimates, within a Bayesian framework, the point of abnormality of the patient's score (PA) and the associated 95% credible limits (CL). In addition, the PA provides the percentage of the healthy population obtaining a score lower than the patient's. Then, in case of deficit, a second analysis was performed (e.g., Bayesian standardized difference test) (Crawford and Garthwaite, 2007; Crawford et al., 2010), using the software DissocsBayes_ES.exe[2], to test whether the patient's performance reduction is significantly lower than other scores of the same task, configuring a strong or classical dissociation (Crawford and Garthwaite, 2005). Since we expected that FF was impaired in these tasks, one-tailed tests were used. This method of analysis was applied to PANAS, emotion recognition from a prosody task, the emotional gestures recognition task, and SGT.

The facial emotion recognition task was first analyzed with one-sample *t*-tests (one-tailed) vs. chance level with the software Jamovi[3] to test whether participants performed above chance level at any intensity of emotional expressions. Secondly, the patient's and controls' performances were compared. Since participants were asked to choose between six options in the task (anger, disgust, fear, joy, sadness, and shame) in four trials for each emotional intensity, the chance level was set to 0.07. The patient's performances on this task were considered at chance level if their total accuracies for each emotional intensity were equal to 0 or 1, while they were considered above chance if the score was 2, 3, or 4. Then, given the complexity of the design, the patient's and controls' performances on facial emotion recognition task were compared with mixed-effect models (MMs), using the program R[4] and the package lme4[5]. MMs represent a powerful tool in the analysis of single-case data, allowing us to compare the patient's and controls' performances even in complex study designs, such as repeated-measure designs (Huber et al., 2015; Wiley and Rapp, 2018). Specifically, we used a generalized mixed-effect model (function glmer) on the accuracy of the facial emotion recognition task (binomial) using the subject and the identity of the actor in the stimuli as random factors and the group (patient and controls), the emotion type (anger, disgust, fear, joy, sadness, and shame), the emotion intensity, and their interactions as fixed factors. Then, we removed stepwise any fixed factors not inducing any significant loss of fit to the model (tested with the likelihood ratio test). The final model included as fixed factors the interaction between group and emotion and the interaction between emotion and intensity. To explore the interactions, we performed a planned contrast between the patient's and controls' scores for each emotion type (*lsmeans*[6]). Then, similar to the analyses of the other tasks, in case of deficit, we tested whether the patient's performance reduction on one emotion was significantly different from those of other emotions. Specifically, we contrasted the difference in the patient's and controls' performances on each impaired emotion and those related to other emotions. Bonferroni corrections were also applied.

RESULTS

Neuropsychological Assessment and Questionnaires

FF's results are summarized in **Table 1**. He was impaired at the Wisconsin's card sorting test and similarities subtest of the WAIS. battery, suggesting a deficit affecting abstraction abilities. His performances on phonological and semantic fluencies were also poor, while on alternate semantic/phonological fluency, it was at the average level. The patient's score on Benton's facial recognition test was in the borderline range. The affective state of FF, measured by the positive and negative scores of PANAS, was not different from that of healthy controls [positive affect score: FF = 37, controls = 29.92 $\pm$ 7.43, $Z = 0.95$, PA = 81.17 (60.92–94.51), $p > 0.1$; negative affect score: FF = 18; controls = 18.33 $\pm$ 7.28, $Z = -0.05$, PA = 48.30 (27.84–69.16), $ps > 0.1$].

Social Cognition Battery

The emotion attribution task (see **Table 2**) revealed that FF was impaired in attributing sadness and disgust to characters of brief stories, while his performance on fear, shame, happiness, anger,

[1]www.beatricedegelder.com/

[2]https://homepages.abdn.ac.uk/j.crawford/pages/dept/psychom.htm

[3]https://www.jamovi.org/

[4]https://www.r-project.org/

[5]https://cran.r-project.org/web/packages/lme4/

[6]https://cran.r-project.org/web/packages/lsmeans/index.html

TABLE 2 | Patient's scores on the social cognition battery.

Test	Score	Range	Cutoffs
Theory of mind	**12**	**0–13**	**≥ 12**
Emotion attribution			
-Sadness	**5***	0–10	≥ 6
-Fear	10	0–10	≥ 8
-Shame	10	0–12	≥ 8
-Disgust	**1***	0–3	≥ 2
-Joy	9	0–10	≥ 10
-Anger	9	0–10	≥ 6
-Envy	3	0–3	≥ 1
Social situations			
-Identification of correct social behaviors	**12***	0–15	≥ 13
-Identification of social violations	**20***	0–25	≥ 22
-Rating of the entity of violations	45	0–75	≥ 45
Moral/conventional distinction			
-Moral behaviors	6	0–6	≥ 6
-Conventional behaviors	6	0–6	≥ 5

**Impaired performance.*

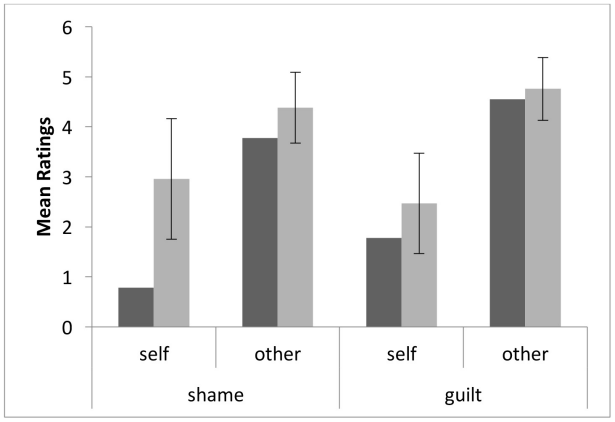

FIGURE 2 | Patient's (dark gray) and healthy controls' (light gray) scores on the SGT. The error bars indicate standard deviations.

and envy was above the cutoff. It is worth noting that errors in sadness and disgust attributions included mainly anger (errors on sadness: 80% anger, 20% shame; errors on disgust: 100% anger). On the social situation task, FF showed impaired abilities in identifying normal social behavior and social violations, while his evaluation of the severity of the social violation was just above the cutoff. The patient's performances on both the theory-of-mind task and the moral/conventional distinction task were in normal ranges.

SGT

FF's shame ratings (see **Figure 2**) on the "social standards" condition were marginally lower than those of healthy controls (FF = 0.78, healthy controls = 2.96 ± 1.20, Zcc = −1.82, PA = 5.28, superior CL = 15.00, $p = 0.053$), and his ratings on the "harming others" condition were within the control level (FF = 3.78, healthy controls = 4.38 ± 0.71, Zcc = −0.85, PA = 21.58, superior CL = 38.44, $p > 0.1$). Moreover, patient's ratings of guilt were not different from those of controls in any condition (social standards: FF = 1.78, healthy controls = 2.47 ± 1.00, Zcc = −0.69, PA = 25.95, superior CL = 43.41, $p > 0.1$; harming others: FF = 4.56, healthy controls = 4.76 ± 0.63, Zcc = −0.32, PA = 38.25, superior CL = 56.27, $p > 0.1$. The reduction in shame ratings for the "social standard" condition was also significantly different than guilt ratings on the same condition (Z-dcc = −1.90, PA = 4.65, superior CL = 20.41, $p < 0.05$), while it was not significantly different than shame ratings on the "harming others" condition (Z-dcc = −1.03, PA = 17.12, superior CL = 44.55, $p > 0.1$).

Facial Emotion Recognition Task

Healthy individuals recognized all the emotions above chance level when the intensities ranged between 40 and 100% (all ps < 0.05). When the intensity was 20%, controls' performances on anger were also above chance level ($p < 0.01$), but this was not the case for all the other emotions (all ps > 0.05) (see **Figure 3** and **Table 3**). Patient FF showed a similar pattern to that of healthy controls when emotions were expressed at the 20% intensity, except for sadness, which was recognized above chance level, and for disgust at 60%, which was recognized at chance level. In addition, FF recognized shameful facial expressions at chance level at any intensity of presentation, while he performed at chance level when fear was expressed at 40, 60, and 80% intensities.

The mixed-effect generalized linear model (logLik = −854.2, marginal $r^2 = 0.39$, conditional $r^2 = 0.44$) revealed a significant main effect of emotion [$\chi^2(5) = 48.18$, $p < 0.001$] and intensity [$\chi^2(1) = 232.85$, $p < 0.001$] and significant interactions of group * emotion [$\chi^2(5) = 27.34$, $p < 0.001$] and emotion * intensity [$\chi^2(5) = 49.21$, $p < 0.001$]. Participants were overall more accurate in recognizing faces displaying joy than all other emotions (joy vs. sadness: $z = 2.71$, $p = 0.07$, all other ps < 0.05), except for those displaying anger ($p > 0.1$). Shame and fear were recognized less accurately than all the other emotions (all ps < 0.05). However, no significant difference was evident from the comparisons between FF's and controls' performances for any emotion displayed (all ps > 0.05). Indeed, even though FF recognized shame and fear at chance level, while controls performed above chance, the difference among their performances did not reach significance level (fear: $z = -2.43$, $p = 0.088$; shame: $z = 2.55$, $p = 0.063$).

Emotional Gestures Recognition Task

FF's performance on emotional gesture recognition task (see **Table 4**) did not differ from that of healthy controls in any of the emotions investigated (all ps > 0.01), highlighting that the patient was not impaired in recognizing emotions from body gestures.

Emotion Recognition From Prosody

The analyses of emotion recognition of auditory stimuli did not show any significant difference in patient's and controls' performances (all ps > 0.1) (see **Table 4**).

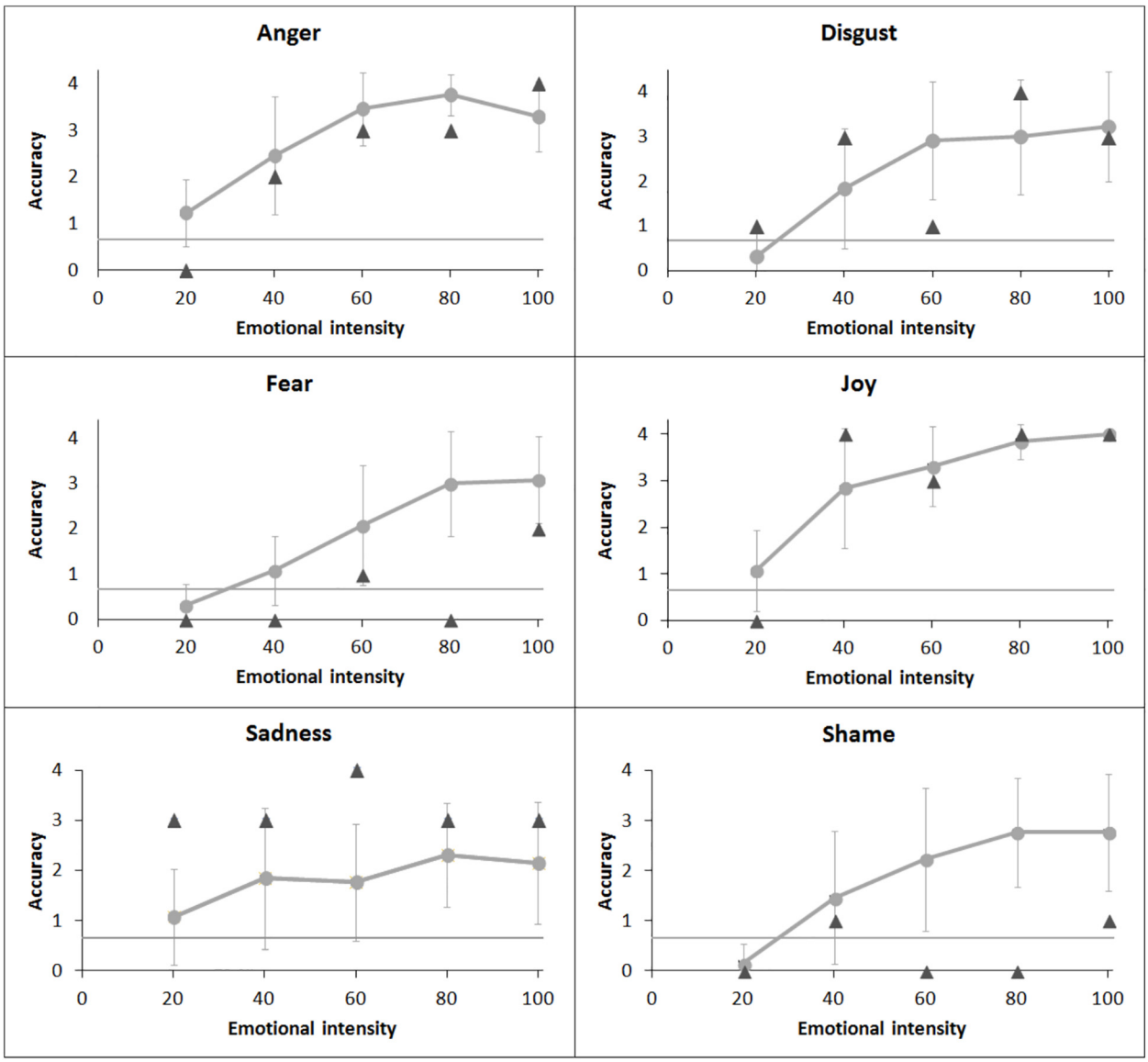

FIGURE 3 | Patient's (dark gray triangle) performance and healthy controls' (light gray dot) mean performance on emotional facial recognition task. Bars indicate standard deviations.

TABLE 3 | FF's and controls' performance in the Facial Emotion Recognition Task for all intensity levels.

Emotion	Intensity														
	20%			40%			60%			80%			100%		
	HC	FF	Zcc	HC	FF	Zcc	HC	FF	Zcc	HC	FF	Zcc	HC	FF	Zcc
Anger	1.23 ± 0.73	0	−1.7	2.46 ± 1.27	2	−0.36	3.46 ± 0.78	3	−0.59	3.77 ± 0.44	3	−1.75	3.31 ± 0.75	4	0.92
Disgust	0.31 ± 0.63	1	1.1	1.85 ± 1.34	3	0.86	2.92 ± 1.32	1	−1.46	3.00 ± 1.29	4	0.77	3.23 ± 1.24	3	−0.19
Fear	0.31 ± 0.48	0	−0.64	1.08 ± 0.76	0	−1.42	2.08 ± 1.32	1	−0.82	3.00 ± 1.15	0	−2.6	3.08 ± 0.95	2	−1.13
Joy	1.08 ± 0.86	0	−1.25	2.85 ± 1.28	4	0.9	3.31 ± 0.85	3	−0.36	3.85 ± 0.38	4	0.41	4.00 ± 0.00	4	/
Sadness	1.08 ± 0.95	3	2.02	1.85 ± 1.41	3	0.82	1.77 ± 1.17	4	1.91	2.31 ± 1.03	3	0.67	2.15 ± 1.21	3	0.70
Shame	0.15 ± 0.38	0	−0.41	1.46 ± 1.33	1	−0.35	2.23 ± 1.42	0	−1.57	2.77 ± 1.09	0	−2.54	2.77 ± 1.17	1	−1.52

TABLE 4 | FF's and controls' accuracy scores in the different emotion recognition tasks.

	FF	Controls		Zcc	PA (Upper CL)
		Mean	*SD*		
Body emotion recognition accuracy					
Anger	6	6.90	1.60	−0.56	30.25 (54.87)
Fear	8	7.40	0.70	0.86	78.26 (92.68)
Joy	3	5.10	2.13	−0.99	18.60 (37.39)
Sadness	8	8.00	0.00	–	–
Prosody emotion recognition accuracy					
Anger	4	3.50	0.71	0.70	74.06 (89.85)
Disgust	3	1.90	1.20	0.92	79.76 (93.62)
Fear	4	3.40	0.97	0.62	71.51 (88.00)
Joy	3	3.10	0.99	−0.10	46.28 (66.41)
Sadness	3	3.50	0.53	−0.94	19.60 (30.64)
Surprise	3	3.00	0.94	0.00	50.01 (69.86)

Zcc, effect size; PA, point of abnormality of the patient's score, expressing the percentage of the healthy population falling below FF's score.

DISCUSSION

In the present single-case study, we tested the role of the amygdala in the perceptual and experiential processing of shame. Patient FF, with acquired bilateral amygdala and hippocampal damage, performed several tests tapping subjective emotional experience of shame, emotion recognition, and social cognition.

The assessment of the subjective experience of shame revealed two different patterns of findings. FF experienced less shame than controls when exposed to social standard violations but not to moral violations. FF's and controls' guilt ratings did not differ in any condition. This pattern of results is not congruent with the view of a primary role for the amygdala in shame generation. Indeed, if the amygdala was involved in the generation of a subjective experience of shame, after its lesion, we would expect a reduction of both shame ratings across all situations and not only in association with social standard violations.

However, the selective reduction in FF's shame experience in reaction to social standard violation might be easily explained considering his deficit in recognizing whether a social situation was normal or not in the social cognition battery. Indeed, FF's reduction in the subjective experience of shame might be secondary to the impaired ability to detect whether a social situation is to be considered normal: if an individual is not able to detect the occurrence of a social violation, she will not be able to react properly to such violation. This latter finding might be interpreted at least in two ways. First, the patient lacks social knowledge and, hence, is not able to compare the perceived social stimuli to prior knowledge, and second, he is not able to detect the relevant cues that are necessary for understanding the social situation and that need to be matched with prior social knowledge. While several studies reveal that the crucial region involved in representing social knowledge is the anterior temporal lobe (Olson et al., 2013; Wang et al., 2017) and that a lesion of this area, even sparing the amygdala, leads to pervasive impairments in emotional and social behaviors (i.e., psychic blindness) due to degraded social knowledge (Franzen and Myers, 1973), the amygdala was proposed to be involved in disambiguation, orienting attention to salient cues in order to understand stimulus meaning (Whalen, 1999; Adolphs, 2010). Indeed, neuroimaging studies revealed that amygdala activation was modulated by the ambiguity of the stimulus (Davis et al., 2016; Wang et al., 2017). FF's ability to discriminate between moral and conventional social situations was spared, possibly because the situations presented were less ambiguous, and this is consistent with our interpretation that FF suffers from deficit in disambiguating the stimuli. Even though it is not possible to exclude that the patient's impairment in detecting social violations might be due to the involvement of structures in close proximity to the amygdala, we argue that the role of the amygdala in orienting attention to salient cues to deal with ambiguous social situations might explain this deficit.

In addition, FF also showed impaired performances on some tasks tapping executive functions such as the similarity task, Wisconsin card sorting test, and verbal fluency tasks. However, FF's deficit was not extended to all the tests tapping executive functions, but only to those requiring abstraction abilities. Recent evidence (Saez et al., 2015) suggested not only that frontal lobes are crucial for executive functions (Alvarez and Emory, 2006) but also that the amygdala might contribute to high-order cognitive functions, specifically being involved in representing abstract cognitive information. This interpretation of FF's performance on neuropsychological battery might also better explain the patient's deficit in understanding social situations, which are abstract in nature.

Results on the emotion recognition task revealed that, even though there was no significant difference between the performances of FF and controls, the patient recognized shameful and fearful facial expressions at chance level, while controls performed above chance. This might be attributable to the low number of trials per condition and, consequently, to the low sensitivity of this task to detect mild deficits. However, the inability to recognize fearful and shameful facial expressions of FF, although not different from that of controls, might reflect nevertheless a deficit in recognizing the two emotions. While the deficit at recognizing fearful facial expressions is consistent with previous evidence (Adolphs et al., 1994; Calder, 1996), shameful facial expression recognition has not been systematically investigated before. Social emotion recognition impairment (including moral emotions) from faces was only reported in patients with acquired amygdala damage (Adolphs et al., 2002), without any distinction about the specific facial emotion impaired. The same emotions were not impaired in the emotion attribution task of the social cognition battery, indicating that FF was able to recognize shame and fear from written stories, but he was impaired when faces were used as stimuli. In addition, FF's ability to recognize specific emotions from bodily gestures and from prosody was completely preserved. FF's poor performance on fear recognition, which was limited to facial expression, not involving bodily gestures and prosody, confirms previous research on patients with amygdala damage (Adolphs and Tranel, 1999; Atkinson et al.,

2007; Bach et al., 2013). This pattern of results can be explained with the amygdala being involved in orienting attention to the eye region when presented with a facial stimulus (Jacobs et al., 2012). Indeed, the eye region is diagnostic in the identification of fear (Smith et al., 2005) and is poorly fixated by patients with amygdala damage during face presentation (Adolphs et al., 2005; Spezio et al., 2007).

Although whether the eye region might be diagnostic of shameful expression recognition has never been tested, the action tendencies associated with the shame experience seem to involve gaze movement downward, blushing, and inhibition of speech and movement (Asendorpf, 1990; Keltner and Buswell, 1997). Hence, the deficit of allocating attention toward the eye region might prevent patients with amygdala damage from perceiving a shift of gaze direction downward, typically associated with shameful facial expression.

Different from facial expression recognition, FF performed poorly in sadness and disgust attribution from brief stories on the social cognition battery. Previous studies highlighted the association between disgust and sadness, and amygdala and hippocampus processing. Indeed, a recent study reported that increased variability of a subnetwork formed by the amygdala and the hippocampus correlated with worsening mood and depression (Kirkby et al., 2018). For disgust, a recent study by Pujol et al. (2018) found the involvement of the hippocampus in response to disgusting food, and another experiment (Blanco-Hinojo et al., 2019) showed abnormal responses to disgusting food inside the hippocampus of individuals affected by Prader–Willi syndrome when compared to controls. We might speculate that the patient might have performed poorly in detecting sad and disgusting scenes in the attribution task because a damage of the hippocampus (for disgust) and of the amygdala–hippocampus circuit (for sadness) could have led also to mild deficits in processing sad and disgusting scenes. However, further research is necessary to confirm our findings.

CONCLUSION

The investigation of shame and guilt processing in a patient with acquired damage within bilateral amygdalae and surrounding tissues revealed reduced feelings of shame in self-relevant social situations in association with a deficit in discriminating normal social situations and social violations and impaired performance on the Wisconsin card sorting test and WAIS analogies. In addition, the patient performed poorly in shameful (and fearful) facial expression recognition. This pattern of findings is congruent with a deficit in detecting salient cues in order to understand social situations and, consequently, to generate shame feelings in case of violations. Hence, the amygdala integrity appears to be relevant in the detection of social stimuli but not in the generation of moral emotions such as shame and guilt. These findings are more easily explained assuming a role of the amygdala in ambiguity and uncertainty resolution, as suggested by Whalen (1999). However, further research is necessary in order to better understand the role of the amygdala in moral emotion processing.

Limitations

The present study involves the testing of a patient with a bilateral lesion of the amygdala that extends to the surrounding part of the hippocampus. Hence, the reported deficits might also be attributable to the lesion of both the hippocampus and the amygdala. Moreover, MRI acquisition and cognitive testing occurred at different time points (i.e., 4 months' interval). Hence, the patient's behavioral findings might not correspond strictly to the detected damaged brain areas.

The lack of data about premorbid patient's cognitive performances does not allow us to make causal inferences about the role of the damaged areas in influencing behavior. However, the associations between specific brain lesions and impaired behavioral performances give interesting hints on the role of amygdala. In addition, the findings of single-case studies have low generalizability and need to be confirmed by further group studies. However, the relative rarity of the case described gives an important contribution in the understanding of amygdala functioning.

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 Comitato Etico Unico Regionale (CEUR), Friuli-Venezia Giulia. 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 manuscript.

AUTHOR CONTRIBUTIONS

LP collected the data of the experimental tasks on the patient, analyzed the data, and drafted the manuscript. EP collected the data on the part of the healthy control samples and revised the manuscript. AL collected the neuropsychological data on the patient. MU and IZ interpreted the radiological findings. EP, VP, RR, RJ, and AG revised the manuscript. LP and AG interpreted the results. AG designed and supervised the project. All authors contributed to the article and approved the submitted version.

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Instructed Partnership Appreciation in Depression: Effects on Mood, Momentary Relationship Satisfaction, and Psychobiological Arousal

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Background: Depressive disorders are associated with attentional bias and social anhedonia. There is evidence supporting the hypothesis that depressed individuals participate less in potentially rewarding social situations and exhibit alterations in stress reactivity. With the present study, we aimed at investigating the affective and psychobiological response of couples with a depressed (female) partner in an instructed partnership appreciation task (PAT) that included positive and appreciative communication.

Methods: In a quasi-experimental repeated-measures design, depressive couples (DCs)—i.e., the female partner being diagnosed with a depressive disorder—were compared to non-depressive couples (NDCs). Study outcomes were the PAT-induced changes in state mood, momentary relationship satisfaction, salivary cortisol, and salivary alpha-amylase. Additionally, we assessed psychometric baseline data on depression, relationship quality, social support, and chronic stress. Data was analyzed using multilevel modeling.

Results: A total of 184 individuals from $N = 47$ DCs and $N = 45$ NDCs were included. DCs were characterized by higher depressiveness, lower relationship quality, less actually received social support from the partner, and higher chronic stress than NDCs. Manipulation checks led to the additional exclusion of two couples. Regarding mood, depressed women showed lower baseline scores and no significant differences in mood increase compared to non-depressed women ($p = 0.107$). Increases in relationship satisfaction were significantly stronger in the depressed group ($p = 0.035$). In addition, we found a significantly stronger cortisol increase in depressed women, but only if relationship duration was taken into account as a moderating factor ($p = 0.022$). No significant group differences were found for women's amylase trajectories or for sex-dependent interaction effects on the couple level (all $p > 0.05$).

Conclusions: Instructed engagement in positive couple interaction may require high effort and increased psychobiological arousal, but may finally result in emotional and social

benefits in depressed women. While these findings encourage speculations about the therapeutic application of instructed partnership appreciation, more research is needed on the effectiveness of such interventions and on the moderating role of relationship duration in depression and couple functioning.

Keywords: depression, couple interaction, relationship, social interaction, stress response, cortisol, alpha-amylase

INTRODUCTION

With an estimated incidence of 300 million cases worldwide, the World Health Organization's Global Burden of Disease Study ranks depressive disorders as the single largest contributor to global disability (1, 2). In addition to common symptoms of anhedonia, poor concentration or sleep disturbances, depression can have a detrimental effect on social functioning and the quality of relationships. Moreover, depressive disorders were found to be accompanied by alterations in the neurobiological stress-regulatory systems, including the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS). Hence, it seems crucial to take into account an integrated "bio-psycho-social" perspective—addressing psychobiological dysfunctions, subjective emotional and cognitive strain, and impaired social relationships equally—to approach a comprehensive understanding of depressive disorders (3).

Social Dysfunction in Depression

Receiving promising support from neuroimaging studies, the social brain hypothesis has highlighted the importance of the social domain of human behavior and cognition. Depressive disorders were specifically proposed as an entity where the social constraints need to be taken more into account (4, 5). In general populations, a growing body of research has provided evidence for the health promoting effects of adaptive social relationships (6–8). In couple constellations, the physical health of one partner predicts the quality of life of the other, even after controlling for one's own status (9, 10). Depressive patients, in contrast, were reported to benefit less from these health promoting effects (5). Moreover, there seems to be a bi-directional association between depression and relationship quality (11): On the one hand, relationship conflicts were proposed as a relevant contributor to depressiveness, on the other hand, symptoms of depression such as social withdrawal or loss of interest are a serious challenge for existing relationships (12, 13). Some authors proposed this association, in turn, to be moderated by relationship duration. Marital happiness was found to decline over the years (14, 15), while the risk for depressiveness is increased in long-term relationships (16, 17).

In particular, a substantial proportion of acute depressive episodes is accompanied by social anhedonia, i.e. the reduction of interest in or pleasure from social engagement (18). Previous research looked into both the internal processing and behavioral manifestations of social anhedonia. Regarding the first, a generally heightened focus on internal states was reported to reduce engagement with the social environment and to lead to interpersonal difficulties (18). In addition, a meta-analysis on eye-tracking data found that individuals suffering from depression spent significantly more processing time on dysphoric and less time on positive information than healthy controls (19). Moreover, studies suggest that this attentional maintenance bias transfers to socially relevant stimuli such as emotional facial expressions and is present in both acute and remitted forms of depression (19–21). These associations could be grounded in alterations of the reward system, with depressive individuals showing less motivation and capacity to respond to rewarding stimuli (19, 22).

With regard to behavior, a recent network analysis of RFID-based position tracking in a student camp revealed that that depressive symptoms were associated with a reduction of time spent in social interactions in general and particularly with friends, as well as with an increase of time spent with similarly depressed others (23). More specifically, depressed individuals showed impaired communication and interaction skills (24, 25) as well as difficulties in empathy and perspective taking (26). Social anhedonia manifest itself in reduced attempts to approach social situations (18). In general populations, women with high levels of depression were found to anticipate less positive response from social interaction and to engage less in approaching behavior (27). Reduced engagement in rewarding social interaction, in turn, impedes potential effects from positive social feedback (27). The described pattern of socially relevant depressive behavior may be due to self-serving biases including the tendency to avoid threatening social upward comparison (28), reduced attributed trustworthiness in interaction partners (25), and the fear of social rejection (5, 29).

For the majority of adults, a satisfying romantic relationship is the main source for social support (30) and a key determinant of quality of life (31). Unsurprisingly, the abovementioned social dysfunctions were also found in couple research. A recent longitudinal study found evidence for a possible causal effect of marital discord on the emergence of depressive symptoms (32). Moreover, more negative communication styles including accusation, hostility or aggression and less positive styles such as problem-solving behavior and self-revelation were observed in couples with depression than in control couples without depression (33, 34). These effects remained robust after controlling for general marital/relationship distress. In a study using a non-clinical sample, depressiveness in the female partner was associated with less empathic accuracy towards unpleasant feelings of the male partner (35). Moreover, individuals with higher depression scores underestimated the partner's commitment and overestimated his/her negative behavior (36).

Another series of studies suggests that the intimacy and trust of a relationship may buffer the use of these maladaptive emotion regulation strategies (37).

Altered Stress Regulation in Couples With Depression

Both social isolation and depression in general are associated with decreased physical health. A lack of social connectedness was found to be a risk factor for immune dysfunction (38) and premature mortality (7, 8). On the other hand, meta-analyses revealed high marital quality as a predictor for general health (11). Physical touch and emotional intimacy from a romantic partner, in particular, were found to buffer cortisol response in healthy females in the Trier Social Stress Test (TSST) (39, 40) and in couples' everyday life (41). Similarly, depression is associated with poor health outcomes in couples including the risk for cardiovascular diseases and general mortality (9). Stress and its underlying neuroendocrine, autonomic, and immune regulation processes have been introduced as a crucial mediator in the multi-directional association between depression, social functioning, and health (9). For instance, satisfying couple relationships buffer the adverse effects of stressful life events on the development and maintenance of physical and mental diseases, while marital conflict itself can serve as a powerful stressor and exacerbate depressive symptoms (38, 42).

Further, acute and recurrent depressive disorders seem to alter multiple biological stress-regulatory systems and the level of general arousal (43, 44). Besides inflammatory processes, research focused mainly on dysregulation of the HPA axis and ANS (9). Dysfunction in glucocorticoid regulation, particularly regarding the steroid hormone cortisol, is one of the most frequently studied phenomena in this context (45, 46). Altered circadian rhythms of cortisol release were associated with sleep disturbances, and increased cortisol secretion in the morning was found to be a risk factor for depressive diseases (47, 48). Moreover, meta-analytic syntheses showed generally elevated levels of cortisol secretion in depressed patients across multiple assessment methods (49), and an increase in reactivity towards psychosocial stressors, in particular (50). The magnitude and direction of effects, however, depends on moderating variables such as sex, diagnosis, type of stressor, and measurement plan. Cortisol release in response to the TSST, for instance, was blunted in women with remitted major depression compared to healthy controls, but not in men (51). A longitudinal study showed cortisol levels to be associated with the persistence of depressive symptoms (52). Moreover, depressed women showed weaker associations between morning cortisol increases and the occurrence of social interactions and perceived these interactions as more negative than healthy women (53). Regarding romantic couples, women's depression scores were positively related to their partners cortisol output (54) and high depressiveness in women predicted an attenuated cortisol response after a relationship conflict discussion with the partner in another recent study. In male participants, however, cortisol levels were generally elevated if depression scores were high (55). Hence, the question of HPA hypo- vs. hyperactivity in couples with depression is still subject to controversy, and it seems crucial to take sex differences into account.

Recent research has emphasized the complex and dynamic interplay between the HPA axis and the ANS in the regulation of chronic and acute stress, and it has been recommended to monitor both systems simultaneously in the study of the human stress response (56). Besides feasible cardiovascular, autonomic markers such as heart rate variability, salivary alpha-amylase (sAA) has been introduced as a promising biomarker of sympathetic arousal (57–59). sAA is an enzyme produced by the parotid glands in response to acute adrenergic innervation. It has thus been studied as a proxy for the sympatho-adreno-medullary (SAM) branch of the ANS in stress research (57, 60–62). Previous studies showed an sAA increase in response to the TSST (63), after pharmacological stimulation of adrenergic receptor systems (61) and after different psychologically or physically induced arousal paradigms (59). A systematic review identified substantial alterations in sAA-reactivity in the context of mental illness including depression (64). Moreover, an elevated release of sAA was associated with increased feelings of depression and shame in general populations (57, 65). Individuals with a current episode of depression showed higher levels of sAA than remitted patients (66) and an elevated sAA reactivity to an electrical stimulation stressor compared to healthy controls (67).

Rationale and Aim of the Study

Taking into account the abovementioned complex dynamics, we followed an integrated approach to the understanding of social behavior in depressed couples. This study compared the psychological and psychobiological response of depressed and non-depressed romantic couples in an instructed partnership appreciation task (PAT) that included positive and appreciative communication. The rationale for the use of the PAT in our study was influenced by two directions of previous literature on instructed social interactions between romantic partners, namely couple therapy (68) and experimental mood induction tasks (69). Inspired by couple therapy research, we developed a list of positively connoted conversation topics and asked couples to express appreciation for each other and to share positive experiences with the idea to increase positive reciprocity (70, 71). At the same time, this task was intended to induce positive mood in a naturalistic couple setting [as opposed to e.g. mood induction by auditory or visual stimuli, (69)]. The hypothesized differences in the psychobiological response are based on the abovementioned literature on the connection between depression and the responsiveness of stress-reactive systems in social situations (53). I.e. both cortisol and sAA were described in previous literature as markers of physiological arousal in response to stressful situations (44, 58), and both may show altered functioning over the course of a depressive disorder (53, 72). We expected that—due to social anhedonia and the evident phenomena of positive interactions occurring less frequently in everyday life and being perceived as less pleasant (23, 53)—engaging in an instructed PAT would require high internal resources and induce (or alter) physiological arousal in

depressed individuals who would usually tend to avoid PAT-like situations.

Hence, with the observation of (close to) naturalistic behavior between real-life partners and the emphasis on positive instead of negative interaction, we aimed at extending previous research that rather focused on conflict behavior, non-intimate laboratory stressors, or non-interpersonal mood induction. The integrated monitoring of psychobiological arousal was a novel aspect in this study, and the general hypothesis was that couples with depression, and the depressed female index-patients in particular, would benefit less from instructed positive couple interaction, in comparison to healthy controls. We expected this pattern to lead to different changes in the ratings of state mood and momentary relationship satisfaction and to different HPA and SAM activation trajectories in response to the PAT. The study hypotheses are specified below (section *Multilevel Modeling for Hypotheses Testing*).

MATERIALS AND METHODS

Study Design and Ethics

In a quasi-experimental, repeated-measures design, we compared so-called "depressive couples" (DCs; i.e. couples with the female partner being diagnosed with a depressive disorder) to non-depressive couples (NDCs) with regard to their psychobiological stress response in the PAT. This study received approval by the Ethics Committee of the Medical Faculty at Heidelberg University (S-021/2016). All participants gave written informed consent in accordance with the declaration of Helsinki.

The present analysis is based on the first part of the SIDE (Social Interaction in Depression) study series. The SIDE studies contained a cross-sectional, first part in which self-report, psychobiological, and eye-tracking data was collected from DCs and NDCs, and an interventional, second part where participating DCs were randomized to either a 10-week Cognitively Based Compassion Training (CBCT®) for couples or to a control treatment. Procedures and methods of this randomized controlled trial (RCT) can be found in the published study protocol (73). No protocol was pre-registered for the cross-sectional part, which is reported here, but many of the present methods (e.g. sample size calculation, outcome measures) were influenced by the consideration to later conduct the RCT with partly overlapping samples (NDCs were not included in any subsequent study). The reasons for the overlap in methods in the SIDE studies were to address well-known recruitment challenges in clinical trials in couples with psychopathology, and the assumption that financial incentives alone would not ethically justify the required assessment effort in some severely distressed couples.

Participants

Recruitment strategies for couples in both groups involved newspaper advertising, posters and flyers in public places, advertising in public transport, social media, and university mailing lists. For the recruitment of DCs, we additionally contacted registered doctors, psychiatric and psychosomatic clinics, as well as regional outpatient centers for counseling and psychotherapy. Due to the abovementioned sex differences with regard to stress-reactivity in depression, the study focused on the inclusion of female patients suffering from depression and their romantic partners. Inclusion and exclusion criteria for DCs and NDCs are listed in **Table 1**.

Procedures and Tasks

This study was conducted at the Institute of Medical Psychology at Heidelberg University Hospital in Germany. Interested couples initially participated in a brief, standardized telephone interview for a first screening of eligibility (e.g. relationship status and duration). Afterwards, couples were invited to our Social Interaction Lab for a laboratory assessment on two consecutive days. On lab day 1, participants were informed about the study goals, procedures, potential risks and benefits, and were asked to sign the consent form. Participants were then screened for the presence of any mental disorder and depression in particular by use of the Structured Clinical Interview for DSM-IV (SCID) and the Hamilton Depression Rating Scale (HDRS) (74, 75). While one partner was interviewed, the other was asked to fill out questionnaires on demographic and health data (including information on education, income, employment, physical activity, health status, and on menstrual cycle for female participants) and a number of clinical psychometric scales (see *Additional Clinical Measures*). Questionnaire data was collected with a tablet computer and the online software SoSci Survey (76).

On lab day 2, we carried out an interview and measurements on possible confounding variables recommended for cortisol research including body mass index (BMI), current medication, caffeine/alcohol/nicotine intake, and physical exercise (77). Afterwards, participants received an instruction for the PAT. Couples were seated on opposite sides of a table and read a list

TABLE 1 | Inclusion and exclusion criteria.

	Inclusion	Exclusion
DCs—Women	• SCID diagnosis: Depressive episode or recurrent depressive disorder (F32.X, F33.X, F34.1) • HDRS score ≥ 12 • Age ≥20 years • In a romantic, heterosexual relationship for ≥2 years	• Psychotic symptoms • Bipolar disorder • Acute suicidal tendency • Present substance abuse
DCs—Men	• Age ≥20 years • In a romantic, heterosexual relationship for ≥2 years	• Psychotic symptoms • Bipolar disorder • Acute suicidal tendency • Present substance abuse
NDCs—Women	• Age ≥20 years • In a romantic, heterosexual relationship for ≥2 years	• Any current psychiatric diagnosis (SCID) • HDRS score ≥12
NDCs—Men	• Age ≥20 years • In a romantic, heterosexual relationship for ≥2 years	• Any current psychiatric diagnosis (SCID) • HDRS score ≥12

DCs, depressive couples; NDCs, non-depressive couples; SCID, Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders; HDRS, Hamilton Depression Rating Scale.

with 23 conversation themes (e.g. attractiveness, trust, tolerance). Themes were adopted from the problem list used in research on couple conflict (71), but were modified to have a positive instead of negative connotation (e.g. loyalty instead of jealousy). Couples were instructed to speak only about positive content, to be supportive and appreciative, and to switch to another theme if they noticed any upcoming conflict or unpleasant feelings. The experimenter then left the room for 10 min, while the partners were asked to start the interaction. Conversations were video-taped and rated for adherence to the instructions by three independent, blinded research assistants on a scale ranging from (1) *very negative* to (5) *very positive*. Instruction materials for the PAT can be found in the **Supplemental Materials** of this publication.

We collected a total of four saliva samples from each participant: (T1) 20 min before PAT, (T2) immediately before PAT, (T3) immediately after PAT, (T4) 20 min after PAT (**Figure 1**). Psychobiological assessments on lab day 2 were carried out at standard times in the afternoon between 2 p.m. and 5 p.m. Additionally, participants were asked to fill out a brief questionnaire on acute mood states and a single-item scale on perceived relationship satisfaction at that moment, immediately before (T2) and after the PAT (T3). The post-PAT (T3) assessment also contained a single item asking for the individual's perception of the previous conversation on a 5-point scale ranging from *(1) very negative* to *(5) very positive*, for the purpose of manipulation check. After the PAT, participants completed the second part of the tablet-based psychometric assessment.

Outcomes

The study outcomes encompassed PAT-related changes in state mood (MOOD) and momentary relationship satisfaction (RELSAT), both measured pre- (T2) to post PAT (T3). Moreover, we repeatedly measured the HPA and SAM response to the PAT *via* salivary cortisol (sCORT in ng/ml; T1–T4) and salivary alpha-amylase (sAA output in U/min; see (78); T1–T4).

State Mood and Momentary Relationship Satisfaction Scale

Participants rated their state mood on three bipolar scales (1–5) based on the Multidimensional Mood Questionnaire's (MDBF) mood subscale (79, 80): *annoyed–in a good mood, content–discontent, happy–unhappy*. Item responses were averaged for calculation of a total score (MOOD), with higher values indexing more positive mood. Additionally, participants were asked for their momentary perception of state relationship satisfaction (RELSAT) from (1) *very dissatisfied* to (5) *very satisfied*. This single-item assessment was adapted from the Relationship Assessment Scale (RAS), which showed adequate internal consistency and validity in previous studies (81, 82). Both scales were assessed once before and once after the PAT. Modification of existing scales was necessary to enable brief assessments and change sensitivity in the very short measurement time course and has been shown to be feasible in a previous study (79).

Cortisol and Alpha-Amylase Assessment

We used the passive drool method and SaliCab® tubes (RE69985, IBL, Hamburg, Germany) to collect four whole saliva samples per participant. Participants were asked to collect saliva for one minute and to salivate through a plastic straw into the collecting tube. Saliva samples were stored at -80°C until laboratory analysis. sCORT was analyzed using a commercially available enzyme-linked immunosorbent assay (DES6611; Demeditec Diagnostics, Kiel, Germany) according to the manufacturer's protocol. sAA was analyzed using a kinetic colorimetric kit with reagents from Roche (Roche Diagnostics, Mannheim, Germany). Biological data were analyzed in the stress biomarkers lab at the Institute of Medical Psychology, Heidelberg. The intra-assay coefficient of variation (CV) was 3.35% for sCORT and 3.36% for sAA. The inter-assay CV was 7.20% for sAA and 6.28% for sCORT.

Additional Clinical Measures

For the purpose of sample characteristics description and statistical control of unintended variability in the outcome data, several psychometric scales were assessed once at either lab day 1 or 2. A complete list of all scales collected in the SIDE studies can be found in the RCT's protocol (73). The following scales were used in the present study: The Patient Health Questionnaire (PHQ-9), the Partnership Questionnaire (PFB), the Berlin Social Support Scale (BSSS), and the Trier Inventory for Chronic Stress (TICS).

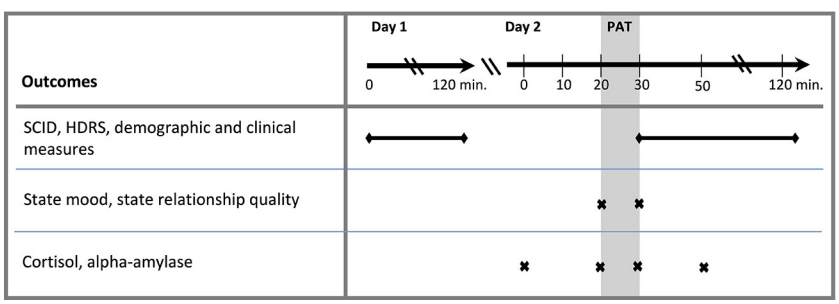

FIGURE 1 | Assessment plan. SCID, Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders; HDRS, Hamilton Depression Rating Scale; PAT, positive social interaction.

The PHQ-9 is a brief, self-report screening tool for depression severity consisting of nine items on a 4-point scale (83). Validation studies reported high reliability and an acceptable one-factor model fit for the German version (84). The PFB is a diagnostic instrument for the assessment of partnership quality frequently used in German-speaking countries, with adequate internal consistency and validity (85, 86). The questionnaire uses 30 items on a 4-point scale to measure partnership related behavior and attitudes on the subscales "quarreling", "tenderness", and "similarity/communication". The BSSS measures social support in the course of a stressful event (e.g. coping with a disease). Responses to 34 items on a 4-point scale can be aggregated to one of six available subscales (perceived, actually received and actually provided support, need for support, support seeking, protective buffering). Reliability and validity were reported to be sufficient for the BSSS (87). Moreover, to measure the presence of chronic stress in our participants, we used the 12-item (0–4) screening subscale of chronic stress (SSCS) of the TICS. Adequate psychometric properties were reported in a German validation study (88).

We used total sum scores of all scales for sample description purposes, except for the BSSS, which does not allow for calculation of a total score. Here, we used the "actually received social support" subscale (calculated as mean), as it asks specifically for support by a romantic partner (87). For all reported scales, higher numeric values indicate a higher score on the labeling construct: high depression (PHQ-9), partnership quality (PFB), social support (BSSS), and chronic stress (TICS).

Analytical Plan

Preliminary Analysis and Handling of Covariates

With regard to the manipulation check, observer-ratings of the PATs were averaged across raters. For both the self- and observer-ratings, we calculated means and 95% confidence intervals (CIs), first for the entire sample and then for study groups separately (DCs and NDCs). Couples, whose self-ratings and averaged observer-ratings were all below 3, were considered "non-compliant" to the PAT instructions, and thus, were deleted from the outcome models.

Before calculating the outcome models, a number of potential confounders and moderators were tested for their association strength with the study outcomes. These variables were derived from guidelines on stress biomarker research (77), from the clinical scales used in this study (PHQ-9, PFB, BSSS, TICS), and from preselected demographic/health screening variables that were relevant to the research question (e.g. blood pressure, age, relationship duration, medication intake). Balancing between statistical control and model convergence, we decided to consider caffeine intake (no/yes), smoking (no/yes), and BMI (in kg/m^2) as time-invariant covariates for the psychobiological outcomes, and age for all outcomes. Since associations between relationship duration (RELDUR) and the study outcomes were particularly consistent, we chose to explore its potentially moderating role in the course of multilevel modeling. Additionally, associations of RELDUR with other relevant study data were exploratively analyzed by Pearson product-moment correlations and 95% CIs calculated *via* Fisher's *z* (back-) transformation. Further statistical procedures and handling of predictor variables are described in the following paragraph.

Multilevel Modeling for Hypotheses Testing

Given the nested structure of the data (measurements nested in individuals and individuals nested in dyads), statistical analysis was conducted using multilevel modeling (89, 90). To test the study hypotheses, we decided to follow a two-step analytical strategy: In the first step, the primary hypotheses (see below) were tested in a women-only data subset, eliminating the couple level. This analysis was of primary interest as we hypothesized differences in the PAT response between female index patients and non-depressed female controls. In a secondary step, we included the data of male partners, but eliminated the measurement level (TIME) by collapsing repeated measures into a change score or area under the curve with respect to increase (AUCi). Change scores were calculated by subtracting pre from post scores for state mood (MOOD_d) and relationship satisfaction (RELSAT_d). AUCi's were computed for sCORT and sAA according to standard procedures in psychoneuroendocrine research (91). In addition to outcome hypotheses testing, AUCi's were used for illustrative purposes in the graphical outputs. If single measurements were missing within one person, they were imputed by use of the R package Amelia II (92) before calculation of the AUCi's.

Hence, multilevel models were built to test the following focal predictors and hypothesis:

1. Primary hypotheses: Women's PAT response (with regard to MOOD, RELSAT, sCORT, and sAA) is moderated by GROUP * TIME (Models 1 to 4)
2. Exploratory hypotheses: GROUP * TIME effects in women are moderated by relationship duration (GROUP * TIME * RELDUR)
3. Secondary hypotheses: PAT response of all participants (with regard to MOOD_d, RELSAT_d, sCORT AUCi, and sAA AUCi) is moderated by SEX*GROUP (Models 5 to 8)
4. Exploratory hypotheses: SEX * GROUP effects in all participants are moderated by relationship duration (SEX * GROUP * RELDUR)

Models were fitted in the statistical environment R (93) *via* the "lme" function of the "nlme" package (94) with a restricted maximum likelihood method of estimation (REML). The distribution of every outcome variable was examined. In case non-normality became evident, transformation techniques were applied, given that this helps to approximate normality of the model residuals. All continuous predictors, except TIME (0 to 1 for MOOD and RELSAT, 0 to 3 for sCORT and sAA) were centered on their grand mean. Dichotomous predictors were entered as factors. To account for the nested structure of the data and to minimize standard errors (95), random intercepts were added in each model. Random slopes were only considered for models with more than two lower-level units nested in higher level units (Models 3 and 4). We graphically assessed each final

model for violations of central model assumptions regarding the distribution of residuals and random effects (96).

To test hypotheses 1.a, we built two-level models with TIME nested in individuals (women only). Both, sCORT and sAA data were positively skewed. To enable an approximate normality of the model residuals, both were transformed to the natural logarithm. Thereafter, outliers beyond three standard deviations of the mean were excluded. In the process of model fitting, we allowed the effect of time to vary across individuals only in the sCORT model, since this provided the best model fit as indicated by likelihood ratio tests for nested models as well as by the Bayesian information criterion (BIC). For testing of hypothesis 2.a, we built two-level models with individuals (all participants) nested in couples for the composite outcomes MOOD_d, RELSAT_d, sCORT AUCi, and sAA AUCi. Only MOOD_d was found to be positively skewed and was transformed to the natural logarithm (adding 5 as a constant first, because negative change scores would have been transformed to NA otherwise). The potentially moderating role of relationship duration was explored in all models (Models 1–8, hypotheses 1.b and 2.b). Only if the focal predictor in these models was statistically significant, final models including this interaction effect are reported.

Sample Size

Sample size calculations for the SIDE studies were tailored for the conduction of the subsequent RCT that would further include the DCs who participated in the present study. Analyses with G*Power (97) were described in the study protocol and revealed an optimal total sample size of $N = 50$ DCs, accounting for assumed attrition (73). In the present study, we aimed at recruiting an equal amount of $N = 50$ additional NDCs for the comparison of PAT responses. Power analyses showed that this sample size would allow us to detect small-sized effects ($> f = 0.1$) between DCs and NDCs in a repeated-measures design with $k = 4$ observations, a correlation between repeated-measures of $\rho = 0.6$, $\alpha = 0.05$, and $(1 - \beta) = 0.8$ (97). Sample size calculation for multilevel modeling is more complex, but it is reasonable to assume that the G*Power analyses represent a conservative estimate, as previous simulation work has shown that a sample of $n \geq 50$ subjects on level-2 allows for unbiased estimates of model coefficients, standard errors, and variance components (98).

RESULTS

Sample Characteristics and Manipulation Check

A total of $N = 116$ heterosexual couples and $n = 232$ individuals were recruited ($N = 65$ DCs and $N = 51$ NDCs). $N = 24$ couples were excluded as they did not meet the requirements with regard to the presence or non-presence of a depressive diagnosis as defined in **Table 1**, or because no biodata was available at all. This resulted in a total of $n = 184$ individuals from $N = 47$ DCs and $N = 45$ NDCs to be included in the study. Additional individual data points were excluded in the course of psychobiological data preparation (see analysis sections and tables). With an overall mean of $M = 4.26$ ($CI = [4.13; 4.39]$) the total sample rated the PAT as positive on average. This was true for both DCs ($M = 4.11$, $CI = [3.93; 4.29]$) and NDCs ($M = 4.42$, $CI = [4.24; 4.60]$). The observer-based manipulation checks revealed similar results: Blinded raters on average perceived the PAT as positive ($M = 4.22$, $CI = [4.03; 4.42]$), and the difference between study groups was small in magnitude (DCs: $M = 4.15$, $CI = [3.87; 4.43]$; NDCs: $M = 4.31$, $CI = [4.04; 4.58]$). Interaction behavior in two couples (1 DC and 1 NDC), however, received ratings lower than 3 in both the self- and observer-ratings, leading to subsequent exclusion of this data from the outcome models.

As **Table 2** shows, the study groups differed with regard to both age and relationship duration. DCs on average were $M = 42.5$ ($SD = 14.8$) years old and in the relationship for $M = 11.3$ ($SD = 10.5$) years, while NDCs were $M = 36.7$ ($SD = 17.3$) years old and in the relationship for $M = 9.0$ ($SD = 11.9$) years. Hence, both variables were considered potential covariates in the subsequent analyses. None of the included men in the DCs was diagnosed with a current form of depression *via* SCID. $N = 7$, however, had a HDRS rating ≥12. Moreover, $N = 7$ men in the DCs, $N = 4$ men in the NDCs, and $N = 6$ women in the NDCs reported a lifetime history of depression (fully remitted). **Figure 2** illustrates sex and group differences with regard to clinically relevant measures. As expected, women in the DCs had the highest PHQ-9 scores, but their female partners also reported moderately elevated depressiveness with an average of $M = 5.51$ ($SD = 4.33$) compared to the NDCs. Moreover, both partners in the DCs reported lower overall relationship quality (PFB) and actually received social support by the partner (BSSS) than NDCs (**Figures 2B, C**). A similar pattern of baseline differences occurred for the assessment of chronic stress with the TICS (**Figure 2D**): Both male and female partners indicated a higher stress level, if they belonged to the DCs group compared to NDCs, while sex-dependent differences within study groups on clinical measures other than the PHQ-9 were rather small.

PAT Response in Depressed vs. Non-Depressed Women

Table 2 includes means and standard deviations of all study outcomes (sCORT, sAA, MOOD, RELSAT), and trajectories of raw data means and standard errors over the course of the PAT are shown in **Figure 3**. Women in both groups showed increases in MOOD and RELSAT after the PAT. Baseline means were lower and mean increases were stronger in depressed women for both variables (**Figures 3A, B**). The tested TIME * GROUP effect was statistically significant for RELSAT ($p = 0.035$), but not for mood ($p = 0.107$). Hence, depressed women's momentary relationship satisfaction increased significantly stronger, while the between-group differences in MOOD slopes over time were in the same direction but failed to reach significance. Relationship duration was not a significant moderator of

TABLE 2 | Descriptive statistics of sample characteristics and outcome data.

	Sex	DCs		NDCs	
		N	*M (SD)*	*N*	*M (SD)*
Age	**Women**	46	41.24 (14.13)	44	34.95 (16.38)
	Men	46	43.98 (15.84)	44	37.09 (17.60)
Relationship duration in years	**Women**	46	11.27 (10.80)	44	8.84 (12.21)
	Men	46	11.17 (10.64)	44	8.80 (11.94)
Depression (PHQ-9)	**Women**	46	13.54 (4.72)	44	3.00 (3.12)
	Men	46	5.33 (4.19)	44	2.84 (3.23)
Relationship quality (PFB)	**Women**	45	54.20 (16.75)	44	67.41 (13.45)
	Men	45	54.89 (13.16)	43	64.95 (14.37)
Social support (BSSS)	**Women**	44	3.23 (0.63)	43	3.48 (0.49)
	Men	44	3.15 (0.51)	44	3.37 (0.55)
Chronic stress (TICS)	**Women**	44	24.50 (11.74)	43	14.86 (8.62)
	Men	44	22.16 (10.56)	44	13.57 (8.89)
State mood (MOOD) —Pre PAT	**Women**	46	3.28 (0.83)	44	4.19 (0.71)
	Men	46	3.88 (0.63)	44	4.19 (0.79)
State mood (MOOD) —Post PAT	**Women**	46	3.91 (0.80)	44	4.55 (0.62)
	Men	46	4.20 (0.69)	44	4.53 (0.68)
Momentary relationship satisfaction (RELSAT)—Pre PAT	**Women**	46	3.57 (1.17)	44	4.45 (1.00)
	Men	46	3.83 (0.97)	44	4.55 (0.90)
Momentary relationship satisfaction (RELSAT)—Post PAT	**Women**	46	4.09 (1.07)	44	4.75 (0.53)
	Men	46	4.30 (0.70)	44	4.45 (1.13)
sCORT_1	**Women**	44	3.33 (1.52)	44	3.12 (1.96)
	Men	44	3.61 (1.72)	44	3.76 (2.53)
sCORT _2	**Women**	45	3.30 (1.45)	44	3.08 (1.50)
	Men	45	3.88 (1.89)	43	3.89 (2.32)
sCORT _3	**Women**	45	3.80 (2.81)	43	3.26 (1.91)
	Men	45	4.01 (2.18)	44	4.28 (2.96)
sCORT _4	**Women**	45	3.07 (1.86)	44	3.03 (2.00)
	Men	43	3.63 (2.13)	43	3.67 (2.37)
sAA_1	**Women**	43	69.92 (104.83)	44	74.40 (104.25)
	Men	44	98.28 (111.88)	44	80.87 (76.85)
sAA_2	**Women**	43	102.10 (184.69)	41	58.36 (39.92)
	Men	43	116.39 (162.32)	42	95.39 (89.36)
sAA_3	**Women**	43	114.17 (101.24)	43	112.57 (171.28)
	Men	44	137.50 (174.29)	44	104.11 (107.15)
sAA_4	**Women**	43	91.99 (91.83)	42	91.76 (93.97)
	Men	44	113.69 (130.18)	42	100.97 (99.14)
sCORT AUCi	**Women**	45	4.72 (59.73)	44	0.14 (56.68)
	Men	45	7.12 (61.85)	41	10.43 (64.55)
sAA AUCi	**Women**	44	885.11 (2235.90)	40	739.00 (2269.15)
	Men	43	797.96 (2901.10)	41	860.42 (2484.32)

M, mean; SD, standard deviation; PHQ-9, Patient Health Questionnaire; PFB, Partnership Questionnaire; BSSS, Berlin Social Support Scales—actually received support; TICS, Trier Inventory for Chronic Stress—screening subscale; PAT, Partnership Appreciation Task; DCs, depressive couples; NDCs, non-depressive couples; sCORT, salivary cortisol (in ng/ml); sAA, salivary alpha-amylase (in U/min); AUCi, area under the curve with respect to increase.

MOOD or RELSAT change in women (both p >0.050) and was therefore not included in the final Models 1 and 2 (**Table 3**).

Averaged sCORT trajectories of women in the NDCs group showed little change over time, while depressed women's sCORT levels, in contrast, particularly increased from pre-PAT (T2) to post-PAT (T3; **Figure 3C**). Multilevel modeling showed that sCORT increases were significantly stronger in depressed women, but only if relationship duration was taken into account (**Table 3**). Hence, while we did not find a significant TIME * GROUP effect (p = 0.214), the three-way interaction TIME * GROUP * RELDUR was statistically significant (p = 0.022), indicating that the higher sCORT increase in depressed females was particularly pronounced in longer-term relationships. This effect is illustrated in **Figure 4**, where the sCORT AUCi was used as the outcome for illustrative purposes.

sAA increased from T1 to T3 and decreased after the PAT in depressed women (**Figure 3D**). Non-depressed women's trajectories revealed comparable mean values at T1, T3, and T4, but a lower score at T2. Multilevel modeling showed a significant sAA increase in response to the PAT in all women regardless the study group (TIME, p = 0.009). We did not find a significant TIME * GROUP interaction (p > 0.050), however, and RELDUR was not a significant moderator in this analysis (p > 0.050) and was therefore not included in the final Model 4 (**Table 3**).

Sex Differences in Depressed vs. Non-Depressed Couples' PAT Response

State mood increases were observed in all study groups including men. In DCs, men's MOOD levels were higher than those of their female partners (**Figure 3A**). Concerning RELSAT, both men and women in the DCs reported lower scores than NDCs, and between-group differences decreased after the PAT. Men in NDCs had the highest initial ratings and they were the only subgroup showing a slight decrease in RELSAT (**Figure 3B**). Models 5 and 6 in **Table 4** present the estimates and significance values with regard to the moderating role of sex in MOOD_d and RELSAT_d group differences. The tested SEX * GROUP effects failed to reach significance in both the change scores of state mood and momentary relationship satisfaction (MOOD_d, RELSAT_d, both p > 0.050).

Men's average sCORT and sAA AUCi were positive and the sCORT AUCi's were descriptively higher than those of their female partners (**Table 2**). Trajectories were comparable between men in the DCs and NDCs group with regard to sCORT and sAA, while sAA levels were higher in DCs (**Figures 3C, D**). However, none of the tested, interaction effects were statistically significant in multilevel modeling of sCORT AUCi and sAA AUCi (both p > 0.050, **Table 4**). Moreover, RELDUR was not a significant moderator of any SEX * GROUP effect in Models 5–8, and therefore, final models without RELDUR and its higher-order interactions were reported in **Table 4**.

Explorative Associations of Age and Relationship Duration

Given the identified moderating role of relationship duration in women's cortisol response, we explored its associations with other psychological and psychobiological variables in this study to gain a deeper understanding into the meaning of this finding (**Table 5**). Unsurprisingly, relationship duration was strongly related with age in all participants (r = −0.71). Furthermore, we found longer relationship duration to be associated with lower partnership quality (PFB) and lower actually received social

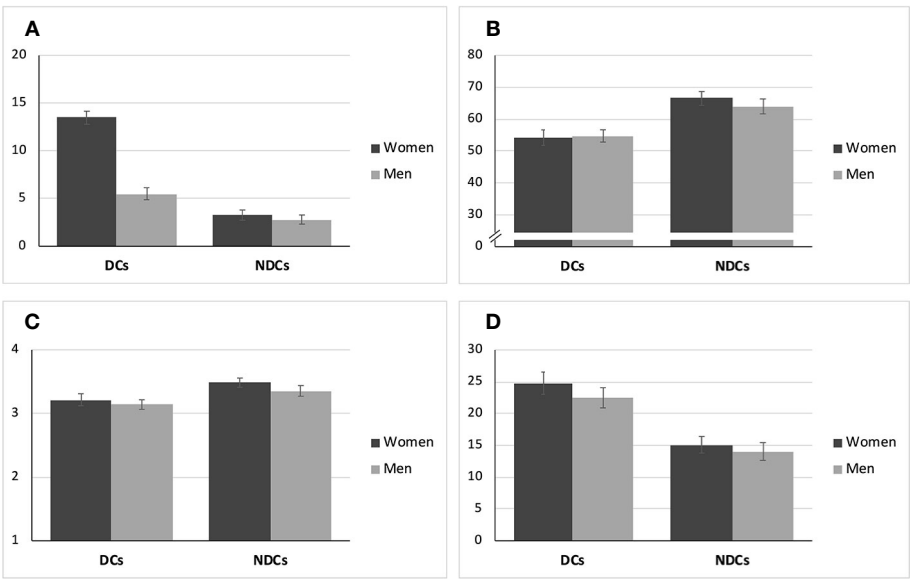

FIGURE 2 | Means and standard errors of psychometric scales at baseline. **(A)** Depression (PHQ-9, Range: 0-27). **(B)** Relationship Quality (PFB, Range: 0-90). **(C)** Social Support (BSSS, Range: 1-4). **(D)** Chronic Stress (TICS, Range: 0-48). DCs, depressive couples; NDCs, non-depressive couples; PHQ-9, Patient Health Questionnaire; PFB, Partnership Questionnaire; BSSS, Berlin Social Support Scales (actually received support); TICS, Trier Inventory for Chronic Stress (screening subscale).

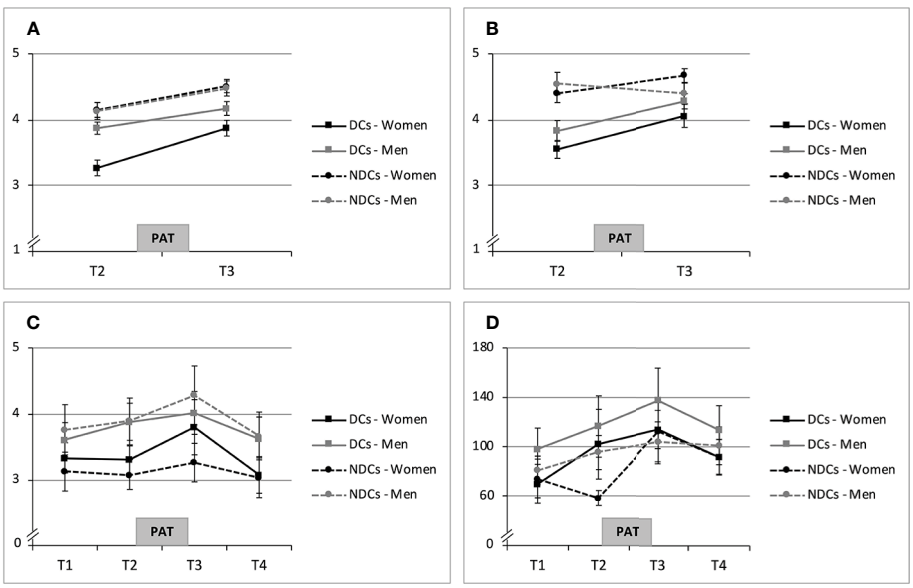

FIGURE 3 | Means and standard errors of PAT response. **(A)** State Mood (Range 1-5). **(B)** Momentary Relationship Satisfaction (Range: 1-5). **(C)** Cortisol (sCort in ng/ml). **(D)** Alpha-Amylase (sAA in U/min). DCs, depressive couples; NDCs, non-depressive couples, PAT, partnership appreciation task.

TABLE 3 | Multilevel modeling of outcome data (observations nested in individuals), women only.

Fixed effects	Model 1: MOOD		Model 2: RELSAT		Model 3: sCORT		Model 4: sAA	
	Est.	*p*	Est.	*p*	Est.	*P*	Est.	*p*
INTERCEPT	**4.135**	**<0.001**	**4.484**	**<0.001**	**0.988**	**<0.001**	**3.821**	**<0.001**
TIME (0, 1, 2, 3)	**0.364**	**<0.001**	**0.210**	**0.038**	–0.012	0.525	**0.130**	**0.004**
GROUP (0 = NDCs, 1 = DCs)	**–0.725**	**<0.001**	**–0.708**	**<0.001**	0.030	0.762	–0.173	0.454
RELDUR (years)	–		–	–	0.000	0.957		
AGE (years)	**–0.017**	**<0.001**	**–0.017**	**0.001**	0.006	0.240	0.013	0.078
CAFFEIN INTAKE (0 = no, 1 = yes)	–		–	–	0.105	0.330	0.004	0.986
SMOKING (0 = no, 1 = yes)	–		–	–	0.260	0.143	0.163	0.659
BMI (kg/m^2)	–		–	–	0.011	0.378	–0.010	0.697
TIME * GROUP	0.186	0.107[a]	**0.302**	**0.035**[a]	–0.033	0.214[a]	0.014	0.823[a]
TIME * RELDUR	–	–	–	–	–0.001	0.689	–	–
GROUP * RELDUR	–	–	–	–	–0.008	0.320	–	–
TIME * RELDUR * GROUP	–	–	–	–	**0.005**	**0.022**[b]	–	–
Random effects (variances)								
INTERCEPT	0.322	–	0.428	–	0.164	–	0.687	–
TIME	–	–	–	–	0.010	–	–	–
Residual variance	0.143	–	0.213	–	0.023	–	0.405	–
BIC	361.599	–	413.504	–	232.554	–	892.014	–
Number of observations	177	–	173	–	340	–	332	–
Number of individuals	89	–	87	–	86	–	85	–

MOOD, state mood; RELSAT, momentary relationship satisfaction; sCORT, salivary cortisol (in ng/ml); sAA, salivary alpha-amylase (in U/min); RELDUR, relationship duration; BMI, body mass index; Est., Estimate; BIC, Bayesian information criterion; bold effects were statistically significant on the level of p <0.05; [a]tested in hypothesis 1.a; [b]tested in hypothesis 1.b.

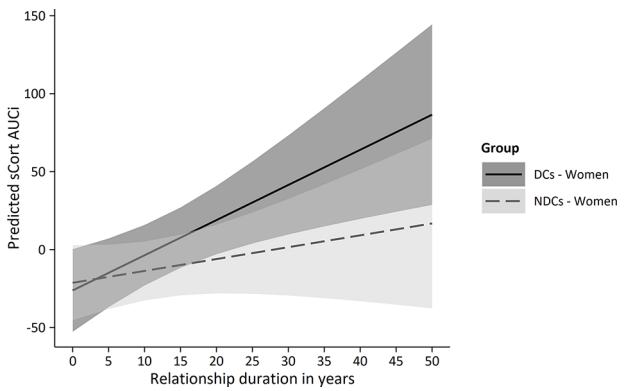

FIGURE 4 | Predicted sCORT_AUCi by group and relationship duration in women. PAT, partnership appreciation task DCs, depressive couples; NDCs, non-depressive couples; sCORT, salivary cortisol (in ng/ml); AUCi, area under the curve with respect to increase.

support (BSSS), and correlations were stronger in depressed women (PFB: $r = -0.41$, BSSS: $r = -0.39$) than in non-depressed women (PFB: $r = -0.21$, BSSS: $r = -0.02$). Interestingly, while non-depressed women's relationship duration was associated with a stronger increase in PAT-induced mood ($r = 0.16$) and a lower sCORT AUCi ($r = -0.23$), the opposite direction of associations was found in depressed women: Here, longer-term relationships were associated with less positive mood changes ($r = -0.22$) and a higher cortisol output (sCORT AUCi: $r = 0.38$).

DISCUSSION

Summary and Interpretation of Findings

With the present study, we aimed at investigating the affective and psychobiological response of couples with depression in an instructed dyadic interaction setting in the lab. Couples with the female partner suffering from depression (DCs) and non-depressed controls (NDCs) were asked to perform an instructed PAT sequence that included positive and appreciative communication between romantic partners. Mood, momentary relationship satisfaction, and biological indicators of stress and arousal were repeatedly assessed during and following the task.

Our primary analyses focused on differences in PAT-induced trajectories between depressed and non-depressed women. Previous research in general populations showed that positive social interaction can increase mood and activate reward-related central nervous system mechanisms (99, 100). Social feedback from the partner, as the most relevant person to most adults, has been shown to substantially affect mood in laboratory studies and in couples' everyday life (41, 101). We expected depressed women to benefit less from positive interaction with their partners due to social anhedonia and the usual tendency to avoid these situations (23). Increases in state mood, however, were comparable in magnitude between depressed and non-depressed women and differences were not significant. Hence, the presence of a depressive diagnosis did not lead to women evaluating the interaction as unpleasant, despite previous evidence from eye-tracking studies suggesting that depressed individuals avert positive (social) stimuli (19). In contrast, depressed women

TABLE 4 | Multilevel modeling of outcome data (individuals nested in couples), all participants.

Fixed effects	Model 5: MOOD_d		Model 6: RELSAT_d		Model 7: sCORT AUCi		Model 8: sAA AUCi	
	Est.	*p*	Est.	*p*	Est.	*p*	Est.	*p*
INTERCEPT	**1.670**	**<0.001**	0.116	0.253	−1.793	0.877	650.086	0.100
SEX (0 = men, 1 = women)	0.004	0.817	0.113	0.419	−12.845	0.264	−55.720	0.885
GROUP (0 = NDCs, 1 = DCs)	−0.005	0.818	0.247	0.083	3.839	0.748	363.831	0.391
AGE (years)	0.000	0.851	0.005	0.111	**−0.569**	**0.049**	−8.256	0.451
CAFFEIN INTAKE (0 = no, 1 = yes)	–	–	–	–	15.455	0.128	−328.631	0.344
SMOKING (0 = no, 1 = yes)	–	–	–	–	−25.031	0.089	294.816	0.565
BMI (kg/m^2)	–	–	–	–	−1.180	0.227	−11.418	0.737
SEX * GROUP	0.039	0.151[a]	0.002	0.993[a]	3.243	0.837[a]	5.291	0.992[a]
Random effects (variances)								
INTERCEPT	0.003	–	<0.001	–	256.78	–	659,935	–
Residual variance	0.008	–	0.403	–	2600.78	–	2692.464	–
BIC	−236.17	–	383.79	–	1849.55	–	2819.53	–
Number of individuals	177	–	172	–	171	–	161	–
Number of couples	90	–	90	–	90	–	87	–

MOOD_d, change in state mood; RELSAT_d, change in momentary relationship satisfaction; sCORT, salivary cortisol (in ng/ml); sAA, salivary alpha-amylase (in U/min); AUCi, area under the curve with respect to increase; BMI, body mass index; Est., Estimate; BIC, Bayesian information criterion; bold effects were statistically significant on the level of p <0.05; [a] tested in hypothesis 2.a.

TABLE 5 | Explorative correlations [95% confidence intervals] for relationship duration.

	All (N = 184)	DCs—Women (N = 47)	NDCs—Women (N.=.45)
Age	**0.71 [0.63; 0.77]**	**0.74 [0.57; 0.84]**	**0.73 [0.55; 0.84]**
Relationship quality (PFB)	**−0.34 [−0.46; −0.21]**	**−0.41 [−0.21; −0.14]**	−0.21 [−0.47; 0.09]
Social Support (BSSS)	−0.26 [−0.39; −0.12]	**−0.39 [−0.61; −0.12]**	−0.02 [−0.31; 0.28]
MOOD_d	−0.08 [−0.22; 0.07]	−0.22 [−0.48; 0.07]	0.16 [−0.14; 0.43]
sCORT AUCi	−0.10 [−0.24; 0.04]	**0.38 [0.10; 0.60]**	−0.23 [−0.49; 0.07]

PFB, Partnership Questionnaire; BSSS, Berlin Social Support Scales—actually received social support; MOOD_d, change in state mood; sCORT, salivary cortisol (in ng/ml); AUCi, area under the curve with respect to increase; DCs, depressive couples; NDCs, non-depressive couples; bold correlations were medium or large effects (r >0.30 or r < −0.30).

reported affective benefits from appreciative conversation with their partners. Moreover, increases in relationship satisfaction were even stronger in depressed than in non-depressed women, indicating that the engagement in positive interaction with the partner directly entailed social evaluative processes regarding the partnership. It should be noted that depressed women had the lowest baseline scores in both mood and relationship satisfaction. While this shows that the chosen outcomes were apt to clinically characterize the study groups at baseline, there is also the possibility of statistical regression-to-the-mean effects. However, these effects seem rather unlikely here, as these baseline variability was not due to extreme values or outliers but to theoretically expected differences in clinically distinguishable groups. Therefore, the findings show that depressed women's mood and relationship satisfaction improve from participation in appreciative communication and that the PAT can reduce pre-existing baseline differences in these variables compared to non-depressed women.

As depressed women usually tend to avoid PAT-like situations, we hypothesized that the instructed (or "forced") participation in positive communication would require high mental and affective effort and that this would transfer to a pattern of psychobiological arousal or stress response. This assumption partly received support with regard to cortisol trajectories: Depressed women showed a higher increase in cortisol in response to the PAT, but this effect was only significant if relationship duration was considered as a moderating factor. Hence, the identified increase in cortisol output was particularly pronounced for female partners in long-term relationships. sAA levels also increased over the course of the PAT in depressed women, but differences between the groups were not significant. On a descriptive level, the T1–T2 decrease in non-depressed women's sAA may reflect adjustment to the experimental situation after initial arousal, which was not found in depressed women. Hence, the increased psychobiological arousal observed in both the sCORT and sAA trajectories in depressed women may well contain an anticipatory stress component. Taken together, these results support the idea that the unfamiliar involvement in positive couple interaction requires higher effort and leads to arousal in depressed women (particularly in longer-term relationships), but that successful engagement in the PAT offers potential affective and social benefits with regard to the partnership.

As the psychobiological arousal effects were not found independent of relationship duration, we explored associations of RELDUR with other relevant variables in order to better

understand the nature of this finding. Interestingly, longer-term relationships were associated with a weaker increase in subjective mood and a stronger increase in cortisol in depressed females, while the opposite direction of associations was found in non-depressed women. Moreover, we found negative correlations between relationship duration and partnership quality (PFB) and actually received social support by the romantic partner (BSSS), particularly in depressed women. Hence, longer relationship duration was associated with impairments in marital/relationship functioning, which is consistent with previous research (14, 15). With increasing duration, couples were found to report less companionship, sexual interaction, relational satisfaction, and commitment on the one hand, and higher frequency of conflict and arguing on the other hand (102). The effect received further support by longitudinal data from a female sample showing not only a decline in relationship quality after 10 years, but also an increased risk for the later occurrence of depressive symptoms if relationship quality was initially low (16). More broadly, marital strain seems to accelerate the typical decline in general health over time (103), and HPA and SAM dysfunctions were found in partners with insecure attachment styles (104). Other studies, in contrast, reported a protective effect of relationship duration on mental health (105), but these were found only in individuals younger than 30 years. In the present study, depressed women in long-term relationships already had developed a mental disorder despite the potentially protective effect of partnership in early years of a relationship, and then showed an increased HPA activation in the PAT. As the moderating role of relationship duration was identified in exploratory analyses, inferences should be drawn cautiously and future studies should be conceptualized to directly test this effect in depressed couples.

A secondary set of analyses in this study included data from male partners. Descriptively, male partners in the DCs showed higher scores of depressiveness on average than men in the NDCs (**Figure 2A**). This is in line with previously reported findings suggesting depressive disorders to affect not only the individual, but whole social systems, particularly including romantic partnerships (5, 106). Notably, the average PHQ-9 score of $M = 5.51$ ($SD = 4.33$) for males in the DCs group would pass the cut-off for a mild depression according to common classifications (107) and $N = 7$ men had a HDRS rating ≥12. Moreover, both partners in the DCs descriptively reported lower partnership quality (PFB), less actually received social support from the partner (BSSS), and higher chronic stress (TICS) than NDCs, and sex-differences within DCs were rather neglectable (**Figures 2B–D**). Hence, DCs as an entity were not only characterized by depression-related symptoms, but also revealed further impairments in social functioning and stress when compared to NDCs. Previous research identified similar profiles in couples with depression, showing reduced quality of life, less perceived social support, higher occurrence of stressful events, and impairments in family or marital functioning (108). These comparable patterns in couple-related functioning and chronic stress may help to explain the paucity of observed sex-dependent group effects in the dyadic analyses. In fact, we did not find any significant SEX * GROUP interactions with regard to mood, relationship satisfaction or stress/arousal markers. Men in both groups improved in mood and patterns of change in RELSAT, sCORT, and SAA did not differ significantly from the female partners or from each other. While these non-significant findings may also depend on sample size and high variability in psychobiological data, they also suggest that both partners are noticeably affected by the mental disorder, and that it is worthwhile to consider the couple as an important unit in depression research and treatment. Taken together, the couple data suggest that instructed positive interaction may lead to affective and psychosocial benefits in couples with depression and encourage speculations about the usefulness of PAT-like interventions as a therapeutic tool. With the aim of challenging social anhedonia behavior and reduced attempts to approach socially rewarding situations in depression (5, 18, 22, 23, 27), couples might be instructed to use positive feedback under a therapist's supervision.

Limitations

A major strength of this research was the integration of complex data within a comprehensive bio-psycho-social approach to the study of positive interaction in depressed couples. However, the study faced a number of limitations which need to be considered. First, DCs on average were 5.8 years older than NDCs. We became aware of this imbalance between groups at an early stage of the study and identified the high percentage of participants in a students' age in the NDCs as a possible reason. While the financial incentive may have been appealing particularly for younger, healthy subjects, DCs' participation in the SIDE studies may have been driven more by the opportunity to benefit from the subsequent CBCT® couple therapy (73). Despite the development of strategies to recruit older couples in the NDCs group (e.g. by offering incentives such as mindfulness courses free of charge and by tailoring the advertising strategy to older participants), we were unable to eliminate this possible source of bias completely. As we intended our findings to remain as unbiased as possible, all subsequent analyses were statistically adjusted for age. Second, to test whether the PAT (instead of conflict conversations or the TSST) would result in a psychobiological stress response in depressed individuals was a novel, previously untested paradigm. It is reasonable to assume that even in depression, stressfulness of positive conversation is lower than a "classical" stress task and that increases in stress biomarkers may rather represent global arousal. In addition, the identification of relationship duration as a potential moderator in the cortisol response was data-driven and the reported findings should therefore be considered exploratory. More confirmatory research is needed to verify these results. Moreover, residuals of the model fitted to predict RELSAT_d were found to be leptokurtic compared to a normal distribution and only moderate overall model fits were observed for models predicting both MOOD_d and RELSAT_d. We decided to accept these limitations given the fact that no significant effects

were observed, and the danger of reporting false positive results could thus be neglected. Lastly, inferences on the potential therapeutic benefits of the PAT need to be drawn cautiously, as we did not implement a randomized control group for a direct evaluation of effectiveness (i.e. depressed couples who were assessed but did not participate in the PAT).

Conclusions

Contrasting expectations based on attentional bias and social anhedonia reported in depression, we found depressed women to respond to and benefit from a positive and appreciative interaction with their romantic partners with regard to state mood and momentary relationship satisfaction. At the same time, depressed women had a higher cortisol output in the PAT than healthy controls, particularly if they were in a longer-term relationship. Relationship duration in depressed women was associated with lower relationship quality, less social support, weaker PAT-induced mood increases and stronger increases in cortisol. Male partners of depressed women reported increased distress with regard to depressiveness, social support and chronic stress, and PAT-related trajectories did not significantly differ between men and women, favoring the considerations of the couple as an important unit in depression research and treatment.

Instructed engagement in positive couple interaction, which depressed women usually tend to avoid, may have required high internal resources and led to increased psychobiological arousal, before offering the chance to emotionally and socially benefit in case of successful completion. While these findings encourage speculations about the therapeutic application of instructed partnership appreciation, more research is needed to evaluate the effectiveness of such interventions, for instance in randomized trials using ecological momentary assessments or to clarify the moderating role of relationship duration.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: heiDATA repository: https://doi.org/10.11588/data/UNWRFN.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

CA-R, MJ, and BD designed the research study. CA-R, MW, and FW performed the study. MS and MW analyzed the data. MW, MS, and BD drafted the first version of the manuscript. All authors contributed to the article and approved the submitted version. All authors agree to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00701/full#supplementary-material

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Childhood Maltreatment Alters the Neural Processing of Chemosensory Stress Signals

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Accumulating evidence suggests that childhood maltreatment (CM) confers risk for psychopathology later in life by inducing hypervigilance to social threat cues such as fearful faces. However, it remains unclear whether the modulatory impact of CM extents to the olfactory domain of social communication in humans. To address this question, we examined whether CM modulates the neural processing of chemosensory threat signals in sweat and whether CM affects the stress-reducing effects of oxytocin (OXT) in this context. In a randomized, double-blind within-subject functional MRI study design, 58 healthy participants (30 females) received intranasal OXT (40 IU) or placebo (PLC) and completed a forced-choice emotion recognition task with faces of varying emotion intensities (neutral to fearful) while exposed to sweat stimuli and a non-social control odor. Axillary sweat samples were collected from 30 healthy male donors undergoing an acute psychosocial stressor (stress) and ergometer training (sport) as control in a pre-study. CM was assessed by the 25-item Childhood Trauma Questionnaire (CTQ). The final fMRI analysis included 50 healthy participants (26 females). Regression analysis showed a stress-specific association of CTQ scores with amygdala hyperreactivity, hippocampal deactivation, and increased functional connectivity between the amygdala and the hippocampus, medial orbitofrontal cortex, and the anterior cingulate cortex (ACC) under PLC. Furthermore, we observed a positive association of CTQ scores and the dampening effects of OXT on stress-related amygdala responses. Our findings suggest that CM may induce hypervigilance to chemosensory threat cues in a healthy sample due to inefficient frontolimbic inhibition of amygdala activation. Future studies should investigate whether increased recruitment of the intralimbic amygdala-hippocampus complex reflects a compensatory mechanism that prevents the development of psychopathology in those who have experienced CM. Furthermore, the results reveal that the stress-specific effects of OXT in the olfactory domain are more pronounced in participants with increasing levels of CM exposure.

Keywords: amygdala, childhood maltreatment, fMRI, hypervigilance, olfaction, oxytocin

INTRODUCTION

Childhood maltreatment (CM) presents a leading risk factor for the later development of psychopathology (1), with CM exposure accounting for over 30% of adult-onset psychiatric disorders (2). Recent efforts to identify etiological mechanisms that mediate this association, suggest CM experiences become biologically embedded (3) in altered trajectories of neurodevelopment (4) and behavior (5). Specifically, burgeoning data underscore the notion that a history of CM is linked to changes in sensory systems (6) and the neural circuitry underlying emotion regulation and threat responsivity (4).

One of the most frequently reported neuroimaging finding in individuals with a history of CM is exaggerated amygdala reactivity to threatening faces (fearful and angry) (7–9). Furthermore, individuals with a history of CM exhibit increased amygdala functional connectivity (FC) with the anterior cingulate cortex (ACC) (10) and with regions of the prefrontal cortex (PFC), in particular the orbitofrontal cortex (OFC) (11) during the exposure to threatening faces. The amygdala represents a key node in threat detection and in the coordination of adaptive behavioral and autonomic responses to these threat signals (12). Aberrant amygdala activations are observed across psychiatric disorders (13) and the amygdala threat detection process has been suggested to mediate the relationship between CM and psychopathology later in life (14, 15). Both the ACC and the OFC feature reciprocal functional and anatomical connections with the amygdala (16) and co-activations of the ACC and OFC with the amygdala are central to efficient emotion regulation by enabling a down-regulation of amygdala reactivity to threatening stimuli (17–19). These findings show that CM is associated with a dysregulated threat circuitry manifested in a phenotypic hypersensitivity towards social threat cues. However, it remains unclear whether the modulatory impact of CM extents to the olfactory domain of social communication.

Phylogenetically one of the most ancient senses, olfaction is essential for survival due to its alarm function. In humans, the ability to identify olfactory threat cues in the environment and respond to them in an adaptive manner is well developed (20). Olfaction plays a key role in the modulation of behavior and interpersonal relationships (21), with accumulating evidence indicating social chemosignaling in humans (20, 22–24). Human social chemosignals have been shown to convey information with respect to kin recognition (20), mother-infant bonding (25), disease detection (26), aggression (24) and emotional states (23). A recent line of research demonstrates that chemosensory communication of threat cues in axillary sweat modulates cross-modal emotion perception of ambiguous threatening facial stimuli and produces widespread neural threat responses in the amygdala, ACC, hippocampus, the prefrontal cortex, and fusiform face area (FFA) (27–30). These effects are even more pronounced in individuals with heightened stress vulnerabilities such as patients with anxiety disorders (31, 32). The olfactory system and the emotion circuitry are largely intertwined and share neuroanatomical pathways *via* the amygdala, hippocampus, and OFC (33). Thus, olfactory stimulation directly evokes emotions and autonomic responses *via* these pathways (34). Furthermore, there is evidence suggesting a separate representation of pleasant and unpleasant odors in the medial and lateral parts of OFC (35). The overlap of brain regions showing aberrant threat-induced activation patterns in CM studies and olfactory projection areas render the olfactory domain a potential pathogenic pathway following CM exposure. Recent findings have linked CM to altered activation in a widespread network of neocortial areas including the OFC and hippocampus during non-threatening olfactory stimuli presentation in females (36). Another study observed significant reductions of olfactory bulb volume and olfactory function in women with a history of CM (37). Moreover, olfactory dysfunctions and altered processing of non-social olfactory threat cues have been observed in individuals with post-traumatic stress disorder (PTSD) (38–40). However, whether CM modulates the processing of social olfactory cues remains unclear.

The hypothalamic peptide hormone oxytocin (OXT) has been increasingly recognized as a promising therapeutic candidate for stress-related disorders such as major depressive disorder and PTSD due to its role in stress regulation and social behavior (41). Animal models demonstrate long-term consequences of early life experiences in the oxytocinergic system, with rodents exhibiting lower OXT receptor expression in the amygdala and hypothalamus after receiving less maternal care (42, 43) and increased serum and hypothalamic OXT levels in maternal separation models (44). Likewise, human studies observed lower OXT concentrations in the cerebrospinal fluid of men (45) and women with a history of CM (46). Interestingly, a particularly strong effect was identified for emotional abuse. However, less severe forms of CM were positively associated with urine OXT levels in adults (47). In line with this, women with a history of sexual abuse during childhood exhibited higher blood OXT levels in response to a laboratory psychosocial stressor, i.e. the Trier Social Stress Test (TSST) (48) compared to controls (49). Furthermore, human intranasal administration of OXT enhanced the stress-buffering effects of social support during the TSST (50, 51) and we recently found that the peptide reduces amygdala reactivity to social chemosensory threat signals (27). Importantly, a plethora of studies observed that the effects of intranasal oxytocin vary as a function of social context and interindividual variables such as childhood experiences (52, 53). For instance, the stress-buffering effects of OXT after the TSST were only evident in women with higher levels of adverse childhood experiences (51), while the peptide had no significant effect on handgrip force in reaction to an infant crying in women with harsh parenting experiences (54). However, it remains to be investigated whether CM affects the effects of OXT in the context of social chemosensory threat cues.

Given the adverse behavioral and health consequences of CM (55, 56), there is a pressing need to identify neurobiological compensatory mechanisms that help individuals to maintain or rapidly regain mental well-being in the aftermath of CM (57). Notably, a significant proportion of individuals with a history of CM function well and are clinically resilient despite CM-induced

neurobiological changes (4, 58). This suggests that additional neurobiological mechanisms may be present that enable these individuals to effectively compensate for CM-induced brain changes (4). Potential compensatory mechanisms for CM-associated hypervigilance have recently been examined in response to threatening facial stimuli revealing a heightened intra-limbic FC between the amygdala and the hippocampus in resilient adults (59). However, it remains unclear whether CM also modulates threat responsivity in the olfactory domain and which potential compensatory mechanisms may be observed in a resilient sample.

The current study consists of a secondary analysis utilizing an existing data set of a randomized, double-blind, placebo (PLC)-controlled trial by Maier et al. (27) that was collected to explore the oxytocinergic modulation of chemosensory communication of stress. The functional magnetic resonance (fMRI) study involved 58 healthy volunteers completing a forced-choice emotion recognition task with facial stimuli of varying emotion intensities (neutral to fearful) while exposed to sweat stimuli and a non-social control (raspberry odor) after intranasal PLC and OXT administration, respectively. Axillary sweat samples were obtained from healthy male donors undergoing an acute psychosocial stressor (stress) and ergometer training (sport) as control in a pre-study. In this secondary analysis, we investigated the modulatory effect of CM on the processing of chemosensory threat signals and whether CM affects the anti-stress effects of OXT in this context. The measure relevant to the current hypothesis was the Childhood Trauma Questionnaire (CTQ) (60). Our primary hypothesis was that CM would be associated with increased neural reactivity and increased frontolimbic as well as intralimbic FC to chemosensory threat signals. Secondary, we assumed that CM also modulates the effects of OXT on the processing of chemosensory stress cues.

METHODS

The original randomized, double-blind, PLC-controlled, within-subject, cross-over trial (n = 58) by Maier et al. (27) was conducted between 2015 and 2017 at the Division of Medical Psychology of the University of Bonn, Germany. The study methods were previously described in full detail (27) and are summarized here.

Participants

The study sample included 58 healthy (26 females, mean ± SD age, 24.90 ± 3.11 years), right-handed, heterosexual, non-smoking volunteers recruited from the local population *via* online advertisement and public posting. The Mini-International Neuropsychiatric Interview (MINI) (61) was used to screen for a history of psychiatric or physical disease prior to study enrollment. Furthermore, participants were screened for anosmia using the Sniffin'Sticks test battery, which comprises an odor identification and discrimination test (Burghart GmbH, Burghart Wedel, Germany). Participants were lifetime naïve to prescribed psychoactive medication and none of the participants were pregnant or used hormonal contraceptives during the study. MRI contraindications were additional exclusion criteria. CM experiences were assessed using the 25-item retrospective CTQ (60). The CTQ measures five types of adverse childhood experiences: emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse (62). A 5-point Likert scale is used for responses ranging from 1 (*never true*) to 5 (*very often true*) and scores ranging from 5 to 25. In addition, depressive symptoms within the previous 2 weeks and subjective anxiety for the past month were assessed using the Beck Depression Inventory–II (63) and the State-Trait Anxiety Inventory (STAI) (64). Autistic-like traits were measured *via* the Autism Spectrum Quotient questionnaire (AQ) (65). Demographic and psychometric sample characteristics are listed in **Table 1**. Eight participants had to be excluded from the fMRI analysis due to technical malfunctions or excessive head motion (>3 mm/°) during scanning, leaving 50 participants (26 females, mean ± SD age, 24.54 ± 3.09 years) for the fMRI data analyses.

The study was conducted in accordance with the latest version of the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Bonn. All participants provided written informed consent before screening and were reimbursed for participation.

Study Design

In a randomized, double-blind, PLC-controlled, within-subject crossover design, participants received either OXT (Novartis, Basel, Switzerland) or PLC intranasally in two separate experimental sessions of at least 24 h apart. At the beginning of each fMRI testing session, participants self-administered a single intranasal dose of 40 IU synthetic OXT or PLC under the supervision of an experimenter following a standardized protocol (66) (5 puffs balanced across nostrils, at an inter-puff interval of 50 seconds to allow the solution to be absorbed into the nasal epithelium). The amount of administered substance was weighed and was supplemented by an additional puff if it fell below a set minimum (40 IU = 1000mg). The PLC solution contained identical ingredients except for the peptide itself. Functional MRI scanning

TABLE 1 | Demographic and psychometric sample characteristics.

	Mean ± SE (Range) (*N* = 58)
Age (years)	24.9 ± 0.41 (19–31)
Sex (F/M)	30/28
Education (years)	16.83 ± 0.38 (12–25)
CTQ sum score	33.98 ± 0.75 (29–53)
CTQ emotional neglect	7.55 ± 0.35 (5–16)
CTQ emotional abuse	6.66 ± 0.29 (5–16)
CTQ physical abuse	8.66 ± 0.16 (6–13)
CTQ physical neglect	5.86 ± 0.18 (5–9)
CTQ sexual abuse	5.26 ± 0.22 (5–18)
BDI	2.09 ± 1.07 (0–12)
STAI Trait	31.45 ± 0.92 (22–52)
AQ	13.81 ± 0.65 (2–28)

Childhood maltreatment experiences were assessed by means of the CTQ.
CTQ, Childhood Trauma Questionnaire; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory; AQ, Autism Spectrum Quotient.

started 30 min after nasal administration and was followed by an anatomical scan. Participants abstained from caffeine and alcohol intake for 24 hours prior to arrival. Participants' olfactory functioning was verified after nasal spray administration in both scanning sessions using a staircase olfactory threshold test (Burghart GmbH, Wedel, Germany) [67) (for full description, see (27)].

Olfactory Stimuli and Presentation

During the fMRI experiment, participants were exposed to three different olfactory stimuli: male axillary sweat obtained from an independent sample of 30 healthy donors (mean ± SD age, 23.30 ± 2.67 years) who underwent both the (i) TSST (stress sweat) (48) and (ii) ergometer training (sport sweat), and as a non-social control (iii) chemically synthesized raspberry (Burghart GmbH, Wedel, Germany) [for detailed description of stimuli generation, see **SI** and (27)]. Sweat donors experienced significantly greater stress during the TSST compared to the physical exercise condition manifested in elevated salivary cortisol levels and state anxiety ratings (27). Chemosensory stimuli did not exhibit detectable differences in odor quality between treatment scan sessions, which was validated by an independent sample of participants who rated the pleasantness, intensity, and familiarity of the stimuli (27).

Olfactory stimuli were administered *via* a three-channel, computer-controlled, MRI compatible air-dilution olfactometer (OG001, Burghart GmbH, Wedel, Germany). Odorant flows (5 lpm) were directed *via* 10 *m* tubes through an odorless oxygen mask, which participants wore inside the scanner. At stimuli offset, participants breathed ambient air through the exhalation ports of the oxygen masks. The odor channels were triggered using a specialized proprietary olfactometer control software (OG Control, Burghart GmbH, Wedel, Germany).

Respiratory Signal Recording

Respiratory compliance was monitored online throughout fMRI scanning *via* an MR-compatible chest-strap-based respiration transducer (Biopac, RX-TSD221-MRI) to ensure that inhalations (i.e. thoracic expansions) were temporally aligned with odor delivery. Respiration signals were recorded using a Biopac MP150 system and the accompanying AcqKnowledge Acquisition & Analysis Software (Version 4.3.1) applying a sampling frequency of 1000 Hz. Noise was removed by means of a hardware-based filter included in the amplifier with a low pass filter of 1 Hz and a high pass filter of 0.05 Hz.

fMRI Task

For the fMRI scan, an adapted version of an established emotion recognition paradigm was utilized (29). In a forced-choice paradigm, male facial stimuli were briefly presented at four emotion intensity levels (neutral, low fearful, medium fearful, and high fearful). Participants were instructed to identify whether the stimuli depicted a neutral or fearful expression while they were exposed to stress sweat, sport sweat or raspberry (non-social control odor). Odor delivery *via* the olfactometer was synchronized with respiratory cues (green fixation cross) and participants were instructed to breathe orthonasally and inhale on cue throughout the experiment. In each trial, odor delivery spanned the duration of the inhalation cue (1300 ms) as well as the emotional facial stimuli (200 ms) for a total duration of 1500 ms and was preceded by an exhalation cue (red fixation cross, 2000 ms). Experimental trials were separated by a jittered inter-stimulus interval (black fixation cross, 4,000–6,000 ms) and a new trial started immediately after the response was recorded or after 2000 ms if no response was made. Each of the three olfactory stimuli were presented 48 times in a random order, resulting in 144 trials and an experiment duration of about 20 min (for full description of the fMRi task, see **SI** and (27).

Image Acquisition

A Siemens MAGNETOM Trio MRI system (Siemens, Erlangen, Germany) operating at 3T and equipped with a 32-channel phased-array head coil (Siemens, Erlangen, Germany) was used to acquire T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast (TR = 2500 ms, TE = 30 ms, pixel size: 2 x 2 x 3 mm, slice thickness = 3.0 mm, distance factor = 10%, FoV = 192 mm, flip angle = 90°, 37 axial slices). High-resolution anatomical reference images were obtained on the same scanner using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 2.54 ms, matrix size: 256 x 256, pixel size: 0.8 x 0.8 x 0.8 mm, slice thickness = 0.8 mm, FoV = 256 mm, flip angle = 9°, 208 sagittal slices).

fMRI Data Analysis

Functional imaging data were realigned and spatially normalized to the standard Montreal Neurological Institute (MNI) space and smoothed (Gaussian kernel, 6mm FWHM) using SPM12 software (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2010b (MathWorks, Natick, Massachusetts) [for further detail, see **SI** and (27)].

Onsets and durations of the 24 experimental conditions (treatment (PLC, OXT) × odor (stress, sport, raspberry) × emotion intensities (neutral, low fearful, medium fearful, high fearful) were modeled by a stick function convolved with a hemodynamic response function, with the trial onset defined as the onset of odor delivery. Respiratory noise correction was performed using the PhysIO toolbox (68). The movement parameters (realignment parameters) and respiratory noise regressors were included as nuisance regressors in the design matrix. For the fMRI statistical analysis, we used a two-level random-effects approach based on the general linear model as implemented in SPM12 [for full description, see **SI** and (27)].

On the group-level we performed multiple regression analysis. Due to the absence of specific neural effects of emotion intensity, chemosensory-induced responses were averaged across all intensity levels. The modulatory effect of CM on the processing of chemosensory threat signals was measured by regressing CTQ sum scores on the differential contrast between blood-oxygen-level-dependent (BOLD) signal response to stress relative to sport odor [(Stress $_{(PLC)}$ > Sport $_{(PLC)}$)]. To explore whether CM moderates the stress-specific effects of OXT on the processing of chemosensory threat signals, CTQ scores were regressed on neural

responsiveness to the contrast [($Stress_{(PLC)}$ > $Sport_{(PLC)}$) – ($Stress_{(OXT)}$ > $Sport_{(OXT)}$)]. Furthermore, we also tested potential modulatory effects of CM on the neural processing of the non-social odor (raspberry) by regressing CTQ sum scores on the BOLD signal response to the contrasts [($Raspberry_{(PLC)}$)] and [($Raspberry_{(PLC)}$ > ($Raspberry_{(OXT)}$)]. The fMRI analysis focused on a set of *a priori* defined bilateral regions of interest (ROIs) consisting of the amygdala, hippocampus, ACC, FFA, lateral OFC (lOFC) and medial OFC (mOFC). All ROIs were anatomically defined according to the Wake Forest University PickAtlas, version 3.0. *P*-values were corrected for multiple comparisons (family-wise error (FWE)) based on the size of the ROI, and $P < 0.05$ was considered significant. Parameter estimates were extracted from significant clusters of the BOLD response analysis (for full description, see **SI**).

Connectivity Analysis

To explore the modulatory effects of CM on the functional interplay of brain regions showing significant CM-associated changes in neural responsiveness to chemosensory stress cues in the BOLD analysis, we regressed CTQ sum scores on the FC between these regions and the *a priori* defined ROIs (amygdala, hippocampus, ACC, FFA, lOFC and mOFC). For this purpose, we carried out a generalized psychophysiological interaction [gPPI; (69)] in SPM12. Seed regions were identified as significant clusters of the BOLD analysis. All target ROIs were anatomically defined using the Wake Forest University PickAtlas, version 3.0. On the first level, hemodynamic deconvolution was performed on the extracted time series to remove the effects of the canonical hemodynamic response (HRF). The resulting time series were multiplied by the psychological variables and reconvolved with the HRF to obtain the PPI interaction terms. The gPPI analysis for each subject was performed on the first level and included the same task regressors as specified for the BOLD analysis. On the second level, we regressed CTQ sum scores on the FC between seed and target regions for the contrasts [$Stress_{(PLC)}$ > $Sport_{(PLC)}$] and [($Stress_{(PLC)}$ > $Sport_{(PLC)}$) – ($Stress_{(OXT)}$ > $Sport_{(OXT)}$)]. Results were considered significant at $P_{FWE} < 0.05$ (peak-level inference) adjusted to the size of the ROIs. Given that FC is susceptible to small frame-to-frame head movements, we calculated the mean frame-wise displacement (FD) (70) for each subject in each session. The FD has been shown to have a strong association with motion-induced artifacts in functional connectivity (71). Results revealed that all subjects exhibited FDs below the recommended threshold for task-based FC of 0.9 mm (72) during scanning in both testing sessions, respectively.

Statistical Analysis

Statistical analyses were conducted with SPSS, version 24 (IBM, Armonk, N.Y.). Linear regression analyses were performed to estimate the effect of CM on emotion recognition during axillary sweat presentation. For these regression models, CTQ sum scores were used as the predictor variable and the differences in fearful recognition ratings of the emotional facial stimuli (range: 0 faces rated as fearful - 12 faces rated as fearful) between the stress and the sport condition for each emotion intensity level (neutral, low fearful, medium fearful, and high fearful) served as the criterion variables, respectively. The resulting four regression analyses were performed for the PLC condition and the modulating effects of OXT (OXT < PLC). For the regression models testing the effect of CM on emotion recognition during the presentation of the non-social control odor raspberry, CTQ sum scores served as the predictor variable and fearful recognition ratings for each emotion intensity level functioned as the criterion variables, respectively. These four regression analysis were computed for the PLC condition and the modulating effects of OXT (OXT > PLC). Furthermore, we tested multiple regression models predicting CM-related behavioral (emotion recognition rating) and neural responses (extracted parameter estimates) by the five CTQ subscales in order to explore maltreatment-specific predictions in the current sample. Pearson's product-moment was used for correlation analyses. Reported *P*-values are one-tailed for directional analyses and two-tailed for all non-directional analyses.

Mediation and Moderation Analysis

To control for the influence of possible confounding variables on our observed CTQ-associated response pattern, moderation, and mediation effects were assessed for the covariates subjective anxiety, depressive symptoms, autistic-like traits, age, sex and education time using the PROCESS macro for SPSS, version 3.1 (model 1 and model 4) (73). For all regression analyses, CTQ sum scores served as the predictor variable, respectively. CTQ-associated differences in fearful recognition ratings of the emotional facial stimuli between the stress and the sport condition and parameter estimates extracted from significant clusters of the BOLD analysis to the contrasts [($Stress_{(PLC)}$ > $Sport_{(PLC)}$)] and [($Stress_{(PLC)}$ > $Sport_{(PLC)}$) – ($Stress_{(OXT)}$ > $Sport_{(OXT)}$)] served as the criterion variables, respectively. Using heteroscedasticity-consistent standard errors and mean-centering, the significance of indirect effects was examined using 95% bootstrapped (10,000 bootstrap samples) symmetric confidence intervals (95% CIs). Indirect effects were considered significant when the upper and lower bound of 95% CI did not contain zero. As the underlying mediation framework of PROCESS does not support dichotomous mediators, we explored a potential mediation effect of sex by employing the Baron and Kenny four steps regression approach (74). A moderation effect was assumed when the interaction term between the predictor variable CTQ and a moderation variable was significant. For these analyses the level of statistical significance was set at $P < 0.05$ and all reported *P*-values are two-tailed.

RESULTS

Behavioral Results

Regression analyses revealed that CTQ sum scores were associated with an increased stress-specific recognition of high fearful faces under PLC, ($\beta = 0.29$, $P = 0.015$), with 8% of the

variation explained by the model (R^2 = 0.08, $F_{(1,57)}$ = 5.03, P = 0.015) (cf. **Figure 1**; for further detail, view **SI and Figure S1**). After Bonferroni-correction, we observed a trend toward significance for this association (P = 0.06). Salivary oxytocin levels were significantly increased after intranasal OXT administration relative to intranasal PLC administration, which we reported in (27). However, CTQ sum scores did not predict the modulatory effect of OXT on stress-specific fearful recognition ratings across all four emotion intensity levels (all Ps > 0.05; for more detail, view **SI**). Moreover, CTQ sum scores did not predict fearful recognition ratings for all emotion intensities during trials in which subjects were exposed to the non-social control odor raspberry under PLC (all Ps > 0.05; for more detail, see **SI**).

Correlation analyses did not yield significant associations between CTQ sum scores and post fMRI pleasantness, intensity, and familiarity ratings of either social or non-social odor stimuli (all Ps ≥ 0.05; for further detail, view **SI**). Thus, CM did not influence the perception of odor quality.

fMRI Results

Regression analyses yielded a positive association of CTQ sum scores and stress-specific right amygdala hyperreactivity (peak MNI coordinates x, y, z: 26, −6, −12; $t_{(48)}$ = 3.51, P_{FWE} = 0.015) (cf. **Figure 2A**) and a negative association of CTQ sum scores and stress-specific left hippocampal hyporeactivity (−30, −40, 0; $t_{(48)}$ = 3.96, P_{FWE} = 0.017) (cf. **Figure 2B**) under PLC (for further detail, view **Figure S2**). Furthermore, CTQ scores were positively associated with the stress-specific effect of OXT in the right amygdala (24, −6, −14; $t_{(48)}$ = 3.41, P_{FWE} = 0.038) (cf. **Figure 3**). Stress-associated increases in amygdala reactivity suggest CM may induce hypervigilance to chemosensory threat cues in the present sample. Moreover, stress-specific attenuating effects of OXT in the amygdala appear to be more pronounced in participants with increasing levels of CM exposure.

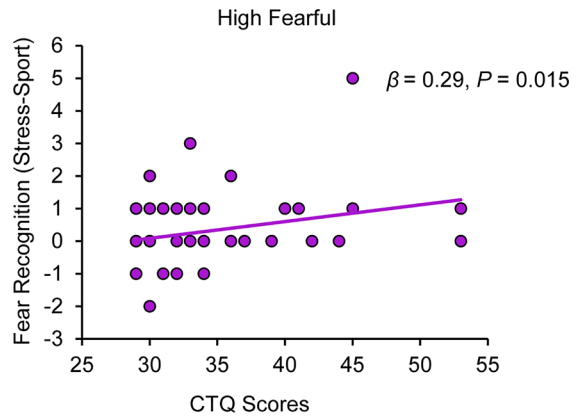

FIGURE 1 | Childhood maltreatment and the impact of chemosensory stress signals on fear recognition. Childhood Trauma Questionnaire (CTQ) scores are positively associated with a stress odor induced bias in the recognition of high fearful faces (range: 0 faces rated as fearful - 12 faces rated as fearful). CTQ, Childhood Trauma Questionnaire.

Connectivity Results

For the right amygdala seed region (26, −6, −12), the gPPI analysis revealed a stress-specific positive association of CTQ scores and functional coupling with the left mOFC (peak MNI coordinates x, y, z: −6, 40, −14; $t_{(48)}$ =4.09, P_{FWE} = 0.019, ACC (−10, 36, −8; $t_{(48)}$ = 4.08, P_{FWE} = 0.039) and hippocampus (−32, −24, −10; $t_{(48)}$ =3.87, P_{FWE} =0.046) under PLC (cf. **Figure 4**). Furthermore, we observed a positive association of CTQ scores with OXT effects for the functional coupling between the right amygdala seed region (26, −6, −12) and the left mOFC (−2, 28, −12; $t_{(48)}$ = 4.41, P_{FWE} = 0.008) in the stress relative to the sport condition. There were no CTQ-associated changes in FC for the hippocampus as a seed region. The CTQ-associated increase in FC may reflect an inefficient top-down regulation of the amygdala *via* the ACC and the mOFC. Administration of intranasal OXT appear to reinstate the frontolimbic regulatory mechanism.

Mediation and Moderation Effects

We did not detect significant mediation or moderation effects for any covariate. All 95% confidence intervals of indirect effects overlapped with zero and all interaction terms between CM and moderation variables were non-significant (all Ps > 0.05). Thus, the observed modulatory effect of CM on the behavioral and neural levels were not significantly moderated or mediated by sociodemographic factors, depression or anxiety levels.

Effect of Maltreatment Type

Multiple regression analyses with the five CTQ subscales as predictors revealed an association of emotional neglect (β = −0.36, P = 0.04) and emotional abuse (β = 0.54, P = 0.004) with the chemosensory induced bias in the recognition of high fearful faces under PLC (β = 0.31, P = 0.016). Stress-specific amygdala hyperreactivity was associated with emotional neglect (β = 0.53 P = 0.002) and physical neglect (β = 0.29, P = 0.022). Entering all five subscales into the model did not reveal an association of hippocampal hypoactivation with a specific subscale (all Ps > 0.05). Stress-specific FC between the amygdala and the hippocampus was associated with emotional abuse (β = 0.43, P = 0.019). Multiple regression analysis revealed no association of amygdala-ACC FC with a specific CM subscale. Stress-specific FC between the amygdala and the mOFC was associated with sexual abuse (β = 0.29, P = 0.043). We observed no significant association between the stress-reducing effects of OXT and specific CM subtypes. Correlation analysis revealed that the subscale emotional neglect highly correlated with the subscale emotional abuse (r = 0.64, P < 0.001) and moderately correlated with physical neglect (r = 0.3, P = 0.023).

DISCUSSION

In the present study, we primarily examined the modulatory impact of CM on the processing of chemosensory threat signals in axillary sweat. Given the long-term consequences of CM on the oxytocinergic system, our secondary aim was to investigate

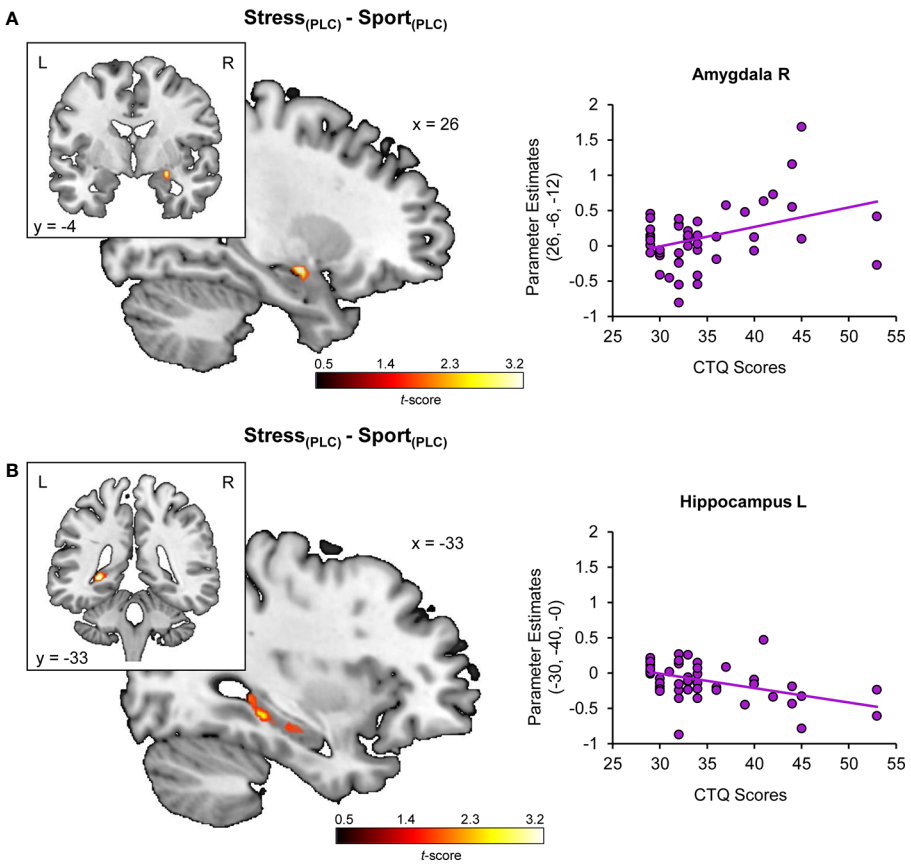

FIGURE 2 | Childhood maltreatment and the impact of chemosensory stress signals on **(A)** amygdala and **(B)** hippocampus reactivity. Childhood Trauma Questionnaire (CTQ) scores are associated with a stress-specific amygdala hyperreactivity and hippocampal deactivation. CTQ, Childhood Trauma Questionnaire; PLC, placebo; L, left hemisphere; R, right hemisphere.

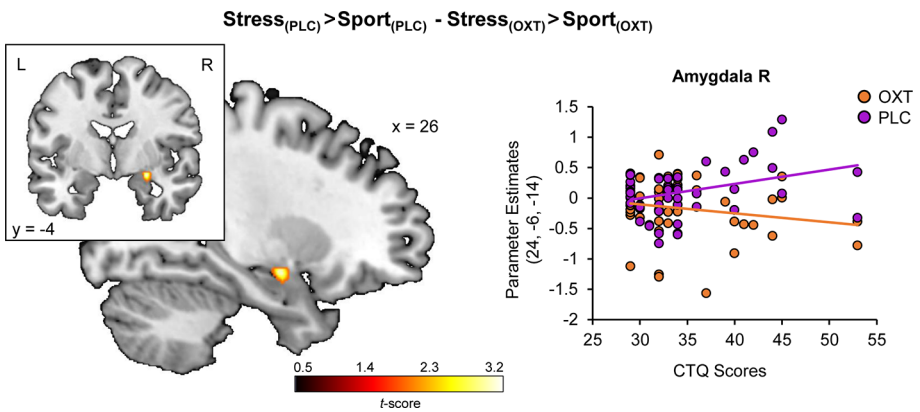

FIGURE 3 | Childhood maltreatment and the modulatory effect of oxytocin on stress-specific amygdala reactivity. Childhood Trauma Questionnaire (CTQ) scores are associated with a stress-specific dampening effect of oxytocin in the amygdala. OXT, oxytocin; PLC, placebo; L, left hemisphere; R, right hemisphere.

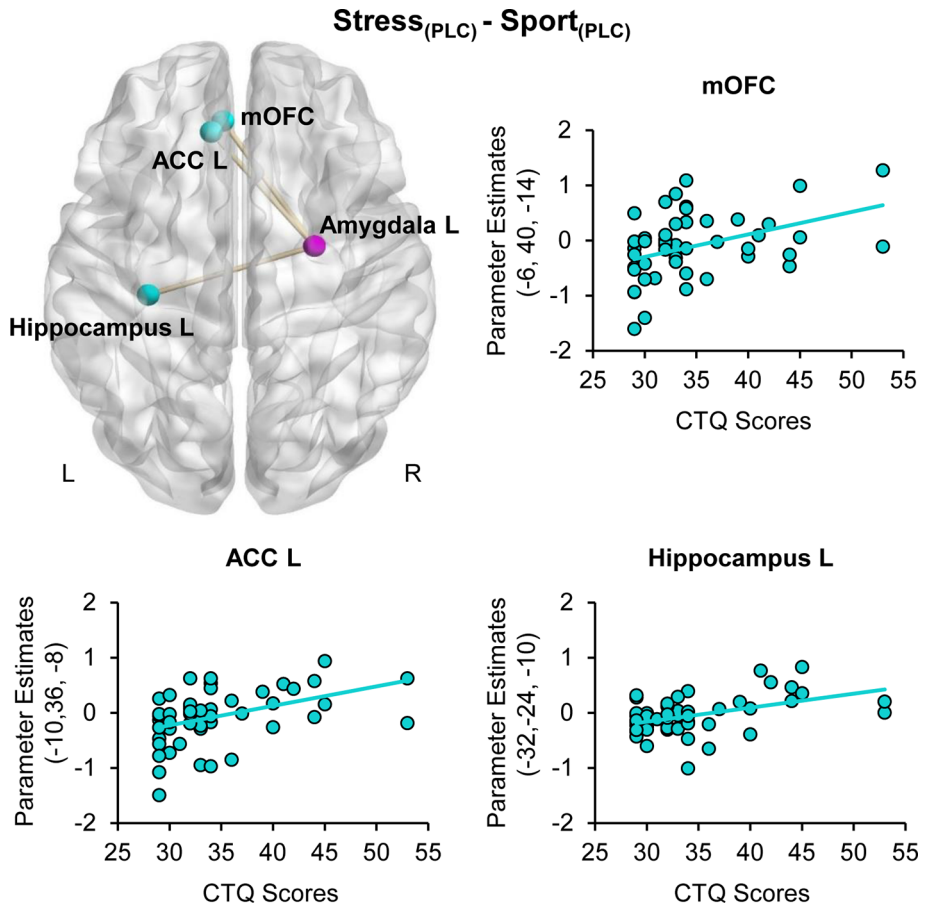

FIGURE 4 | Childhood maltreatment and stress-specific functional connectivity. Childhood Trauma Questionnaire (CTQ) CTQ scores were associated with a heightened functional connectivity between the amygdala (purple sphere) and the medial orbitofrontal cortex (mOFC), the anterior cingulate cortex (ACC) and the hippocampus (blue spheres) when subjects were exposed to stress sweat. ACC, anterior cingulate cortex; CTQ, Childhood Trauma Questionnaire; mOFC, medial orbitofrontal cortex; PLC, placebo; L, left hemisphere; R, right hemisphere.

whether CM affects the stress-attenuating effects of OXT in this context. As expected, a secondary analysis of our recent study (27) revealed a modulating role for CM in the olfactory domain of social threat communication. CM was associated with increased amygdala reactivity, decreased hippocampal activation and increased FC between the amygdala and the hippocampus, ACC and mOFC during exposure to threat-associated olfactory signals. This neural response pattern was paralleled by a threat-related increase in the recognition of high fearful faces. Furthermore, in line with our second hypothesis, we found that CM moderated the effects of OXT on threat-related processing of these olfactory signals. The observed response pattern was not moderated or mediated by sociodemographic factors, current depression or trait anxiety levels. Here, we extend previous evidence of a phenotypic hypervigilance in adults with a history of CM (4) to the olfactory domain, highlighting an underexplored vulnerability pathway to psychopathology in those affected.

Our finding of CM-associated amygdala hyperreactivity to social olfactory threat cues is directly in line with frequently reported elevated amygdala responses to threatening faces in individuals with a history of CM (7–9). Moreover, converging evidence demonstrates changes in frontolimbic FC following CM both at rest (75) and during emotional face processing tasks (10, 11, 59). While this response pattern may reflect a mechanism mediating resilience when measured at rest, increased task-based FC between the amygdala, the ACC and the OFC has been linked to an inefficient regulatory system in adults following CM (56). It is well established that the amygdala, hippocampus, ACC, and PFC are central to efficient threat and fear regulation (76, 77). Both the ACC and the mOFC exert top-down control on limbic and endocrine systems through mechanisms such as attentional control and contextual processing (16–18, 77). Our findings suggest that threat-associated amygdala activation prompted individuals with a history of CM to up-regulate activations of cognitive control regions. In healthy adults, increased FC between the amygdala and the OFC as well as the ACC was associated with threat-induced anxiety (78) and in trauma-exposed adolescents increased amygdala-ACC connectivity was paralleled by a reduced ability to regulate emotional conflict (79). In the current sample,

elevated amygdala reactivity and concomitantly increased frontolimbic FC might reflect hypervigilance to the threatening properties of the olfactory signals used in the fMRI paradigm. Further, our data support the notion that CM is associated with long-term downstream perturbations of frontolimbic emotion circuits (1, 4). Previous data show hippocampal hypoactivation both following psychosocial stress induction (80) and in response to masked fearful faces (81) in individuals with a history of CM. By contrast, other studies found increased activation of the hippocampus in response to threatening faces (82, 83). These conflicting findings may arise from variations in the operationalization of CM, time between trauma exposure and data collection and psychiatric comorbidities. However, accumulating evidence suggests CM-related hippocampal deactivation in response to emotional faces may represent a mechanism of resilience (57). The hippocampus and the amygdala are highly susceptible to adaptions following early life stress (4) and subtle interactions between these structures are central for forming representations of emotional significance and contextually modulating physiological threat responses (77, 84). Furthermore, amygdala-hippocampal FC is crucially involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) (85) axis and has been shown to predict the capacity of the HPA axis to restore homeostasis of the stress response after perturbations (86). Along this line, there is evidence showing that upon induction of psychosocial stress, deactivation of the hippocampus plays an essential role in initiating a stress response (87). Notably, recent evidence demonstrates that CM-related differences in amygdala-hippocampus FC in response to threatening facial stimuli are linked to adult adaptive functioning (59). Thus, we propose that enhanced recruitment of the amygdala-hippocampus complex during exposure to social olfactory threat cues might reflect a compensatory mechanism for inefficient frontolimbic circuitry in individuals with a history of CM. Resilient individuals with a history of CM may exhibit an enhanced capacity for contextualizing social olfactory threat signals due to an amygdala-dependent increased presentation of these cues in the hippocampus (77). Enhanced encoding of these signals may allow resilient individuals with a history of CM to adaptively refine physiological stress responses in a safe context.

In the current sample, CM-related neural responses to social olfactory threat signals were paralleled by increased recognition of fearful faces. This shows that the cross-modal sensory integration of visual and olfactory threat cues is modulated by a history of CM. Previous findings revealed that effective olfactory-visual emotion integration results in biased detection of fear that is accompanied by enhanced amygdala responsiveness and increased functional connectivity between the amygdala and the OFC (88). Moreover, the ACC and the OFC have been suggested to be part of a network that initiates increased sensory responses during cross-modal sensory integration of fear (89). Thus, given their hypervigilant sensory profile, individuals with a history of CM may exhibit increased evaluation of social olfactory threat cues that leads to biased emotion detection. (7). Enhanced cross-modal fear detection during the exposure of social olfactory threats may represent an adaptive mechanism, by which individuals accentuate their automatic response in a threatening environment (4).

Burgeoning evidence implicates the oxytocinergic system in CM (1). Mechanistically, a stronger effect of OXT on threat-specific amygdala activation in individuals with a history of CM appears to be rooted in a reinstated top-down regulatory function of the mOFC over the amygdala, thereby emulating a more normative response to social olfactory threat cues in individuals with a history of CM (16–19, 76). Evidence corroborating this interpretation comes from studies demonstrating that OXT reduces threat hypersensitivity in women with Borderline Personality Disorder (90, 91) which is frequently associated with CM. Likewise, OXT enhanced the stress-buffering effects of social support in women with more severe CM exposure (51). The oxytocinergic system is highly sensitive to the adverse effects of CM, with most studies reporting decreased levels of peripheral and central OXT in a dose-dependent manner following CM exposure (44–46). These findings could reflect a downregulation of the OXT system and increased OXT sensitivity in individuals with higher levels of CM exposure. However, previous studies also reported diminished stress-attenuating (92) or prosocial (93) effects of OXT in individuals who have experienced CM. Thus, the moderating role of CM on OXT effects is also evident in the olfactory domain, but the direction of this moderation seems to vary depending on baseline differences and sample characteristics.

The stress-specific chemosensory effects were predominantly associated with emotional and physical neglect as well as emotional abuse subscales. However, given the high intercorrelation of the subscales, these results need to be interpreted carefully. Importantly, our moderation and median analyses revealed that CM-associated symptoms, such as depression and anxiety, did not significantly influence the observed pattern of results. Furthermore, recent findings of CM-related structural and functional alterations (37) as well as aberrant responses to non-social olfactory threat cues (94) corroborate the notion of an etiological olfactory pathway to psychopathology in individuals with a history of CM. Consistent with this idea, enhanced amygdala reactivity to threatening facial stimuli has been found to mediate the link between CM and the development of adult anxiety disorders and PTSD (14, 15). Thus, future work is warranted to examine whether the observed alterations of the social olfactory pathway precipitate a latent vulnerability to later psychopathology in the context of CM.

There are a number of limitations in this study that need to be addressed in future research. First, the retrospective and self-report assessment of CM may be subject to misreporting of CM. While we did thoroughly control for current anxiety and depression levels, which may provoke a negative recall bias (95), we cannot exclude that a recall-related underreporting of CM in the present healthy sample may have influenced our results (96). Second, we were not able to ascertain whether the observed alterations in olfactory processing were associated with specific types of maltreatment due to the interrelatedness of CM types in the present sample. Given that various forms of CM frequently co-occur (2), future studies employing a longitudinal design are needed to probe the associations between specific forms of CM, neural responses to olfactory threat cues, and psychopathology. Third, while the study

used a well-controlled healthy sample, subjects of the study exhibited mild CM, limiting the interpretation of the findings to the context of less severe forms of CM. However, given the robust finding of dose-dependent effects of CM, we speculate that a neural threat response to olfactory signals may also be observed in individuals with a history of severe CM exposure. Fourth, here we report that CM is associated with altered responses to social olfactory stress cues compared to sport-related social olfactory cues. However, in contrast to the difference scores, we did not observe a significant association between CM and parameter estimates of the amygdala and hippocampus responses to stress and sport odor cues compared to baseline (cf. SI). Thus, it is conceivable that a differential response to sport odor cues contributed to the observed CM-associated changes. Future studies should include additional non-stress-related social control conditions in their design to further investigate the specificity of stress-related responses in subjects with a history of CM. Finally, while the fMRI analysis did not include a correction for small frame-to-frame head movements, an additional control analysis demonstrated that subjects in the present sample exhibited no critical head movements during scanning.

In conclusion, we extend prior findings of a phenotypic hypervigilance to social threat signals in individuals with a history of CM to the domain of social olfactory signals. We propose that CM disrupts the neural circuitry of threat detection by weakening top-down regulatory systems. Increased intralimbic connectivity may reflect an effective compensatory mechanism in resilient individuals. Furthermore, CM moderates the effects of OXT on the processing of chemosensory stress signals. The current study highlights a potential vulnerability pathway in individuals with a history of CM that needs to be addressed in future work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission an der medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM and DS designed the experiments. AM and LH-L conducted the experiments. AM, LH-L, and DS analyzed the data. All authors wrote the manuscript. All authors contributed to the article 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/fpsyt.2020.00783/full#supplementary-material

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Intrinsic Functional and Structural Brain Connectivity in Humans Predicts Individual Social Comparison Orientation

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Social comparison orientation (SCO), the tendency to compare oneself with others, is universal, varies widely across individuals, and predicts important life and health outcomes. However, the neural mechanism underlying individual differences in SCO is still not well-understood. In the present study, we identified intrinsic neural markers of SCO in healthy young adults (n = 42) using a multimodal neuroimaging approach that included diffusion tensor imaging and resting-state functional MRI data. We found that higher SCO was associated with weaker structural and functional connectivity (SC, FC) strengths between the ventral striatum and the medial prefrontal cortex, which are core regions of the brain reward network. Additionally, individual SCO was negatively associated with neural fluctuations in the intraparietal sulcus (IPS), part of the frontoparietal network, and positively with FC between the IPS and anterior insula/amygdala cluster. This finding was further confirmed by the observation of independently-defined, large-scale, inter-network FC between the frontoparietal network and cingulo-opercular network. Taken together, these results provide novel evidence for intrinsic functional and structural connectivity of the human brain associated with individual differences in SCO.

Keywords: diffusion tensor imaging, functional connectivity, resting-state fMRI, social comparison orientation, structural connectivity

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INTRODUCTION

Social comparison—comparing one's own opinions and abilities with those of others—is a constant and ubiquitous experience that occurs throughout life. People use social comparison to evaluate or groom their social reputation and relationships (1, 2). However, individuals vary in their tendency to engage in social comparison, and a person's tendency to compare oneself with others is referred to as social comparison orientation (SCO). This can be measured using the Iowa-Netherlands Comparison Orientation Measure (INCOM) (3). Understanding individual differences in SCO is important, because higher SCO is associated with a variety of real-life behaviors and outcomes, including several psychological dimensions such as poorer self-perception and lower self-esteem (4), lower job satisfaction (5), more altruistic/helping behavior to unfamiliar others (6), and an increased

susceptibility to mental illness such as depression (7). Despite its importance, the neural markers that may underlie individual differences in SCO have been only sparsely investigated.

Over the past decade, researchers have observed links between social comparison and reward processing at both the psychological and neurological levels. For example, social comparison is associated with increased activity in the ventral striatum (VS) and medial prefrontal cortex (MPFC) (8–12), both of which are considered core regions of the brain reward system (13–15). More recent studies have reported that functional communication between the VS and MPFC is critically involved in social comparison and may underlie individual differences in SCO (16, 17).

Besides the reward-related neural network, several other neural structures may be involved in general comparison in both social and non-social domains (12, 18). These regions include the intraparietal sulcus (IPS), anterior insula (aINS), and anterior cingulate cortex (ACC). The IPS is known to play a role in encoding numerical quantities and the activity of the region can be modulated by the distance between two magnitudes (i.e., comparison of numbers, size, luminance, or height) (19–21). The activity of the aINS and ACC increases when people compare themselves to better-off others, and it is stronger for self-other than for familiar-other comparisons (22, 23). However, it is not yet clear whether structural and functional features of these areas at rest are linked to individual variability in SCO.

Recently, several studies have used task-independent neural measures to predict specific behaviors. These measures are more likely to be of practical use, because they are likely less tied to a specific context and are therefore relatively stable over time (24, 25). However, to our knowledge, no neuroimaging studies have yet investigated task-independent neural markers of individual differences in SCO. In the present study, we thus examined neural predictors of individual differences in SCO using a multimodal, task-independent neuroimaging approach, including diffusion tensor imaging (DTI), and resting-state functional magnetic resonance imaging (RS-fMRI), that focused on individual variations in the brain's intrinsic structural and functional network architecture. Because the reward network plays a central role in social comparison, we first aimed to identify potential associations between individuals' SCO scores and the strength of structural connectivity (SC) and resting-state functional connectivity (FC) between the VS and the MPFC, which are the central components of the reward network (i.e., intra-network connectivity within the reward network). For exploratory purposes to test whether SCO is associated with other areas and networks outside the reward network, we next performed the following additional analyses at the whole-brain voxel level using data-driven approach examining RS-fMRI and DTI data. In other words, to identify neural signatures of SCO at the whole-brain voxel level, we searched for brain areas associated with individual SCO in terms of local features (e.g., local connectivity and local fluctuation) in neural activity and in SC. This analysis highlighted the IPS, the neural structure previously linked to aspects of general comparison. To further characterize this association, we searched for neural regions whose FC strength with the IPS is associated with SCO, by using seed-based FC analysis, and found a significant association between the IPS–aINS/amygdala FC strength and SCO. Given that core areas of the frontoparietal network (FPN) and of the cingulo-opercular network (CON) include the IPS and aINS (26, 27) respectively, we investigated whether individual SCO scores are associated with the inter-network FC between these two large-scale functional networks. Finally, linear regression analyses with identified neural variables showed that each of the identified features, particularly that from the RS-fMRI data, uniquely explains the variance in SCO. These results provide a set of unique multi-modal intrinsic neural markers associated with individual differences in SCO.

MATERIALS AND METHODS

Participants

A total of 47 participants were recruited from Korea University and the surrounding community. From each participant, we collected high-resolution T1-weighted anatomical MRI, RS-fMRI, DTI, and fMRI during an incentive delay task in the context of social comparison. In this study, we focused on task-independent measures of brain function and structure (i.e., RS-fMRI and DTI data) to examine the link between individual variations in SCO and individual differences in intrinsic functional and structural brain features. Among all, 43 had both DTI and RS-fMRI data available, and four participants were lost due to technical problems. One additional participant was excluded due to excessive head motion during RS-fMRI—that is, > 2.5 mm of translation or 2.5° of rotation and > 0.24 mm mean frame-wise displacement (FD; > 2 standard deviations from the group mean) (28). Ultimately, the data of 42 participants [27 women, 15 men, age (mean ± SD): 22.29 ± 3.04 years, all right-handed, SCO: 3.79 ± 0.58] were used in the final analyses. We confirmed that the final sample size was rational to obtain scientifically meaningful results, based on a power analysis performed before data analysis using G*Power software (29). Assuming an effect size of 0.5, an alpha level of 0.05, and a power of 0.90 to ensure correlation with the bivariate normal model, the G*Power analysis resulted in a required sample size of 37. All study procedures were approved by the Institutional Review Board of Korea University, and all participants provided written informed consent.

Measuring Social Comparison Orientation

The degree of SCO for each participant was assessed using the Iowa-Netherlands Comparison Orientation Measure scale (INCOM) (2, 3), which is a widely used scale to test an individual's SCO. It consists of 11 items, each scored using a 5-point Likert scale (1 = I disagree strongly, 5 = I agree strongly). The INCOM measures an individual's tendency toward social comparison (e.g., "I often compare myself with others with respect to what I have accomplished in life"). All participants

filled out the debriefing questionnaires, including the INCOM, scale before completing the scans.

Image Acquisition

All images were scanned using a 3-T scanner (Siemens Magnetom Trio; Erlangen, Germany). High-resolution, T1-weighted anatomical images were acquired using a 3D magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) sequence [repetition time (TR) = 1,900 ms, echo time (TE) = 2.52 ms, flip angle (FA) = 9°, voxel size = 1.0 × 1.0 × 1.0 mm, 192 sagittal slices]. Next, functional images were obtained using T2*-weighted, echo-planar imaging (EPI; TR = 2,000 ms, TE = 20 ms, FA = 90°, voxel size = 3.0 × 3.0 × 3.0 mm, 42 interleaved axial slices, and 155 volumes). During RS-fMRI, participants were instructed to keep their eyes open and maintain fixation. An eye-tracker mounted on a head coil was used to monitor the participants' eyes and ensure they did not fall asleep during the scan. Finally, DTI data were acquired with a 32-channel head coil using a single-shot, multiband EPI sequence (TR = 3,000 ms, TE = 70 ms, FA = 90°, multiband acceleration factor = 3, phase partial Fourier = 6/8, voxel size = 2.0 × 2.0 × 2.0 mm, 75 interleaved axial slices, and 64 diffusion directions with b-values of 1,000 s/mm^2 and 8 images with b-values of 0 s/mm^2).

Structural Connectivity Analysis Within the Reward Network

DTI data were preprocessed using PANDA v1.3.1 (30) (https://www.nitrc.org/projects/panda/): a pipeline tool for diffusion MRI that uses the processing functions of established packages, including FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and the Diffusion Toolkit (https://www.nitrc.org/projects/trackvis/). Briefly, a brain mask was made using the b0 images. Diffusion images were registered to the average of the b0 images using an affine transformation to correct for eddy current-induced distortions and simple head-motion. Whole-brain fiber tracking was performed using the fiber assignment by continuous tracking (FACT) algorithm (31), with the fractional anisotropy threshold set at 0.20 and the tracking turning angular threshold set at 45°. Afterwards, spline filtering was applied to smooth the streamline tractography. To quantify the degree of connection between the left VS and MPFC, as well as between the right VS and MPFC in the native space, we first identified these three regions-of-interest (ROIs) based on a previous meta-analysis involving the valuation system in the human brain (**Figure 1A**) (32). Next, these ROIs were transformed from the Montreal Neurological Institute (MNI) space to each subject's native space. The number and average length of the fibers connecting each pair of ROIs were then calculated (**Figure 1B**). To normalize the fiber number, we divided it by the average volume and length of the two connecting regions. This counteracted bias where it was larger; closer brain regions inherently project/receive more fibers. Because the values were non-normally distributed, they were log-transformed before subsequent statistical analysis. We performed partial correlation, with age and sex as covariates, between SCO scores and normalized fiber numbers.

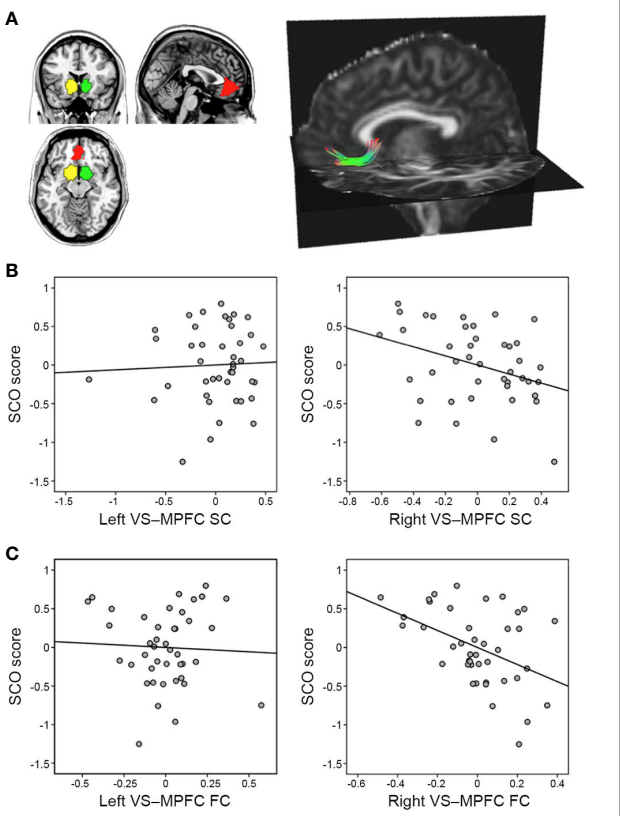

FIGURE 1 | Associations between social comparison orientation (SCO) and the reward network. **(A)** The right panel shows three regions of interest—the left ventral striatum (VS; yellow), the right VS (green), and the medial prefrontal cortex (MPFC; red). The left panel displays a single subject's tracking map between the right VS and the MPFC, identified using tractography analysis (for illustration purposes only). **(B)** Partial correlation scatterplot between SCO score and normalized fiber number, displayed as the strength of structural connectivity between the VS and MPFC. **(C)** Partial correlation scatterplot between SCO score and VS–MPFC functional connectivity strength (z-transformed). For illustration purposes, **(B, C)** were generated using Pearson's correlation analysis between residuals after age and sex were regressed out.

Functional Connectivity Analysis Within the Reward Network

In the case of RS-fMRI data, the first five volumes were discarded to avoid instability in the initial data signal. Preprocessing steps, which included slice-acquisition timing, motion correction, nuisance signal regression, and spatial normalization, were performed using SPM12 (www.fil.ion.ucl.ac.uk/spm) and DPARSFA toolbox (33) (www.rfmri.org/DPARSF). To remove the effects of head motion and non-neuronal fluctuations on signals, as in recent studies (34), the following nuisance parameters were included as regressors within the general linear model: Friston 24-motion parameters, five principal components estimated from both the white matter and cerebrospinal fluid regions using a component-based noise correction method (35), mean global signal, head motion scrubbing regressors one volume before and two volumes after the

bad time point (root mean square volume-to-volume displacement > 0.25) (36), and two polynomial trends (linear trend and quadratic trend). The spatially normalized residual images were smoothed using a 6-mm Gaussian kernel and band-pass filtering (0.01–0.1 Hz). The Pearson correlation coefficients were then computed between the mean time series of an ROI pair (i.e., MPFC, left VS, and right VS) as the strength of FC. The correlations were then converted to z-values using Fisher r-to-z transformation. We also performed partial correlation (covariates: age, sex, and motion indexed by mean FD) between SCO scores and z-transformed FC values, with the following co-variates.

Exploratory Voxel-Level Whole-Brain Analysis

To ensure the study was complete and identify the brain areas or networks, mentioned in the *Introduction*, that are associated with individual SCO, we performed multiple regression analysis on data-driven structural and functional brain maps generated from DTI and RS-fMRI data together with SCO scores. Specifically, for voxel-level whole-brain DTI analysis, preprocessed DTI images were used to estimate four DTI metrics in the DTIFIT function of FSL: fractional anisotropy (FA), which measures the directionality of water diffusion, axial diffusivity (AD), which measures diffusion parallel to the white matter tract, radial diffusivity (RD), which measures diffusion perpendicular to the tract, and mean diffusivity (MD), which measures the diffusion speed of water molecules. The MD was estimated as the mean of all three eigenvalues [(λ1+ λ2+ λ3)/3], RD as the mean of the second and third eigenvalues [(λ2+ λ3)/2], and AD as the principal eigenvalue (λ1). To estimate the voxel-wise values of the DTI metrics of each subject's skeleton, we performed tract-based spatial statistics (TBSS) (37). All the subjects' FA images were aligned into the MNI standard space using the non-linear registration tool FNIRT. Next, a mean FA image was created and skeletonized/thinned to produce an image representing the center of all tracts common to the group (threshold = 0.2) (**Figure S1**). Each subject's aligned data (including FA, AD, RD, and MD) were then projected onto this skeleton. Finally, for the FA, AD, RD, and MD maps, we performed permutation-based statistics (using FSL's randomize with 5,000 permutations) to determine the areas in which DTI metrics were associated with SCO. Age and sex were included as covariates. Threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons (corrected $p < 0.05$).

For voxel-wise, whole-brain RS-fMRI analysis, the following local FC maps were generated with a default setting of DPARSFA: i) regional homogeneity (ReHo)—a measure of localized intraregional connectivity (38), ii) DC—a measure of local network connectivity (39, 40), and iii) fractional amplitude of low-frequency fluctuations (fALFF)—a measure of the relative contribution of specific local frequency fluctuations in neural activity to the whole frequency range (41). The ReHo maps were created using the Kendall coefficient of concordance of each voxel's time series with those of its 26 neighboring voxels (38). The DC maps were obtained by summing of the weights of the significant connections ($r > 0.25$) (39, 40) for each voxel. For each of these three RS-fMRI maps, we implemented multiple regression analysis in SPM to identify areas in which the values of each map were associated with SCO, controlling for age, sex, and mean FD as covariates.

Using the IPS cluster that had significant fALFF activity in the whole-brain RS-fMRI analysis, we generated and analyzed seed-based FC maps that were seeded using IPS. The maps were regressed against SCO scores to identify regions that were functionally coupled with IPS as a function of individual SCO differences. All results were corrected for multiple comparisons to a significance level of $p < 0.05$ [uncorrected height threshold of $p < 0.001$ combined with a family-wise error (FWE)-corrected extent threshold of $p < 0.05$].

Mediation Analysis With the Neural Features From the Exploratory Whole-Brain Analyses

To further examine the relationship between SCO and the above IPS findings (i.e., IPS fALFF and IPS–aINS/amygdala seed-based FC), we tested whether the direct effect of the IPS fALFF strength (X) on SCO (Y) could be explained in terms of the indirect influence of IPS–aINS/amygdala FC strength (M) as a mediator. To this end, we used the M3 Mediation Toolbox (https://github.com/canlab/MediationToolbox). Age, sex, and mean FD were included as covariates. Bootstrapping with 10,000 resamples was used for statistical inference in each path ($p < 0.05$).

Inter-Network Connectivity Between the Frontoparietal and Cingulo-Opercular Networks

Based on the results of the multiple regression analysis with the above seed-based FC maps, we hypothesized that SCO is associated with functional interactions between two largely independent neural networks: the FPN and the CON, also often referred to as the salience network, because the IPS and aINS/amygdala clusters reported above are the core regions of these two networks, respectively (26, 27). To validate this hypothesis, we evaluated the data within a network framework. Specifically, the nodes of each network (25 nodes in the FPN and 14 nodes in the CON) consisted of 6-mm radius spheres centered on the coordinates taken from the corresponding networks in the Power-264 atlas, as defined in terms of the task-based fMRI and resting-state FC techniques (28). Next, to estimate inter-network FC, we extracted the mean time series from each of the nodes, computed the average connectivity across all node-to-node connections between the two networks using Pearson's correlation, and converted the correlations into z-values using Fisher r-to-z transformation. For exploratory purposes, we also computed the average connectivity across node pairs within the same network, defining this as intra-network FC. We then performed partial correlation (covariates: age, sex, and mean FD) between SCO scores and z-transformed FC strengths.

Testing the Effectiveness of Neural Predictors of Social Comparison Orientation

Finally, we examined whether the neural features found in this study (i.e., right VS–MPFC SC, right VS–MPFC FC, fALFF in the IPS, IPS–aINS/amygdala FC, and inter-network FC between FPN and CON) explain independent or overlapping variance in SCO. This was done by performing a multiple linear regression analysis including all of the neural features as independent variables to explain the variance in SCO. Notably, significant features in the multiple regression model explain variance in SCO over and above that explained by all other remaining features (25). We used SPSS Statistics version 25 to perform the linear regression analysis on each brain variable alone, as well as on all five identified brain variables together. Before performing this statistical analysis, the effects of age and sex were regressed out of all the neural variables.

RESULTS

Intrinsic Structural and Functional Connectivity Within the Reward Network

The SCO scores were negatively associated with both SC ($r = -0.350$, $p = 0.027$) and FC ($r = -0.479$, $p = 0.001$) between the right VS and the MPFC, whereas no correlation was found in the left hemisphere (SC: $r = 0.044$, $p = 0.787$; FC: $r = 0.054$, $p = 0.734$) (**Figure 1**). There were no significant correlations between the strengths of SC and FC ($r = -0.134$, $p = 0.399$ for the left VS–MPFC connection; $r = 0.133$, $p = 0.403$ for the right).

Exploratory Voxel-Wise Whole-Brain Analysis

Voxel-level whole-brain RS-fMRI analysis revealed that the fALFF value in the right IPS (peak MNI x, y, z coordinates = 60, −42, 42; peak z-value = 4.45) was negatively associated with SCO score (**Figure 2A**). No regions showed any significant correlation with other voxel-level whole-brain RS-fMRI maps including ReHo and DC maps at an uncorrected significance level of $p < 0.001$ and a FWE-corrected extent of $p < 0.05$.

Further multiple regression analysis using seed-based FC maps, with the right IPS acting as the seed point, revealed that SCO score was positively associated with FC strength between the right IPS seed and right aINS extending to amygdala (referred to as "aINS/amygdala" cluster here), areas belonging to the FPN and CON respectively (x, y, z coordinates = 30, 3, −18; z-value = 3.95; uncorrected significance level $p < 0.001$; FWE-corrected extent $p < 0.05$; **Figure 2B**).

No regions showed any significant correlation with the whole-brain structural maps created using DTI data (FA, MD, AD, and RD TBSS maps).

Mediation Effect

Figure 2C shows the mediation effect of IPS–aINS/amygdala FC on the relationship between SCO score and fALFF in the IPS. In particular, fALFF was negatively correlated with the FC between IPS and aINS/amygdala (path a). The same FC was positively correlated with SCO score (path b). Finally, IPS–aINS/amygdala FC exhibited a negative mediation effect (negative path a*b) that resulted from an IPS fALFF-associated reduction in IPS–aINS/amygdala FC (negative path a), and there was a positive relationship between IPS–aINS/amygdala FC and SCO score (positive path b). This finding indicates that stronger FC between the IPS and the aINS/amygdala mediates the reduced fALFF in the IPS among individuals with high SCO scores.

Social Comparison Orientation Associated With Inter-Network Connectivity

In line with our hypothesis, SCO score correlated positively with inter-network connectivity strength between the FPN and CON ($r = 0.393$, $p = 0.013$; **Figure 3**). An exploratory analysis with intra-network connectivity revealed that there were no associations between SCO score and intra-network connectivity ($r = 0.282$, $p = 0.082$ for the FPN; $r = 0.223$, $p = 0.173$ for the CON).

Regression Models Predicting Individual Difference in Social Comparison

A linear regression model using all neural variables revealed that the FC within the reward network (right VS–MPFC FC), neural fluctuation (i.e., fALFF) in IPS activity, and the FC between the IPS and aINS/amygdala were significant predictors ($p < 0.05$) of SCO (**Table 1**). In such a combined model, significant measures explain the variance in SCO more than all other measures. We also ran linear regressions with each of the measures individually, allowing us to compare the variance explained by each measure (**Table 1**). The variance (R^2) estimated from these analyses, arranged in ascending order, was as follows: 0.12 for the right VS–MPFC SC alone, 0.14 for the FPN–CON inter-network FC alone, 0.19 for the right VS–MPFC FC alone, 0.45 for the fALFF in the IPS alone, and 0.52 for the IPS–aINS/amygdala FC alone. The variance of the combined model was 0.75.

DISCUSSION

In the present study, we investigated whether individual differences in social comparison, as measured by SCO, were related to multimodal, context-independent, brain measures, estimated using DTI and RS-fMRI data. In so doing, we identified several intrinsic functional and structural neural markers of SCO. Most importantly, individuals with higher SCO showed weaker SC and FC between the right VS and the MPFC—regions belonging to the reward-related neural network. We also found several exploratory results from the whole-brain voxel level analyses and network analysis. Individuals with higher SCO showed reduced spontaneous neural activity in the IPS—a region belonging to the FPN, increased FC between the IPS and aINS/amygdala, and large-scale inter-network FC between the FPN and CON. Of these measures, right VS–MPFC FC, fALFF in IPS, and IPS–aINS/amygdala FC contributed most to the neural prediction of SCO. The predictive model using all neural markers identified in the present study was highly effective

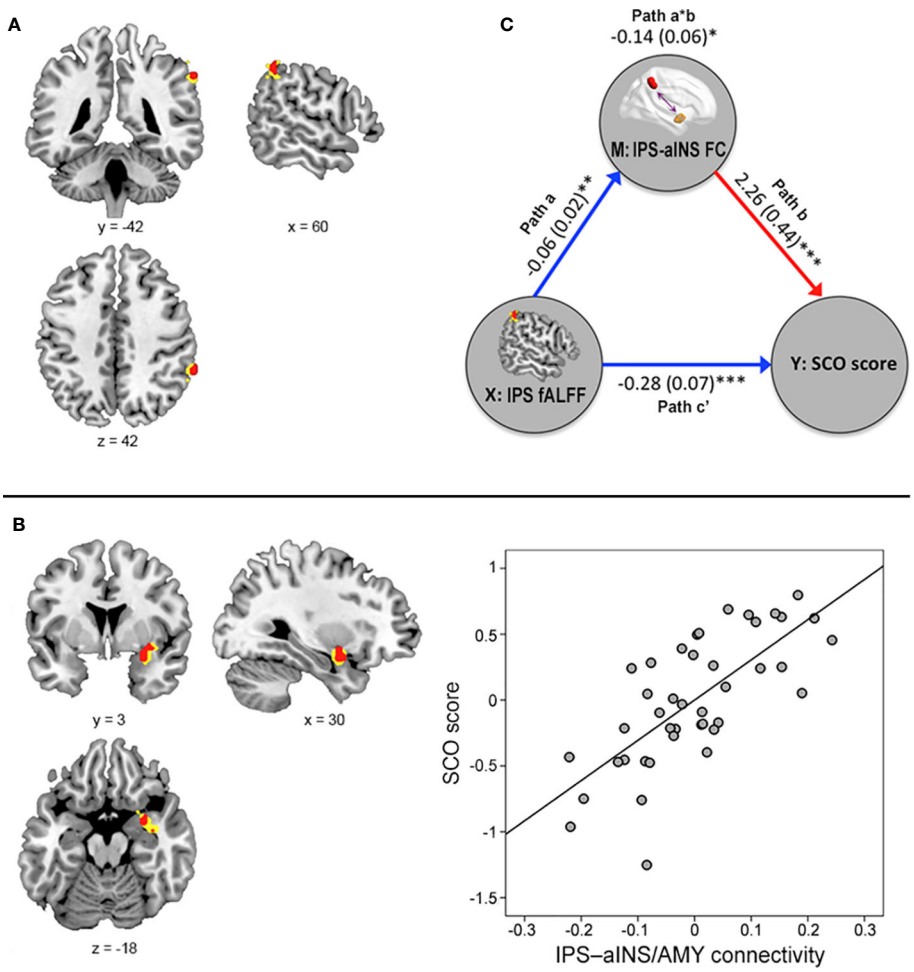

FIGURE 2 | Results from the voxel-level, whole-brain resting-state functional magnetic resonance imaging analyses. **(A)** The fractional amplitude of low-frequency fluctuation (fALFF) value in the right intraparietal sulcus (IPS) was negatively associated with social comparison orientation (SCO) score [height $p < 0.001$ (red) or $p < 0.005$ (yellow)]. **(B)** Functional connectivity strength between the right IPS seed and right anterior insula (aINS)/amygdala cluster was positively associated with SCO score [height $p < 0.001$ (red) or 0.005 (yellow)]. For illustration purposes, this scatterplot was generated by performing Pearson correlation analysis between residuals age, sex, and motion were regressed out. **(C)** The mediation effect of functional connectivity strength in the IPS–aINS/amygdala on the right IPS fALFF and SCO scores. All paths (paths a, b, and c') and mediation effects (path a*b) are labeled with path coefficients and their standard errors in parenthesis. Blue and red arrows indicate negative and positive relationships, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

—accounting for a substantial amount of variance in SCO (R^2 = 0.75). Taken together, these findings suggest that individual differences in social comparison can be characterized in terms of specific patterns in neural structures as well as intrinsic neural activity, particularly in the neural networks engaged in reward processing and comparative processing of external stimuli.

Our findings of SC and FC between the right VS and MPFC are broadly consistent with previous studies linking the same markers with reward processing. Both the VS and MPFC play a critical role in reward processing, showing elevated activity in response to both primary (e.g., food) and secondary reward stimuli (e.g., money) (43, 44). Importantly, these two regions contribute to the appraisal or representation of the subjective value of either social or non-social rewards (32, 42, 45, 46), providing strong evidence for a common neural currency (47, 48). Relatedly, activity in the VS and MPFC are modulated by the absolute outcome and by the relative payoff differences derived from social comparison (8, 9, 49), and this mechanism can vary depending on cultural membership (17). Several studies have indicated that functional interaction between the VS and MPFC reflects variability in the behavioral changes caused by social comparison (16, 17). For example, in one study, the VS response to social gains (winning more than a counterpart) during the earlier outcome phase predicted MPFC activity during the subsequent decision phase, and experienced social gains induced behavioral changes in later trials (16). In addition, the VS-MPFC FC strength predicted individual variability in the degree to which participants' decisions were affected by relative income (17).

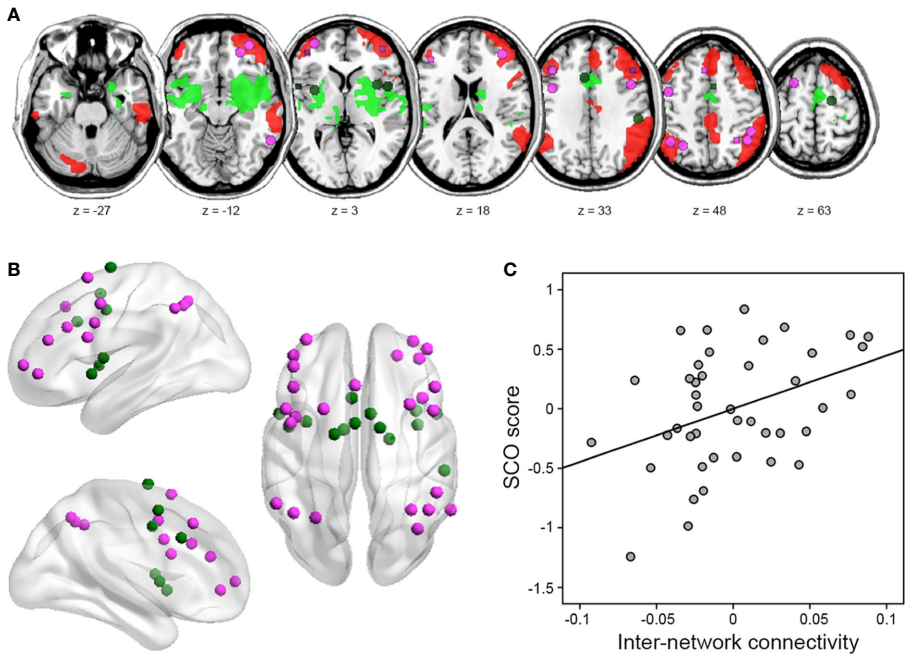

FIGURE 3 | Results of inter-network connectivity analysis. **(A)** Figure illustrating the location of regions (i.e., nodes) in the frontoparietal network (FPN) (violet) and cingulo-opercular network (CON) (green), identified from the atlas by Power *et al*. (42). **(B)** Identified nodes overlaid on within-group seed-based functional connectivity map of each right IPS and right aINS/amygdala seed, identified from voxel-level whole-brain analysis (uncorrected height $p < 0.001$ and FWE-corrected extent $p < 0.05$). **(C)** Partial correlation between SCO score and FPN–CON inter-network connectivity strength. For illustration purposes, this scatterplot was generated using Pearson correlation analysis between residuals after age, sex, and motion were regressed out.

TABLE 1 | Summary of linear regression models with each brain measure individually[1] and together.

	Model with VS–MPFC SC	Model with VS–MPFC FC	Model with fALFF in IPS	Model with IPS–aINS/AMY FC	Model with FPN–CON FC	Model with allbrain variables
Constant	–2.38E–5 (0.07)	–2.46E–5 (0.07)	–2.38E–5 (0.06)	–2.24E–5 (0.05)	–2.18E–5 (0.07)	–2.25E–5 (0.04)
VS–MPFC SC	–0.59 (0.25)*	–	–	–	–	–0.12 (0.15)
VS–MPFC FC	–	–1.10 (0.36)**	–	–	–	–0.51 (0.22)*
fALFF in IPS	–	–	–0.43 (0.08)***	–	–	–0.26 (0.06)***
IPS–aINS/AMY FC	–	–	–	3.05 (0.47)***	–	1.83 (0.42)***
FPN–CON FC	–	–	–	–	4.18 (1.64)*	1.56 (1.02)
R^2	0.12	0.19	0.45	0.52	0.14	0.75

[1]Linear regressions with each individual measure were performed for comparison purposes, with the amount of the variance (R^2) explained in terms of the model with all brain variables. Data are given as unstandardized coefficients, B (standard errors).

*Coefficients significantly different from zero are indicated by asterisks: *p < 0.05, **p < 0.01, ***p < 0.001.*

R^2 values indicate the amount of variance, explained by the model.

VS–MPFC SC, structural connectivity strength between right ventral striatum and medial prefrontal cortex, as part of the reward network; VS–MPFC FC, functional connectivity strength between right ventral striatum and medial prefrontal cortex; fALFF in IPS, fractional amplitude of low-frequency fluctuation in intraparietal sulcus; IPS–aINS/AMY FC, functional connectivity strength between IPS and anterior insula/amygdala; FPN–CON FC, inter-network functional connectivity between the frontoparietal network and cingulo-opercular network.

In this study, the association of SCO with SC and FC between VS and MPFC was significant only in right hemisphere. Though this was not expected, many previous studies have proposed hemispheric specialization of the reward network and of social processing. For instance, a recent functional MRI meta-analysis study shows that hemispheric dominance of striatum activation varies across different types of reward, including food, erotic, and money stimuli (50). In addition, a right-lateralized connectivity of the VS to the parietal cortices during resting-state has been reported (51). Studies in different types of social contexts demonstrate right hemisphere superiority in processing and detecting social stimuli (e.g., voices, faces, and gestures) (52, 53) as well as understanding the intentions behind other's actions (54, 55). Future neuroimaging studies combining both behavioral task on social comparison and resting-state fMRI with a larger sample size will help to verify the observed hemispheric lateralization of FC associated with social comparison.

The present study showed that higher social comparison was associated with weaker VS-MPFC FC during resting-state. Previous studies have reported the involvement of VS-MPFC FC in the manifestation of clinical symptoms, such as addiction and depression (56, 57), as well as reward learning and valuation

(16, 58). In the studies on social comparison, an increased activity and FC within the reward network have been observed specifically when people compare themselves to worse-off others (referred to as downward comparison), which is often associated with positive feelings (17, 23). Thus, it can be speculated that such a hypo-connectivity in the reward network during resting-state observed in the present study may reflect reduced baseline intrinsic reward sensitivity, which may cause people to seek excessive extrinsic social rewards possibly through increased social comparison to others, leading to positive (downward comparison) as well as negative (upward comparison) feelings. In line with this explanation, patients with hyperactivity or increased reward-seeking behavior showed reduced neural responsiveness in the VS, a key part of the reward network (59). Notably, usage-dependent selective synapse elimination (60) is often observed as an example of day-to-day experience-dependent neural plasticity (61), which may be the mechanism underlying decreases in neural activity and cortical thickness after training (17). Another possible explanation is that the reduced SC and FC between the VS and MPFC may indicate that the number of available alternatives is reduced because subjects engage in the excessive pursuit of a limited number of rewards. One good example of such a state may be approval addiction, which involves the excessive pursuit of approval to gain superior social status to others (i.e., downward comparison). The desire of social approval may be the main cause of social comparison. Though we speculate above on interpretations for our findings, we caution against these interpretations as we did not have any behavioral data to prove these interpretations. Therefore, further study may be necessary to investigate whether weaker resting-state VS–MPFC FC is associated with FC in the same circuit during certain social comparison behavior. Such research would provide a more accurate understanding of the functional implication of VS–MPFC FC in social comparison.

In the present study, individuals with higher SCO exhibited less fALFF in the right IPS, which is part of the FPN. While FC quantifies temporal synchrony between remote brain areas, the fALFF indicates quantifiable magnitudes of spontaneous regional neural activity across the whole brain (41). In other words, the fALFF allow us to probe local brain regions where individual differences in resting state activity are correlated with their phenotype (in this case, SCO) across the whole brain at voxel level. The IPS plays a crucial role in visuospatial attention and arithmetic processing (62), and it activates during cognitive and perceptual comparison of stimuli that differ in various ways (e.g., number, size, or luminance) (19–21). Notably, previous studies have demonstrated that the degree of IPS activity increases with the difficulty of comparison (20, 63). IPS activity is also increased during the comparison of social status (63), as well as during comparison of one's own height against those of acquaintances (26). Interestingly, using the IPS as the seed region, further regression analysis between the IPS seed-based FC maps and the SCO revealed that higher SCO was associated with greater FC between the IPS seed and the aINS/amygdala cluster. Additionally, IPS–aINS/amygdala FC partially mediated the link between fALFF in the IPS and the SCO. Therefore, our findings suggest that the SCO is associated with various features of intrinsic neural activity in the IPS, including the power of local neural activity and the patterns of FC.

Considering that the IPS and aINS/amygdala are the core regions of the FPN and CON, respectively, we examined inter-network FC between the FPN and CON, which were independently identified in a previous study (28). Thus, we confirmed that higher SCO scores are associated with stronger inter-network FC between the FPN and CON. The aINS/amygdala cluster, which comprises key elements of the CON, together with the ACC, has been strongly implicated in social and non-social emotions, including disgust (64), pain (65), unfairness (66), and empathy (67), and interoceptive and emotional awareness (68–70), as well as in saliency detection (71). Relevant to the present study, the aINS is often engaged during social comparison (22, 23). In particular, a recent meta-analysis of functional neuroimaging studies emphasized the roles of the aINS and ACC in upward comparison (23). Previous studies have reported competitive and cooperative interactions between FPN and CON (72, 73). For example, Dosenbach *et al.* (72) suggested that these networks communicate with each other, and that each of them carries out dissociable control functions, such as adaptive control in the FPN and stable set-maintenance functions in the CON. Furthermore, the interaction between FPN and CON may be involved in the integration of salient cognitive and affective information to promote goal-directed behavior (74, 75). Thus, we cautiously speculate that the tendency toward higher social comparison can be characterized in terms of increased FC between the CON and FPN, and that this increased FC integrates affective and cognitive/comparative information in the pursuit of self-promotional goals, even during resting periods. Given that the SCO showed negative association with VS–MPFC FC and positive association with IPS–aINS/amygdala FC, we also speculate that individuals with higher social comparison operate more within the external valuation system (IPS-aINS/amygdala FC) and less within the internal valuation system (VS–MPFC FC) than those with lower social comparison during rest. However, there is a lack of additional data supporting this speculation, so future studies should clarify this issue by using functional neuroimaging data obtained simultaneously with behavioral indices of social comparison.

For the exploratory whole-brain analyses, significant relationships of SCO were found only with the RS-fMRI measures but not with the DTI measures. While DTI measures quantify properties related to the direct anatomical links (i.e., white matter fibers) between voxels, RS-fMRI measures quantify the voxel itself and local or remote connections between voxels, especially in the absence as well as in the presence of direct anatomical links. From this point of view, our results for IPS connectivity may reflect FC derived from indirect anatomical connections (76). ROI approach has the advantage of alleviating the multiple comparisons problem by the limiting the number of statistical tests when there are specific hypotheses. Therefore, because of the aforementioned advantage, it may be that the relationship with SC in the present study was found in ROI analysis, but not in voxel-level analysis. In this regard, another possible interpretation is that our DTI measures may be less sensitive in detecting relationships with SCO at the whole-brain

level due to more stringent threshold. SC estimation is challenging owing to complex fiber orientations, such as crossing fibers within a voxel. This problem may cause false-positive and false-negative connections, generating spurious and overlooked links of fiber tracts, respectively. In this regard, the current spatial resolution and analytical techniques for DTI data are not sufficient to solve the issue referred to as the "crossing-fiber problem." Future studies using data with more gradient directions (e.g., high angular resolution diffusion imaging, HARDI) (77) and multiple tensor models (e.g., Q-ball) (78) will clarify the relationship between SCO and SC without the crossing-fiber problem.

The present study had some limitations that should be addressed in future research. Firstly, our interpretations of the findings were necessarily limited by the paucity of information about the directionality of SC and FC. Secondly, it is unclear whether the observed associations reflect the causes or the results of the different levels of social comparison, mainly because the study was cross-sectional in design. The strength of VS–MPFC FC during rest declines with age (79), so future research with longitudinal design should address whether the observed associations change with age. Finally, because the exploratory nature of additional analyses to test whether SCO is associated with certain areas and networks outside the reward networks, hence no further correction for the number of all analyses performed (including mediation analysis, SCO and inter-network connectivity, and regression models) was performed, though each of all these separate analyses was corrected for multiple comparisons.

In conclusion, to our knowledge, the present study was the first to demonstrate that task-independent neural markers can explain individual variabilities in social comparison. Using multimodal, task-independent neuroimaging data, including DTI and RS-fMRI data, we identified several brain networks associated with individual differences in SCO, including the reward network (comprising the MPFC and VS), the FPN (containing the IPS), and the CON (containing the aINS/amygdala). These networks have previously been implicated in either social comparison or general comparative information processing. The present study provides novel and important insights regarding the neural mechanisms underlying individual differences in SCO, suggesting that social comparison is a multidimensional process that engages the networks associated with various motivational, affective, and cognitive components.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

HK and WJ designed the research. WJ analyzed the data. All authors contributed to the article 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/fpsyt.2020.00809/full#supplementary-material

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A Multidimensional View on Social and Non-Social Rewards

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Social rewards are a broad and heterogeneous set of stimuli including for instance smiling faces, gestures, or praise. They have been widely investigated in cognitive and social neuroscience as well as psychology. Research often contrasts the neural processing of social rewards with non-social ones, with the aim to demonstrate the privileged and unique nature of social rewards or to examine shared neural processing underlying them. However, such comparisons mostly neglect other important dimensions of rewards that are conflated in those types of rewards: primacy, temporal proximity, duration, familiarity, source, tangibility, naturalness, and magnitude. We identify how commonly used rewards in both social and non-social domains may differ in respect to these dimensions and how their interaction calls for careful consideration of alternative interpretations of observed effects. Additionally, we propose potential solutions on how to adapt the multidimensional view to experimental research. Altogether, these methodological considerations aim to inform and improve future experimental designs in research utilizing rewarding stimuli, especially in the social domain.

Keywords: social reward, non-social reward, reward dimension, primacy, tangibility, familiarity, reinforcement learning

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SOCIAL AND NON-SOCIAL REWARDS

Rewards are desired, appetitive, and positive outcomes of motivated behavior that *can* increase and maintain the frequency and strength of the behavior they are contingent on (1). They often serve as reinforcers, i.e. positive (or in other cases negative) stimuli or events that *actually* change the probability of that behavior's occurrence or its strength in the future (2). Because humans do not live in isolation, many rewarding experiences stem from social interaction and relationships. *Social rewards* are a broad set of stimuli, which instigate positive experiences involving other people, including a vast repertoire of verbal and non-verbal behaviors, gestures, and feelings (3) such as a smile (4), praise (5), a thumbs-up (6), acquisition of good reputation (7), etc. However, despite the considerable heterogeneity of social rewards and abundance of research utilizing them, it is not clear what constitutes rewards as social and there has been surprisingly little systematic discussion on how we can conceptualize them. Nevertheless, regardless of lacking a clear definition of social rewards, there is a large body of literature discussing them in relation to non-social ones.

Social rewards have been studied by two different lines of research. The first line of research aims to address the "privileged" nature of social rewards, arguing that there are dedicated, special

mechanisms that subserve social functioning, including social rewards. These studies often contrast them against non-social rewards to demonstrate if and how they are processed differently from non-social environmental rewards. For example, autism, which is characterized by pervasive social impairments (8), has been taken as an example of atypical responsiveness to social cues. Researchers have hypothesized impaired processing of social, and preserved processing of non-social rewards [social motivation hypothesis; Chevallier et al. (9)] and have been testing this prediction by comparing responses to social and non-social rewards [for a review, see Bottini (10)]. The comparison is also common in other fields with non-clinical populations [e.g., Kohls et al. (11)].

Another line of research has indicated that social and non-social rewards may be processed in a similar manner. This is supported by economic theories proposing that behaviors stem from the desire to maximize the ratio of rewards to costs (12) and this applies to non-social as well as to social rewards [social exchange theory, Thibaut and Kelley (13)]. Indeed, many studies investigating the neural basis of reward processing found that social and non-social rewards are processed in the same brain areas of what is referred to as the *reward network* [i.e. a cortico-basal ganglia circuit, Haber and Knutson (14)], especially in the striatum, supporting the assumption of an "extended common currency schema" (15). However, researchers have also emphasized specific activity differences in line with the idea of "social-valuation-specific schema" (15), which assumes dedicated brain circuits for social rewards. For instance, a study comparing the rewarding properties of receiving money or positive social feedback found that both rewards activated the striatum, especially the left nucleus caudate, and that this region also showed a linear activity increase towards both reward values (7). A reanalysis of the same data using machine learning, however, yielded a fairly small correlation between classifier weights for social and monetary rewards, suggesting that only a subset of neurons in the caudate nucleus encodes both rewards, whereas also distinct populations of neurons are involved for social and for non-social rewards separately (16). Thus, although both types of rewards can be processed in similar structures of the reward network in the brain [e.g. Izuma et al. (7); Spreckelmeyer et al. (4); Wake and Izuma (16)]; Smith et al. (17); Levy and Glimcher (18); Lin et al. (19), there has also been accumulating evidence for differences in neural processing between social and non-social rewards [e.g. Izuma et al. (7); Smith et al. (17); Sescousse et al. (20); for a recent review of literature discussing overlaps and differences in neural processing of social and non-social rewards, see Ruff and Fehr (15)].

These studies suggest that there are both similarities and differences in neural processing between social and non-social rewards. However, we argue that research comparing social and non-social rewards often neglects important dimensions that can be conflated with the sociality dimension. For example, comparing brain responses to receiving a smile or money may potentially reveal a difference between social and non-social rewards as well as between intangible and tangible rewards. In this article, we propose a more comprehensive, multidimensional view on rewards in experimental settings, which allows more informed and better-controlled comparisons of social and non-social rewards.

DIMENSIONS OF REWARDING STIMULI

Research contrasting social and non-social rewards implicitly assumes a binary categorization of those rewards. However, monetary reward is considered as non-social, but money could be regarded as a "social construct" in the sense that it would not exist without society and a collective agreement of their function [social constructionism, e.g. Galbin (21)]. Thus, binary categorization of social and non-social may be an oversimplification, and a continuous dimension may provide a more accurate conceptualization. Moreover, we suggest that there are other dimensions to describe rewards, e.g. tangibility and primacy, and that considering them can offer alternative interpretations of observed differences between social vs. non-social rewards. This section describes these dimensions of rewarding stimuli (see **Figure 1** for an overview). Our goal is not to provide a complete list of all possible dimensions, but to outline the scope of this multidimensional view with several examples, which we consider particularly relevant for social vs. non-social reward processing: primacy, temporal proximity, duration, familiarity, source, tangibility, naturalness, and magnitude. Importantly, we discuss how each of these dimensions interacts and confounds with social vs. non-social dimension.

Primacy

Primacy is a dimension categorizing rewards [after theories of operant conditioning, Skinner (22)] depending on whether they stem from innate or biologically pre-programmed reinforcing states (hunger satisfied by food or mother's closeness satisfying the need for touch of an infant) on one hand (i.e. primary rewards), or having rewarding properties through learned or acquired associations with primary reinforcers (money as a means to acquire food, a Facebook thumbs-up to gain social appreciation) on the other hand [i.e. secondary rewards; Delgado et al. (23)]. Thus, primary and secondary rewards can be found in both, social (touch, thumbs-up) and non-social (food, money) domain. Studies have shown that even though there is a partial overlap in the ventromedial prefrontal cortex (vmPFC) representing the anticipatory value of primary and secondary rewards (18, 24), there is also additional activity specific to primary (i.e. hypothalamic regions) and secondary rewards [i.e. posterior cingulate cortex; Levy and Glimcher (18)], respectively. Since primacy can be linked to distinct neural processing, it is important to choose rewards of the same primacy nature when comparing social and non-social ones.

Temporal Proximity

Temporal proximity describes the temporal relationship between motivated behavior and reward reception (e.g., immediate vs. delayed). There is evidence that they are processed distinctly in the human brain [e.g., Ballard and Knutson (25); for a review, see

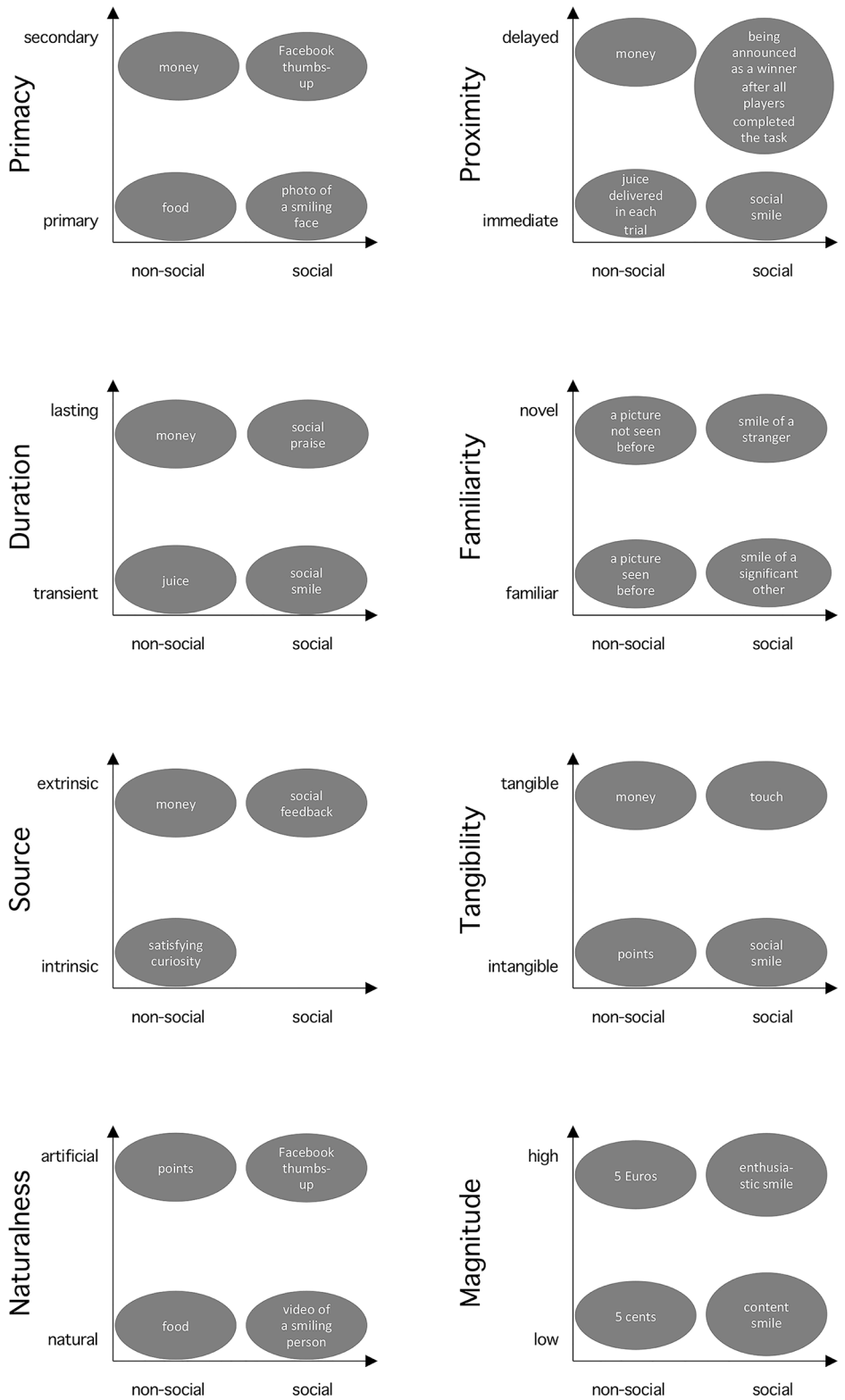

FIGURE 1 | Interplay of the sociality and other reward dimensions. The x-axis represents the sociality dimension. The provided cases illustrate examples of rewards used in psychology and neuroscience placed along the dimensions discussed in this article. The spatial distance between the cases does not directly depict differences in their rewarding value.

Bermudez and Schultz (26)]. Specifically, midbrain, striatum, frontal cortex, and amygdala are all sensitive to time of reward occurrence (soon or later). Moreover, temporal discounting may lead to a preference for sooner smaller compared to later larger rewards. Social rewards are usually delivered immediately at the end of the trial in the form of a smile or social feedback, aligning simultaneous reception and consumption of reward. However, in the non-social domain, there is often a difference between reward reception in an experimental trial (e.g. a picture of a coin) and the actual consumption of the reward after the experiment (i.e., receiving the physical money). Note that sometimes the amount of points won in trials is not even directly translated to actual money gains (27). Thus, comparing social rewards with non-social rewards may trigger brain responses reflecting differences in the temporal proximity dimension in addition to the sociality dimension.

Duration

The dimension of duration distinguishes between lasting and transient rewards. Unlike transient rewards (consumed/appreciated while presented), lasting ones may entail accumulation over time, which affects economic decision making and activity in vmPFC (28). While social ones most often are transient (a smile lasts only while presented, but praise may have longer-lasting effects generating feelings of appreciation), non-social rewards are more dependent on the experimental context. For example, money received in a task is still available after the end of the experiment, whereas juice delivered on a trial-by-trial basis is immediately consumed. Thus, when comparing social and non-social rewards, duration needs to be considered to avoid confoundedness.

Familiarity

Familiarity differentiates novel from familiar stimuli and is signaled in the striatum and the midbrain (29). While novelty is rewarding in non-social stimuli (29), it may be the opposite in the social domain, where familiar and socially relevant faces are more rewarding than faces of strangers (30). In fact, it has been shown that familiar faces are processed differently than faces of unknown people, due to different visual representations stored in memory, personal knowledge, and personal relevance (31). Furthermore, "familiarity" in the context of social rewards has multi-faceted meanings and there may be qualitative differences between familiarity with relatives, celebrities, and experimentally learned individuals (31), which can potentially lead to inconsistencies through differential engagement in experimental tasks (32). Altogether, familiarity may modulate social and non-social rewards differently, which should be considered in study designs.

Source

Source relates to whether the rewarding nature originates internally (i.e. intrinsically within a person, e.g. feeling curious) or externally (i.e. extrinsically by receiving food or praise). While psychological theories consider them as distinct [e.g., Deci and Ryan (33)], neuroscientific studies show that rewards from both sources activate the reward network (34), with additional brain regions specific for intrinsic rewards [the anterior insula; Lee (35)]. This can be a potential confound for the sociality dimension, as non-social rewards could stem from both sources (satisfying curiosity or receiving money), but social rewards are by definition extrinsic as provided by others (e.g. social feedback).

Tangibility

Tangibility refers to the property of a stimulus to be touched or consumed, with more abstract stimuli being less tangible. Studies suggest differential reinforcing and motivating effects of tangible and intangible stimuli (36), often *via* differential engagement of intrinsic and extrinsic motivation (37). For example, in a study with tangible monetary and intangible verbal rewards on intrinsic motivation, only the latter showed positive and prolonged effects (38). Because social rewards are most often intangible (like verbal praise) and non-social rewards are tangible (e.g. money), the interaction of sociality and tangibility is a potential confound.

Naturalness

Some studies use natural stimuli such as chocolate (18) or verbal praise (39) as rewards, whereas other studies use more arbitrary, symbolic stimuli such as Facebook thumbs-up icon (6) or a picture of a coin (11). Naturalness is especially important for social rewards. For example, there is an increasing number of studies using avatars [e.g. Kim et al. (40)] and cartoon representations of faces [e.g. Gonzalez-Gadea et al. (41)], which convey the social nature through the resemblance to their natural equivalences (faces). In fact, computer-generated and natural faces have been shown to elicit similar emotional processing in the amygdala, but also differential activation in the fusiform face area (42). Again, the interaction of sociality and this dimension should be considered and controlled for by choosing both social and non-social rewards to be either natural or representational.

Magnitude

The magnitude of a reward can be defined as the extent of its objective and subjective value. Studies have shown that activity in the ventral striatum correlates with the objective magnitude of both monetary [increasing amounts; Knutson et al. (43)] and social rewards [happy face expressions with increasing intensity level; Spreckelmeyer et al. (4)], and vmPFC correlates with the subjective magnitude of rewards (19). Critically, rewards with higher magnitude are likely to elicit larger responses in wider areas of the brain in comparison to rewards with lower magnitude [e.g. Smith et al. (44); Diekhof et al. (45)]. Differences in magnitude between rewards should thus be avoided to allow interpretation of the observed effects in terms of social vs. non-social (and not low vs. high magnitude).

In addition to the dimensions above, some other aspects contrast social rewards against other rewards. For example, social stimuli are usually complex and can be more ambiguous than non-social ones: The same smile may be interpreted as a friendly reaction or as a ridicule, depending on the context. Thus, it is important to take into account biases in the interpretation of ambiguous social stimuli linked to internal states [e.g. negativity

bias in depressive states; Dai et al. (46)]. Also, psychological traits and conditions [like autistic traits and social anxiety; Cox et al. (47) and Cremers et al. (48), respectively] have been shown to modulate responses to social rewards specifically. Likewise, visual complexity may introduce altered processing: Non-social rewards are often less visually complex than their social counterparts (6, 49), introducing a perceptual bias and neural differences (50). Furthermore, it may be more challenging to uniformly induce a rewarding value of social stimuli than of non-social ones, as the rewarding value of social stimuli depends on a certain context around participant and reward. In fact, a smiling face seen on the screen can be rewarding for a participant performing a task only when they believe to some extent that this smile is contingent on their action, as it happens in natural interactions. Simply instructing participants that a smiling face indicates positive feedback might not make it sufficiently socially rewarding; this requires a perceived social context between the participant and the person on the screen, entailing that "social interaction must not inherently be rewarding due to the appearance of positive social stimuli" [Krach et al. (51), p.1]. Although some studies suggest that bottom-up processes are involved in the privileged processing of social stimuli (52), for a stimulus to be *socially rewarding*, it is not enough to be a representation of human likeness/gesture carrying positive feedback. Social rewards require the component of intention and direction from the observer to the observed, even if there is no direct (face-to-face) interaction between those two. In fact, one could consider social rewards that are delivered without a social visual stimulus. For example, in Kujawa et al. (53) participants saw a green checkmark (abstract symbol) as signifying social acceptance, a salient social reward (54). This is especially important considering recent attempts to bring experimental research closer to reality, which includes the use of dynamic stimuli (55, 56) and implementing a second-person approach in (neuroscientific) research on social cognition (57). Although instantiating social context may come at the cost of losing experimental control, some promising designs aiming to ensure ecological validity and experimental control have been proposed [e.g. Drimalla et al. (58)].

IMPLICATIONS OF THE MULTIDIMENSIONAL VIEW ON REWARDING STIMULI IN EXPERIMENTAL DESIGNS

As discussed, rewards can be described on multiple dimensions and each of them can be linked to different neural correlates and psychological processes. Thus, research interested in comparing social against non-social rewards should carefully control for other dimensions that may conflate the dimension of interest instead of ascribing the observed effects to a single one, like sociality. However, research has rarely considered these additional aspects of rewards [but see the discussion of primacy and tangibility of money and juice, Kim et al. (24); or praise, Wake and Izuma (16)]. For example, many studies simply compare smiling faces and monetary outcomes to examine the differences of social vs. non-social processing (59–62). However, both outcomes differ not only on the social – non-social dimension, but also in terms of their 1) tangibility: a smile is not tangible, but money as a reward in the form of coins and notes is; 2) primacy: a smile is a primary reward[1], money is secondary; 3) proximity and duration: a smile is immediate and transient (its rewarding value lasts as long as its exposure), whereas money is lasting and distant, as it will be delivered at the end of the experiment. Hence, from this multidimensional perspective observed differences between responses to smiles and money cannot be fully ascribed to the social vs. non-social contrast but could also stem from differences in tangibility, primacy, proximity, and duration.

How can empirical research overcome these potential limitations? One strategy is to incorporate these dimensions as additional factors in an experimental design [e.g. visual complexity in Pfabigan et al. (50)]. However, this exponentially increases the number of conditions, which substantially boosts the length of the experiment and/or required sample size. An alternative solution is to use stimuli that match in other dimensions than sociality as much as possible. Previous research has shown that pleasant odors can engage the reward circuits (64, 65, 66) which could be used in a comparison with social rewards like smiling faces. Both rewards would be balanced in terms of temporal proximity (both immediate), tangibility (both intangible), source (both external), and they can be matched with respect to their primacy, duration, familiarity, naturalness, and magnitude. Another approach could be to condition social and non-social rewards with neutral stimuli. For instance, Lehner et al. (67) matched reward magnitude of chocolate, money, and social smile with thumps-up using a willingness-to-pay paradigm and later paired them with neutral stimuli (matched in color, luminance, and complexity) to then measure the response to those stimuli. Finally, another potential solution would be to assess other dimensions as much as possible (e.g. using subjective ratings) and statistically control for these effects in the analysis. This strategy can also address potential individual differences in the interpretation of social stimuli.

Another implication of this multidimensional view is noteworthy for one of the most widely-used paradigms that compare social and non-social rewards: Monetary [MID; Knutson et al. (43, 68)] and Social [SID; Spreckelmeyer et al. (4)] Incentive Delay tasks. In these tasks, participants are presented with a cue indicating possible outcomes in a given trial: a gain or loss, or no outcome (control condition). After a variable anticipation delay, they perform a task after which feedback (i.e. the amount of reward or punishment) is delivered depending on participants' performance. An advantage of the incentive delay paradigm is that it allows targeting both reward anticipation triggered by an incentive cue indicating a possible future reward, and reward reception, elicited with a rewarding stimulus after task performance (43, 68). It has been shown that both phases (anticipation and reception) involve different brain regions and they are modulated differently by the domain of rewards (social and non-social), with reception being more

[1] In this article, we consider smile as a primary reward as suggested by infants' preference for smiling faces (63), but other interpretations are possible.

domain-specific than anticipation (69). This paradigm has intuitive appeal to contrast social and non-social rewards, but our multidimensional view suggests the potential difficulty in interpreting the results in terms of anticipation and reception, especially in the context of comparing social and non-social rewards.

For example, Kohls et al. (59) used a picture of a smiling face as both incentive cues and rewards in the SID task. However, a smile is an immediate reward (participants are being smiled at the moment), which entails that as an incentive cue it triggers not only anticipation as intended, but also reception of this reward. Moreover, in the MID task, a picture of a coin is normally presented as a signal that the trial was successful and thus participants receive a monetary reward. However, in reality, participants receive physical money at the end of the experiment, not immediately after each trial (money is a distant reward in such settings). Hence, a picture of a coin intended to represent a reception of reward may actually trigger another anticipation. In other words, when considering the dimension of temporal proximity, for both cases, the distinction between the reward processing phases becomes rather arbitrary. Confounding these two factors (reward processing phases and domain) has serious consequences on how we should interpret the results because both phases are associated with distinct brain areas (70). Disentangling of those factors could be achieved by using neutral, non-rewarding incentive cues to trigger anticipation [e.g. Matyjek et al. (71)], or by matching social and non-social rewards on the temporal proximity dimension (i.e. immediate vs. delayed rewards). For instance, to match social rewards, which are often immediate (e.g. a smile), their non-social counterparts can be delivered on a trial-by-trial basis, e.g. in form of juice (24) or direct online bank transfers. Similarly, to match non-social rewards, which have often delayed reception (e.g. money), the social condition could include trial-by-trial symbolic indications of positive feedback, which translate into social appreciation at the end of the experiment in a form of positive adjectives describing the participant (7), given by an "observer".

At a broader level, one important implication of the proposed multidimensional perspective is that it highlights a more nuanced relationship between social and non-social rewards than what researchers have previously assumed. As indicated earlier, while many studies seek neural correlates specialized to social processes, another body of literature focuses on the similarities among different types of rewards (including social), suggesting that there is a common valuation network in the brain. These two lines of research seem contradictory: One argues that social and non-social rewards are different and the other suggests that they are the same. However, the proposed multidimensional view provides a simple integration (see also Murayama (34), in the context of the distinction between intrinsic and extrinsic rewards). While social and non-social rewards are both reinforcers with the potential to guide behavior, their differential effects are (at least in part) attributable to properties on other dimensions on which rewards can be described (e.g., temporal proximity, familiarity, etc.). Using the multidimensional view as a starting point, we can thoroughly reflect upon mechanisms underlying the processing of social rewards, being able to go beyond the simple assertion that social rewards and non-social rewards are either similar or different.

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REVIEW
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Calming Effects of Touch in Human, Animal, and Robotic Interaction—Scientific State-of-the-Art and Technical Advances

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Small everyday gestures such as a tap on the shoulder can affect the way humans feel and act. Touch can have a calming effect and alter the way stress is handled, thereby promoting mental and physical health. Due to current technical advances and the growing role of intelligent robots in households and healthcare, recent research also addressed the potential of robotic touch for stress reduction. In addition, touch by non-human agents such as animals or inanimate objects may have a calming effect. This conceptual article will review a selection of the most relevant studies reporting the physiological, hormonal, neural, and subjective effects of touch on stress, arousal, and negative affect. Robotic systems capable of non-social touch will be assessed together with control strategies and sensor technologies. Parallels and differences of human-to-human touch and human-to-non-human touch will be discussed. We propose that, under appropriate conditions, touch can act as (social) signal for safety, even when the interaction partner is an animal or a machine. We will also outline potential directions for future research and clinical relevance. Thereby, this review can provide a foundation for further investigations into the beneficial contribution of touch by different agents to regulate negative affect and arousal in humans.

Keywords: safety signal, stress axis, cortisol, oxytocin, amygdala, C-tactile, HRI (human robot interaction), heart rate variability

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INTRODUCTION

The tactile sense is one of the first that a human develops. A newborn child has the first contact with its environment, such as its clothes or its cradle. In particular, touch by the parents has been proposed to be important for development, e.g., feeling their touches on its skin, but also by feeling tactile input when it actively moves toward them, with an important impact on the child's development (1, 2).

Even in adulthood, being touched and touching others is a central element of social interaction and social relationships (3). It has been suggested that social touch is one mechanism for beneficial health effects of social relationships. The effects of positive social interaction, in general, show effect

sizes equaling or exceeding those of well-established behavioral factors, such as smoking cessation or sports (4); some of them might be due to touch or intimacy. Touch has also been ascribed as important functions during bonding [e.g., (5)], communication (6–8), and reward [e.g., (9, 10)].

It has often been proposed that social touch can buffer stress and has calming effects [e.g., see overviews by Burleson and Davis (11) and Morrison (12)], but the underlying preconditions and mechanisms of this positive effect are not sufficiently investigated yet. Several studies show a reduction of psychobiological fear or stress responses in neuro-physiological and endocrine outcomes after touch [e.g., (13–15)]. Here we would like to put forward the possible mechanism that touch acts as a social signal for safety, which communicates to the receiver that "things are ok," and thereby inhibits fear and stress responses. The assumed neural processes in terms of responses to touch signals and their mediation of attenuated fear and stress responses will be outlined below.

Of course, touch can also occur as an act of aggression or in order to threaten an interaction partner. In these negative interaction situations, both the expectations and the physical properties are different (6, 7, 16), with violence as an extreme form of touch and physical pain as a potential consequence. There is surprisingly little research on the stress-inducing effects of touch. For example, during a physical examination, the medical doctor's announcement of pain may induce stronger pain than the touch itself; this is mostly investigated in the context of placebo- and nocebo-research (17). However, in order to determine the potential beneficial effects of touch by agents other than humans, it is crucial to also evaluate whether and when it can be experienced as negative.

The increased use of intelligent robots as service machines, especially in the medical context, makes human–robot interactions more and more frequent in daily routine as well as in healthcare. This raises the question of whether the beneficial effects of touch depend on the social source of the tactile stimulation or whether they can also be elicited by mechanical or robotic devices. This question is also generally important in medical situations since most humans experience illness, physical examinations, and surgery as threatening. Therefore, robots interacting with humans in a way that supports mental and physical well-being have the potential for directly supporting individuals at risk and also the healthcare system in general. With the current demographic development, more and more people, including the elderly, also live alone. At the same time, when deprived of social touch, e.g., lonely persons or patients in self-isolation or quarantine, humans show higher levels of stress and more symptoms of mood, and anxiety disorders (18). This poses the question of whether an absence of human touch can be (partly) compensated for by an animal companion or a machine. In many of the studies on gentle touch perception, the stimulation is performed by a machine and is evaluated as similarly pleasant by healthy participants than when performed with the hand (19). This suggests that touch by actors other than humans can give rise to comparable hedonic experiences.

The goal of this conceptual review is to give an overview of experimental research on the calming effects of touch, taking into account different interaction partners. In the following discussion, the evidence for stress-reducing effects of touch by humans, animals, and even robotic machines that might be of relevance for clinical contexts will be summarized. Supporting the view of at least partly comparable effects, we propose joint underlying neurobiological mechanisms. These will be outlined in the following section.

Neural Mechanisms Underlying the Calming Effects of Touch

In the following paragraph, we will describe two possible neural circuitries which might mediate touch acting as safety signal: inhibition of the amygdalar fear response *via* the posterior insula and activation of the reward system for facilitating approach behavior. In the latter, stress dampening effects are assumed to be less dominant. Both the bottom-up processing of the tactile experience and the top-down regulation of the fear/stress response are displayed in **Figure 1**.

Regulation of Fear and Stress Responses

The state of literature on fear inhibition describes a down-regulation of amygdala activity through the input of the prefrontal cortex (PFC) and the insula. Evidence suggests that, in particular, the pathway *via* the insula is also involved in the stress-reducing effects of touch.

The amygdala is widely known as the neural center of fear, although being involved in various other functions (20, 21). Mostly animal literature, but also human studies, shows that the amygdala is not a homologous structure but is composed of subnuclei with different functions. The lateral amygdala, the primary sensory input site, and the basal amygdala (together BLA) are involved in fear learning, while its central nucleus (CeA) is involved in the expression of fear (22). The expression of fear results in the activation of two stress axes (see "Section Neuroendocrine mediators and stress response" below) for a flight or fight response, which is measurable in endocrine or psychophysiological outcomes.

The amygdalar neurons within the subnuclei are under the inhibitory control of local GABAergic interneurons (23) and the medial intercalated neurons (24). Control from other brain regions comes from the infralimbic ventromedial prefrontal cortex (25) and the insula (26, 27). The inhibitory control of the amygdala *via* the PFC and the insula, together with the amygdala, is a network for top-down and bottom-up emotion generation. Bottom-up processes describe the information flow starting from the stimulation of specific receptors to subsequent neural reactions. Top-down processes describe, e.g., modulating influences from the PFC (associated with cognitive influences such as appraisal or evaluation) on the perception and processing of touch.

The posterior insula, termed sensory insula, exhibits convergent responses to simultaneous multisensory stimulation (28) and has afferent intracortical and thalamocortical as well as efferent amygdala connections (26, 29). The insula is therefore

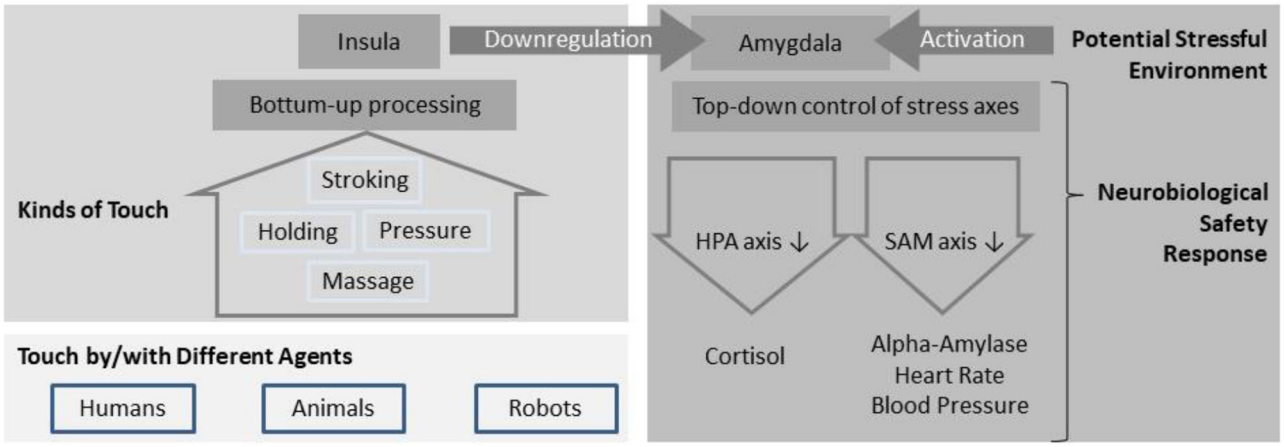

FIGURE 1 | Mechanisms of touch potentially acting as safety signal: In a dangerous environment, the amygdala is activated in order to allow for rapid reactions via the stress axes (e.g., fight or flight response). Tactile perception from different social and non-social contexts is processed in the insular cortex, which has a regulating influence on the amygdala and can therefore dampen the stress response. A calming or relaxing effect of touch might therefore be based on signaling safety (absence of danger) on a neurobiological level.

well-suited to modulate amygdala activation based on both top-down and bottom-up input. Such input could be triggered from a particular "all-clear" signal or, in other words, a safety signal.

Neural Processing of Safety Signals

Few studies have investigated the neural response to—mostly visual—safety signals and point to an involvement of both the posterior insular cortex and the striatal reward system in the processing of visual safety cues. Safety signals, in general, have been first described by (30) as one form of internal inhibition of conditioned reflexes, with a former neutral stimulus predicting the non-occurrence of an aversive event after a learning process. It can be assumed that social stimuli such as social touch can not only be learned to predict safety but also to have the property to "prepare for safety," analogous to some stimulus types that include preparedness for fear (31). Everyday life examples for safety signals would be, e.g., a calm voice and also the face of the romantic partner (32).

Based on the findings on inhibition of fear, Kong et al. (33) have proposed a regulatory model stating that the posterior sensory insula projects to BLA which orchestrates CeA and bed nucleus of striatum terminals that subsequently mediate the behavioral output in response to a safety signal. This is supported by animal studies showing that a knock-out of the posterior insula leads to deficient inhibition of fear (27, 34).

On the other hand, very early work by Dickinson and Pearce (35) suggested a further mechanism by which safety signals could act. These authors suggested that safety signals inhibit the aversive system while at the same time disinhibiting the appetitive system. Safety signals would thereby facilitate approach behavior and act as reinforcers. These possible rewarding effects of safety signals led Pollak et al. (36) to suggest them as "behavioral antidepressants." Other studies supporting this idea showed that a safety signal increased the slope and the amplitude of conditioned stimulus-evoked field potentials in the caudatoputamen (37), reduced the activity in the amygdala, and increased the activity in the striatum (38). The reward system itself has regulatory influences on the stress axes [e.g., (39, 40)]. This raises the possibility that safety signals activate the reward system which then downregulates amygdala activation. Thus, touch as a safety signal might also execute its stress-inducing effect *via* reward system activation.

Neural Processing of Tactile Information

Several human imaging studies revealed that touch activates a broad neurocircuitry including the insula, orbitofrontal cortex, and anterior cingulate cortex (41–43).

An especially "social" experience of touch has been described as being conveyed by low-threshold unmyelinated peripheral afferent fibers [C tactile (CT) fibers]. These fibers respond preferentially to gentle, slow, caress-like stroking at skin temperature (44), and their activation is generally perceived as pleasant (45). CT afferents project to the posterior insula (46, 47). For instance, Gordon et al. (48) showed that CT–targeted affective touch to the arm activated the insula and the mPFC/dorsal–anterior cingulate cortex (dACC). Lesions of the insula in turn, impair the perception of affective touch (49). Recently, the insula was shown to be also activated by A-beta afferents (50). Thus, bottom-up input from different mechanoreceptors reaching the insula has the potential to dampen the stress response. Connectivity analyses with a mPFC/dACC seed revealed co-activation with the left insula and amygdala. These studies therefore suggest regulation of the amygdala by touch acting as safety signal *via* mediation of the insula.

In addition to bottom-up influences, top-town influences have also been discussed, for example, expectations. This influence can affect the valence of the touch perception from prefrontal and limbic regions (51). It remains still to be determined how bottom-up and top-down influences on touch processing interact

to modulate the stress response. The involvement of the reward system in this process also needs to be clarified. One region coding for the reinforcing aspect of touch is the ventral striatum (52). Our own work has shown a joint activation of the insula, putamen, and caudate (53) during CT-targeted touch. This involvement of the striatum may point to the second neural mechanism of touch acting as safety stimuli *via* the reward system. However, striatum activation is only found occasionally in studies on pleasant touch, so more evidence is needed.

Taken together, inhibition of amygdala fear *via* the insula is a highly plausible underlying mechanism of touch acting as safety signal. Potentially, amygdala inhibition is furthermore due to reward system projections. Since research on safety signal processing is limited to visual signals so far, it has to be investigated yet whether tactile safety signals act on the same processes. On the other hand, opposite mechanisms may account for the stress-inducing effects of touch in negative contexts *via* increasing the amygdalar responses, yet this remains to be investigated as well.

Neuroendocrine Mediators and Stress Response

In addition to neuroanatomical connections, mediating neuromodulators, and neurotransmitters such as oxytocin and dopamine released in response to touch may be regulating the above-mentioned limbic and reward areas (54–56). Especially oxytocin has been shown to be released during intimate touch (57–60), while dampening stress and fear (61, 62). Administered exogenously, oxytocin increases the neural and subjective response to touch (15, 56). Histological investigations show a high density of oxytocin receptors in the human insula, striatum, and amygdala (63), which constitutes an additional regulatory mechanism of the neural circuitry mentioned above.

Stress Axes

The fear and stress response triggered by the amygdala reaches the periphery by two main axes of stress hormones, the hypothalamic–pituitary–adrenocortical (HPA) axis (64) and the sympathetic–adrenomedullary (SAM) system [(65); see also **Figure 1**]. HPA axis responses are mediated through a cascade of hormones from the central nervous system (corticotrophin-releasing factor), which then stimulate adrenocorticotropic hormone and cortisol secretion in the periphery. As dynamic negative feedback of the HPA axis, the increase of cortisol will—*via* the activation of mineralocorticoid and glucocorticoid receptors—reduce further activation and, in turn, initiate the recovery from stress (66). Cortisol in saliva is one established key marker for assessing stress levels (67). The SAM system, on the other hand, facilitates a fast reaction to acute threat *via* the adrenal medulla releasing catecholamines. The parasympathetic component of the SAM influences, e.g., the heart rate (HR) *via* the vagus nerve or salivary alpha-amylase as a product of beta-adrenergic activity (68). The heart rate variability (HRV) is an established marker for a healthy adaptation to stress (69) that is regulated by the autonomic nervous system, both by its parasympathetic branch that is known for the "fight or flight response" and its parasympathetic branch.

Taken together, touch has the potential to exert a calming and stress-dampening effect *via* these neurobiological mechanisms. Indeed the findings from many studies suggest that such an effect might be observed across a variety of different contexts due to a joint phylogenetic basis. We assume that the evolutionary circuitries underlying touch as a safety signal are activated through all kinds of touch, yet context and personal factors can moderate the effects. In order to systematically explore these effects, we performed a literature search and will summarize the findings in the consecutive sections for the different contexts.

METHODOLOGICAL OVERVIEW

With a focus on basic research, we chose to include studies in healthy human adults published in English. We searched the platforms Pubmed.gov, Web of Science, and Google Scholar with the search terms "touch," "massage," "stress," "fear," "cortisol," "heart rate," "arousal," "blood pressure," "animal," "pet," "machine," "physical contact," "tactile," among others, individually or in combination. Boolean operators were used to search with multiple terms. Further papers were retrieved from the reference lists of papers found this way. Given the large number of results, we decided at this point to set up further exclusion criteria and to only include studies that fulfilled the following criteria: (1) outcomes were measured in adult humans (not infants), (2) measures of stress, anxiety (subjective and/or physiological), or negative affect were used, and (3) the extent, type, and duration of tactile contact was explicitly stated. This excluded studies, for example, where the information was restricted to the statement that the participants "interacted" with a (robot) animal without it being clear whether this included touch. Both self-initiated touch situations (active touch) and other-initiated touch situations (where the human receives passive touch) are discussed. Based on these criteria, the following sections "Human-Human Touch", "Touch between Human and Animal", and "Touch between humans and artificial object" will give a summary on the most relevant experimental studies reporting physiological, hormonal, neural, and subjective indicators of the positive role of touch in different contexts on stress, arousal, and negative affect.

HUMAN–HUMAN TOUCH

When analyzing human-to-human touch, behaviors as listed in **Figure 1** (i.e., stroking, holding, pressure, massage) can be interpreted. In addition, in 2018, Lee Masson and Op de Beeck (70) published a socio-affective touch expression database, based on video sequences, to be rated on the dimensions naturalness and valence. This database can help in structuring human-to-human touch experiences but has not systematically been tested with regard to different relationship types. Being touched by another human can yield substantially different responses depending on the personal relationship. In a study investigating touch between close friends, Kawamichi et al. (71) found that the participants evaluated hand-holding with a close female friend as more relaxing than holding a rubber hand and showed parallel dampening effects on neural activation when processing aversive

visual stimuli while in an fMRI scanner. In order to account for the effects of personal relationships between the persons touching and being touched, we will summarize studies separately for different relationship forms (romantic, professional). Apart from parent–infant touch (which is not in the scope of this review), human touch studies focused mostly on touch between adult romantic couples and on touch in a medical context, particularly the effects of massage.

Touch Between Romantic Partners

Studies on touch between romantic partners suggest that affective touch can reduce subjective and psychobiological stress levels during standard stress in the laboratory (13, 72) and in couples' everyday life (73, 74). Couples who reported more physical intimacy in everyday life had lower cortisol levels on a momentary basis (73) and higher oxytocin levels in plasma at baseline before a lab stress test (75). In another study, higher levels of non-verbal affection in intimate relationships (parents, partner) were associated with lower HR and blood pressure levels (76). In a functional MRI study, Coan et al. (77) found that hand-holding—the partner's hand in particular—during the anticipation of pain reduced unpleasantness and bodily arousal as well as the neural threat response in $N = 17$ women. In another study, pupil dilation during the Stroop test was interpreted as an arousal marker, and study participants who held hands with their partner showed accelerated habituation to stress and less pupil reactivity (although this was not a tonic pupil response) than those in the non-hand-holding condition (78). Being stroked by the partner also decreased HR, and the decrease was related to the quality of the relationship (14). Furthermore, 10-min hand-holding with the partner while watching a romantic video reduced subsequent blood pressure during public speaking (79). Overall, affective touch between partners can reduce stress levels and psychobiological stress reactivity as measured with different markers of arousal. Of note, however, is that, so far, affective touch between romantic partners has not been related to the duration of the relationship. During the beginning of a romantic relationship, overall increased stress and arousal have been found (80). Based on this, it might be assumed that touch during the beginning of an erotic or intimate relationship would rather increase arousal and psychobiological stress levels than reduce stress.

Beyond this, touch not only serves as a calming agent but can also communicate specific emotions (6) and thereby even serve to communicate anxiety or aggression (45). So far, we are not aware of systematic research on the effects of positive affective touch in comparison to aggressive touch or physical violence in intimate relationships. It could be assumed that touch might serve as an intensifying factor of both bonding and affiliative behavior on the one side and anxiety and stress on the other side, thereby acting either as a safety or a threat signal.

Touch in Professional Relationships

Studies on non-romantic human touch have used both highly controlled standardized touch movements and also static holding/ hugging or complex massages [e.g., Thai massages; (81)].

Using such a standardized design in an early study and with a small sample size only, an experimenter touched the wrist of $N = 8$ healthy subjects for 30 s (82). This led to a decrease in HR, indicating relaxation. Touching the wrist by the subject him/herself with their other hand did not decrease HR. A similar effect of 60-s wrist-holding by an experimenter also occurred when the subjects ($N = 20$) were confronted with a cold pressor stressor (83). HR was also reduced by 5 min of CT-touch (N = 29) (10), as well as skin conductance response ($N = 34$) as a measure for unspecific arousal (84).

In a within-subject design, von Mohr et al. (85) compared different stroke frequencies and found that the partner's slow touch (in comparison to fast touch) reduced pain levels to standard pain in the laboratory. This data was in line with earlier results from the same group (however, not in couples) that slow affective touch reduced feelings of social exclusion during the Cyberball task (86). In a patient sample ($N = 29$ individuals with coronary illness), different kinds of touch led also to reduced HR and lower blood pressure (87). Taken together, these studies indicate a regulatory influence of simple static touch on autonomous nervous system activity.

Massage Studies

Classical Western or also traditional Eastern massage usually involves large parts of the body and is combined with treatments such as aroma oils or relaxing music. Therefore, the effects of music, odors, and oils are often not clearly separable from the effects of the touch itself. In addition, massage touches not only the skin and stimulates the tactile system but also the deeper tissue and muscles, which might also account for some of the beneficial effects on well-being. As all these effects cannot be disentangled from the sole effect of touch, we only refer to few exemplary studies in the following discussion. The effects of massage on stress relief become evident in patients with various conditions.

A 7-min standardized hand massage by an unknown experimenter led to a decrease in cortisol levels in 29 healthy volunteers as compared to simply holding an object in their hand while the experimenter was present (88). In a subgroup of highly self-critical individuals, the hand massage additionally decreased alpha-amylase levels. Likewise, receiving a 5-min hand massage reduced subjective stress, anxiety, and fatigue in $N = 40$ healthcare professionals (89). In palliative care patients, salivary chromogranin A, as another biomarker for stress by SAM activation, was reduced after a hand massage as well (90). When waiting for ambulatory surgery, a 5-min hand massage reduced anxiety in $N = 45$ patients as compared to controls without a medical intervention pending (91). This finding indicates a function of safety especially in the presence of acute threat.

A classical (whole body) massage for 30 min reduced cortisol and subjective stress levels in 34 breast cancer patients (92). Patients ($N = 24$) suffering from back pain receiving two 30-min sessions of massage therapy reported experiencing less pain and anxiety and showed higher serotonin and dopamine levels than controls in a relaxation intervention (93). On the other hand, actively giving a massage also shows stress-dampening effects: elderly retired volunteers showed lower anxiety scores,

salivary cortisol, and long-term catecholamine levels after giving a standard massage to infants in a hospital (94).

Taken together, these studies indicate a potential positive effect of not only being massaged but also of giving massages on subjective stress and neuroendocrine response, yet these have to be interpreted with caution due to the multifaceted uses of touch.

Pressure

An osteopathic technique called deep touch, using larger pressure of 44 N toward the rear head muscles for 90 s, led to an increase in HRV in $N = 35$ healthy participants (95). A deep hands-and-feet massage with pressure of about 2.5 N and a velocity of 1–5 cm/s for 80 min in 63 volunteers, on the other hand, led to a decrease in HRV and HR, together with a reduction in cortisol and insulin levels (96). In a study with 15 min of light and moderate pressure massage in $N = 20$ (97), the participants who received the moderate pressure massage exhibited a parasympathetic nervous system response characterized by an increase in high frequency (HF), suggesting increased vagal efferent activity, and a decrease in the low frequency/high frequency (LF/HF) ratio, suggesting a shift from sympathetic to parasympathetic activity that peaked during the first half of the massage period. On the other hand, those who received the light pressure massage exhibited a sympathetic nervous system response characterized by decreased HF and increased LF/HF. Therefore, pressure also seems to regulate the autonomous stress axes.

TOUCH BETWEEN HUMAN AND ANIMAL

Touch with an animal—trained or untrained—is an element of animal-assisted therapy, a non-pharmacological intervention aimed to improve human health in a wide range of conditions and patients. This type of therapy has become more and more popular for clinical conditions such as dementia, depression, and post-traumatic stress disorder, among others. Whereas studies appear to point at the beneficial effects of animal-assisted therapy for many health outcomes, they often address parameters other than stress reduction and, in part, suffer from methodological problems [e.g., as reviewed in Charry-Sánchez et al. (98)]. In the following discussion, we will focus on summarizing experimental studies meeting more rigid criteria with regard to the variation of the touch stimulus and the outcomes.

In the studies meeting our criteria, the animal of choice was usually the dog. In one such early study, HR and blood pressure were collected in 60 participants during different types of interaction with a dog (tactile, verbal–tactile, conversation in the presence and the absence of a dog, and rest) which each lasted for 6 min (99). For the tactile condition, the participants were instructed to fondle and pat the dog or let it sit on the lap while refraining from talking to it. Blood pressure was lower in the tactile and rest condition than during the verbal and verbal–tactile condition. Blood pressure was also higher during the conversation than during all other conditions. Thus, patting the dog and resting appear to have had similar effects, with no clear advantage of touch.

In a related study, 10 dog owners and 10 controls participated (100). The dog owners sat in a chair and petted, stroked, and talked to their dog for 3 min, whereas the controls just sat there. Levels of cortisol and HR to measure activation of the autonomic nervous system were assessed during the interaction/sitting still and the subsequent 57 min. In addition, insulin was measured to reflect vagal nerve tone and oxytocin to investigate the interaction's effect on stress and arousal. The cortisol and the insulin levels decreased in both groups, whereas HR only decreased in dog owners. At the same time, the dog owners' oxytocin levels increased shortly after the interaction. Thus, the decreased HR in dog owners could have been due to the touch itself or due to bonding with their dog. As cortisol also decreased in the group sitting still without a dog, the study only provides weak evidence for a specific beneficial effect of a dog on the stress response.

Whereas, the majority of studies was performed with a dog as touch target, there is also one study with a horse. HR and subjective arousal were measured in 18 participants before, during, and after stroking a horse for 90 s (101). HR was highest during the first 10 s of stroking and decreased steadily across the remaining time. Subjective arousal decreased as well, and tiredness increased. However, as no control condition was administered, it is not known whether the HR changes were specific to the stroking. Therefore, evidence of stress-dampening effects of touching an animal is not very strong in these studies so far.

Comparing Animal Touch With Quiet Reading

The role of the relationship with the dog was investigated in a study using quiet reading as a control condition (102). Here blood pressure, HR, and respirator rate were measured in 24 participants while they petted an unknown dog, a known dog, or read quietly for 9 min in three sessions. Blood pressure decreased more for petting the known dog than the unknown dog. *Post hoc* comparisons were only performed for the two dog conditions, but it appears as if the decrease in blood pressure was similar for the known dog and reading and that blood pressure was overall lowest for reading. Similarly, HR and respiratory rate appear to have been lowest for reading compared to the other two conditions where the values were rather similar. Thus, whereas petting a known dog had positive effects on arousal, quiet reading had the same calming effect.

In a similar study using an unknown dog only, blood pressure and HR were compared in 20 subjects during 11 min of reading and 18 min of petting a dog without any verbal interaction, preceded by 5 min of greeting the dog (103). Blood pressure, but not HR, was lower while petting the dog than while reading. However, since the duration of the two conditions differed by 7 min plus a "greeting period" of 5 min, it is not clear whether the change in blood pressure was due to the tactile contact with the dog or the passage of more time.

Reading aloud and quiet reading served as a control condition to petting and talking to a dog for 10 min in a study with 92 students (104). Before and afterwards, blood pressure, mean arterial pressure, HR, and state, and trait anxiety were measured. Mean arterial pressure, blood pressure, and HR were lower when

petting the dog than during all other activities. State anxiety was lower for quiet reading and petting compared to the other activities. Descriptively, all these measures were lowest for quiet reading. Petting the dog had, again, no clear advantage regarding stress reduction over quiet reading. However, this does not mean that tactile interaction with a dog is ineffective, but that quiet reading as a measure of stress reduction presumably has been underestimated. It is not clear if the mechanisms underlying these effects are similar. At least the bottom-up mechanisms are different since different sensory receptors and processes are involved.

Yielding similar results, a different study measured blood pressure and several hormones, among which is cortisol, in 18 participants before and after they read quietly or interacted with one of 18 dogs (105). This interaction included talking, stroking, playing with the dog, and scratching its body and ears for 30 min. Both conditions induced similar changes in all measures, and there were no significant differences in blood pressure, levels of cortisol, phenyl acetic acid, and dopamine. All these measures decreased similarly following reading and interacting with the dog. Only beta-endorphins, oxytocin, and prolactin increased more following an interaction with the dog than during reading. This points more at bonding than on specific effects on stress relief.

Nevertheless, all these studies indicate that petting a dog, optimally one that is familiar to the touch provider, can have calming effects that become obvious in various measures. This points at the potential of dogs to act as safety signals. Studies that investigated touch effects following stress induction can provide more insight into this potential, and three more recent ones will be described in the following section.

Touch Following Arousal Induction

One such study investigated the effect of petting a dog vs. a teddy bear on coping with a stressful situation in a large sample of 223 students (106). Blood pressure, state anxiety, and HR were assessed before and 10 and 20 min after the Trier Social Stress Test (TSST) (107). The participants had 5 min to prepare a short speech to be presented in front of a panel, followed by an arithmetic task. During both tasks, the participants were instructed to continuously pat the dog (experimental group) or a dog-size teddy bear (control group). Blood pressure was lower for all participants who had petted the dog compared to the teddy bear. State anxiety was lower for the group who had patted the dog. This effect was mainly driven by participants with high trait anxiety at the timepoint of 10 min after the TSST. HR was lower for the participants with high trait anxiety who had petted the dog compared to the teddy bear, but not for those with low trait anxiety. Thus, participants with high anxiety benefitted from touch with a living furry animal. However, it is also possible that the stuffed animal in itself already had a stress-reducing effect. This question was addressed in a different study where 58 participants were presented with a tarantula spider and told that they might be asked to hold it (108). Following this announcement, the participants split into five groups and asked to either pet a rabbit, a turtle, a toy rabbit, a toy turtle, or wait for 2 min (control group). State anxiety was measured at baseline, after stress induction, and after petting one of these objects or waiting. The participants who had petted an animal reported lower state anxiety compared to those who waited, whereas the anxiety scores of the participants who had petted a stuffed animal did not differ from the control group. The state anxiety scores following petting a real rabbit or a real turtle or soft- vs. hard-shelled animals/objects did not differ. The authors inferred that it is not the texture of the petted object or petting *per se* that lead to anxiety reduction, but only petting a living animal. Thus, this study provides evidence for the stress-reducing effects of touching a rabbit and even a turtle.

However, a further study where stress was induced by preparing and giving a speech, there was no evidence for the stress-reducing effects of petting an animal. In this study, blood pressure, HR, and state anxiety were compared in a sample of 36 participants that either kept a dog on their lap during preparation and the speech itself or not (109). While holding the dog, the experimental group was also allowed to talk to the dog and pet it. Whereas, preparing and holding the speech increased blood pressure, HR, and state anxiety, the presence of a dog did not affect these measures.

To conclude, the listed animal studies are difficult to compare due to a large variety of comparison conditions. Different animals were also used, and even the familiarity with these animals varied. Verbal interaction while petting may be a confounding factor due to the associated arousal. Measures of physiological arousal are often found to be lower during quiet reading than during interaction with an animal, but it appears difficult to draw conclusions regarding the stress-reducing effects from these setups. A better approach may be to first induce arousal and subsequently measure the effect of touch. Studies with this approach show some, however inconclusive, evidence for the stress-reducing effects of living animals compared to toy animals.

TOUCH BETWEEN HUMANS AND ARTIFICIAL OBJECT

In the study of Robinson et al. (110), participants from a residential care facility interacted with and touched the robot seal "Paro" (111) for 10 min (see **Figure 2A**). Paro responds to visual, auditory, and tactile stimuli by moving or making small noises. Blood pressure and HR were measured before and directly after the interaction and 5 min later in 14 participants who interacted with Paro. Whereas, all these participants touched Paro during the 10 min that they interacted with him, it is not specified how much time of these 10 min was devoted to touch. Compared to a control group of seven residents who did not interact with Paro, the experimental group's systolic and diastolic blood pressure decreased from baseline, and their HR also decreased over time. Diastolic, but not systolic, blood pressure increased again 5 min after the robot had been removed. Whereas, these results are promising, the low number of participants warrants replication.

A similar kind of furry-animal like device is the "Haptic Creature" (112). The Haptic Creature (see **Figure 2B**) recognizes touch and responds by different forms of breathing, purring, and ear stiffness. Following a baseline where 38 healthy participants

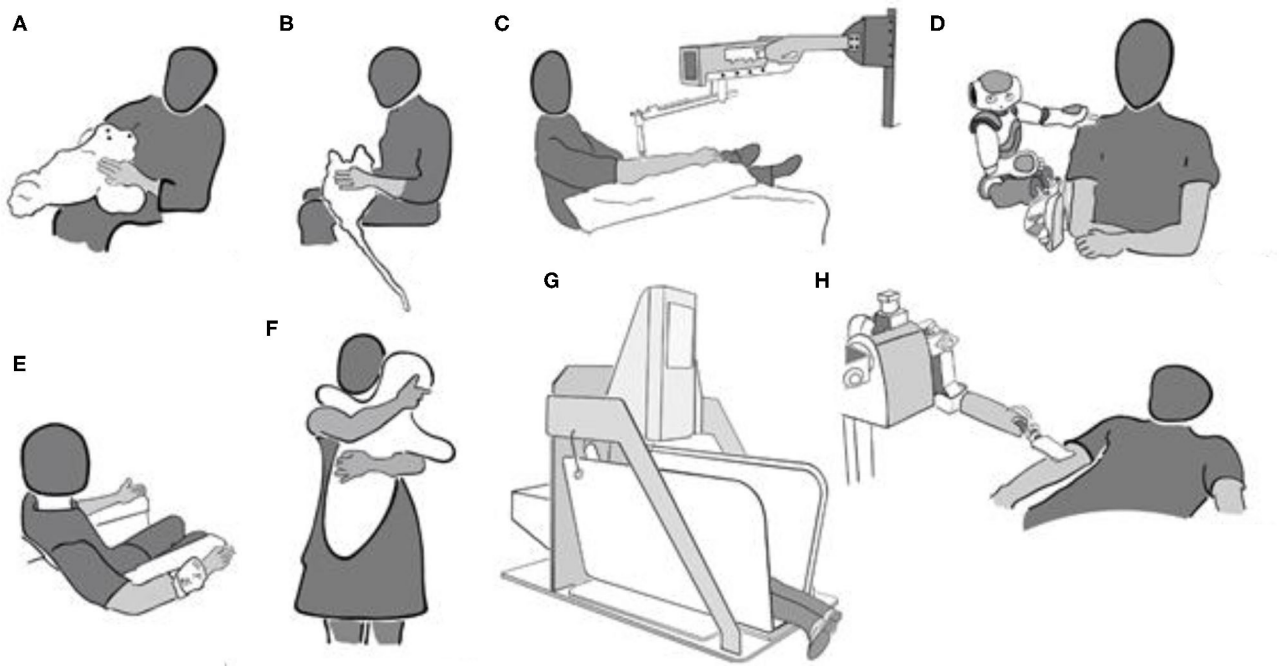

FIGURE 2 | (A–H) Schematic overview over devices used to perform touch.

were sitting alone with the robot out of sight, the Haptic Creature was placed on their lap either turned off or while simulating the breathing of an animal (112). Galvanic skin response (GSR), respiration level, and HR were recorded during stroking and baseline, each lasting for 75 s. One hand was used to stroke the robot, and the other was kept on its side where the breathing can be felt. Subjective reports of arousal, emotional valence, and anxiety were collected after baseline and after interaction with the active or inactive furry robot in a within-subject design. When the robot was breathing compared to be inactive, respiration rate, HR, and state anxiety were lower, whereas emotional valence was more positive. Differences between baseline and interaction periods were not analyzed, but descriptive data suggest that GSR increased for both active and inactive interaction compared to baseline, whereas subjective arousal and valence were only affected by active interaction. HR and respiration rate also increased for the Haptic Creature being switched on or off, but more so when it was inactive. State anxiety also increased for the inactive robot compared to baseline, but it decreased for the active robot. Thus, it was not the mere presence of the Haptic Creature that produced relaxing effects (apart from those captured by GSR), but the fact that it was animated.

Investigating the effect of longer-lasting touch on autonomic function, Triscoli et al. (14) used a paintbrush attached to a robotic device (linear tactile stimulator; Dancer Design; St Helen's, United Kingdom) which delivers stroking at a highly replicable force (**Figure 2C**). The participants were stroked on their forearm with a slow CT-targeted velocity of 3 cm/s for about 35 min. This type of stimulation intends to mimic a gentle human caress, and the healthy participants rated it as similarly pleasant as touch at the same velocity performed by hand (19). HRV increased during stroking touch, but not during vibration at 100 Hz in a comparison group. This might indicate improved cardiovascular reactivity by stroking touch. At the same time, subjectively reported stress was not different following any type of touch compared to before. Cortisol levels decreased for both types of stimulation, leaving the question open on whether the changes in cortisol were due to lying still for a long time or to having been touched.

Touch Following Arousal Induction

Several studies assessed the potential beneficial effects of touch after inducing arousal or some form of stress. In the study of (113), 67 healthy participants were touched by a "NAO" - robot while viewing movies with multiple startling scenes (see **Figure 2D**). GSR, HR, HRV, and respiration rate were recorded during a baseline in which a neutral movie was shown and compared to the activity during the scary movie. For eight times during the movie, the robot touched the participant on the shoulder and the upper arm for between 10 and 40 s. At the end of the touch, the robot also uttered some calming words ("Luckily, it is just a movie"). The participants in a control group watched the movie with the robot being present and moving in a similar way, but without making physical contact. Subjective ratings on different scales were collected before and after the scary movies. HR increased for the participants who did not receive touch, whereas it decreased for the participants who received touch. It appears as if there was no difference in the other measures. The subjective ratings regarding arousal and positive and negative affect were also not different. Thus, there is some evidence

for arousal reduction through touch, but as touch always was combined to calming words, the respective contributions to the observed effect are not known.

In a similar experiment by the same group, additional saliva samples were collected and respiration rate was measured (114). Touch lasted here between 30 and 55 s. In this experiment, no differences between touch and the control condition were found for any of the measures (cortisol, GSR, HR, HRV, affect scores, and respiration rate). As a potential explanation for the discrepant findings in these two studies, the authors suggest that the participants in the 2019 study were already familiar with the robot before the experiment began. Getting acquainted with the robot may have promoted the stress-reducing effects by its touch. This is a plausible explanation given the differences found in animal studies between dogs known to the participant and unknown dogs.

Also using an emotional film, Cabibihan and Chauhan (115) performed a study on 30 healthy (student) participants. Ten of them received touch by their partner, 10 received no touch, and 10 received tele-touch (see **Figure 2E**). With this tele-touch system, pressure, and temperature information from the experimenter's hand are transmitted and presented to the participant *via* a cuff-like device as vibration, heat, and tickle. HRV and GSR were collected while the participants looked at an emotion-eliciting film. Touch was applied during the film scene that had shown the highest heart rate in pilot studies and lasted until the end of the movie (for 3 min and 29 s). HRV and GSR variations were higher in the control group than in the human and tele-touch groups. HRV for human touch and tele-touch did not differ, but GSR variation was higher for tele-touch than for human touch.

Several studies assessed the effect of "Hugvie," a cushion with the shape of a minimalistic human (see **Figure 2F**) during telephone conversations with an unknown human—which may be considered an arousing situation. A sample of 18 women (mean age, 64) was split into two groups that had a 15-min conversation with a stranger either with a mobile phone ($N = 9$) or with the mobile phone placed inside Hugvie ($N = 9$). The cortisol levels were lower for the participant group who had used Hugvie (116), whereas subjective reports of calmness and positive and negative affect did not differ between the two groups. In a similar study with 29 healthy elderly participants (men and women with a mean age of 65 years), state anxiety following the conversation was lower when Hugvie had been used (117). State anxiety was lower following conversation in the group of 14 participants that had used Hugvie, but there was no difference in subjective stress and cortisol levels. In a further study, 19 participants listened to stories when they were transmitted *via* a speaker placed inside Hugvie or through a speaker in the absence of Hugvie (118). When the speaker was inside Hugvie, the participants hugged it while listening. Global field power, power in all frequency bands, and permutation entropy were lower during listening and hugging Hugvie than during listening alone and during rest. This was interpreted as indicating higher levels of relaxation when using Hugvie.

Taken together, the evidence points at some positive effects of robot interaction on stress-related measures, but only in some and not all measures. As the measures used also differed in almost every study, the results are difficult to compare.

Mechanic Pressure Devices

Other studies have looked into the stress-reducing effects of mechanic devices applying a constant pressure. For example, HR and state anxiety were compared in a group of 23 healthy students when they self-administered deep-pressure touch during 15 min while they were sandwiched in an apparatus called "Hug'm" (for "hug machine") and when they just lay in the apparatus without deep pressure (119) (see **Figure 2G**). State anxiety and HR were not different in the two conditions. There was a trend for a larger anxiety reduction in participants with high trait anxiety when the machine was "on" compared to "off" than in participants with low trait anxiety. Using a similar machine, but with the squeeze being applied laterally and a larger amount of pressure, 40 healthy students were asked to describe their experience in the so-called squeeze machine (120); 45% of them used terms such as "relaxing." Furthermore, ratings of relaxation were collected from 18 participants following stationary pressure and fast and slow rhythmic pressure of 3 min each. Relaxation was rated as being highest for slowly pulsating and stationary pressure compared to fast pulsating pressure.

Very recently, a series of experiments in healthy volunteers ($N = 78$ in total) evaluated the effects of pulsating pressure delivered with a sleeve-like device. Oscillating low compression of 30 mmHg resulted in a subjective decrease of anxiety similar to that obtained by slow CT-targeted stroking (121). High compression of 65 mmHg did not have such an effect.

Whereas, such pressure machines may not be assigned any human qualities such as intention, this appears to be different for devices with human-like features such as language. In this case, the beneficial effects of machine touch might be modulated by the assumed intention behind the touch. This is indicated by a study in which 56 healthy participants, divided into four groups of 14 participants each, received touch from a robotic nurse that verbally either gave a warning before the touch or not and, in case of the warning, gave reasons for the touch (122). The robot used a spatula-like end effector that was covered with a towel for moving across the participants' arm (see **Figure 2H**). Before or after the touch, depending on the condition, the participants received verbal information by the robot that they were going to get cleaned or received a comforting statement ("Everything will be alright; you are doing well.") Affective touch was rated as more arousing than instrumental touch. Positive and negative affect did not differ for the two touch types. Touch preceded by information was also rated as more arousing compared to when the information was given afterwards, and positive affect was lower for touch preceded by information. GSR increased following contact and during the touch in all four conditions, independent of whether the participants had received information before. At the same time, 10 out of 28 participants who had received comforting touch reported that they would have preferred if the robot had not touched them. In the group receiving instrumental touch, only one participant would have preferred no touch. This may point at the low acceptance of robotic touch which is explicitly performed with the attention

to comfort. In the case of human touch, the assumed intention also determines touch perception and its effects (123, 124). On the other hand, the findings may have to do with the way the information was conveyed, as the authors themselves point out. More controlled experiments on such contextual effects are needed.

As with the animal studies, the low number of studies meeting our criteria and the different effect measures used (see also **Supplementary Table 1**) make it difficult to compare their results. However, altogether one may conclude that touch by various non-human agents either has no or a small calming effect, which might be modulated by the assumed intention of the agent. Presumably, the appearance of the robot also plays a role here, as a too-human-look of robots can also have an opposite, negative effect on the interaction partner. This has been described as the "uncanny valley" effect [e.g., Moore (125)], where a robot resembling a human almost, but not perfectly, induces feelings of unfamiliarity and eeriness.

CURRENT TECHNICAL ADVANCES IN ROBOTICS

While in classical industrial robotics the situation of a robot touching a human was considered as an emergency and had to be avoided, new research fields of human–robot interaction (HRI) and human–robot collaboration have emerged, where robots are expected to work side by side and even interact with humans similarly to a social interaction between two humans. Therefore, it is of highest relevance to evaluate these new and innovative systems also in regard to their psychological effects.

Assistive robots can be classified into two main categories (126): On the one hand, there are rehabilitation robots like smart wheelchairs (127) and exoskeletons, which can perform, e.g., a movement of a paralyzed hand by moving the hand for the patient (128). There is a collaboration with the human, yet no cooperation (129). The robot touch lies in the realm of HRI, as robots only act on a human and there is, normally, no joint effort with a human [e.g., handshaking; Shiomi et al. (130)].

On the other hand, there are socially assistive robots that directly interact with humans (131). This category includes service robots that can perform tasks, like handing an object and also washing or feeding (132, 133), and companion-like robots (111, 112). Both kinds of socially assistive robots have physical contact with humans; therefore, their touch can be expected to have psychological effects, and could be designed to act calming.

In general, from a technical view, humans are often considered as non-deterministic factors (134), that is, systems with unpredictable outputs despite identical inputs. This makes the development of HRI systems highly challenging and requires interdisciplinary collaboration between robotics experts, cognitive scientists, and psychologists in order to make human behavior at least, to some amount, more predictable by determining regularities and defining preferences.

Until now, robotic touch has been mostly investigated in the context of social robotics with humanoid robots (see "Section Touch between humans and artificial object") when the robot actively touched a human, but there are also a number of studies where the robot is touched by a human and responds with different forms of feedback (110–112). The feedback of the robot may be important for shaping the experience of the touch provider, as indicated by the results from the animated vs. non-animated Haptic Creature (112) and also from a living animal vs. a stuffed animal toy (108). When programming and building social robots, studies in which a robot is the toucher and a human user is the touchee are of high interest to determine the effects of different kinds of robotic touch on stress outcomes. Ideally, there are identifiable characteristics of the touch, the robot, and the situation, which allow specifying when robotic touch can be experienced as a safety signal and when not.

Although robotic touch is usually associated with humanoid robots (135), plain touch arousal is feasible with just a one degree-of-freedom (DOF) linear actuator (45, 136). In this basic research experiment with a machine without human appearance, the trajectory, the moving speed, and the contact force were predefined and had no variance. However, it is arguable if variations in trajectory parameters are beneficial for a natural feeling of repetitive touch. On the other hand, in the study of Willemse and van Erp (137), a humanoid robot "NAO" with 25 DOF, touch sensors, and cameras were used. This allowed for very different and sophisticated movements toward and pressure onto a person who might move herself. For the touch experiment, a teleoperation mode was utilized. The operator was initiating a social touch using one robot (master), while the unaware participants were touched on the shoulder by another robot (slave) connected to the first one. It is worth investigating whether these differentiated ways of touch influence its stress-reducing effects.

A simplified robotic touch process is similar to a grasping action and can be divided into the following steps (see **Figure 3**): (1) perception of the area of interest (e.g., human forearm), (2) path planning and end-effector movement from the initial position to the pre-touch position, (3) searching contact with human body, (4) trajectory/surface following, and (5) disengagement and moving back to the initial position. Whereas, the movement to the pre-touch position (step 2) can be realized with a simple position controller, an interaction control policy is necessary for the trajectory/surface tracking (step 4). A survey of interaction control schemes with static and dynamic model-based compensation is presented by Chiaverini et al. (138). Especially in steps 2–4, technical adjustments can be done to optimize the effects of touch. This indicates the complexity of parameters that has to be taken into account.

One step into this direction was the study of Reed and Peshkin (139), where the authors attempted a "Haptic Turing Test" in an experimental setup with a two-handled crank with a hidden motor. A Turing test assesses a machine's ability to exhibit intelligent behavior comparable to or even indistinguishable from human behavior. For the investigation of dyadic physical communication, the authors designed a simple task of mutually acquiring a one-DOF visual target. In one of the experiments, 10 out of 11 participants who worked with a hidden robot in the presence of a confederate were under the impression that

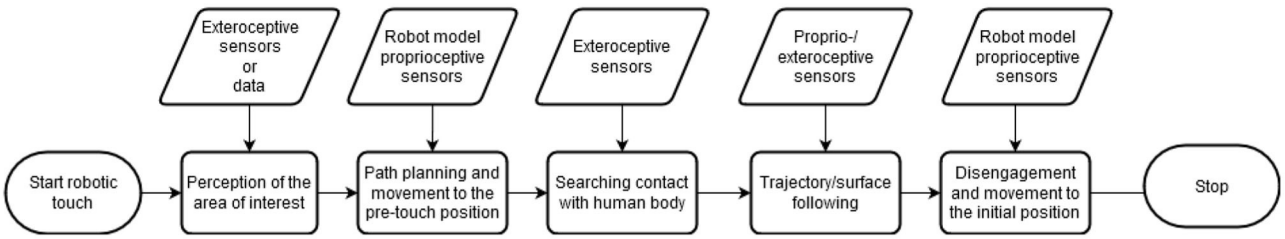

FIGURE 3 | Flow chart of a simplified robotic touch. Steps 2 to 4 are expected to crucially influence the perception of touch and, therefore, its role as safety signal.

they were working with another human. A "Touch Turing Test" can also be designed. The human visual and auditory systems provide powerful sensory input that complicates isolated touch experiments with humanoid or industrial robots visible to the participants. The Touch Turing Test with an autonomous robot executing variable touch motions in the presence of a confederate could help investigate the hypothesis on whether or not a robot is able to simulate human touch motion sufficiently well to deceive human participants—and whether deception is a good idea in this case. In addition, recent technological advances in virtual reality (VR) (140) offer a new modality for touch experiments. Humans can be touched by a robot in reality, and a digital twin in the form of a humanoid robot, robotic arm, or even a human could be shown to the participant in VR. Similar to the experiments with the "Repliee Q2" (141), the "uncanny valley" effect (see "Section Mechanic pressure devices") can be investigated with addition of the tactile sense and underlining the relevance of taking the psychological context of touch into account. Studies making use of these possibilities could provide important insight into the optimal properties of robotic touch.

In an overview of interpersonal touch, Gallace and Spence (142) point out that surprisingly little systematic scientific research has been conducted on this topic. The characteristics of tactile stimulation that are needed for the touch to be perceived by a human as interpersonal rather than as mechanical are still unknown. Furthermore, in order to realize an autonomous robotic touch in the context of physical HRI, it is essential that the robot can use sensory feedback and perception. Besides the visual (e.g., RGB and depth cameras) and force-torque sensor technologies already widely used in HRI, tactile and proximity sensors could enhance the performance of the robotic touch system. Multi-modal tactile proximity sensors (143, 144) can be applied for the searching contact phase (step 3 of **Figure 3**) and during the trajectory tracking phase for the pressure/force feedback.

Finally, latest breakthroughs in artificial intelligence research can be employed both as a control policy model [e.g., reinforcement/machine learning (145)] and as a feedback to the robotic system using artificial emotional intelligence (146), therefore already allowing to adapt the kind of touch during the interaction. For instance, facial expression recognition can achieve very high accuracy (∼97%) under laboratory conditions (147). Facial expressions or acoustic speech can be perceived by robot sensory systems and used as a feedback or reward signal for unsupervised learning. In a technically similar manner, a robotic system will be able to learn a personalized robotic touch based on the emotional feedback of the human participant and could account for individual preferences or clinical contexts. For example, the robot could adjust pressure based on the facial expression of the touch receiver. Such a dynamical adaptation to an individual's response would allow for greater flexibility and therefore presumably increase the likelihood of positive effects in the receiver.

Advances in robotics research as well as technological progress in hardware development bring robots from structured factory environments to human homes and enable new communication modalities for improved HRI. One of the important aspects in physical interaction and yet to become a growing research field in HRI is robotic touch, bringing robotics and psychology experts together.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Taken together, the majority of previous research reviewed in this article indicates a calming/stress-relieving effect of touch, irrespective of the agent that is touching or being touched: effects have been shown both after actively touching, and being touched. Humans, animals, and even robotic devices may induce a cascade of reactions from tactile perception to insular control of the amygdala and subsequent regulation of the stress axes, resulting in dampened arousal. Both from onto- and phylogenetic perspectives, the health-related beneficial effects of physical interpersonal contact seem plausible, as they might signal safety from harm in the presence of the family or the community. Therefore, we propose that, under appropriate conditions, touch from various agents can act as social signal for safety and support mental and physical health. Clinical implications can be drawn for touch as a treatment for an acute physical or mental health problem under consideration of the disorder-specific reactions to touch and also for preventive applications during phases of high stress in order to reduce the chance of stress-induced diseases (148).

Interpersonal touch during medical treatments has been evaluated in a number of studies and suggests that touch can

improve treatment outcomes [for a recent review, see (149)]. In their overview on the potentially beneficial effects of touch for patients treated in an intensive care unit, Harris et al. suggest that interpersonal touch is most effective when provided by a relative in a lightly moving way (in contrast to static touch) and that dimmed light might increase the calming effects. These conclusions are in line with research that light massage and touch can improve psychobiological stress levels and decrease pain in older patients with dementia (150) and patients with pain due to cancer (151). A touch therapy program in autistic children has been suggested to improve parent–child communication (152). Harris et al. (149) also support the notion that, rather than interpersonal touch *per se*, it is the affective level and the interpretation of an adequate physical contact as a gesture of support and closeness which can attenuate stress. This is in line with studies suggesting that some individuals (e.g., those who are anxious or traumatized) might prefer to have no physical contact to others or physical contact in a controlled setting only (19, 106). Above this, skin contact is associated with increased levels of intimacy and can bear the risk of re-traumatization after sexual trauma. Therefore, touch in a medical context (e.g., prior to surgery, during intensive care, or in a nursing home) should be well-elaborated in order to act beneficial. In line with this, in some vulnerable situations, being touched by a machine might be preferred over touch by an unknown person, such as when being washed. Another solution would be personalized touch that can be controlled by the individual's feedback itself.

Machine-based touch might also be helpful as a preventive procedure for lonely individuals or individuals in quarantine who cannot rely on human touch. This review article focuses on the basic research question of touch by different agents acting as safety signal; therefore, we did not discuss studies on infants or clinical patients in detail. However, this would, of course, be important for future applications of touch.

Expectations, beliefs, and the whole context of the interaction need to be taken into account, not only in clinical settings but in general, in order to determine the beneficial effects of touch [see (51)]. For example, sex/gender, and the romantic attraction to the interaction partner (153) have been found to influence the touch experience. The preference for physical contact with another human or an animal also differs between individuals (154–156) and is subject to personal experience such as trauma [e.g., Strauss et al. (19), Maier et al. (157)], touch deprivation (158), and attachment style (155).

Thus, various interindividual and context factors can also influence the effectiveness of touch as a safety signal. As stated by Older (159): "Appropriate touch becomes inappropriate when given at the wrong time, in the wrong dose, or to the wrong person." Nevertheless, actual negative interaction situations have barely been investigated. Stress- or fear-dampening effects can only occur if the touch and the touching agent are not experienced as threatening or potentially dangerous. To the best of our knowledge, however, no study has yet focused on these different aspects of positive vs. negative anticipation of touch and the type and the quality of the relationship between the touching person or agent and the individual receiving the touch. Rather than the objective characteristics of the touch itself, it might be the interpretation and the social situation which makes touch either act as a safety signal or a threat. To disentangle these effects, research systematically testing different contexts, and expectations would be necessary. Nevertheless, when reviewing the literature, it becomes clear that this field of research is facing several challenges. In studies of human touch, there is a large heterogeneity of the way touch was performed or instructed. In ecologically more valid studies such as those regarding touch in close relationships and therapeutic touch, e.g., massages or animal-assisted therapy, the effects of touch may be intermixed with the effects of other experiences in this social interaction. In some studies, other aspects such as visual appearance or verbal communication are not controlled for or there is no control group at all. Therefore, the results have to be treated with caution in regard to the basic research questions on touch as a safety signal.

Regarding the stress- or fear-markers assessed, there is also a lot of variance. Cortisol, as an established marker of HPA activity (67), is the most widely used physiological measure, which improves comparability among studies, yet studies reporting other outcomes are difficult to integrate (see **Supplementary Table 1** for an overview over the measures used). Another limitation of some studies is the critically small sample size that may hamper the generalization of the results. However, despite these limitations, the sum of research points toward similar effects, which is the regulation of the stress axes by touch. Future research needs to address the issues listed above to provide a clear picture on the physical conditions in which touch acts as stress-dampening and by which underlying neural pathway it affects the stress axes. Our recommendations are both to design systematic research studies comparing different kinds of touch and also use established measures in the field.

Technical advances also open new research innovative directions: advances in machine learning and artificial emotional intelligence will allow the development of feasible robotic systems, which can account for individual preferences in terms of personalized touch. Such touch by robots or machines might provide new options for individuals with an aversion for touch by another human [e.g., Hielscher and Mahar (154), Strauss et al. (19)].

In conclusion, the broad and multifaceted range of research on touch given by several agents can be summarized as a promising field, yet only at its very beginning. From a clinical perceptive though, robots or machines giving stress-relieving touch could be of high potential in healthcare, e.g., in patients in spatial isolation of quarantine, in individuals refusing touch by another person, in lonely people, or in nursery homes.

AUTHOR CONTRIBUTIONS

ME and US conceived the presented idea. ME led the review and the development of the manuscript, searched and summarized

literature on human–human touch and on the neurobiological foundations of stress regulation. BD searched and summarized literature on touch in relationships. IM contributed with technical expertise and wrote on advances in the field of robotics. US searched and summarized literature on human–robot and human–animal studies. All authors have written and proofread the manuscript. ME and US revised the manuscript following the reviewers' comments.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.555058/full#supplementary-material

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Graded Empathy: A Neuro-Phenomenological Hypothesis

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The neuroscience of empathy has enormously expanded in the past two decades, thereby making instrumental progress for the understanding of neural substrates involved in affective and cognitive aspects of empathy. Yet, these conclusions have relied on ultrasimplified tasks resulting in the affective/cognitive dichotomy that was often modeled and overemphasized in pathological, developmental, and genetic studies of empathy. As such, the affective/cognitive model of empathy could not straightforwardly accommodate and explain the recent surge of neuroscientific data obtained from studies employing naturalistic approaches and intergroup conditions. Inspired by phenomenological philosophy, this article paves the way for a new scientific perspective on empathy that breaks thorough the affective/cognitive dichotomy. This neuro-phenomenological account leans on phenomenological analyses and can straightforwardly explain recent neuroscience data. It emphasizes the dynamic, subjective, and piecemeal features of empathic experiences and unpicks the graded nature of empathy. *The graded empathy hypothesis* postulates that attending to others' expressions always facilitates empathy, but the parametric modulation in the levels of the empathic experience varies as a function of one's social interest (e.g., via intergroup or inter-personal cues) in the observed other. Drawing on multiple resources that integrate neuroscience with phenomenology, we describe the potential of this graded framework in an era of real-life experimentation. By wearing lenses of neuro-phenomenology, this original perspective can change the way empathy is considered.

Keywords: empathy, neurophenomenology, magnetoencephalography (MEG), intergroup conflicts, cognitive empathy, affective empathy, empathy dichotomy, phenomenology

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PHILOSOPHICAL OUTLOOK ON EMPATHY

Phenomenological Definition

Empathy is a multifaceted phenomenon with several meanings depending on the context and discipline in which it is used. Contemporary debates in the philosophy of mind ascribe this term to our ability to grasp other subject-expressed mental states (1). This suggestion is in line with (2) concept of the German word "Einfühlung," which was translated into English as empathy by (3). From a phenomenological perspective, empathy primarily amounts to direct perception of other subjects' mental states by attending to their facial expressions, gestures, and bodily patterns (4). (5) clarify this idea, noting: "I can attune to others' intentions and emotions on the basis of what I perceive of their behaviors and bodily expressions.… To the extent that I understand their intentions and emotions

in this way, that just is what phenomenologists call empathy." Nonetheless, for phenomenologists, empathy is not restricted to a basic sensory–motor attunement, but can extend to higher layers of interpersonal understanding (6, 7) that unfold as a function of the social situation at hand (8, 9); this will be detailed in the following sections.

Inner Modeling (Simulation/Mentalizing)

Philosophers discuss the term empathy in the context of the question how we understand other minds. Contemporary debates in the philosophy of mind propose that emphatic understanding rests on either reflection (i.e., simulation) or introspection (i.e., mentalizing) [e.g., (10, 11)], both of which go beyond primary sensory–motor attunement (12). These approaches are based on the cartesian view that the mental is hidden and individualistic, and therefore the subject's emotions and attitudes are not accessible to other people.

Reflectionists suggest that empathy operates through a self-experience-based model. According to this hypothesis, which is known as "simulation theory," attending to others' embodied behaviors generates a process of inner imitation. Consequently, the subject can understand others' attitudes and intentions from a first-person perspective without the need for mentalizing (9, 13). Proponents of introspectionism (i.e., mentalizing), which is known as "theory–theory" suggest that empathy unfolds at a higher level of intersubjectivity through a process of inference that is based on the acquisition of a "theory of mind" during the early phases of childhood. This ontogenetic transition occurs when children around the age of 4 years develop a capacity to infer others' beliefs and intentions [e.g., (14)]. Establishing a third-person point of view allows subjects to grasp others' motives through observation, and this facilitates empathic resonance (15).

Beyond the Inner-Modeling Dichotomy

In contrast to both of these approaches, interaction theory, which is rooted in the phenomenological concept of direct perception (16), emphasizes the constitutive role of embodied engagements in fostering empathic understanding (17). Interactionists maintain that the socio-enactive character of humans' encounters (18) allows to immediately grasp others' embodied mental states without the need to employ self-experience-based model or reflect on their intentions and beliefs (9, 12). In other words, at a primary level, empathic understanding is manifested simply by attending to others' bodily behaviors within a social context. The focus on the role of environmental and intersubjective factors in driving interpersonal resonance downplays the dichotomy between the perceiver and the perceived (19). Interactionism shows that empathy is established through a dynamic process comprising a shared context, bodily expressions, and the impressions that these expressions trigger [(20), p. 33]. This approach emphasizes that in social encounters, we are not passively gathering information about other people. Rather, others' embodied behaviors are manifested and grasped in relation to the context of the encounter and the dynamics of our engagement (8, 21, 22). While "theory of mind" views in the philosophical literature emphasizes things that have an epistemic quality such as beliefs, intentions, and judgments, interactionists suggest that primary empathy can already unfold in young infants through attuning to rhythms and dynamics in dyadic interactions (23, 24). Interactionalism helps to unpick the graded nature of empathy by emphasizing that this early form of empathic resonance can extend in later ontogeny to include advanced types of interpersonal understanding (20).

NEUROSCIENTIFIC OUTLOOK ON EMPATHY

The Affective/Cognitive (i.e., Simulation/Mentalizing) Dichotomy

Along with the technological progress in neuroimaging, in the past couple of decades emerged the scientific research on the neural correlates of empathic responses. During the first decade of this millennium, evidence gradually accumulated to distinguish between affective (a.k.a., emotional, embodied simulation, or resonance) and cognitive (a.k.a., mentalization, theory of mind) empathy (25, 26). Accordingly, *affective empathy* (i.e., *simulation*) was ascribed to automatic processes reflecting vicarious pain and feelings; it was thought to emanate from sensorimotor and affective neural substrates: the sensorimotor cortex area, the anterior insula, and the anterior cingulate cortex. By contrast, *cognitive empathy* (i.e., *mentalizing*) was ascribed to higher-order processes reflecting vicarious mental states and understanding; it was proposed to emanate from higher-order cortices including the prefrontal cortex, temporo-parietal junction, and the superior temporal sulcus. Drawing parallels to other dichotomous models such as the lexical/phonological model of language (27, 28), the affective/cognitive model leaned on lesion studies (which are in themselves dichotomous) demonstrating direct mapping between specific neural systems and impairments in affective and cognitive empathy (25), and has allowed to explain various manifestations of empathy and its origins. For instance, different mental disorders like autism (29), schizophrenia (30) and psychopathy (31), or heritability variance (32). Further, studies on empathy development implemented the dichotomous framework to study the developmental trajectories of affective and cognitive empathy. For instance, it was claimed that the first emerges early in development (33), whereas the second has a more prolonged developmental course from childhood to adulthood (34, 35). Likewise, rudimentary neural networks are mostly in place by the end of infancy, whereas frontal areas reach maturity by young adulthood (36). This explains neurodevelopmental patterns of empathy: a complex change in the affective–cognitive empathy balance that matures with age both at the neuroanatomical-functional (37) and the neuro-rhythmicity (38–40) levels.

Moving Beyond the Affective/Cognitive Dichotomy: Ecological Validity, Neural Mechanisms, and Phenomenological Considerations

Despite being paramount for the understanding of empathy, the dichotomous framework gradually revealed several limitations. First, it did not accommodate phylogenetic evidence pointing

to the interconnected nature of the two components along evolution and across species (41). Second and perhaps more important to the current manuscript, dichotomous reports often leaned on simplistic designs and dualistic approaches that consolidated the validity of this dissociation. For instance, findings from numerous empirical experiments relied on simplistic artificial stimuli in tightly controlled lab contexts that convey distinct cerebral mapping patterns and that isolate one of the two components (42). Likewise, even in lesion studies (25), there was no direct dichotomous matching between the lesion and the behavioral outcome (43). Research on the multiple facets of empathy: neuroscience, development, heritability, and psychopathology—typically applied artificial and simplified experimental settings or models. In a way, methodology (e.g., questionnaires, coding schemes, stimuli) was developed and designed to pre-target the two components; hence, it was not surprising that findings straightforwardly matched the model. This parsimonious approach was crucial for neuroscientists to gain traction on the contribution of elemental socio-cognitive components (i.e., affective and cognitive) to the phenomenon of empathy (44). However, relying on overly simplified models (i.e., affective/cognitive dichotomy) did not allow drawing broader conclusions about empathy in more ecologically valid contexts, in particular, during interpersonal interaction (45) and intergroup contexts (46).

At the onset of the second decade of this millennium, a gradual emergence of naturalistic experimental settings began to establish in the cognitive and social neurosciences (47, 48), including in the neuroscience of empathy (44). This paradigm shift gradually conveyed the notion that this dichotomy is somewhat artificial and overestimates the dual distinction in live empathic encounters that are dynamic and interactive. As such, in 2015, a new lab paradigm was suggested to investigate the two systems in parallel (49). Further, the shift toward naturalistic experimentation showed a growing body of evidence that could no longer be accommodated by the dichotomous framework. For example, Goldstein et al. investigated brain-to-brain coupling during interpersonal empathic encounter and found that it was associated with the level of empathic accuracy of the empathizer (45). In another study, Levy et al. investigated the impact of intergroup representations on neural empathy and empathic behavior; the study found that empathy brain response was expressed by various rhythmic events occurring at different timings, and was amplified and synchronized as a function of intergroup representations and the emotions that they arose (46). These findings were hard to accommodate by the dichotomous model of empathy, and attempting to do so would miss important facets of the data. This is not surprising because in comparison to simplified and controlled experiments, experiments that involve naturalistic aspects of social life engage qualitatively different patterns of neural activity (50). Hence, to capture non-dualistic neural mechanisms, instead of relying on anatomical segregation, more advanced methods (e.g., multi-rhythmic temporal representations in MEG) should be employed (51, 52).

Beside the shift in methodology, phenomenological investigations, which by definition focus on lived experiences, also pointed out the need to move beyond dichotomy. For example, phenomenological studies of psychopathology suggest that anomalies of empathy in mental disorders do not necessarily rely on the affective–cognitive dichotomy, but rather unfold and amplify at both levels—often simultaneously (53). In autism, for instance, reduced capacity for attuning to affective cues (54) involves modification in the capacity to grasp others' mental states toward a shared context, and this amounts to difficulties in establishing gestalt perception of social scenes (55). The interplay between different aspects of empathy is also evident in other disorders: Schizophrenic patients show oscillations of self-other perspectives that diminish their ability to effectively follow others' embodied mental patterns and to discern their intentions (56, 57). In borderline personality disorder, and most likely in social anxiety disorder and posttraumatic stress disorder, the affective response to the bodily presence of others is altered, and this involves modifications in what are considered as "cognitive" aspects of empathy. Specifically, subjects with these types of disorders tend to overemphasize negative affective cues at the expense of other socio-affective stimuli (58), and this impacts interpersonal resonance and consequently the way the world appears to them (59).

Moreover, recent neuroimaging studies show that dichotomous modeling fails to accommodate empirical evidence that integrates lived experiences. A good example is the study by Grice-Jackson and colleagues on pain empathy (60, 61), which is basically elicited by observing others in painful situations (62). Typically, neuroscientists interpret pain empathy by implementing the dichotomous framework, thereby arguing that the vicarious perception of pain triggers simulation (63), while no mentalizing is elicited unless participants are explicitly instructed to take the targets' perspective (64, 65). By contrast, Grice-Jackson and colleagues examined empathy in the brain while integrating lived experiences (i.e., neuro-phenomenology) and found a graded phenomenon. The first group of participants (i.e., experiencers) reported no conscious experience of vicarious pain, the second group reported experiencing affect, and the third reported experiencing a sensorial and localized experience of pain while perceiving vicarious pain (61). This is a very good example of the difficulty in implementing the dichotomous affective/cognitive framework while relating to lived experiences of human beings. Noteworthy, a similar approach was recently conducted in two MEG studies while instead of investigating empathy, they addressed conscious perception (66, 67). In brief, while previous accounts claimed that conscious perception is dichotomous, that is, all-or-none [for a review, see (68)], phenomenal evidence pointed to a rather graded experience of conscious perception (69, 70). Similar the study of empathy (60, 61), by implementing a neuro-phenomenological approach, conscious perception was empirically demonstrated as a graded phenomenon (66, 67). *Altogether, inspired by a recent phenomenological outlook on levels of empathy that we describe in the following section, we contend that a new neuro-phenomenological framework is needed*

to accommodate the methodological paradigm shift and the necessity to integrate empirical measures with lived experiences.

THE PHENOMENOLOGICAL ACCOUNT OF GRADED EMPATHY

The focus on the experiential features of empathy suggests that it is a multilevel process (7). Empathy can range from basic motor attunement to extended social understanding (12, 22), in accordance with the situation at hand and group factors (8, 9). (20) suggests that empathy consists of three levels of interpersonal understanding. In what follows, we draw on the phenomenological view on empathic understanding to develop a graded account, which emphasizes the crucial role of group contexts in shaping the levels of empathy.

Primary Empathy

From a phenomenological perspective, the first layer of empathy is direct perception (71). Phenomenologists emphasize that in direct face-to-face encounters, we can immediately grasp other subjects' basic mental states by attending to their facial expressions and embodied patterns (16). This primary type of social understanding does not rely on imitation (i.e., simulation) or reflection (i.e., mentalizing). That is, primary empathy essentially amounts to a second person perspective process (72). A capacity for direct perception seems to be based on intersubjective predispositions such as fast detection and the prioritization of social stimuli that develop in the early stages of life (45, 73). These tendencies require mechanisms that allow the subject to quickly locate and discern others' embodied expressions (74–76).

A phenomenologically informed account of social understanding suggests that direct perception is enabled by the fact that the subject's mental world is not necessarily obscure from us (20). For phenomenologists, an expression is not a one-way process in which our inner world is on display; rather, our feelings are sometimes constituted and amplified by our embodied behaviors (77). In other words, bodily manifestations of emotions and intentions do not merely reflect an inner mental state, since the body also plays a constitutive role in shaping and communicating our experiences. Consequently, when attending to the expressions of others, we can actually see some of their mental operation (70). Furthermore, expressions have socio-communicative value. Expressions of emotions also unfold to provide others with information regarding the shared environment (21). This approach fits well with evolutionary theories that suggest that humans had evolved to share their emotions with others through facial expressions and embodied behaviors (78, 79).

Another feature that supports the capacity for direct perception is the participatory nature of social understanding (80). Phenomenological approaches to social cognition suggest that empathic resonance is attained through a dynamic process, which involves two (or more) lived bodies (9, 18, 81). By virtue of the unique phenomenal structure of intersubjectivity, social perception is phenomenologically and ontologically distinct, to begin with (82) and (83). When encountering other subjects, we immediately recognize a differentiated subjectivity (6). This occurs because the other person's body, like my own, is not experienced as an inanimate object, but rather as a field of their lived experiences. (22) clarifies this idea noting that the other's body is "present to me as a field of expression for his subjective experience" (p. 163). This allows the subject to quickly and effectively gain other subjects' perspectives by locating and following their embodied patterns and facial expressions. (22) analysis also shows that social understanding is not necessarily a one-way street. The perception of others' mental operation is intensified by the socio-dynamic nature of the encounter. In everyday life, the social background of our interpersonal engagements typically facilitates a two-step process (12). First, the other's expressive behavior, such as expressions of anger, triggers bodily arousal, which precedes other types of operation (24). Then, the observer bodily responses drive an interactive set of feedbacks, comprising expressions and impressions (19, 20, 84). This socio-affective cycle allows a dynamic space (85), in which empathic understanding derives from the subjective framework of the encounter.

These considerations suggest that empathy does not necessitate at the primary level inner-imitation or reflection [e.g., (9, 11)]. Empathic understanding is enabled, primarily by the fact that it is directed at a differentiated subjectivity. As (9) explains: "To have a feeling of oneself and to know that another has it are two fundamentally different things. The first is not conditioned in the second, nor the second in the first" (1979, p. 25)[1]. Investigations into the phenomenal structure of humans' interpersonal encounters show that attention to others' embodied expressions always triggers minimal empathy. This idea is illustrated in the "*boulevard example*" [(21), p. 389]: Imagine a situation where I walk down the boulevard and a person approaches me from the opposite direction. While we pass, I notice her/his slightly bent posture and part of her/his reddish sad face. Attention to the expressive behavior in these situations triggers a minimal type of empathy in the sense that I pre-reflectively grasp the other's sadness (16), regardless of any imitation, reflection, or social operation (87, 88).

This example demonstrates that primary empathy requires nothing more than detecting and following others' expressions; this is precisely what the first level of empathy amounts to. This view gains support from empirical studies that suggest that empathic understanding is established and regulated at early developmental stages through sensory–motor attunement

[1]Gurwitsch, one of the key figures in the phenomenological tradition, offers a conceptual understanding of the subjective structure of empathy. Gurwitsch philosophical definition of the experience of others' basic mental states is aligned with the scientific research on subjects with congenital insensitivity to pain (CIP) that suggest that although CIP patients cannot refer to their own experience of pain, they show normal responses to observed pain (86).

to others' embodied patterns (45, 89). *Hence, the primary type of empathic response that arises in social encounters is immediate, does not rely on simulation or mentalizing, and is unconditioned by any kind of social operation.*

Secondary Empathy

Empathy, however, can go beyond the primary level; this occurs when direct perception opens the door to deepen empathic understanding. Typically, the amplified forms of empathy are driven by communal predispositions (18, 81). In everyday situations, my emotional attachment and commitment to the people I encounter influences my interest in their expressions and this leads to heightened types of empathy (9, 90). Specifically, the incorporation of broadened affective ties[2] into social perception constitutes extended empathic layers, these layers comprise: (A) envisioning how the world appears from the other person's perspective (i.e., secondary empathy), and (B) the other's stance toward me during the emphatic encounter, which is typical of conditions of group cohesion (i.e., tertiary empathy) (7, 20).

Phenomenologists emphasize that regardless of the level of empathy that attention to others triggers, empathic experiences always stem from the self-other distinction (19). That is to say, empathy is directed at other subjects' experiential world and recognizes their differentiated embodied selfhood. As [(88), p. 92] puts it, "The phenomenologists would consequently reject the view that imitation, emotional contagion or mimicry should be the paradigm of empathy." This approach does not necessarily rule out the possibility that empathic understanding extends by my interest in the other subject (91). Indeed, it is precisely because empathic processes are other-directed that empathy can increase by virtue of the nature of our we-relationship (22); the more I am emotionally attached to the person I attend to, the more I am interested in their mental states, and correspondingly empathy amplifies [for the impact of emotions on social cognition see in (92)].

At the phenomenal level, variations to the empathic process are induced by a social factor (i.e., commitment or attachment). In the previous *boulevard example*, due to my social interest in the person walking past me, I sometimes also take her/his position toward the situation through an imaginary process or even go deeper to reflect on her/his motives. Both cases cannot merely rest on imitating the others' emotional state as proponents of the simulation theory claim (9, 13) [3].

The first experiential step toward a fully amplified empathic response that emotional commitment induces go through taking the other's perspective. This entails an imaginative operation, which manifests itself as an *as if* scenario (20). By virtue of this operation, I experience the other person's sadness, also by taking their stance. Secondary empathy often unfolds in situations where I have more interest in the attended other (7). [(20), p. 38] suggests that this materializes in cases of disturbances, such as a misunderstanding or irritation. Yet, it seems that the second level of empathy is generated primarily by the fact that I am emotionally committed or attached to the attended other, and therefore, I am driven to take their position by employing an imaginary model.

Usually, to explicate others' experiences in a way that includes taking their perspective, i.e., *as if* I were in their shoes, requires some degree of emotional attachment/commitment. This intersubjective component allows the incorporation of an implicit socio-attentional process (53), with an explicit operation that is based on the capacity to grasp others' differentiated perspective (93). In everyday situations, including in cases of disturbances, the amplification of the empathic process is intimately related to the nature of our relationship. Social ties often trigger an *as if* imaginary process, which increases empathy. For example, when the expressions of the person I encounter suggest that she/he is irritated, the expressive behavior and the social context allows primary empathy (12). Nonetheless, in order for me to experience how I would feel and react if I were in her/his place requires an additional empathic step. This secondary intersubjective phase necessitates that I have an interest in the other subject, which transcends the temporal encounter. Social interests that amplify empathic underspending are typically constituted by communal concerns. These concerns may involve manifold social relationships (9). Aroused by a pre-reflective induced communal-based interest, subjects are more prone in some situations to employ a socio-imaginary operation, which is incorporated into the empathic process. This secondary layer extends, as we show next, in cases of increased social attachment. Hence, *secondary empathy is driven by a communal-based interest and requires the process of perspective taking.*

Tertiary Empathy

In comparison to the first and second levels that relate to individual targets, the third empathic level is driven by group factors (i.e., intergroup relations) (c.f., **Figure 1**). Phenomenologists suggest that the third level of empathy consists of an experiential structure in which I perceive myself from the other's perspective as she/he perceives me attending to her/his expressions (20). In these cases, the nature of our relationship drives interpersonal understanding that goes beyond an *as if* scenario. (7) maintains that at this phase of empathy, the other's expression is given to me as an intentional object that I can reflect upon (91). We argue that tertiary empathy unfolds in two types of encounters that are colored by intense group interest: those that do not necessitate mutual emphatic awareness, and those that rely on it. The first unfolds in situations that involve a strong sense of social cohesion (94), such as a case in which one observes a member of her/his group in conflict situations (even if she/he is not aware of the other's attention to her/his expressive behavior). In these settings, a fused perspective provoked by increased emotional commitment is fueled by the scene's circumstances and manifests itself as tertiary empathy. That is, the strong sense of identification with the other person incorporated with my attention to the scene triggers an amplified empathic process. This concept is nicely illustrated by what we label as "*the protest example*": a situation where I participate in a protest against the government's corruption. At some point, I notice that a member

[2] In the sense that they exceed the basic dyadic types of inter-affectivity (45).

[3] For simulation theory, subjects gain access to others' minds by running an inner simulation of their behavior (as-if scenario), which is then attributed back to the encountered other (20).

of the group is dragged by police officers. Even if the other person is not directly aware of my attention to the scene (or even of my presence), my empathic experience will typically go beyond placing myself in his/her shoes to include motives and beliefs that led to the situation.

The second type of tertiary empathy is based on increased sense of social interest, which is broadened through mutual awareness. As we suggest in the previous subsection, extended types of empathy are often triggered by social ties. Manifestations of tertiary empathy require that this critical factor significantly intensifies. Reframing tertiary empathy in the *boulevard example*, let us assume that it turns out that I am attached to the sad person approaching me in the boulevard by virtue of increased group interests (e.g., family, friendship, or other close ingroup ties). While we pass, she/he observes me attending to her/his sadness. Typically, this situation stimulates an imaginary operation, where I take the other's perspective. However, it also can drive deeper emphatic responses. This occurs as a result of mutual awareness, which is amplified by group-based-factors[4]. Consequently, this emphatic step will address motives and events (both actual and fictional) that are beyond my direct experiential reach (7). Hence, *tertiary empathy typically arises in the context of heightened social cohesion.*

GRADED EMPATHY THROUGH THE LENSES OF NEURO-PHENOMENOLOGY

In the previous section, we formulated that social bonding increases empathic responses and shed light on the graded nature of empathy, thereby undermining the affective/cognitive dichotomy in certain contexts. The constitutive role of group factors in determining the levels of empathic understanding, which is indicated by phenomenological analyses of social encounters (9, 90), shows that the amplification of empathy involves increased group ties with broadened cognitive operations. Altogether, our phenomenal typology suggests that in its fully amplified form, empathy involves three steps that are spontaneously activated during the encounter. As was highlighted in the "*boulevard example*," the more I am emotionally engaged (i.e., via interpersonal or intergroup representations) with the target of empathy, the more empathy is amplified. In the present section, following in the footsteps of Francisco (95) concept of neuro-phenomenology, we integrate this phenomenological account with neuroscientific findings. Varela coined the term to describe a research area "in which lived experience and its natural biological basis are linked by mutual constraints provided by their respective descriptions" [(95), p. 112]. The phenomenological outlook described in the previous section emphasizes the lived encounters, feedback, dynamic, and graded parametric aspects in empathic encounters, and therefore, a graded framework better accommodates real-life experiences compared to a dichotomous view.

[4]I.e., I perceive the other's awareness of my perception of her/his expression.

In the Moving Beyond the Affective/Cognitive Dichotomy: Ecological Validity, Neural Mechanisms, and Phenomenological Considerations section, we detailed the limitations of the affective/cognitive approach in accommodating data that describe intergroup conditions, naturalistic designs, and phenomenological approaches. We now turn to detail how neural mechanisms in these recent data can be explained according to the graded framework. As outlined above, primary empathy is a basic intrinsic perceptual process unconditioned by social operation, and this can be explained by the almost immediate (i.e., ∼100-ms poststimulus onset) neural response to empathy-evoking targets (96). This response is amplified as a function of social factors, as can be evidenced in numerous studies investigating the neural empathic response (39, 40, 46, 65, 97–103). Yet, these findings are also explained by the dichotomous framework of empathy, for instance, by explaining differences in neural substrates (i.e., lower vs. higher-order cortices) and chronometry (i.e., early vs. late response) as a function of the affective and cognitive components of empathy, respectively. However, in contrast to this dichotomous model, the graded framework straightforwardly accommodates recent empathy neuroimaging experiments that integrate phenomenological reports (60, 61), as well as experiments targeting complex interpersonal and intergroup contexts and employing naturalistic experimental settings.

For instance, the ingroup representations amplify empathy to the tertiary level by triggering a strong sense of social cohesion and emotional attachment between the empathizer and the target. From a biological perspective, our brain has an innate and instinctual propensity to distinguish between friend and foe (104, 105), resulting in amplified empathy for kin (i.e., the ingroup) compared to non-kin (i.e., outgroups) (106). In recent years, there is a growing body of neuroscientific research on intergroup empathy, so this topic can provide ample empiric evidence for the amplification of empathy, particularly toward the tertiary level. Early neuroimaging studies that examined empathy in intergroup contexts showed that the neural empathic response is difficult to interpret in the affective/cognitive terminology particularly while using naturalistic stimuli and real-life design, but can be explained via the graded framework. For example, Hein et al. showed that the more one's empathy toward ingroup targets was amplified, the more one was willing to engage in costly helping toward the ingroup target (107). In a more recent similar study, MEG was used and this enabled to track over time the amplification of various neural empathic mechanisms toward ingroup and outgroup targets (46) (see **Box 1**). In another study that emphasized ecological validity, brain-to-brain coupling was measured during real-life interpersonal empathic encounters (45); as in the intergroup study (46), the encounter involved strong social cohesion, but this time due to romantic partnership. The authors found that interbrain coupling in the alpha-band reduces partners' pain and is amplified by empathic accuracy. Another study that investigated interbrain coupling during mother–child encounter, while using naturalistic and, at the same time, controlled experimental settings (108); once again, the social cohesion

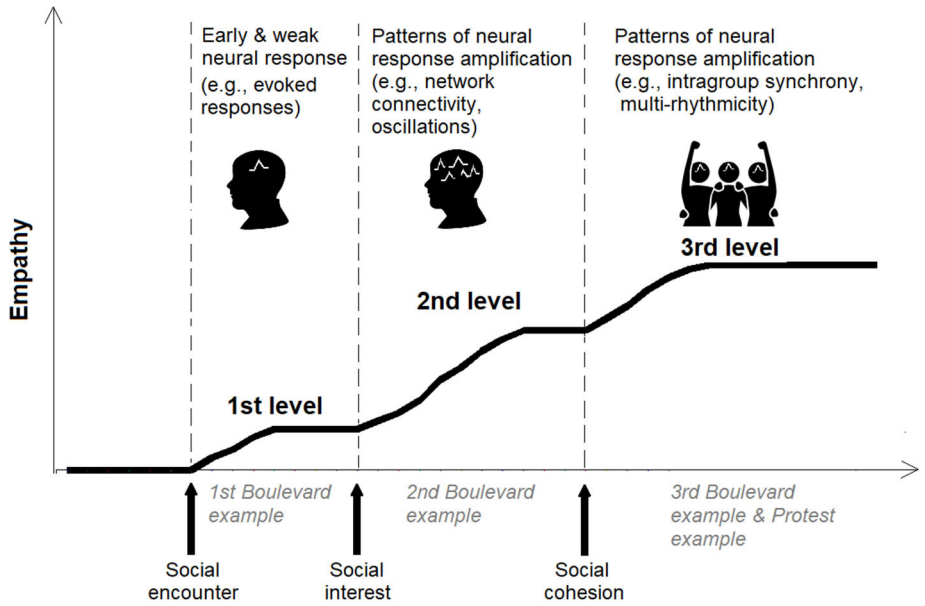


FIGURE 1 | Illustration of the neuro-phenomenological graded empathy framework. The first level of empathy is elicited by the empathic encounter (evoking a minimal neural response). If there is social interest in the target, enhanced neural activity is elicited (involving heightened complexity in terms of neural rhythms and sources), while during intense social cohesion (the target is perceived in group contexts), the neural response is further amplified while conveying patterns of neural cohesion. Real-life examples (i.e., the Boulevard and the Protest examples) are provided in The Phenomenological Account of Graded Empathy section of the manuscript to further illustrate the three levels.

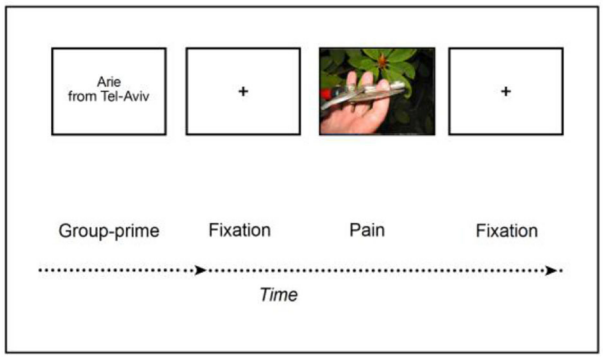
factor was enhanced due to the strong mother–child bond. The authors found interbrain coupling and activation in the gamma-band, conveying empathy being amplified by cohesion (i.e., reciprocity and synchrony). Altogether, we illustrate in **Figure 1** the graded empathy framework and the suggested neural mechanisms that convey the amplification as a function of social factors.

Finally, the idea that empathy operates in a graded manner, pending on social circumstances, might also benefit the design of prevention program for individuals with difficulties in empathic understanding, in that it suggests that it could be useful for treatment models to pay more attention to group behaviors (such as collective intentionality) rather than solely focusing on mentalizing capacities. Several strategies have been proposed to promote empathy, including literary fiction (109), virtual reality (110), or intergroup dialog (111, 112). The success or failure of these interventions may additionally address a central question: whether empathy is innate or, alternatively, whether it can be learned and fostered. In the context of the hypothesis raised in the current manuscript, we emphasize the importance of integrating neuroscience and phenomenology into empathy-building intervention studies. We will end by raising several outstanding questions regarding the graded framework for empathy. Are there specific neural signatures for each of the three levels? What is the nature of the interaction between these levels from a neuronal perspective? Does the framework apply to other social phenomena? What experimental designs can further advance the mapping between phenomenology and empathy neuroscience? Would the graded framework highlight specific neural patterns in psychopathology, development, and heritability? Would future neuroscience findings propose additional levels to the model? More empiric research is needed to address these questions and build upon this framework in the future. The answers to these questions can also be informative for further understanding the operation of empathy in daily circumstances.

To conclude, by providing this neuro-phenomenological framework, we address the recent call (113) for social neuroscience to connect basic neurocognitive processes to a broader array of intergroup contexts and their real-world outcomes. Our model's novelty lies in the fact that (a) it explains why in real-life situations it is insufficient to solely rely on the cognitive/emotional dichotomy to describe the experience of empathy, in (b) suggesting an original conceptualization explaining the amplification of empathic responses, which is something that the prevailing accounts, as yet, have failed to achieve, and finally, (c) it distinguishes empathic experiences as a function of their social/group context; this stands out in comparison to the dichotomous account that rather relies on simulation/mentalizing or bottom–up/top–down considerations. Nevertheless, the model proposed here does not "negate" the cognitive/emotional framework; instead of dichotomizing, the novel model offers a dynamic and graded outlook that can change the way empathy is considered, particularly in intergroup contexts and while implementing real-world experimentation.

BOX 1 | Empirical illustration of the *Graded Empathy Hypothesis*.

In our recent study, we investigated empathy among 80 adolescent high-school students. The adolescents lay down during an MEG neuroimaging session, while facing a screen projecting stimuli of hands or feet in painful (vs. non-painful as control) situations, thereby probing participants' empathy brain response to others' pain in general, or as a function of targets' group membership (**Figure 1**). Following the MEG session, participants interacted with each other and we monitored their social behavior (46). Findings revealed that adolescents' brain response to the pain of others emerged early (<200 ms) after stimuli onset by a neural mechanism of alpha-band suppression; this early neural response remained unchanged as a function of group context. This early, yet weak response of the brain to vicarious pain matches the assumption of a first layer of empathy (i.e., primary): (a) elicited almost immediately following the empathic encounter, and (b) unconditioned by any social operation. Further to the early neural response, a later (>500 ms) and more robust response emerged as a second neural mechanism (i.e., alpha-band rebound), and only toward ingroup targets. Importantly, the latter mechanism was amplified as a function of intergroup interest (i.e., hostility). Finally, another level of intergroup interest (i.e., lack of empathy) strongly amplified a third mechanism—group neural synchrony. These two latter neural mechanisms corroborate the phenomenological assumption that social interest, and in particular social cohesion, act as strong amplifiers of the empathic response.



DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

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

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The icons in **Figure 1** were taken from thenounproject.com and slightly modified; these are under CC attribution and include the following: Protest icon by Claire Jones GB and Man icon by Jule Steffen and Matthias Schmidt, DE.

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Potential Neural Mediators of Mom Power Parenting Intervention Effects on Maternal Intersubjectivity and Stress Resilience

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Stress resilience in parenting depends on the parent's capacity to understand subjective experiences in self and child, namely intersubjectivity, which is intimately related to mimicking other's affective expressions (i. e., mirroring). Stress can worsen parenting by potentiating problems that can impair intersubjectivity, e.g., problems of "over-mentalizing" (misattribution of the child's behaviors) and "under-coupling" (inadequate child-oriented mirroring). Previously we have developed Mom Power (MP) parenting intervention to promote maternal intersubjectivity and reduce parenting stress. This study aimed to elucidate neural mechanisms underlying the effects of MP with a novel Child Face Mirroring Task (CFMT) in functional magnetic-resonance-imaging settings. In CFMT, the participants responded to own and other's child's facial pictures in three task conditions: (1) empathic mirroring (Join), (2) non-mirroring observing (Observe), and (3) voluntary responding (React). In each condition, each child's neutral, ambiguous, distressed, and joyful expressions were repeatedly displayed. We examined the CFMT-related neural responses in a sample of healthy mothers ($n = 45$) in Study 1, and MP effects on CFMT with a pre-intervention (T1) and post-intervention (T2) design in two groups, MP ($n = 19$) and Control ($n = 17$), in Study 2. We found that, from T1 to T2, MP (vs. Control) decreased parenting stress, decreased dorsomedial prefrontal cortex (dmPFC) during own-child-specific voluntary responding (React to Own vs. Other's Child), and increased activity in the frontoparietal cortices, midbrain, nucleus accumbens, and amygdala during own-child-specific empathic mirroring (Join vs. Observe of Own vs. Other's Child). We identified that MP effects on parenting stress were potentially mediated by T1-to-T2 changes in: (1) the left superior-temporal-gyrus differential responses in the contrast of Join vs. Observe of own (vs. other's) child, (2) the dmPFC-PAG (periaqueductal gray) differential functional connectivity in the same contrast, and (3) the left amygdala differential responses in the contrast of Join vs. Observe of own (vs. other's) child's joyful vs. distressed expressions. We discussed these results in support of the notion that MP reduces parenting stress via changing neural

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activities related to the problems of "over-mentalizing" and "under-coupling." Additionally, we discussed theoretical relationships between parenting stress and intersubjectivity in a novel dyadic active inference framework in a two-agent system to guide future research.

Keywords: intersubjectivity, empathy, parenting intervention, parenting stress, amygdala, dorsomedial prefrontal cortex, PAG = periaqueductal gray, Bayesian active inference

INTRODUCTION

Parent-child interactions are crucial for child development and sources of joyful or distressed experiences in the dyad. However, when stress compromises a parent's parenting capacity, parent-child interactions tend to deteriorate and exacerbate parental stress in return (1, 2). Parental intersubjectivity, described below, has been identified as a key resilience factor, and a target of parenting interventions, to buffer the adverse effects of parental stress or depressive moods on parent-child interactions (3, 4).

Intersubjectivity is defined here as the understanding of self's and other's internal, covert states (e.g., internal models, intention, and feeling). Parental intersubjectivity enables a parent to feel what a child's subjective experience or mind *is like*, while maintaining the distinctive awareness of self and child's subjective experiences (first-person and second-person subjectivity). Synonymous to interpersonal understanding (5) and some, but not all, definitions of empathy (6), parental intersubjectivity lies in the core of several parenting-related constructs, such as parental empathic attunement (7), parental reflective functioning (8, 9), parental sensitivity (10, 11), and parental embodied mentalizing (12). All these complex constructs point to a parent's capacity to utilize dyadic interactions to achieve valid attributions of the child's covert states underlying overt behaviors. Thus, in lieu of other terms, the term *intersubjectivity* is used here to emphasize its reliance on person-person interactions (the prefix, *inter*) and its focus on the awareness of self and other's lived experiences (*subjectivity*).

A key attribute underlying intersubjectivity is spontaneous mimicry or voluntary imitation of others' facial expressions or manual gestures. Infants show spontaneous facial mimicry soon after birth (13), which fits the onset of the development of intersubjectivity (14). Mothers with secure parent-child bonding show greater child-oriented face mirroring (15). Notably, mirroring can be performed spontaneously without activating higher-order representations (16). The dissociation between mirroring and higher-order representations points to dissociable processes or systems that may underlie mirroring others' actual behaviors vs. mentally representing (or thinking about) others.

Development of *intersubjectivity* begins in infancy (14), and remains plastic throughout the lifespan, for better or worse, bearing prominent clinical and societal significance (4, 7, 17–20). Mothers exposed to interpersonal violence (21) or suffering depressive mood disorders (4) may show impairment in intersubjectivity, leaving them at risk for excessive parenting stress, as parenting stress is inversely associated with parental intersubjectivity (22).

In this paper, we present a translational neuroscience study to elucidate potential neural mediators of an intersubjectivity-promoting parenting intervention that aims to reduce maternal parenting stress. We address this topic at two levels of analysis, one at an *empirical* level (elaborated here) and the other at an *abstract* level (elaborated in section Abstract Level of Analysis—Toward an Overarching Framework for Research on Intersubjectivity). We begin with the description of two problems that may impair intersubjectivity, namely "over-mentalizing" and "under-coupling" problems, then discuss our parenting intervention, Mom Power (MP), that reverses these intersubjectivity problems. Next, we present brain systems underlying these intersubjectivity problems in two functional magnetic resonance imaging (fMRI) studies utilizing a novel fMRI task. We end with a brief theoretical discussion on the dyadic active inference framework (with extensive elaboration in section Abstract Level of Analysis—Toward an Overarching Framework for Research on Intersubjectivity) to link intersubjectivity with parenting stress, which in turn may theoretically account for the "over-mentalizing" and "under-coupling" problems that are commonly observed in clinical settings.

Intersubjectivity Impaired by "Over-Mentalizing" and "Under-Coupling" Problems

Impaired parental intersubjectivity frequently manifests as a parent's rigid misattributions of a child's unwelcome behavior to malevolence. For example, a mom may think her son's defiance to her requests means ill to her, "*he did it to humiliate me.*" When repeated misattributions of the child consolidate into a rigid belief, the parent may interpret all difficulties in parenting as a character flaw in the child, "*he is mean.*" Such problem is called **"over-mentalizing,"** i.e., the parent overly mentalizes the child into a generalization without relying on situational cues into circular reasoning "*he defies me to humiliate me because he is mean.*" Holding on to such a misbelief, the parent can develop a judgmental stance toward the child, which subsequently predicts chronic rejection, rage toward the child, parent-child bonding problems, and parental depressive moods (23). Furthermore, when parents habitually over-mentalize the child, they ignore situational, emotional, and behavioral cues in the "real-time" parent-child interactions that could otherwise serve as bottom-up data to rectify the parents' misbeliefs (24). Such obliviousness is called **"under-coupling,"** i.e., the parent is disengaged from observing how their physical or verbal actions (e.g., negative judgments or rejections) make their child feel and

may "induce" the observed behaviors. Both "over-mentalizing" and "under-coupling" are undesired mental state manifestations and indicators of impaired parental intersubjectivity. When parents experience heightened parental stress, their defensive reactions (e.g., fight or flight) become sensitized, and "over-mentalizing" and "under-coupling" phenomena can worsen, further exacerbating impairment of parental intersubjectivity in a vicious cycle.

Mom Power—An Intersubjectivity-Promoting Parenting Intervention

To mitigate parenting problems and reduce parenting stress, our team has developed MP, a group parenting intervention that fosters maternal intersubjectivity in clinical settings. For details on the intervention delivery, please see elsewhere (25). Impact on intersubjectivity is thought to be accomplished through (1) interpersonal, interactive exchanges with group peers to facilitate implicit imitations and explicit empathy-boosting exercises, (2) hands-on acquisition of knowledge regarding child's developmental needs to rectify developmental expectations and improve mothers' working models/mental representations of their child, (3) non-judgmental mindfulness practice to support regulation of own distress, which in turn inhibits mothers' defensive reactions to stress, and (4) enhancement of reflective capacity to build the awareness of self and other's lived experiences and needs (24, 26–28). Previously, we have found that MP reduces parenting stress (27), corrects developmentally-inappropriate, distorted working models/mental representations of their child (28), and modulates maternal brain responses to baby cry stimuli as a function of parenting stress (29). Based on this work, we postulate that MP will reverse both maternal intersubjectivity problems, "over-mentalizing" and "under-coupling" (28), which in turn will reduce maternal parenting stress.

Brain Systems Underlying Intersubjectivity

The social neuroscience literature suggests that the recognition and attribution of goals and intentions of another person's behaviors is primarily supported by three distinct but inter-related neural systems, namely ***mirroring system***, ***mentalizing system***, **and** ***salience network***, described below (30–32). **The** ***mirroring system*** becomes active when an agent performs an action or perceives another agent's similar action (33). The co-localization of activities related to perception and action in the brain affords an observer's automatic recognition of the immediate goal of the other agent's actions. This system involves the posterior inferior frontal gyrus (pIFG), dorsal and ventral premotor cortex (dPMC and vPMC), supplemental motor area (SMA), inferior parietal lobule (IPL), superior parietal lobule (SPL), intraparietal sulcus (IPS), superior temporal gyrus (STG), and pericentral cortex (34–39).

The ***mentalizing system*** becomes active when a person is attributing mental states to others and this system involves the precuneus/posterior cingulate cortex (PrC/PCC), dorsal, middle, and ventral medial prefrontal cortices (dmPFC, mmPFC, and vmPFC, respectively), posterior temporal sulcus (pSTS), temporal pole, and temporoparietal junction (TPJ) (32). A meta-analysis suggests that the dmPFC, mmPFC, vmPFC, and PrC/PCC form a loop to generate narrative thoughts related to affective representations of self and other (40). In this loop, interpersonal scripts (autobiographical stories) are generated when the PrC/PCC, as a thought generator (41), connects affective potentials stored in the vmPFC (42) to regions that serve as a proximal-object sketchpad that represents the self (in mmPFC) (43, 44) or a distal-object sketchpad that represents another person (in dmPFC) (43). The dmPFC-dependent functional connectivity preferentially participates in mentalization in verbal, but not in visual, modality, while the TPJ-dependent functional connectivity participates in both modalities (45). Thus, the dmPFC represents others' enduring attributes (a generic image of other's identity) without differentiating self and other's perspectives (40, 46). In contrast, the TPJ represents other's inner thoughts that are different from one's own perspective, with self-other distinction (47) and mediates inferences about others, such as their transient goals, desires and beliefs (48). Moreover, the anterior part of TPJ is involved in joint attention, which requires spatial representation of other's attentional direction (30).

The ***salience network*** includes dorsal ACC, posterior ventral MCC, bilateral anterior insula cortices (IC), and subcortical regions such as PAG, hypothalamus, thalamus, midbrain, striatum, and extended amygdala (49). This network detects internal and external events that are personally meaningful (50) and interacts with the *mentalizing system* to respond to attachment figures (51). Indeed, the salience network largely overlaps with a *maternal caregiving system* that regulates parenting behaviors, including the amygdala, IC, and two motivational sub-systems—one for affiliative motivations that include the hypothalamus, ventral tegmental area (VTA), nucleus accumbens (NAc), and ventral pallidum (VP) and the other for defensive (fight or flight) motivation mediated by the periaqueductal gray (PAG) (52–54). Notably, many of these regions (e.g., the amygdala, PAG, and NAc) are sensitive to *signed prediction errors* of reward or punishment with reference to preceding baselines, i.e., activated when detecting a greater-than-expected level of salience (positive prediction errors of reward or punishment, e.g., the presence of unexpected salience) and deactivated when detecting a less-than-expected level of salience (negative prediction errors of reward or punishment, e.g., the omission of expected salience). For examples, the NAc is sensitive to *signed prediction errors* of reward (55, 56); the amygdala is sensitive to *signed prediction errors* of reward (e.g., desirable liquid) and/or punishment (e.g., undesirable air-puff) (57); besides, the amygdala is also sensitive to the *signed prediction errors* in aversive stimuli, e.g., activated when detecting the presence of unexpected foot shock and deactivated when detecting the omission of expected foot shock (58). Notably, consistent with the notion that NAc and PAG served as opponent motivations of reward-seeking and defense (flight-or-flight) respectively, the NAc and PAG responded in opposite manners to aversive prediction errors, as unexpected pain not only deactivated the NAc (a negative prediction error of reward

as if the unexpected pain was equivalent to the omission of reward), but also activated PAG (a positive prediction error of punishment as if the unexpected pain was equivalent to the presence of unexpected punishment) (59). As described later, the contrast of mirroring the child's joyful vs. distressed expressions in our experimental task is computed to index the sensitivity of *signed prediction errors* specific to maternal mirroring of own child's emotions.

The *mirroring system* largely overlaps with the frontoparietal network (60); the *mentalizing system* largely overlaps with the default-mode network that is more active during resting states (61) and mind wandering (62), as compared to states of actively paying attention to the environments. Spontaneous activities in the default-mode network are often anti-correlated with those in the frontoparietal network (63). Thus, we postulate that empathic mirroring of others encompasses bottom-up perception-action coupling between two agents, which can potentially activate the *mirroring system* and automatically deactivate the *mentalizing system*, as compared to (non-mirroring) observing others.

Moreover, as virtually all cognitive processes depend on the functional connectivity among participating brain networks (64), the functional connectivity among the three aforementioned brain systems, *i.e., mirroring system, mentalizing system, and salience network,* are key to intersubjectivity (45). Indeed, the capacity for intersubjectivity seems to depend on the functional connectivity between the dmPFC (in the *mentalizing system*) and the inferior frontal gyrus (in the *mirroring system*) (65). Notably, the functional connectivity between stress-dependent brain regions (which include the *salience network*) and the child-representing regions, i.e., dmPFC, may underlie the stress-potentiation of the "over-mentalizing" problem. It is through functional connectivity that the *salience network* may switch up or down the activity in the frontoparietal network and the default-mode network *alternately* (66). These results underscore the roles of dmPFC-dependent functional connectivity in representing the child in maternal intersubjectivity. Moreover, the pain-related prediction error signals in the PAG are functionally connected to the dmPFC (59). Thus, we postulate that the functional connectivity between the dmPFC and PAG should reflect the extent to which maternal defensive motivation can influence the representation of the child. In other words, we postulate that the dmPFC-PAG functional connectivity should modulate the maternal mirroring of the child as a function of parenting stress.

The Abstract Level of Analysis to Link Intersubjectivity to Parenting Stress

To provide a theoretical relationship between interpersonal stress and the "over-mentalizing" and "under-coupling" problems at an abstract level of analysis, we postulate a dyadic active inference framework in a two-agent system, which will be elaborated in section Abstract Level of Analysis—Toward an Overarching Framework for Research on Intersubjectivity. Our framework is inspired by Karl Friston's Free Energy Principle (67, 68) and its application to stress (69). In brief, this framework postulates that in a two-agent system, stress ensues in a dyad when an agent's working model of the other agent in the system results in excessive prediction errors in a way that threatens the agent, and the stress worsens when the agent's preconceived working model of the other agent defies, rather than accommodates, the prediction errors. On the basis of this theoretical framework, we are led to postulate that when a mother shows symptoms of impaired intersubjectivity during mother-child interactions, she is at risk for excessive stress, and that her capacity to empathically mirror the child's actions and feelings may be compromised, reducing her sensitivity to the child's feelings, especially when the child's expressions are incongruent to the mother's preconceived working model/mental representation of her child. Thus, when she is stressed and/or in a negative mood, her mirroring of the child's joyful expressions may be diminished (i.e., stress-potentiated "under-coupling"), while her defensive reactions to the child's distressed expressions due to her preconceived working model may be exacerbated (i.e., stress-potentiated "over-mentalizing"). From prior work, we know that MP changes mothers' mental representations/working models toward less distorted/rigid/negative perceptions (28).

The Empirical Level of Analysis in the Present Study

As the brain bases for "over-mentalizing" and "under-coupling" problems may be inferred through various experimental tasks in neuropsychiatric disorders (70), in the present study we employed a face and affect imitation task, namely Child Face Mirroring Task (CFMT) in the fMRI setting, which has been substantially modified from a previously published task (71). The CFMT involves pictorial displays of children's facial expressions, sorted in three independent factors, Child's Identity (Own Child and Other's Child), Emotions (Joy, Distressed, Ambiguous, and Neutral), and Task (Join, Observe, and React). In a full factorial design, each of the two children's pictures displayed four kinds of emotional expressions (Emotions), and all these pictures are repeated in three distinct conditions (Tasks): a face/affect mirroring condition (Join) and a non-mirroring control condition (Observe) to evoke strong and weak mother-child coupling, respectively, and, additionally, a React condition in which mothers respond to child faces as they normally would, to examine whether MP changes mothers' voluntary (un-instructed) responding. Results from two studies are reported here. In Study 1, in a sample of healthy mothers ($n = 45$), we examined the main effects of CFMT. In Study 2, we used CFMT in an randomized controlled intervention study where mother either receive the MP intervention ($n = 19$) or are in Control condition ($n = 17$), and measured maternal parenting stress at both pre- and post-treatment time points (T1 and T2) to identify potential neural mediators of MP effects on parenting stress.

Using CFMT, we computed a family of contrasts, namely Maternal Mirroring Response (MMR), to examine neural underpinning of own-child-specific maternal intersubjectivity. As these contrasts will be included in our predictions, we need to describe them before we prescribe the predictions. To isolate maternal neural responses in child-specific empathic mirroring across all emotions, we construed a MMR(all) contrast, i.e.,

Join[Own vs. Other's child's all emotions] vs. Observe[Own vs. Other's child's all emotions]. We also examine the contrast of positive vs. negative emotion in MMR, namely MMR(j-d), i.e., Join[Own vs. Other Child's Joyful vs. Distressed] vs. Observe[Own vs. Other Child's Joyful vs. Distressed]. The MMR(j-d) contrast approximately indicate the range of signed prediction errors, i.e., the range of MMR = MMR(j) - MMR(d), assuming that mirroring own child's joyful expression MMR(j) and distressed expression MMR(d) should elicit the maximum and minimum of prediction errors respectively in the brain regions that are sensitive to *signed prediction errors*. When these regions' sensitivity to signed prediction errors is diminished, e.g., MMR(j) is not different from MMR(d), then the range of MMR(j-d) should be no different from zero. The reasons for examining MMR(j-d) include: (1) as described above, the amygdala, NAc, and PAG are sensitive to *signed prediction errors* in emotional salience (reward or punishment), we postulate that these regions' MMR responses to positive (joyful) and negative (distressed) expressions may differ in the directions, e.g., relatively activated in MMR(joy) and deactivated in MMR(dis) for the amygdala and NAc, and vice versa for PAG; (2) the child's positive vs. negative facial expressions have been found to differentially activate maternal amygdala (72) as a function of unresolved stress (73), thus the maternal amygdala's sensitivity to the child's emotion during empathic mirroring may vary as a function of maternal stress. Taken together, the literature suggests that the maternal amygdala should be sensitive to MMR(j-d) and parenting stress may diminish the MMR(j-d) in the amygdala.

Predictions

Based on the literature discussed above, we hypothesized that MP can reduce parenting stress by improving the mothers' working models of the child toward more flexible and positive perceptions, which can in turn improve maternal empathic mirroring of the child's joyful expressions (treating "under-coupling") and can prevent the mothers' defensive reactions from coloring their mental representation of the child (treating "over-mentalizing") during empathic mirroring. This hypothesis would be translated to the following group (MP vs. Control) by time (T1 vs. T2) interaction effects in the present study: We predict that, from T1 to T2, MP (vs. Control) will (1) reduce parenting stress measured with parenting stress index (PSI); MP (vs. Control) will rectify the "over-mentalizing" problem by (2) decreasing the *mentalizing system* activities during own-child-specific voluntary responding (React to Own vs. Other's Child); MP (vs. Control) will rectify the "under-coupling" problem by (3) increasing MMR(all) (own-child-specific empathic mirroring) in the *mirroring system* and by (4) increasing MMR(j-d) in the amygdala that mediates *signed prediction errors* of emotional salience. Because parenting stress can potentiate the "over-mentalizing" and "under-coupling" problems, we also predict that (5) the reduction in parenting stress will be associated with the reduction of the "under-coupling" problem, which can manifest as the association between the reduced parenting stress and increasing sensitivity to the *signed prediction errors* in the amygdala's MMR(j-d); (6) the reduction in parenting stress will be associated with the reduction of defensive "over-mentalizing," which can manifest as the association between the reduced parenting stress and decreasing MMR(all)-dependent functional connectivity between the dmPFC (the sketchpad for child representation) and the PAG (the signals for defensive, fight-or-flight motivation). To summarize these predicted effects succinctly, we used non-parametric mediation analyses to identify potential neural mediators of MP treatment effects on parenting stress.

METHODS

Ethics Approval Statement

The research reported in the current study was approved by the Institutional Review Board (IRB) at the University of Michigan, Ann Arbor, Michigan, USA. Informed consent from all participants was obtained. All research was performed in accordance with relevant IRB guidelines/regulations.

Participants

All participants were recruited from low-income community clinics, primary care clinics, and/or community mental health centers. In Study 1, we examined brain responses during CFMT in a sample of healthy, unmedicated participants who underwent the CFMT (see below) for the first time ($n = 45$, age M = 31.78, SD = 7.62, child age M = 2.61, SD = 2.05). As MP's efficacy in reducing parenting stress has been established previously (27, 29), we conducted Study 2 to examine MP effects on intersubjectivity-dependent maternal brain responses and how these responses are associated with reduction in parenting stress. In Study 2, participants ($n = 36$) were randomly assigned to either MP treatment group ($n = 19$) or Control group ($n = 17$) and underwent the CFMT before (T1) and after (T2) MP or Control conditions, with about 14 weeks between scans. The participants in MP and Control groups differed slightly in their age [MP: M = 27.84, s.e. = 1.71; Control: M = 33.35, s.e. = 1.81, $F_{(1, 34)} = 4.92$, MSerror = 55.42, $p = 0.033$], but there was no group difference in the child age [MP: M = 2.25, s.e. = 0.40; Control: M = 3.09, s.e. = 0.42, $F_{(1, 34)} = 2.08$, MSerror = 3.06, $p = 0.16$] and number of offspring [MP: M = 1.63, s.e. = 0.19; Control: M = 1.65, s.e. = 0.20, $F_{(1, 34)} = 0.003$, MSerror = 0.66, $p = 0.96$]. There were three and five participants in MP and control groups, respectively, who were medicated with steady dosing anti-depressants across the study period. Nevertheless, we expected that the potential effects of medication would be canceled out for the following reasons: (1) medicated cases were in the minority and similarly distributed across MP and control groups (Chi-square $Z = 0.963$, $p = 0.33$), and (2) the repeated measures design controlled for the heterogeneity in medication status as participants are compared to their own baseline. As described further in the **Supplementary Materials**, removing medicated participants did not change results.

Child Face Mirroring Task (CFMT)

For the illustration of the task design, see **Figure 1**. In CFMT, participants were presented repeatedly with the same pictures of Own and Other Child in three conditions (Tasks), namely

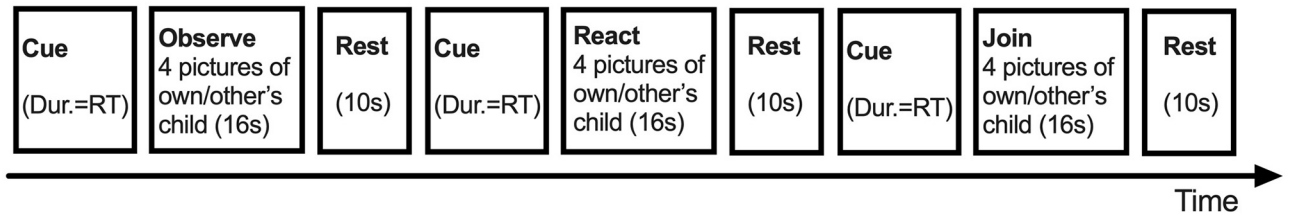

FIGURE 1 | The design of Child Face Mirroring Task. Note that the task order in this figure did not represent the actual order. To protect the privacy, the pictures used in the task are not included here. However, examples of the task stimuli can be found in (71).

Observe, React, and Join. By design, the Observe Task should elicit the participant's unresponsive observation of face-like visual objects (i.e., "look-at-it," a weak coupling condition), React should elicit the participant's usual, voluntary responses to the presented child, and Join should elicit the participant's empathic mirroring of the presented child (i.e., "empathize-you," a strong coupling condition). The task instructions were presented to study participants as follows.

Observe: "You should simply observe the face on the screen. You should NOT make any face or generate any emotion. That is, BE an OBJECTIVE viewer of the faces. DO NOT FOLLOW any feelings depicted or caused by the face."

React: "You should react to the emotion and expression of the child on the screen. You should imagine that you are the caregiver of the child on the screen. That is, you are REACTING to the emotions of the child on the screen as you normally would in your home."

Join: "You should Join your own emotion with that of the emotion and expression of the child on the screen. You should empathize with the emotion depicted on the screen. That is, you are JOINING in the emotions of the child on the screen, with your OWN emotions."

The three Tasks were presented block-by-block in a pseudo-random order. There were four pictures of a single child (one picture each for neutral, ambiguous, Distressed, and joyful expression), presented consecutively in a pseudo-random order, in each block (4 s each picture, 16 s per block). There were 4 blocks per Task for each of the Own and Other Child, with 10-s resting intervals between the blocks. To ensure the participants' wakefulness and readiness for the task, before each block, a single-word cue ("Observe," "React," or "Join") was presented on the screen and participants pressed a button to indicate as soon as they were ready to perform the Task as instructed, without knowing which child's pictures would be presented. The reaction time in pressing the button was defined as Cue Period, reflecting the time required for a participant to be ready to perform the following task. The statistical analysis of the reaction time in Cue period is reported in **Supplementary Materials**.

Task Stimuli

The participants provided all their child's pictures used in the study. The pictures of children unknown to the participants (Other's Child) were drawn from the in-house inventory. The lab staff standardized the stimuli qualities based on specific expressions (neutral, ambiguous, distressed, and joyful). We included these four kinds of expression following pioneering work in the field of parental neuroscience (71). Ratings of the child emotional expression images using Manikin Self-Assessment Scale (74) by four independent female raters confirmed the validity of the valence of the stimuli and the valence and arousal level were matched between the Own and Other Child's pictures, as described in **Supplementary Materials** and **Supplementary Figure 1**.

MRI Procedures

Before each scan, the participants practiced CFMT to ensure their comprehension of the task and minimized effects due to stimuli novelty or learning. In each MRI scan, the participant was positioned in a supine orientation with her head positioned in a head coil. Visual stimuli were presented with E-Prime (PST, Inc., Pittsburgh, PA), via a goggle system and Nordic NeuroLab audio system. Behavioral responses were recorded by a button glove attached to the participant's right hand and linked to the E-Prime system. All fMRI scans were performed with a 3.0 Tesla Philips magnetic resonance imaging scanner using a standard 8-channel radiofrequency SENSE head coil with the following acquisition parameters: (1) A high-resolution T1 scan was acquired to provide precise anatomical localization (TR of 9.8 ms, TE = 459 ms, FA = 8°, FOV of 256 mm, slice thickness of 1.0 mm, 180 slices with 288 × 288 matrix per slice). (2) Two runs of T2*-weighted EPI sequence with BOLD (blood oxygenation level dependent) contrast (190 frames per run, TR = 2,000 ms, TE = 30 ms, FA = 90°, FOV = 220 mm, 42 contiguous axial slices, slice thickness = 2.8 mm with 64 × 64 matrix per slice, voxel size = 3.44 × 3.44 × 2.8 mm^3) were acquired for whole-brain fMRI BOLD signal measures during the experimental task.

MRI Data Processing and Analysis

For both Study 1 and 2, MRI data were pre-processed and analyzed using statistical parametric mapping software (SPM8; Welcome Department of Imaging Neuroscience, London UK). Five images at the beginning of each fMRI run were discarded to account for magnetic equilibrium. Slice timing correction was performed using a middle slice as a reference (slice 21). After slice time correction, images within each run were realigned to the mean image of the first run to correct for movement. Realigned functional images and structural image were spatially normalized using DARTEL method in SPM8. The normalized functional

images were re-sliced to 2 × 2 × 2 mm voxels. Images were then spatially smoothed using a Gaussian filter with a full-width half-maximum value of 8 mm. All the images in the analyses and the figures are in neurological convention, with the left hemisphere presented at the left of an axial image.

First-Level Analysis

For both Study 1 and 2, following pre-processing, two first-level fixed effect General Linear Models (GLMs) were constructed to examine condition-dependent neural responses. The first model consisted of a matrix of regressors modeling 6 trial types (3 Tasks × 2 Child Identities: Observe Own, React Own, and Join Own and Observe Other's React Other's and Join Other's Child), in addition to a regressor for Cue periods (7 regressors total). The second model consisted of a matrix of regressors modeling each of four emotions (Neutral, Ambiguous, Distressed, and Joyful) for each of the six trial types, in addition to a regressor for Cue periods (25 regressors total). Additionally, a generalized Psychological-Physiological Interaction (gPPI) analysis (75) was performed to examine task-dependent functional connectivity with the dmPFC [81 voxels centered at MNI coordinates of [−2, 52, 20]] as the seed. The dmPFC seed cluster was selected because of its roles (as a "sketchpad" representing the child and as a hub whose functional connectivity) in mentalizing, described above, but also the only cluster identified in the conjunction of the Observe > Join main effect and the MP treatment group-by-time interaction effect on React to Own vs. Other Child, which is consistent with its role. Notably, because mathematically a variable's mean magnitude is independent of its correlations with other variables, using the dmPFC as the seed in gPPI analysis did not bias results, as the dmPFC was selected based on its magnitude in certain contrasts, which should be independent of the correlation analysis in gPPI. In gPPI, the physiological variable was estimated to be the average of the first eigenvariate of the BOLD time series of all voxels in the seed throughout the fMRI task. Then, this physiological variable was parsed into 7 condition-specific time-series based on the time window, defined by the onset and duration, of each condition convolved with the canonical hemodynamic response function, wherein the 7 conditions included three for Own Child (Observe Own, React Own, and Join Own), three for Other's Child (Observe Other's, React Other's, and Join Other's), and one for Cue periods. Then, the whole time series of the seed, the 7 condition-specific time series of the seed, the 7 conditions, and 6 motion parameters estimated during the realignment preprocessing were all entered as regressors (21 total) in a first level GLM.

Maternal Mirroring Contrasts

As part of the first-level analysis, we construed a family of contrasts related to maternal mirroring responses (MMR), which is defined as the capacity of the mother to empathically mirror her own child, given her current working model of her own child. There is a family of MMR contrasts based on the following linear combinations of the conditions in CFMT:

MMR(all): We construed MMR(all) as the contrast of [Join(Own Child's all expressions) – Observe(Own Child's all expressions)] – [Join(Other Child's all expressions) – Observe(Other Child's all expressions)] to isolate the mirroring process based on her current working model of child, while controlling for the general effects of looking at face-like visual objects (Join vs. Observe) and general empathic response to any child that is not specific to her own child (Own vs. Other's Child). The removal of the general empathic response is especially important here as the MP intervention aimed to specifically improve the mothers' working model of her child rather than their non-specific empathy.

MMR(j-d): We construed MMR(j-d) as the contrast of [Join(Own Child's Joy vs. Distress) – Observe(Own Child's Joy vs. Distress)] – [Join(Other Child's Joy vs. Distress) – Observe(Other Child's Joy vs. Distress)]. This contrast measured a signed value (vector) of the difference between positive and negative valence in MMR.

MMR(joy/dis/amb/neu): To examine MMR in each kind of emotional expression separately, we construed MMR(joy/dis/amb/neu) as the contrast of [Join(Own Child's joy/dis/amb/neu) – Observe(Own Child's joy/dis/amb/neu)] – [Join(Other Child's joy/dis/amb/neu) – Observe(Other Child's joy/dis/amb/neu)] in only the joy, distressed, ambiguous, or neutral expressions, respectively.

Notably, because all emotional expressions were presented in a random order, the MMR for each emotional expression is directly related to the prediction errors to that expression with reference to the implicit expectation built up during the preceding expression as baseline, which may be based on any other types of expressions. Because MMR(j) should always elicit a response that is more positive in valence than any of its preceding baseline, be it MMR(d), MMR(n), or MMR(a), and, likewise, MMR(d) should always elicit a response that is more negative in valence than any of its preceding baseline, be it MMR(j), MMR(n), or MMR(a). Thus, logically, MMR(j) should elicit the most positive possible prediction errors (the maximum of better-than-expected prediction error) and MMR(d) should elicit the most negative possible prediction errors (the minimum of worse-than-expected prediction error), and therefore MMR(j) - MMR(d) approximates the range of MMRs, i.e., range(MMR) = max(MMR) - min(MMR). Supposedly if a region's sensitivity to signed prediction errors is diminished, e.g., MMR(j) is not different from MMR(d), then the range of MMRs, i.e., MMR(j-d), should be no different from zero. Thus, MMR(j-d) is an index of the sensitivity to *signed prediction errors*. Note that a region that is activated in MMR(joy) but deactivated in MMR(dis) means that the region is sensitive to reward-like prediction errors, resulting in a positive MMR(j-d) in the region, e.g., the NAc (55, 56) and amygdala (57). Conversely, a region that is deactivated in MMR(joy) but activated in MMR(dis) means that the region is sensitive to punishment-like prediction errors, resulting in a negative MMR(j-d) in the region, e.g., PAG (59) and amygdala (57, 58). In other words, MMR(j-d) is a vector indicating the sensitivity of signed prediction errors in a region.

Also, general empathic responses to unknown child were removed from the MMRs to isolate the changes in the mother's own-child-specific empathic responses, because the mothers already have specific preconceived working models of their child, which is believed to be improved by MP. This contrast thus

isolates the responses that are specific to the very mother-child dyad, i.e., the primary focus of the MP dyadic intervention. This is consistent with the notion that intersubjectivity is best investigated in a dyadic framework involving first-person and second-person perspectives (76).

Second-Level Analysis

The contrasts of interest from the first level GLMs were submitted to six second-level random effect GLMs. (1) **CFMT effects:** To establish the effects of the novel CFMT at T1, we examined the main effects of Task, Child and the Task by Child interaction, with the age of the Own Child as a covariate, to control for the children's varying social developmental stages that may influence the maternal responses (77). (2) **MP treatment effects**: In Study 2, we examined MP treatment (vs. Control) by Time interaction effects on MMR(all), MMR(j-d), and React of Own vs. Other Child (i.e., mothers' voluntary response to own child). (3) **Mediation analysis**: To summarize results according to our predictions, we performed X-M-Y mediation analysis, using the MP vs. Control as a categorical predictor (X), T1-to-T2 changes in parenting stress as outcome (Y), and testing three potential intersubjectivity-dependent brain mediators: T1-to-T2 changes in the differential responses in MMR(all) (as M_1), the MMR(all)-dependent gPPI with the dmPFC seed (as M_2), and MMR(j-d) (as M_3). In this analysis, we first identified candidates of potential mediators showing significant effects on both X-M (Path-*a*) and M-Y (Path-*b*), and then submitted the three potential mediators to mediation analysis, controlling for the child age, to compute the 95% confidence interval of indirect effects between X and Y, based on the non-parametric bootstrapping method with 5,000 times of sampling.

Unless specified otherwise, all the second-level models were tested with whole-brain correction at family-wise error (FWE) = 0.05. Besides whole brain analysis, we performed Bonferroni family-wise small volume corrections (s.v.c.), separately, in the subcortical regions known to modulate maternal behaviors (52, 53, 78), with their masks derived from the wfu_pickatlas toolbox (79), including amygdala [as defined in wfu_pickatlas' AAL domain (80)], periaqueductal gray (PAG) (a 8 mm × 6 mm × 8 mm box centered at [0, −28, −12] in MNI coordinates), hypothalamus [as defined in wfu_pickatlas' TD Brodmann areas+ domain (79)], midbrain [as defined in wfu_pickatlas' TD Lobes domain (79)], nucleus accumbens (NAc) [a 18 mm × 8 mm × 10 mm box centered at [0, 10, −14] in MNI coordinates], and striatum [putamen, as defined in AAL (80)].

Procedures in Study 2 Only

Mom Power (MP) Parenting Intervention

MP is a relationship-based parenting group therapy designed to promote positive parenting, reflective capacity, parental mental health and secure child-parent relationships. The curriculum rests on five core pillars paralleling the Strengthening Families Protective Factors Framework (81): (1) attachment-based parenting education, (2) self-care, (3) mother-child interaction practice, (4) social support, and (5) connection to resources. For a detailed description of the intervention, please see **Supplementary Materials**. Women randomized to the MP treatment arm received the 13-session manualized MP parenting intervention (3 individual sessions and 10 group sessions) led by community clinicians trained via a 3-day in person course with model developers. Groups were co-facilitated by two interventionists, at least one being a Master's level clinician, and fidelity was monitored via weekly reflective supervision as well as video review of 20% of all sessions using a fidelity monitoring scale (82). Fidelity was formally assessed using a 5-point Likert scale (5 = highest fidelity) for both content (i.e., fidelity to manual content) and framework (i.e., fidelity to the therapeutic framework dedicated to creating a therapeutic milieu based in attachment theory and trauma informed care). Fidelity was found to be excellent across clinicians for both content ($M = 4.02$, $SD = 0.72$) and framework ($M = 3.85$, $SD = 0.69$).

Control Group

Mothers randomized into the Control group received two individual sessions (pre/post) and 10 weekly mailings of the MP curriculum content without the in-person group components. Mailings included a pre-stamped post card for mothers to send back indicating that the week's material had been read. Participants were compensated $5 for each postcard returned, and an additional $15 if they returned 7/10 postcards.

Self-Reported Measure

Parenting Stress Index (PSI)

The PSI (83) is a 36-item questionnaire designed to measure levels of parenting stress and previously found to be valid, reliable, and sensitive to change across diverse populations (84). The PSI yields a PSI Total Score that was used for present analyses, which has been shown to have excellent internal consistency (Cronbach's alpha = 0.92) and good test-retest reliability (Intraclass Correlation Coefficients = 0.78) (85).

Non-fMRI Analysis and Results

We tested the group differences in demographic variables and the MP treatment effects on parenting stress (as indexed by PSI) in GLMs, using SPSS v.24 (IBM Corp. Armonk NY). We also performed the non-parametric mediation analysis based on the bootstrapping of 5,000 times of re-sampling, with a covariate of Own Child's age, using the macro of PROCESS (86) in SPSS v.24 (IBM Corp. Armonk NY). Due to the space limit, the results of these non-MRI analyses are described in **Supplementary Materials** and **Supplementary Figure 1** (Independent raters' rating on the stimuli), **Supplementary Figure 2** (MP effects on PSI), **Supplementary Figure 3** (Cue period of CFMT), and **Supplementary Figure 4** (robustness check after removing medicated participants in Study 2).

RESULTS

Study 1: Child Face Mirror Task Effects

We first report the results of primary main effects in CFMT. The main effects of Tasks (Observe, React, and Join vs. Rest) and the pairwise planned contrasts (React vs. Observe, Join vs.

TABLE 1 | Task main effects (vs. rest).

Brain region	Side	MNI coordinates			No. of voxels	*Z*-score
		X	Y	Z		
Observe > rest						
Occipital lobe	L	−12	−94	−8	5,373	7.13
	R	14	−96	8		7.05
Hippocampus	R	26	−26	−2	14	5.21
Inferior frontal gyrus (IFG)	L	−44	50	−6	57	5.19
React > rest						
Occipital lobe	L	−12	−90	−10	2,544	7.45
	R	18	−86	−8		7.43
IFG/middle frontal gyrus (MFG)	L	−40	40	−4	1,020	6.79
(including fontal operculum, FOp)	L	−48	14	4	(81)	6.13
	R	54	28	2	142	5.52
Supplemental motor area (SMA)	R/L	−4	10	60	246	6.05
Pericentral gyrus	L	−46	2	46	46	5.29
Lentiform nucleus (pallidum/putamen)	L	−44	50	−6	57	5.19
Join > rest						
Occipital lobe	R	18	−86	−8	1,031	6.91
	L	−36	−58	−22	623	6.44
FOp	L	−46	14	4	178	5.96
SMA	R/L	6	8	62	340	5.65
IFG	L	−42	38	0	192	5.60
Pericentral gyrus	R	48	4	46	95	5.36
	L	−48	2	48	54	5.17
MFG	L	−48	20	28	121	5.32
Lentiform nucleus (pallidum/putamen)	R	22	10	8	6	4.67

Observe, and Join vs. React), pooling across both children, are summarized in **Table 1** and **Figure 2**, with the key brain regions depicted in **Figure 3**. As expected, all three Tasks activated face-related processing in visual cortex and fusiform face area (FFA). Interestingly, the neural responses in some of these visual processing areas were attenuated in both Join vs. Observe and React vs. Observe contrasts. Conversely, both Join vs. Observe and React vs. Observe contrasts activated brain regions involved in the *mirroring system* (32), including pericentral, insular, frontoparietal cortices, and thalamus, and the salience network (49), including striatum, and amygdala.

As summarized in **Table 2** and **Supplementary Figure 5**, the brain regions that were conjunctively implicated in both Join vs. Observe and Join vs. React contrasts included the bilateral pericentral cortices and left inferior parietal lobule (IPL), which were more activated in Join than the other two Tasks, and the occipital and lingual cortices, right hippocampus, and the dmPFC, which were less activated in Join than the other Tasks (also depicted in **Figure 3D**).

The main effects of Child (Own vs. Other Child) are summarized in **Supplementary Table 1**. The neural responses in the occipital, precuneus, angular gyrus, and FIO cortices were greater in Own than Other Child. These regions are largely involved in autobiographical memory, thus consistent with their roles in the *mentalizing system*.

Since there were some Task-by-Child-interaction effects, described below, we examined the simple main effects of Own vs. Other Child in each Task separately (**Supplementary Table 1**). For Observe, we found that the Own vs. Other Child in this Task elicited differential neural responses in the visual face processing areas (FFA) and autobiographical memory-related regions (i.e., FIO, temporal poles and hippocampus), and cognitive regulatory regions (right dorsolateral prefrontal cortex (dlPFC) and supplemental motor area (SMA), which were more active in the main effects of Join (>Observe) and React (>Observe), indicating that the mothers automatically engaged the Own Child with more autobiographical and interactive responses than they did in Observe of Other Child, despite that the task instruction of Observe explicitly discouraged such active child-oriented responses. For React, the Own vs. Other Child elicited differential responses in the subcortical regions, including the thalamus, hypothalamus, striatum, hippocampus, and midbrain, suggesting the mothers responded to Own Child with greater maternal motivation than they did to Other Child. For Join, there were no Own vs. Other Child differences in any regions.

The planned tests related to Task-by-Child interaction effects [including MMR(all) and MMR(j-d)] are summarized in **Supplementary Table 2**. For MMR(all), we found that the precuneus and fusiform gyrus showed greater Own > Other

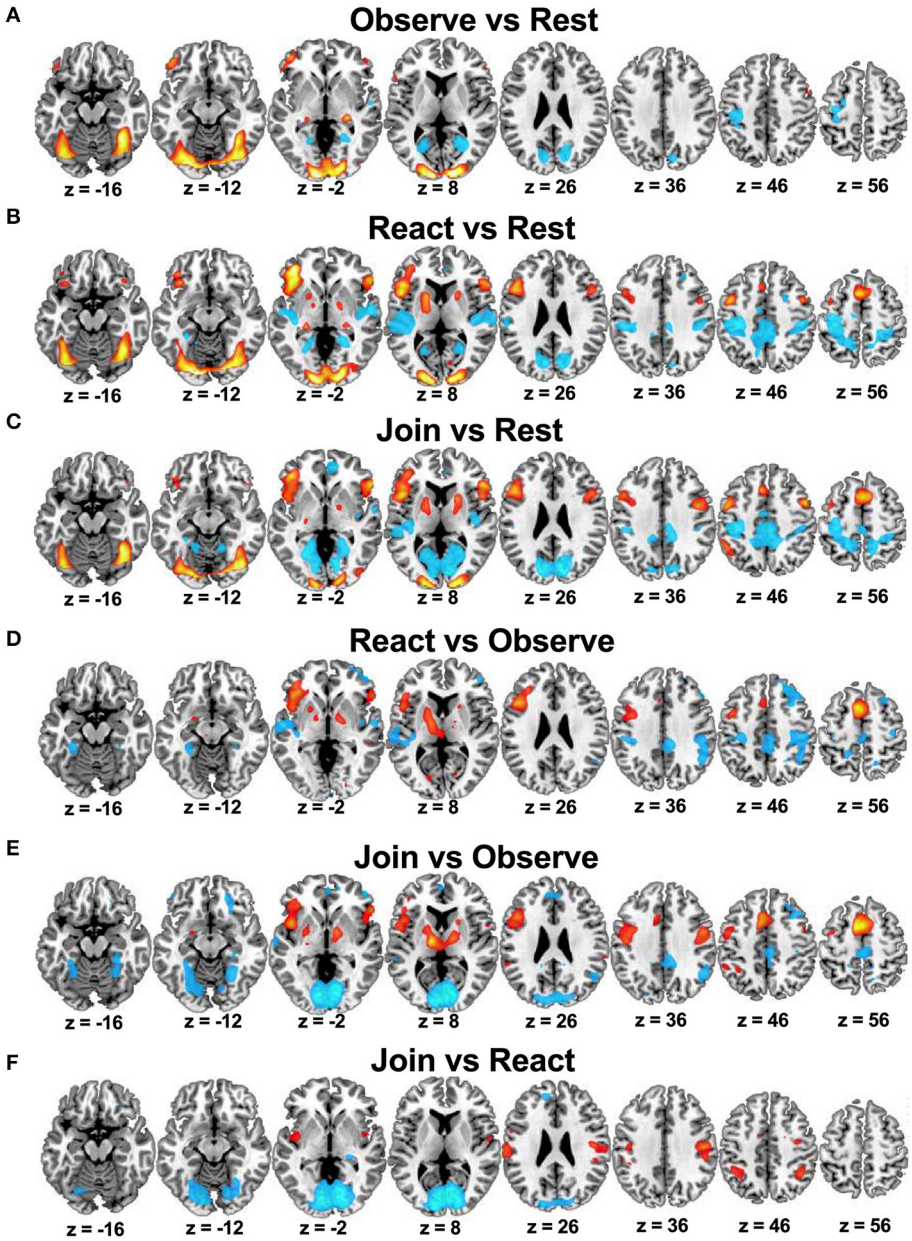

FIGURE 2 | Whole brain results in the reference sample of healthy mothers ($n = 45$) from Study 1: Brain regions that were relatively activated (in hot color) or deactivated (in cool color) in pairwise Task contrasts of Observe vs. Rest **(A)**, React vs. Rest **(B)**, Join vs. Rest **(C)**, React vs. Observe **(D)**, Join vs. Observe **(E)**, and Join vs. React **(F)**.

differential responses in Observe than in Join (Observe > Join)—which is an inverse MMR(all)—suggesting that the Join, as compared to Observe, *reduced* the face processing, mediated by the fusiform gyrus (87), and narrative thinking processing, mediated by the precuneus (41), related to Own Child. We also found that the midbrain, striatum/extended amygdala, and hypothalamus showed greater Own > Other differential responses in React than in Join—suggesting that the own-child-specific maternal motivation responses were stronger in the React than Join. For MMR(j-d), we found that the left amygdala was associated with MMR(j-d) (MNI coordinates: [−26, 2, −24], 15 voxels, $Z = 3.17$, $p = 0.021$ s.v.c.).

Study 2: MP Treatment Effects

We predicted MP treatment effects on parenting stress, maternal voluntary mirroring (probed in the React Condition) and maternal mirroring responses [MMR(all) and MMR(j-d)]. For parenting stress, we found that MP, relative to Control, showed lower PSI total scores at T2 (see **Supplementary Materials**). We examined MP Treatment effects by testing Group-by-Time

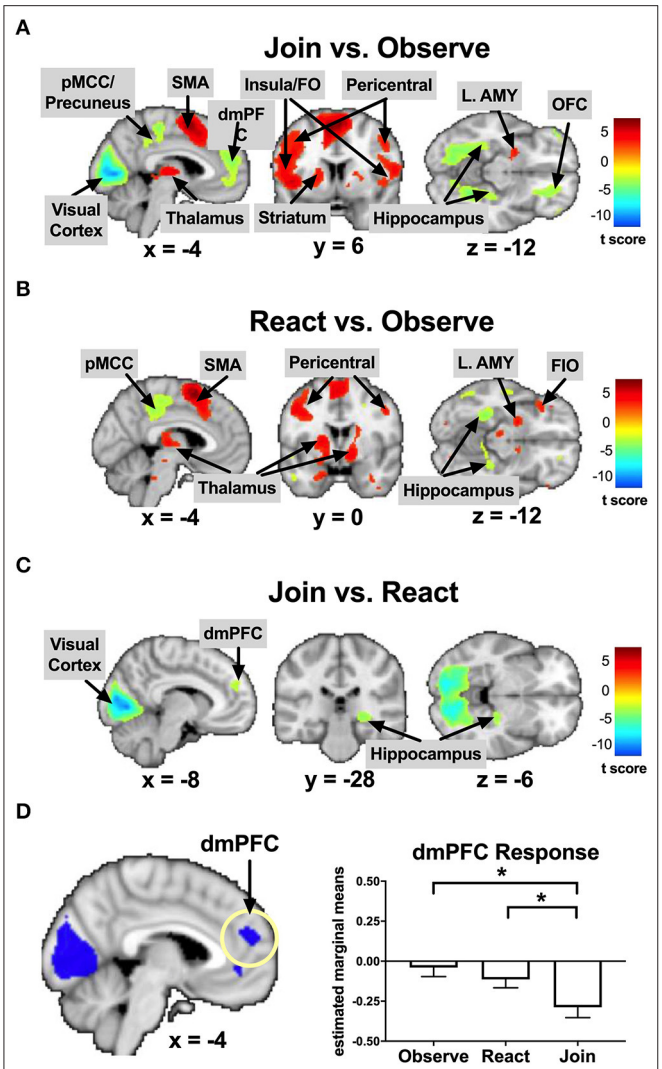

FIGURE 3 | Key results in the reference sample of healthy mothers ($n = 45$) from Study 1: Brain regions that were relatively activated (in hot color) or deactivated (in cool color) in pairwise Task contrasts of Join vs. Observe **(A)**, React vs. Observe **(B)**, and Join vs. React **(C)**. The dmPFC was inhibited in Join vs. Observe and Join vs. React, with the bar charts for each Task's mean (±s.e.) separately **(D)**. pMCC, posterior middle cingulate cortex; SMA, supplemental motor area; dmPFC, dorsomedial prefrontal cortex; Insula/FO, insula/frontal operculum; L. AMY, left amygdala; OFC, orbitofrontal cortex; FIO, frontal inferior orbital. *$p < 0.05$.

interaction effects on three own-child-specific contrasts, i.e., React to Own vs. Other Child, MMR(all), and MMR(j-d).

For React to Own vs. Other Child, we found that, from T1 to T2, MP, relative to Control, decreased React to Own (vs. Other) Child responses in the dmPFC ([−8, 54, 14], 887 voxels, $Z = 3.08$, $p = 0.009$, whole brain cluster-level FWE corrected, **Figure 4**).

As the amygdala mediated MMR(j-d) in the reference sample (**Figure 5A**), there were several Group-by-Time interaction effects on the amygdala as follows. We found that MP, relative to Control, increased the MMR(j-d) in the left amygdala ([−24, −2, −18], 24 voxels, $Z = 2.87$, $p = 0.046$ s.v.c., **Figure 5B**), in which the differential response to own child's Joy expression was increased in MP, but decreased in Control, mothers.

These results suggested that MP mothers, relative to Control, developed stronger capacity not only to activate the left amygdala in response to own child's joyful faces when they were instructed to mirror the children's emotions in the Join condition, but also to inhibit the own-child-specific neural responses in the dmPFC (**Figure 4**) during their voluntary mirroring responses to their own child in the React condition.

For MMR(all), from T1 to T2, MP, relative to Control, increased the MMR(all) in the left frontoparietal regions including the parietal/postcentral ([−56, −26, 42], 357 voxels, $Z = 4.22$, $p = 0.001$, whole brain cluster-level FWE corrected) and dorsolateral prefrontal cortex ([−56, 16, 28], 706 voxels, $Z = 3.48$, $p = 0.001$, whole brain cluster-level FWE corrected, **Figure 6A**), midbrain ([10, −20, −4], 124 voxels, $Z = 3.55$, $p = 0.049$ s.v.c., **Figure 6B**), left NAc ([−8, 16, −12], 26 voxels, $Z = 3.37$, $p = 0.013$ s.v.c., **Figure 6C**), left amygdala ([−28, 2, −22], 12 voxels, $Z = 3.18$, $p = 0.021$ s.v.c., **Figure 6D**), and, marginally, right amygdala ([24, 0, −16], 18 voxels, $Z = 2.85$, $p = 0.057$ s.v.c., **Figure 6E**).

To examine the results in elementary conditions, such as specific tasks and emotions, we unpacked the elements involved in the **Figure 5B** in the **Supplementary Figure 6**. Similarly, we also unpacked the elements involved in the **Figure 6F** in the **Supplementary Figure 7**.

Mediation Analysis

To summarize succinctly the results reported above, we utilized mediation analysis to identify potential mediators of MP effects on reducing parenting stress. We performed mediation analysis using the treatment group as the categorical predictor (X), T1-to-T2 changes in parenting stress (dPSI) as the outcome (Y), and T1-to-T2 changes in MMR(all) and MMR(j-d) as potential mediators (M's). For each of the i'th potential meditator (M_i), we denote the X-M path as Path-a_i, the M-Y path as Path-b_i, the indirect effect as Path-a_ib_i, and the direct effects of X on Y as Path-c'_i.

Firstly, we identified candidates of potential mediators by regressing the T1-to-T2 changes in the MMR(all) against dPSI, controlling for the baseline PSI at T1. We found that the T1-to-T2 reduction of parenting stress was associated with the T1-to-T2 MMR(all) increases in the left superior temporal gyrus (STG) ([−40, 4, −18], 563 voxels, $Z = 3.56$, $p = 0.034$ whole brain cluster-level FWE corrected, **Figure 7A**), right STG ([60, 10, −2], 662 voxels, $Z = 4.30$, $p = 0.016$ whole brain cluster-level FWE corrected, **Figure 7B**), cerebellum ([2, −62, −4], 622 voxels, $Z = 3.86$, $p = 0.022$ whole brain cluster-level FWE corrected, **Figure 7C**), and hypothalamus ([0, −8, −10], 12 voxels, $Z = 3.05$, $p = 0.049$ s.v.c., **Figure 7D**). Among these regions, the MP vs. Control difference in the MMR(all) was significant only in the left STG [$F_{(1, 21)} = 7.61$, $MS_{error} = 0.12$, $p = 0.012$, **Figure 7E**]. Thus, we identified the MMR(all) in the left STG as the first potential mediator, denoted as M_1.

Secondly, we identified candidates of potential mediators by regressing the T1-to-T2 changes in the dmPFC's MMR(all)-dependent psychological-physiological interaction (PPI) against

TABLE 2 | Task main effects in pairwise contrasts*.

Brain region	Side	MNI Coordinates			No. of voxels	*Z*-score
		X	Y	Z		
Join > observe						
SMA	R/L	−6	6	58	2,252	5.83
Thalamus (including hypothalamus)	L	−14	−14	10	483	5.59
	R	12	−10	4	340	4.85
FOp/insula	L	−44	10	2	1,979	5.45
	R	56	28	−4	788	4.68
Pericentral gyrus	R	50	0	38	647	4.52
	L	−36	2	38	1,336	4.38
Lentiform nucleus (pallidum/putamen)	R	14	−4	2	336	4.71
	L	−14	−6	2	513	4.27
Inferior parietal lobule (IPL)	L	−36	−48	44	407	3.68
Amygdala	L	−24	−2	−12	25	3.33
Observe > join						
Occipital lobe (cuneus/calcarine)	R	10	−80	4	7,293	7.72
(including parahippocampal gyrus)	L	−8	−82	2		7.40
Precuneus/middle cingulate cortex (MCC)	R/L	4	−26	50	1,885	4.65
Temporoparietal junction (TPJ)/angular gyrus	R	52	−52	36	693	4.59d
Dorsomedial prefrontal cortex (dmPFC)	R/L	−6	50	18	1,483	4.15
IFG/Fontal inferior orbital (FIO)	R	50	48	−2	235	4.12
Orbitofrontal cortex (OFC)	R	26	36	−12	211	3.84
MFG (BA 8)	R	34	20	46	569	3.80
React > observe						
SMA	R/L	−6	10	58	1,353	5.87
FO/MFG/IFG/precentral	L	−44	12	2	4,287	5.09
(including thalamus/lentiform nucleus)						
Lentiform nucleus	R	14	−4	−6	436	4.36
(including thalamus)	R	18	−16	12	(112)	3.28
Pericentral gyrus	R	50	0	38	647	4.52
	L	−36	2	38	1,336	4.38
IFG	R	54	26	0	303	4.11
FIO/temporal pole	L	−24	18	−24	318	3.99
Observe > react						
Superior temporal gyrus (STG)	L	−56	−10	−2	1,198	4.83
	R	58	−8	−2	201	4.02
Parietal lobe/postcentral	R	48	−28	42	2,293	4.78
MCC/paracentral lobule	R/L	6	−32	40	2,397	4.46
MFG (BA 8)	R	24	32	44	1,070	4.39
IFG/Fontal inferior orbital (FIO)	R	48	50	2	428	4.15
Hippocampus, posterior	L	−28	−40	−12	275	4.11
Join > react						
None						
React > Join						
Occipital lobe (cuneus/calcarine)	R/L	12	−78	8	6,977	>15
dmPFC	R/L	−14	50	28	232	3.64

**Whole brain corrected at false-discovery rate (FDR) = 0.05.*

dPSI, controlling for the baseline PSI at T1. We found that the T1-to-T2 increases in parenting stress was associated with the T1-to-T2 increases in the MMR(all)-dependent PPI between the dmPFC seed and the PAG ([−2, 32, −20], 178 voxels, $Z = 4.36$, $p = 0.002$ s.v.c., **Figure 8A**); conversely, the T1-to-T2 reduction in parenting stress was associated with T1-to-T2 increases in the MMR(all)-dependent PPI between the dmPFC seed and bilateral NAc ([6, 6, −4], 40 voxels, $Z = 3.39$, $p = 0.020$ s.v.c., **Figure 8B**).

Among these PPI results, the MP vs. Control group difference in the MMR(all)-dependent PPI was significant only in the dmPFC-PAG [$F_{(1, 21)} = 14.99$, $MS_{error} = 0.10$, $p = 0.001$, **Figure 8C**]. Thus, we identified the MMR(all)-dependent PPI between the dmPFC-PAG as the second potential mediator, denoted as M_2.

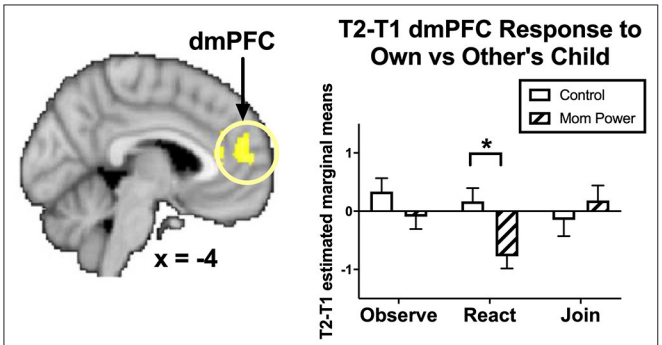

FIGURE 4 | From T1 to T2 in the clinical study sample (Study 2), MP, relative to Control, showed greater inhibition in the dmPFC during React to Own vs. Other Child, with the bar charts for each Task's mean (±s.e.) separately. *$p < 0.05$.

Thirdly, we identified candidates of potential mediators by regressing the T1-to-T2 changes in the MMR(j-d) against dPSI, controlling for the baseline PSI at T1. We found that the T1-to-T2 reduction of parenting stress was associated with the T1-to-T2 MMR(j-d) increases in the left amygdala ([−22, 6, −18], 122 voxels, $Z = 3.62$, $p = 0.014$ s.v.c., **Figure 9A**), right NAc ([8, 4, −8], 30 voxels, $Z = 3.22$, $p = 0.049$ s.v.c., **Figure 9B**), and PAG ([−8, −32, −16], 181 voxels, $Z = 4.34$, $p = 0.001$ s.v.c., **Figure 9C**). Furthermore, when examining each type of expression separately (**Figures 10A–D**), the T1-to-T2 reduction in parenting stress was associated with the T1-to-T2 increases in the differential responses of MMR(joy) in the left amygdala (**Figure 10A**) and right NAc (**Supplementary Figure 8A**) and the T1-to-T2 decreases of MMR(joy) in the PAG (**Supplementary Figure 9A**). Conversely, the T1-to-T2 reduction in parenting stress was associated with the T1-to-T2 decreases in the differential responses of MMR(dis) in the left amygdala (**Figure 10B**) and the T1-to-T2 increases of MMR(dis) in the PAG (**Supplementary Figure 9B**).

Among these regions (the left amygdala, right NAc, and PAG), the MP vs. Control group difference in the MMR(j-d) was significant only in the left amygdala [$F_{(1, 21)} = 11.51$, $MS_{error} =$

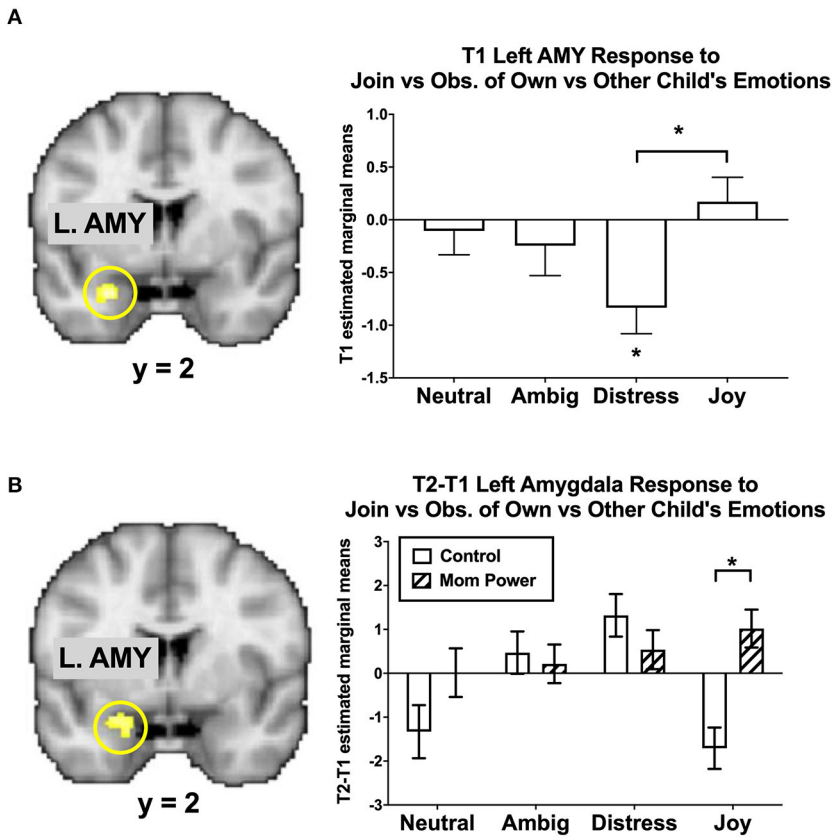

FIGURE 5 | The left amygdala's MMR(all) [Join[Own vs. Other Child] vs. Observe[Own vs. Other Child]] differential responses was activated in Joyful vs. Distressed expression, while it was inhibited in the Distressed expression in the reference sample, with the bar charts of each expression's mean (±s.e.) separately **(A)**. From T1 to T2 in the clinical study sample, MP, relative to Control, showed greater activation in the Joyful expression in the Join[Own vs. Other Child] vs. Observe[Own vs. Other Child], with the bar charts for each expression's mean (±s.e.) separately **(B)**. *$p < 0.05$.

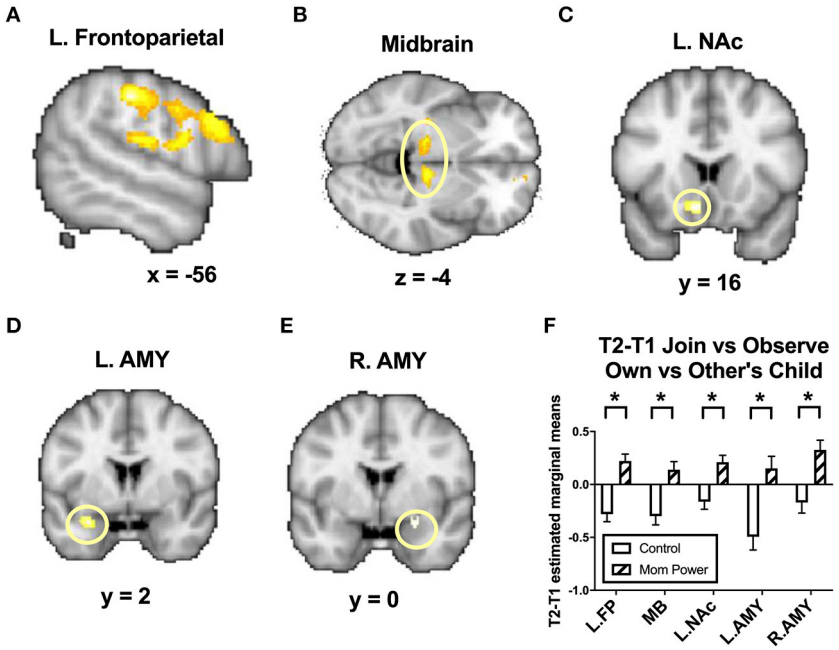

FIGURE 6 | From T1 to T2 in the clinical study sample, MP, relative to Control, showed greater differential responses of MMR(all) [Join[Own vs. Other Child] vs. Observe[Own vs. Other Child]] in the left frontoparietal regions **(A)**, midbrain **(B)**, left nucleus accumbens (NAc) **(C)**, left and right amygdala (AMY) **(D,E)**, with the bar charts of each region's mean (±s.e.) **(F)**. $^*p < 0.05$.

5.79, $p = 0.003$, **Figure 9D**], which was primarily driven by the MP vs. Control group difference in the left amygdala's differential responses of MMR(joy) (**Figure 10E**). Thus, we identified the MMR(j-d) in the left amygdala as the third potential mediator, denoted as M_3.

By running mediation analysis separately for the three potential mediators, M_1 [the MMR(all) in the left STG], M_2 [the MMR(all)-dependent PPI between the dmPFC-PAG], and M_3 [the MMR(j-d) in the left amygdala], we found that each of them potentially mediated the indirect effect of MP treatment (X) on dPSI (Y), with <5% chance that the null hypothesis H_0: $a_i b_i = 0$ is true, as their 95% confidence interval (*c.i.*) did not cover zero. See **Figure 11** and **Table 3** for the statistical results for these three single-mediator models.

When these three mediators were included simultaneously in a three-mediator model, denoted as M'_1, M'_2, and M'_3, respectively, we found that the relative indirect effect of M'_1 [the MMR(all) in the left STG] was potentially stronger than those of M'_2 [the MMR(all)-dependent PPI between the dmPFC-PAG] and M'_3 [the MMR(j-d) in the left amygdala]. See **Supplementary Figure 10** and **Supplementary Table 3** for the statistical results of the three-mediator model.

DISCUSSION

In this translational study, at an empirical level of analysis, we employed the Child Face Mirror Task (CFMT) to examine brain mechanisms underlying maternal intersubjectivity problems, with specific focus on two problem domains of "over-mentalizing" and "under-coupling," and to showcase the MP interventions effects on reversing these "over-mentalizing" and "under-coupling" problems, which ultimately links to reductions in parenting stress. In addition, at an abstract level of analysis to be presented at the end of this paper (section Abstract Level of Analysis—Toward an Overarching Framework for Research on Intersubjectivity), we address the theoretical relationship between the "over-mentalizing" and "under-coupling" problems and parenting stress, using the dyadic active inference framework. By combining both empirical and theoretical levels of analysis, we hope to have provided an enriched conceptual model for future research on intersubjectivity and mother-child interaction. We hereby summarize the results in support of the predictions first in section A Summary in Support of the Predictions and then discuss the results in more details in sections Neural Bases of Empathic Mirroring, The Roles of Dorsomedial Prefrontal Cortex (dmPFC), The Roles of Amygdala, The Roles of Nucleus Accumbens (NAc) and Periaquaductal Gray (PAG), The Roles of Superior Temporal Gyrus (STG), and The Roles of Prefrontal Cortex.

A Summary in Support of the Predictions

We hypothesized that MP can reduce parenting stress by improving the mothers' working models of the child, which in turn improve maternal empathic mirroring of the child's joyful expressions (reversal of "under-coupling") and prevent mothers' defensive reactions from shaping their mental representation

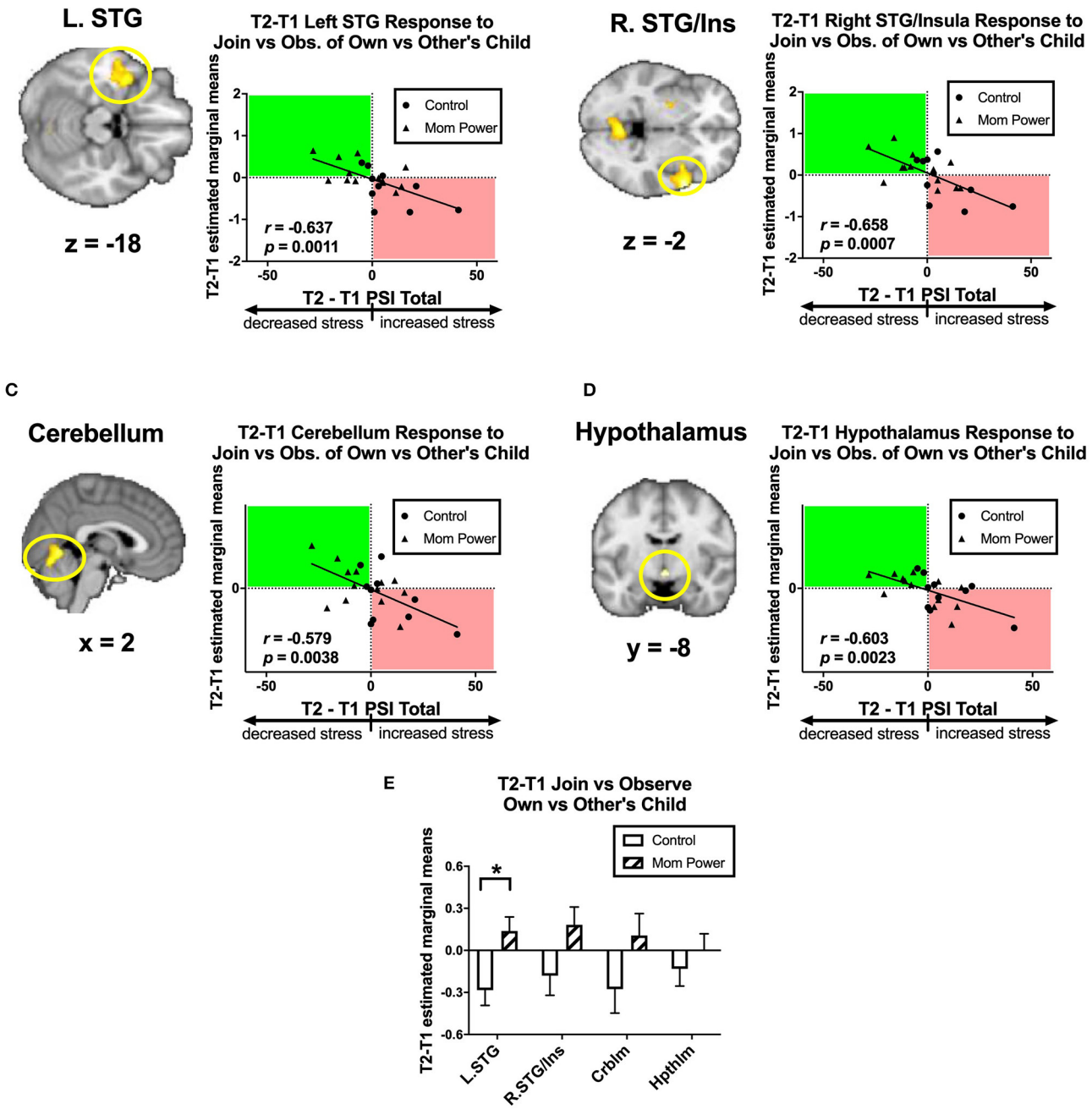

FIGURE 7 | From T1 to T2 in the clinical study sample, the T2-T1 differences in parenting stress index (dPSI) were negatively associated with the concomitant increases in the MMR(all) [Join[Own vs. Other Child] vs. Observe[Own vs. Other Child]] differential responses in the left superior temporal gyrus (STG) **(A)**, right STG/insula **(B)**, cerebellum **(C)**, and hypothalamus **(D)**, each with the dPSI depicted on the x-axis, against the T2-T1 difference in the region's differential response on the y-axis, in the scatter plots. The Pearson's correlation *r* scores and *p*-values are embedded in the plots. The bar charts of each region's mean (±s.e.) are depicted in **(E)**. $^{*}p < 0.05$.

of their child (reversal of "over-mentalizing") during empathic mirroring. The hypothesis was supported by the results in the following group-by-time interaction effects during the CFMT: We found that MP (vs. Control), from T1 to T2, (1) reduced parenting stress (**Supplementary Figure 2**), (2) decreased the dmPFC (in the *mentalizing system*) activities during own-child-specific voluntary responding (React to Own vs. Other's Child), suggesting that MP rectified the "over-mentalizing" problem

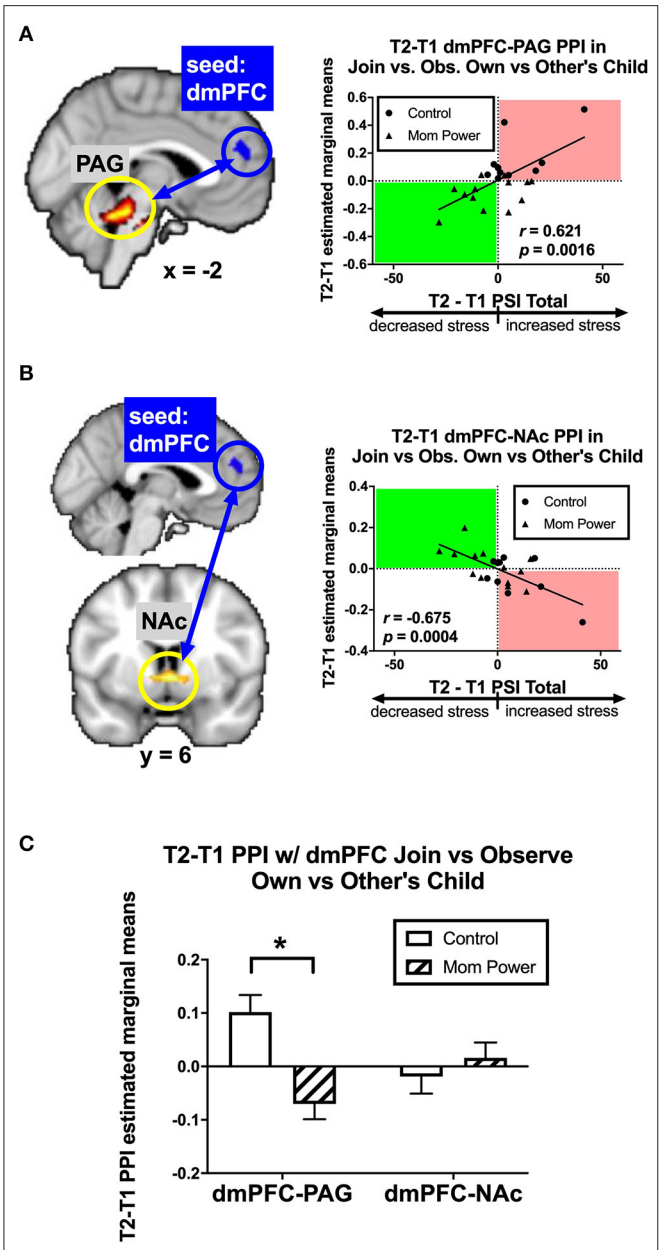

FIGURE 8 | From T1 to T2 in the clinical study sample, the T2-T1 differences in parenting stress index (dPSI) were positively and negatively associated with the concomitant increases in the MMR(all) [Join[Own vs. Other Child] vs. Observe[Own vs. Other Child]] differential functional connectivity [MMR(all)-dependent PPI] between the dmPFC and PAG **(A)** and that between the dmPFC and NAc **(B)**, respectively, each with the dPSI depicted on the x-axis, against the T2-T1 difference in the region's differential response on the y-axis, in the scatter plots. The Pearson's correlation *r* scores and *p*-values are embedded in the plots. The MP vs. Control differed in the MMR(all)-dependent PPI between dmPFC and PAG, but not that between dmPFC and NAc, with the bar charts of each region's mean (±s.e.) depicted in **(C)**. *$p < 0.05$.

(**Figure 4**), (3) increased MMR(all) (own-child-specific empathic mirroring) in the *mirroring system* (**Figure 6**), and (4) the amygdala's MMR(j-d), i.e., the sensitivity to the prediction errors (**Figure 5**), suggesting that MP rectified the "under-coupling" problem. The results also supported our predictions that, from T1 to T2, MP (vs. Control) (5) reversed the stress-potentiated "under-coupling" problem, suggested by the association between the increasing sensitivity to *signed prediction errors* in the amygdala's MMR(j-d) and the decreasing parenting stress index (PSI) (**Figure 9**) and (6) reversed the stress-potentiated over-mentalizing problem, suggested by the association between the decreasing MMR(all)-dependent dmPFC-PAG functional connectivity and the decreasing PSI (**Figure 8**). We also identified three potential brain mediators of the MP treatment effects on reducing parenting stress: (1) the T1-to-T2 increases in the MMR(all) of the left STG, (2) the T1-to-T2 decreases in the MMR(all)-dependent psychological-physiological interaction (PPI) between the dmPFC and PAG, and (3) that the T1-to-T2 increases in the MMR(j-d) of the left amygdala. The results of these potential mediators will be discussed later.

Neural Bases of Empathic Mirroring

In Study 1, the results in the contrast between strong coupling (Join) and weak coupling (Observe) conditions is highly consistent with the predictions deduced from our novel dyadic active inference framework. Specifically, the Join > Observe contrast primarily activated the *mirroring system,* along with the *salience network*, including the SMA, pericentral cortex, inferior parietal lobule (IPL), insula, thalamus, striatum, and left amygdala. Conversely, the Join > Observe primarily deactivated the *mentalizing system*, including the dmPFC, precuneus/posterior middle cingulate cortex, parahippocampal gyrus/hippocampus, and OFC, along with the visual cortex. Furthermore, some of these Join vs. Observe results overlapped with the Join vs. React results. Specifically, the strong coupling condition of Join (vs. both React and Observe) activated the bilateral pericentral cortex and left IPL, but deactivated the dmPFC, primary and secondary visual cortices, and right hippocampus.

The Roles of Dorsomedial Prefrontal Cortex (dmPFC)

According to the affect-object active inference model (40), the dmPFC may mediate the mentalization of others (as a distal-object sketchpad to hold affective active inference of a counterpart), and it has been found that the dmPFC mediated mentalization based on a self-centered, rather than other-centered, perspective (46). The down-regulation of the dmPFC responses during the strong coupling condition (Join) in the healthy mothers in Study 1 probably help preserve their maternal intersubjectivity by preventing the over-mentalizing problem, which may manifest as perspective mistaking that can happen when one overly relies on preconceived beliefs (88). In short, it is probably necessary to suspend (temporarily down-regulate) the prior-driven dmPFC to avoid the over-mentalizing problem and achieve a higher level of intersubjectivity in a strong coupling condition.

The dmPFC has been known to be sensitive to repeated stress (89, 90) and postpartum depression (91). In accord, we previously found that, when listening to own baby's crying, the

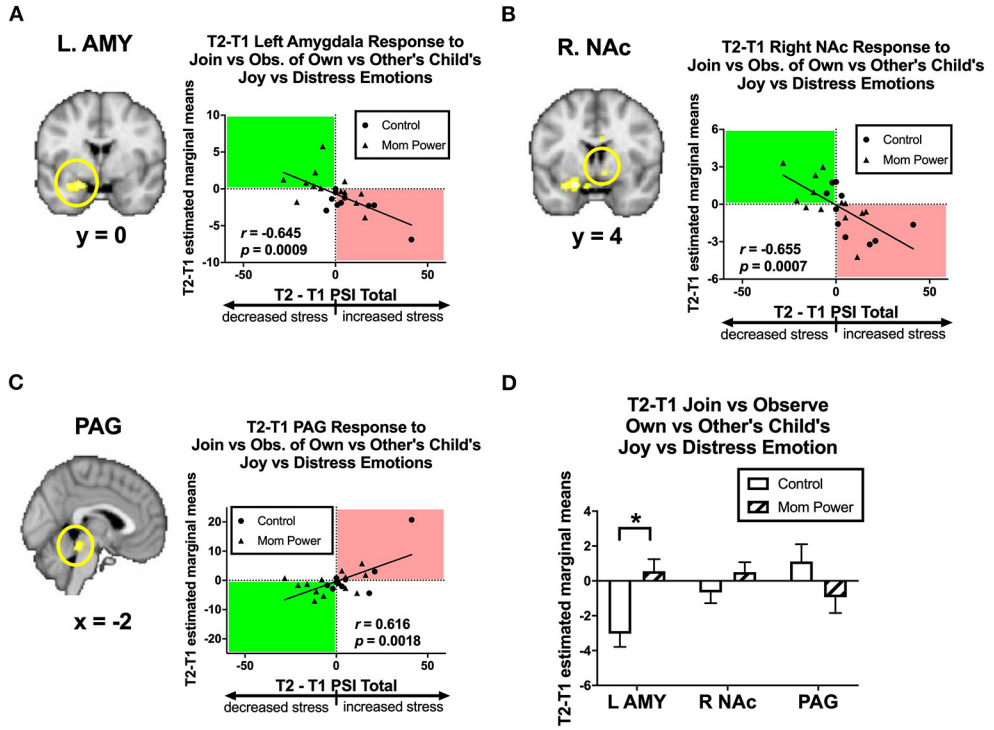

FIGURE 9 | From T1 to T2 in the clinical study sample, the T2-T1 differences in parenting stress index (dPSI) were negatively associated with the concomitant increases in the MMR(j-d) [Join[Own vs. Other Child's Joyful vs. Distressed] vs. Observe[Own vs. Other Child's Joyful vs. Distressed]] differential responses in the left amygdala **(A)** and right NAc **(B)**, but they were positively associated with that in the PAG **(C)**, each with the dPSI depicted on the x-axis, against the T2-T1 difference in the region's differential response on the y-axis, in the scatter plots. The Pearson's correlation *r* scores and *p*-values are embedded in the plots. The MP vs. Control differed in the MMR(j-d) in the left amygdala, but not the right NAc and PAG, with the bar charts of each region's mean (±s.e.) depicted in **(D)**. $^*p < 0.05$.

maternal dmPFC response (92) and its functional connectivity with anxiety-dependent extended amygdala (93) increased with maternal stress-related symptoms. The present study suggested a new insight into the roles of dmPFC in stress resilience, i.e., the dmPFC mediated maternal preconceived beliefs of the child as part of the *mentalizing system*, which should be temporarily suspended when the mothers relied on the *mirroring system* to empathically mirror the child. Moreover, MP enhanced the maternal capacity to down-regulate the dmPFC voluntarily while responding to own child and probably reduced parenting stress by diminishing the influences of PAG-dependent defensive/aggressive motivation signals on the dmPFC-dependent (preconceived) representation of the child. In other words, interpersonal stress can be reduced if defensive signals from the PAG are prevented from influencing the dmPFC, otherwise it would cause the defensive over-mentalizing problem that tends to increase stress.

The Roles of Amygdala

With regard to the amygdala, we found that, in Study 1, (a) the left amygdala was activated in Join vs. Observe and (b) the left amygdala was sensitive to MMR(j-d); in Study 2, (c) from T1 to T2, the left amygdala's MMR(joy) (Join vs. Observe of Own vs. Other Child's Joyful expression) increased in MP, relative to Control, (d) from T1 to T2, the bilateral amygdala (and other regions in the maternal motivation and mirroring component) increased their MMR(all) responses in MP, relative to Control, and (e) T1-to-T2 increases in the left amygdala MMR(j-d) responses mediated the MP effects on reducing parenting stress.

The constellation of amygdala-related results provided more nuanced understanding of the amygdala's role in maternal behaviors, in accordance with the literature documenting the roles of amygdala in parental synchrony in interactions with the infant (94), empathy for the own child (71), positive feelings and attachment to the infant (95), and autobiographical recall of positive and negative emotion cues (96).

The Roles of Nucleus Accumbens (NAc) and Periaquaductal Gray (PAG)

Consistent with the roles of NAc and PAG in maternal affiliative and defensive motivations, respectively (52, 53, 78) and their roles in *signed prediction errors* of reward (55, 56) and pain (59), respectively, we found that these two regions were related to the T1-to-T2 changes in parenting stress in opposite directions. While the T1-to-T2 changes in parenting stress were negatively associated with the NAc's MMR(j-d) and MMR(all)-dependent PPI with the dmPFC, it was positively associated with the PAG's. Consistent with the affect-object active inference model

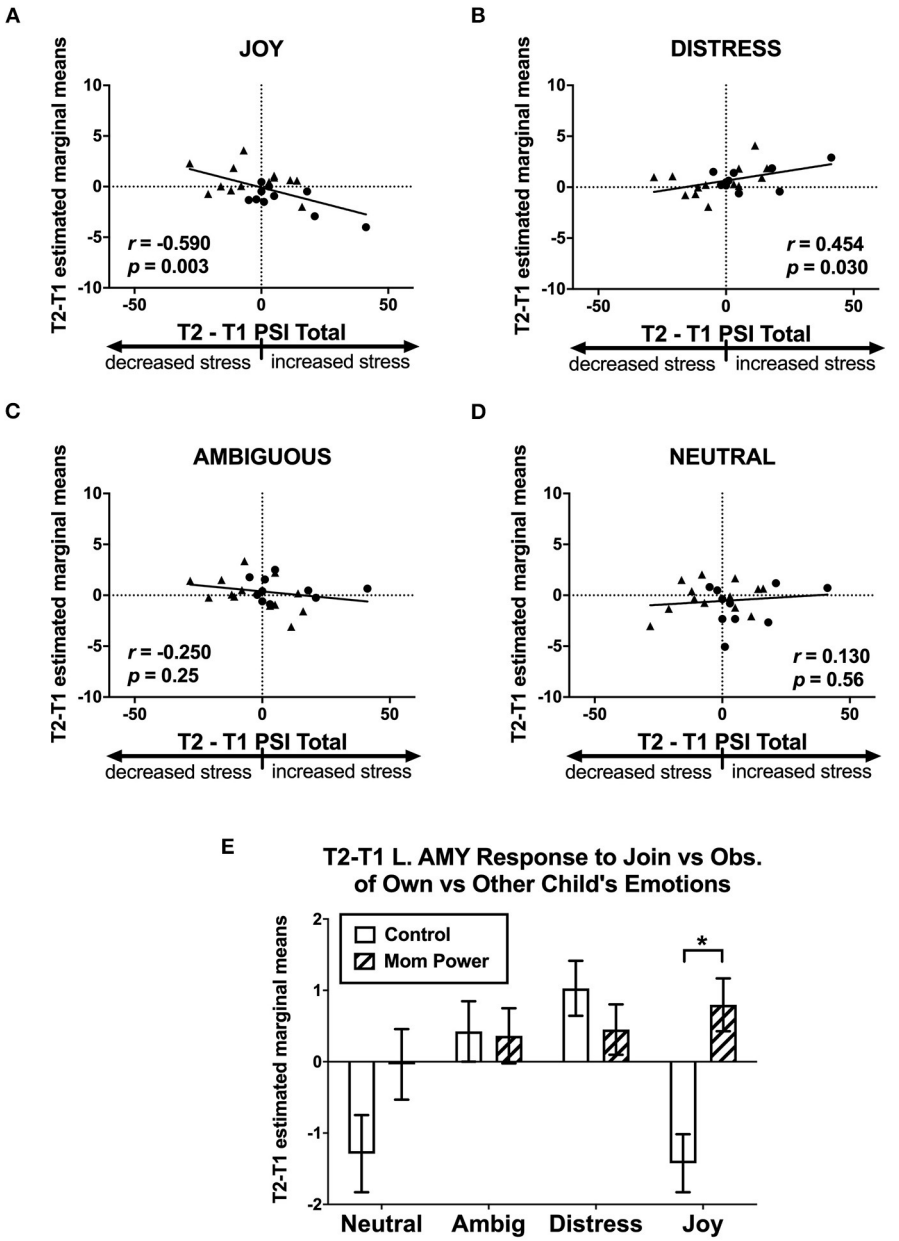

FIGURE 10 | Scatter plots of Study 2 T2-T1 changes in PSI (x-axis) and T2-T1 differential responses in the left amygdala (y-axis) in the contrasts of MMR(joy) **(A)**, MMR(dis) **(B)**, MMR(amb) **(C)**, and MMR(neu) **(D)**. The T2-T1 left amygdala MMR(all) responses were increased in MP but decreased in Control group **(E)**. *$p < 0.05$.

(40), these results highlights the role of dmPFC as a distal-object sketchpad in representing the child and the "coloring" of the representation with affiliative and defensive affective potentials, forming "affect-objects," by its connectivity with NAc and PAG (59), respectively. So, this suggests that the role of affect-object generation during empathic mirroring in parenting stress, i.e., mirroring the child with affiliative or defensive affective potentials can decrease or increase parenting stress, respectively.

The Roles of Superior Temporal Gyrus (STG)

We also found that the T1-to-T2 reduction in parenting stress was associated with the concomitant increases in the MMR(all) in the left STG, right STG/Insula, cerebellum, and hypothalamus. Interestingly, the first three regions were related to music-entrained movement coherences in professional dancers (97), suggesting that increasing coherence in empathic mirroring may be related to parenting stress reduction. In a cross-culture study,

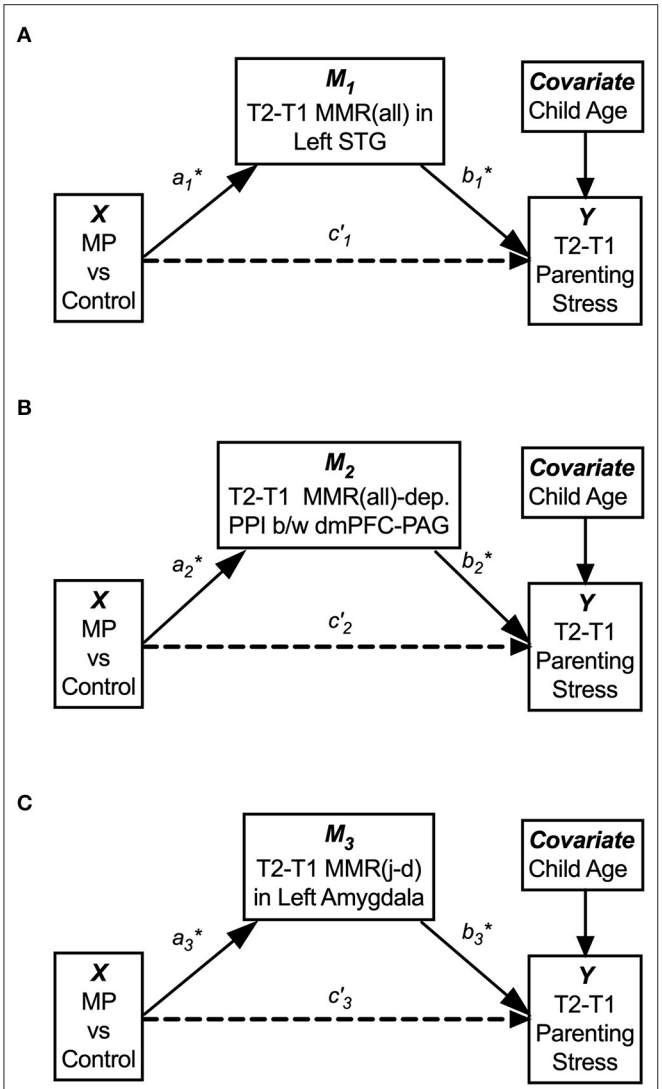

FIGURE 11 | The single-mediator model for each of the three mediators: M_1 = T2–T1 differences in the MMR(all) in the left STG **(A)**, M_2 = T2–T1 differences in MMR(all)-dependent PPI between dmPFC and PAG, **(B)** and M_3 = T2–T1 differences in the MMR(j-d) in the left amygdala showed that each mediator significantly mediated the MP effects on reducing parenting stress from T1 to T2 **(C)**. The age of Own Child was used as a covariate in all mediation models. See **Table 3** for the statistical results of these three single-mediator models.

these brain regions were commonly activated when mothers from different cultures listened to their own baby's cry (98). Consistent with the result that the left STG mediated the MP effects on reducing parenting stress in the present study, we have reported that the T1-to-T2 parenting stress reduction was associated with the concomitant increases in the functional connectivity between the left STG and amygdala, when the mothers responded to own baby's crying (29). Maternal STG responses to own vs. other's infant cry were associated with child-oriented caring thoughts and indirectly with infant development (99). Taken together, these results implicated that parenting stress reduction may depend on increasing the coherence in maternal empathic mirroring of the child, which is potentially mediated by the amygdala-STG neurocircuits, as part of the mirroring system.

The Roles of Prefrontal Cortex

We also found that the left prefrontal cortex was activated in Join vs. Rest (**Figure 2C**), in accord with a recent hyper-scanning study that reported increasing maternal parenting stress was also associated with the differences between mother and child's left prefrontal cortex responses when the dyads watched videos together (100). Considering that the left prefrontal cortex is part of the mirroring system (32), these results suggested that parenting stress may influence the mother-child coupling via the left prefrontal cortex.

Limitations

Several limitations of the present study should be noted. First, although Study 1 established the intended effects of CFMT with whole brain correction in a relatively large sample (n = 45), the sample sizes of MP and Control groups in Study 2 were modest and thus the results should be considered preliminary and warrant future study. Second, there was heterogeneity in medication use in Study 2. Nevertheless, this heterogeneity would cause little confounding because not only it was partially controlled in the repeated measurement effects based on each participant's own baseline, but also the medicated participants were in minority and evenly distributed between the groups. As reported in **Supplementary Materials**, removing all medicated participants in statistical analysis did not qualitatively alter the results reported above. Third, we did not incorporate measurements that are directly linked to the "over-mentalizing" and "under-coupling" problems in the parenting context. Nevertheless, the effectiveness of MP's improvement on the symptoms of "over-mentalizing" and "under-coupling" has been documented (28) and thus the reported Time-by-Group interaction results should be closely related to the correction of "over-mentalizing" and "under-coupling" problems. We will examine the associations between the neuroimaging data and these variables in the future.

ABSTRACT LEVEL OF ANALYSIS—TOWARD AN OVERARCHING FRAMEWORK FOR RESEARCH ON INTERSUBJECTIVITY

In this section, we describe a dyadic active inference framework, at an abstract level of analysis, to address theoretical relationships between the impairment of intersubjectivity and parenting stress we well as to clarify the relationships among the dyadic framework, the MP intervention, and the brain systems. First, we introduce a single-agent active inference framework, namely Free Energy Principle (FEP) (67, 68, 101). Second, we propose a novel *dyadic active inference framework* to account for the link between intersubjectivity and stress resilience in a two-agent system (mother and child dyad). Third, we explain the links between the impairment of intersubjectivity and parenting stress

TABLE 3 | Summary of separate single-mediator models.

Separate models	Path-a_i			Path-b_i			Path-c'_i			Indirect effect (Path-a_ib_i)			
	Coef.	s.e.	*p*	Coef.	s.e.	*p*	Coef.	s.e.	*p*	Effect	s.e.	LLCI	ULCI
M_1	0.431	0.157	0.013	−23.669	7.583	0.006	−2.326	6.247	0.714	−10.192*	5.045	−22.688	−2.172
M_2	−0.171	0.046	0.0013	82.432	25.869	0.005	1.555	6.890	0.824	−14.074*	7.686	−32.478	−2.789
M_3	3.452	1.063	0.004	−3.730	14.080	0.003	0.359	6.345	0.956	−12.877*	6.041	−27.433	−3.233

M_1: T2-T1 MMR(all) in the left STG.
M_2: T2-T1 MMR(all)-dependent PPI between dmPFC-PAG.
M_3: T2-T1 MMR(j-d) in the left amygdala.
**95% confidence interval did not cover zero.*
LLCI/ULCI: Lower/upper limit of 95% confidence interval.

based on the dyadic framework. Fourth, we interpret the MP intervention in light of the dyadic framework. Last, we map brain systems to the components of the active inference framework.

Single-Agent Active Inference Framework

Bayesian active inference (also known as predictive coding) is a computationally powerful framework, as its variants not only can account for perception, cognition, emotions, and consciousness in humans and animals (35, 40, 67, 69, 102–108), but also biologic evolution (109) and even artificial intelligence (110, 111).

According to FEP (67, 68), an agent's predictive-coding engine can be heuristically modeled in a hierarchical network, which contains four nodes (**E**, **S**, **A**, and **M**) in three levels: **E** is Event from environments at the bottom, **S** is Sensation and **A** is Action at the intermediate, and **M** is the internal prior Model at the top level (**Figure 12A**). When an event **E** causes **S** to generate afferent data, **S** causes **M** to predict what the event *means* based on stored prior causal models, and **M** in turn causes **A** to respond to the event, and then the differences between **S** (the afferent data) and **A** (the efferent prediction) are computed, serving as prediction errors in feedback to update the priors in **M**. Because there is no direct contact between **M** and **E** nodes, the engine depends on the prediction errors resulting from the interactions between the agent's **S and A** to infer the events in **E**. The interactions between an agent's **S** and **A** and events (**E**) update the internal model **M** iteratively, until the prediction errors are minimized, and **M** is thus optimized.

Dyadic Active Inference Framework

The notion of human as a social active inference engine has emerged in the recent literature (35, 40, 106, 108). As social interactions lie at the core of intersubjectivity, single-agent active inference framework is simply inadequate to account for intersubjectivity. Thus, we propose a novel *dyadic* active inference framework to model intersubjectivity (**Figure 12B**). In this dyadic framework, in a two-agent coupled system wherein Agent 1 (say, Mom) and Agent 2 (say, Son) are strongly coupled such that one agent's action (**A**) *predominantly* causes the other's sensation (**S**) and *vice versa*, i.e., $\mathbf{A}_{Mom} \approx \mathbf{S}_{Son}$ and $\mathbf{A}_{Son} \approx \mathbf{S}_{Mom}$, each agent's internal model (**M**) will serve as the other's events **E**, i.e., $\mathbf{M}_{Son} \approx \mathbf{E}_{Mom}$ and $\mathbf{M}_{Mom} \approx \mathbf{E}_{Son}$. When Mom's internal model (her working model of the child) approximate Son's (his working model of the mother), $\mathbf{M}_{Mom} \approx \mathbf{M}_{Son}$, she achieves intersubjectivity and minimizes her prediction errors in the dyadic system.

One question arises that if $\mathbf{M}_{Mom} \approx \mathbf{M}_{Son}$, then the mother's working model ($\mathbf{M}_{Mom}$) will be as helpless as the son's ($\mathbf{M}_{Son}$) when the son struggles in distress. This would not be the case if the mother would possess more knowledge or wisdom, i.e., if her working model could access more repertoires or strategies that the son's does not have. *It is important to note that the presence or absence of* $\mathbf{M}_{Mom} \approx \mathbf{M}_{Son}$ *as a state is transactional, not permanent*. Therefore, after the mother achieves the state of $\mathbf{M}_{Mom} \approx \mathbf{M}_{Son}$, she can access additional resources, repertoires, or strategies and then teach the son to expand his working model to solve his issue at hand. Conversely, without first achieving the state of $\mathbf{M}_{Mom} \approx \mathbf{M}_{Son}$, the mother may fail to address what the son needs or to teach him any new strategies effectively because she may have misunderstood what the son actually needs in that current moment.

Linking Intersubjectivity and Stress in the Dyadic Framework: Three Propositions

Our dyadic framework can make sense of why *intersubjectivity* can automatically minimize stress in a two-agent coupled system. Recently, stress has been re-defined as uncontrollable prediction errors (excessive free energy) that threatens the agent as a Bayesian active inference engine (69). Thus, the minimization of prediction errors is equivalent to the minimization of stress. When two or more agents are coupled as a relational whole, if one agent merely projects one's own beliefs about another agent's perception, action, and intention—without relying on data from ongoing dyadic interactions—the prediction errors will tend to increase, as exemplified in *perspective mistaking* (88).

How can imitation facilitate intersubjectivity? In the two-agent system, when the mother imitates the child's action (e.g., smile), their actions are similar and their perceptions are also similar (e.g., joy). By virtue of such reciprocal similarity, the dyad can better predict each other's covert working models underlying their actions and perceptions. Thus, imitation can reduce prediction errors in predicting each other's actions and feelings, which may in turn increase the similarity between their covert working models underlying those actions and feelings, thereby facilitating intersubjectivity. However, when the mother's preconceived working model of the child is fixated in negative

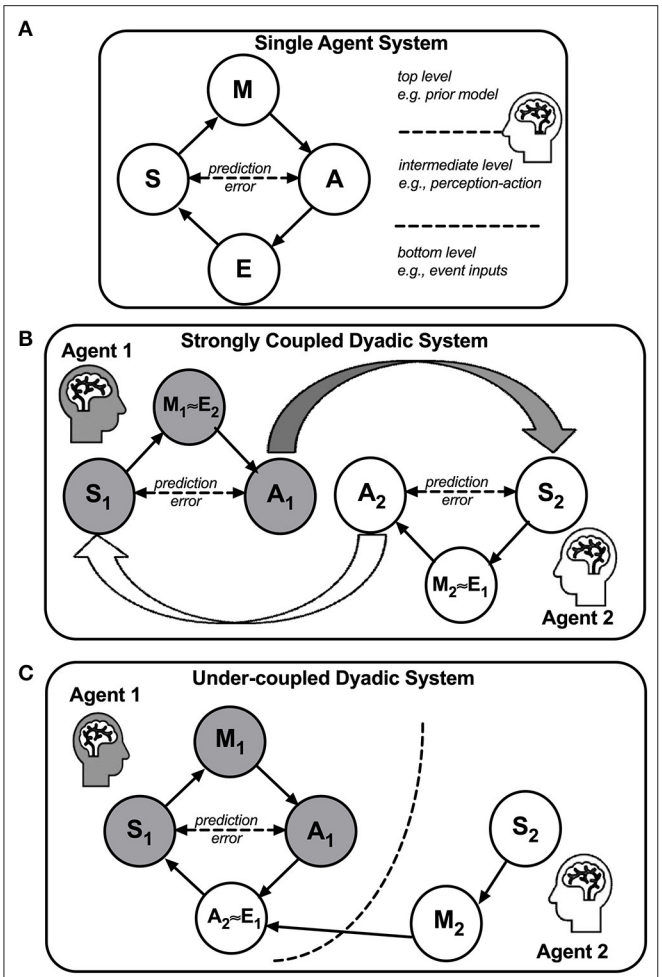

FIGURE 12 | A Bayesian active inference framework for a single-agent system **(A)**, a strongly coupled dyadic system **(B)**, and an under-coupled dyadic system **(C)**. In **(A)**, an agent and its environments form a single-agent system, depicted as a four-node hierarchical network. E, a node representing events from environments at the bottom level; S, a node representing the agent's sensation; A, a node representing the agent's action; M, a node representing the agent's internal model. The S and A nodes are positioned at the intermediate level and the M node is positioned at the top level. The *prediction error*, defined as the difference between the data in the S node and the prediction in the A node, is bounded by free energy. When the free energy is minimized by the M node, the agent can reliably predict the environments, and thus the adaptation of the agent to the environments is optimized. In **(B)**, a strong coupling between two agents is formed when Agents 1 and 2 are coupled by their S's and A's nodes, wherein A_1 causes S_2 and A_2 causes S_1. Due to the coupling, each agent's prediction errors are also coupled and thus the adaptation is optimized when the collective free energy is minimized. In an optimal state, M_1 and M_2 will be highly consistent with one another, indicating a high level of intersubjectivity. In **(C)**, under-coupling ensues when Agent 1 discards Agent 2's M_2 and S_2 and instead only focuses on Agent 2's behaviors A_2 in relation to Agent 1's S_1 and A_1. Due to the under-coupling, Agent 1 tends to misattribute the causes of Agent 2's behaviors.

mood under stress (excessive prediction errors), her capacity to utilize prediction errors to update her working model of the child, which would have helped her better imitate the child's positive affective expressions, is compromised.

We hereby link intersubjectivity and stress in terms of the dyadic active inference framework in three inter-related propositions, namely *dyadic symbiosis*, *under-coupling*, and *over-mentalizing*, as follows:

1) *A strongly-coupled dyadic system is symbiotic*: When a dyad's **S's** and **A's** are strongly coupled ($\mathbf{A}_{Mom} \approx \mathbf{S}_{Son}$ and $\mathbf{A}_{Son} \approx \mathbf{S}_{Mom}$), they function in *symbiosis*, in which the prediction errors are minimized collectively *if*, and *only if*, the prediction error in one agent is minimized without increasing the other's. In such symbiosis, Mom can achieve intersubjectivity ($\mathbf{M}_{\mathrm{Mom}} \approx \mathbf{M}_{\mathrm{Son}}$) by minimizing her prediction errors through communicative interactions with Son. When an agent supports self and other's intentions symbiotically, the agent is considered to be maintaining a stance of intersubjective benevolence.
2) *Under-coupling increases prediction errors*: As depicted in **Figure 12C**, when Agent 1's $\mathbf{S_1}$ and $\mathbf{A_1}$ engage Agent 2's $\mathbf{A_2}$ only, Agent 1 will ignore Agent 2's $\mathbf{M_2}$ and $\mathbf{S_2}$ and thus Agent 1 may fail to achieve intersubjectivity and find it difficult to reduce stress in either agent. For example, when Mom neglects how her harsh reactions ($\mathbf{A}_{Mom}$) make Son feel ($\mathbf{S}_{Son}$) and only focuses on how to change Son's actions ($\mathbf{A}_{Son}$), Mom would fail to recognize Son's internal model ($\mathbf{M}_{Son}$) and therefore Mom's prediction errors about Son's internal model and behaviors would increase. Being ignored or rejected, Son's stress (excessive free energy) would increase, which increases Mom's stress in return.
3) *Stress-potentiated over-mentalizing perpetuates intersubjectivity impairments*: When dyadic stress increases, Agent 1 may become defensive against Agent 2, as if Agent 2 were an enemy, and therefore misattribute Agent 2's disagreeing behaviors to malice or character flaw, i.e., over-mentalizing. For example, Mom may over-mentalize Son's behaviors as "he means to upset me" or "he is mean." When Mom's over-mentalizing explains away Son's actual internal model, she will not even recognize her own ignorance of Son's feelings ($\mathbf{S}_{Son}$) and psychological needs ($\mathbf{M}_{Son}$). Thus, when stress potentiates Mom's over-mentalizing, Son's disagreeing behaviors would only confirm Mom's prior models of stereotypical biases against him, and under this condition, the problems of over-mentalizing, under-coupling, and intersubjectivity impairment will continue in a vicious cycle.

Interpreting MP in Light of the Dyadic Active Inference Framework

We hereby interpret MP intervention in light of the dyadic framework.

1) MP cultivates mothers' knowledge and skills to address a child's psychological needs to promote maternal intersubjectivity through (a) didactic teachings of attachment theory and developmental principles and (b) facilitated mother-child interactions.
2) MP rectifies under-coupling problems by increasing maternal awareness of how a child's overt behaviors ($\mathbf{A}_{Son}$)

may communicate underlying (covert) feelings ($\mathbf{S}_{Son}$) and psychological needs ($\mathbf{M}_{Son}$).

3) MP curbs stress-potentiated over-mentalizing problems via enhancing maternal distress tolerance and non-judgmental stance through teaching mindfulness-based stress regulation skills.

Mapping Brain Systems to the Active Inference Framework

The three systems in the social brain, i.e., the *mirroring system*, *mentalizing system*, and *salience network* can be mapped to three components of the active inference framework. As depicted in **Figure 1A**, social cognition can be modeled as a hierarchical network of active inference engines, which encompasses: (1) an intermediate level involving *mirroring system* as a bottom-up component for automatic perception-action coupling, (2) the *salience network* as a feedback component mediating the surprise (i.e., socially salient prediction errors) detected in the intermediate level, and (3) a top level involving *mentalizing system* as a top-down component for affective and relational model to simulate relationships between self and others.

The functional distinction between the *mirroring system* and *mentalizing system* has gained empirical supports (112). As a bottom-up process, mirroring can be performed spontaneously without activating higher-order representations (16). In contrast, as a top-down process, while the *mentalizing system* can be activated by the theory-of-mind tasks (45), retrospective remembering and proactive imagining of episodic memory (113), and belief-based social attribution (46), it can also be spontaneously active without any inputs or task demands, as part of the default-mode network (61). The roles of the salience network in (a) conflict monitoring (49), (b) switching dynamic oscillations between the frontoparietal network (overlapping with the *mirroring system*) and the default-mode network (overlapping with the *mentalizing system*) during resting (66), and (c) representing *signed prediction errors* of reward (55, 56) and punishment (58, 59) are consistent with its potential role in the prediction errors as a feedback from the *mirroring system* to the *mentalizing system*.

Conclusion

This study advances the science of intersubjectivity and stress resilience on multiple levels. On a theory-generating level, we utilized a promising dyadic active inference framework and offered theoretical relationships between the "over-mentalizing" and "under-coupling" intersubjectivity problems and parenting stress. Further, on an empirical level, we proposed a novel fMRI task to identify neurocircuitry underlying intersubjectivity and potential mediators of the intersubjectivity-oriented intervention (Mom Power). Combined with the within-subject changes afforded by MP intervention, our results point to a two-pronged and potentially generalizable principle, i.e., stress resilience depends on not only mitigating stress-potentiated under-coupling and over-mentalizing problems, but also enhancing a stance of intersubjective benevolence in mirroring others' feelings and serving their well-being in dyadic symbiosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at University of Michigan, Ann Arbor, MI. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH was the principal developer of the theoretical framework and hypotheses and writer of the manuscript. He designed and programmed the fMRI task and conducted the data analysis of the study. He created the figures in the study. MM was one of the developers of Mom Power and contributed to study design and implementation in the community setting, including grant support. She contributed to manuscript development conceptually, and wrote together with SH the first draft, as well as provided ongoing major manuscript edits. KR was also one of the developers of Mom Power. She co-designed and oversaw Study 2 and provided supervision for study clinicians. She contributed to study design and implementation in the community setting. She contributed by writing sections of the manuscript and through ongoing edits. DM contributed to this manuscript with conceptual/content expertise on relationship-based parenting interventions, through contributing to drafting sections of the manuscript, and through providing ongoing edits and feedback. YN collaborated with SH in developing and refining an intersubjectivity-based theoretical framework for understanding how two agents interact with and understand each other. He also provided suggestions for data analysis and ongoing edits in the manuscript. JS was the senior investigator in the study. He co-designed the fMRI task and provided overall supervision on the fMRI studies. He contributed by obtaining grant support for the research and providing theoretical justifications, background, and manuscript edits. All authors contributed to the article 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/fpsyt.2020.568824/full#supplementary-material

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Increased Reward-Related Activation in the Ventral Striatum During Stress Exposure Associated With Positive Affect in the Daily Life of Young Adults With a Family History of Depression. Preliminary Findings

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Background: Being the offspring of a parent with major depression disorder (MDD) is a strong predictor for developing MDD. Blunted striatal responses to reward were identified in individuals with MDD and in asymptomatic individuals with family history of depression (FHD). Stress is a major etiological factor for MDD and was also reported to reduce the striatal responses to reward. The stress-reward interactions in FHD individuals has not been explored yet. Extending neuroimaging results into daily-life experience, self-reported ambulatory measures of positive affect (PA) were shown to be associated with striatal activation during reward processing. A reduction of self-reported PA in daily life is consistently reported in individuals with current MDD. Here, we aimed to test (1) whether increased family risk of depression is associated with blunted neural and self-reported reward responses. (2) the stress-reward interactions at the neural level. We expected a stronger reduction of reward-related striatal activation under stress in FHD individuals compared to HC. (3) the associations between fMRI and daily life self-reported data on reward and stress experiences, with a specific interest in the striatum as a crucial region for reward processing.

Method: Participants were 16 asymptomatic young adults with FHD and 16 controls (HC). They performed the Fribourg Reward Task with and without stress induction, using event-related fMRI. We conducted whole-brain analyses comparing the two groups for

the main effect of reward (rewarded > not-rewarded) during reward feedback in control (no-stress) and stress conditions. Beta weights extracted from significant activation in this contrast were correlated with self-reported PA and negative affect (NA) assessed over 1 week.

Results: Under stress induction, the reward-related activation in the ventral striatum (VS) was higher in the FHD group than in the HC group. Unexpectedly, we did not find significant group differences in the self-reported daily life PA measures. During stress induction, VS reward-related activation correlated positively with PA in both groups and negatively with NA in the HC group.

Conclusion: As expected, our results indicate that increased family risk of depression was associated with specific striatum reactivity to reward in a stress condition, and support previous findings that ventral striatal reward-related response is associated with PA. A new unexpected finding is the negative association between NA and reward-related ventral striatal activation in the HC group.

Keywords: depression, reward, striatum, stress, positive affect (PA), negative affect (NA), ambulatory assessment (AA), fMRI

INTRODUCTION

Major depression disorder (MDD) is a leading cause of disability worldwide, and a research priority in mental health. Having a family history of depression (FHD) is a strong and consistent predictor of MDD development (1–3). In particular, the offspring of parents with MDD have a higher probability of experiencing poorer physical, psychological, or social health (4), as well as a two- to five-fold increased risk of experiencing an episode of MDD, and an increased risk of earlier onset of MDD (i.e., adolescence) (5).

Anhedonia, i.e., the reduced ability to enjoy once-pleasurable activities is a core feature of MDD (6) that could be partially explained by blunted responses to reward at neural level (7–9). Neural responses to reward are processed by a system of cortical and subcortical structures, including among other the striatum, the orbitofrontal and medio-prefrontal cortex as well the anterior cingulate gyrus, with the striatum, in particular the ventral striatum, being one crucial region involved in the anticipation, consumption, and learning from rewarding stimuli (10–14). The term ventral striatum was coined by Heimer (15) and encompasses the continuity between the nucleus accumbens and the ventral part of putamen and of the ventral caudate as well as rostral internal capsule, the olfactory tubercle and the rostrolateral part of the lateral olfactory tract in primates. In the context of reward, the ventral striatum includes the nucleus accumbens, the medial/ventral caudate nucleus, and the medial and ventral putamen (16). A large number of neuroimaging studies reported that individuals with MDD exhibit reduced reward-related activity in the ventral striatum (VS) (17–20). Interestingly, a similar reduced VS activity in response to reward was also found in individuals with FHD before they have met the criteria for a first episode of MDD (21–24). For instance, reduced striatal activation in response to monetary rewards was evidenced in asymptomatic adolescents and children of parents with MDD compared to age- and gender-matched control groups without FHD (25, 26). Thus, blunted striatal response to reward has been postulated to be a potential endophenotype related to MDD (27).

A growing amount of evidence indicates that stress exposure and stress sensitivity are strongly associated with the onset of MDD (28–32). Stress experiences have been shown to affect striatal reward processing in the context of early-life stress, childhood emotional neglect (33, 34), recent life stress (35), and experimental acute stress (36–38). In most cases, stress experiences reduced the activation of the striatum in response to reward. It has been hypothesized that an imbalance between stress and reward reactivity could be a predictor for the development of psychopathology in general (39, 40) and for MDD in particular (9). In line with that hypothesis, a recent study indicated that reward responsiveness measured with event-related potential had a moderator effect on the relationship between life-stress exposure and depressive symptoms in a large sample of young adults (41). Further findings showed that higher VS response to reward was associated with more reported positive affect (PA) in daily life (21, 35, 42), and supporting evidence suggests that this association could buffer the effect of stress sensitivity [e.g., (43, 44)].

Combined findings from daily life measures and neuroimaging techniques, including functional Magnetic Resonance Imaging (fMRI) and positron emission tomography (PET scan) support the idea that dopaminergic activity in VS related to reward response is associated with self-reported PA in daily life (21, 45, 46). The experience sampling method (ESM) is used to collect self-report measures at multiple points in time in natural settings. It offers the opportunity to capture daily life dynamics related to cognitive and affective experiences, including in individuals with MDD (47–49). PA and negative affect (NA)are traits related to the propensity to experience

positive (e.g., happy, confident, joyful) or negative (e.g., sad, angry, ashamed, anxious, lonely) affective states (50) and can be measured with the ESM. PA and NA have been analyzed as both, predictors and outcomes of mental health status (51, 52). Whereas, NA is commonly experienced in almost every mental health disorder (52), there has been an increasing interest in PA in terms of both, its role in daily life and the neuroscientific understanding of psychopathology development and treatment, notably in MDD (21, 45, 51, 53–56). In that context, Forbes et al. (21) showed that reduced reward-related striatal response in adolescents with MDD compared to healthy participants was associated with lower subjective PA in everyday life. In addition, the frequency of reported PA has been conceptualized as an indicator of reward reactivity in daily life (57). Therefore, recording PA in daily life in association with neural measures of reward and stress seems a promising way to investigate the effects of the stress-reward interaction on the development of MDD symptoms, in particular in vulnerable individuals. To our knowledge, one study has examined first-degree relatives of individuals with psychotic disorders (58), but none has investigated first-degree relatives of individuals with MDD.

Based on the above considerations, we propose here an innovative way to investigate the complexity of family risk of MDD by combining neuroimaging measures of reward processing with everyday life reward-related measures, using an ESM protocol in association with fMRI measurements. The aims of this study were: (1) To investigate whether increased family risk of depression is associated with blunted neural and self-reported reward responses. We expected lower neural and self-reported reward sensitivity in individuals with FHD in comparison to healthy controls (HC). (2) To test the stress-reward interactions at the neural level. We expected a stronger reduction of reward-related striatal activation under stress in FHD individuals compared to HC. (3) To explore associations between fMRI and daily life self-reported data on reward and stress experiences, with a specific interest in the striatum as a crucial region for reward processing. Based on the results of (21), we expected positive correlations between PA and reward-related striatal activation to be more accentuated in HC than in FHD participants as well as negative correlations with NA and self-reported stress that would be more accentuated in the FHD group than in the HC group. We focused here on the striatum, in particular the VS, because (1) it is a crucial region in all phases of reward processing (12), (2) it is a region in which differences were reported in the reward-related neural activation between depressed and not-depressed participants (17, 19) as well as between individuals with a family history of depression and controls (22, 23), and (3) this region was reported to be correlated with positive emotions in everyday life (45) #147. We focused on the reward-related activation during the outcome phase, because a recent meta-analysis indicated that differences in the reward-related striatal activation between depressed and control participants were mostly measured activation during the outcome phase (or reward delivery phase) (59) and because robust striatal differences between FHD and healthy participants have been evidenced in this phase in particular (27).

MATERIALS AND METHODS

Participants

Sixteen asymptomatic first-degree relatives with family history of MDD (FHD; 12 females, mean age = 24.31 years, SD = 4.08), and sixteen age-, gender- and socioeconomic status (SES)-matched healthy controls (HC; 12 females, mean age = 25.19 years, SD = 4.79) with no parental history of mental disorder were recruited from the local community by advertisement at the University of Fribourg. The participants of the control group were selected from a larger sample [see (36)] to match for age and gender the group of participants with increased family risk of depression. Participation was compensated in money and/or experimental hours for study plans. The inclusion criteria were: age between 18 and 40 years; good health; good understanding of French; compliance with study procedure; and, for the FHD group, having a first-degree relative with a diagnosed major depressive disorder (MDD), or, for HC group, having no mental health history, as assessed with the Family interview for Genetic Studies (FIGS) (60). General exclusion criteria were: current or past history of any mental disorder, as determined by the Mini International Neuropsychiatric Interview (MINI) (61); history of any endocrinological conditions; history of any neurological condition, epilepsy or head injury; use of psychoactive substances, including alcohol (CAGE) (62), tobacco (Fagerström Test for Nicotine Dependence) (63), and cannabis (CAST) (64); being at risk for pathological gambling (Lie/bet) (65); non-removable metal elements in or on the body; pregnancy, which was confirmed by a urine test on the day of the scan; and being left-handed, as determined with the Edinburgh Handedness Inventory—short form (EHI) (66). Participants were mainly university students (FHD; 87%, HC; 81%) from the Swiss middle-class population. **Table 1** shows that groups did not differ significantly in socioeconomic status (SES). Depressive symptoms were assessed with the Beck depression inventory II (BDI-II) (69), and the Montgomery and Asberg depression rating scale (MADRS) (68), and state and trait anxiety were assessed with the Spielberger State-Trait Anxiety Inventory (STAI) (70). This study was approved by the local ethical review boards of Vaud and Fribourg region (Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD), Study Number 261/14) as well as that of the Bern region (Kantonale Ethikkommission Bern (KEK BE), Study Number 337/14). All participants provided written informed consent that conformed to the guidelines set out in the Declaration of Helsinki (2013).

Procedure

The first meeting included assessment of the inclusion/exclusion criteria. Participants then received detailed explanations of the ESM protocol and we planned the MRI session. ESM material included an iPod 5 Touch (Apple©) with the iDialogPad (Mutz©) app, for collecting real-time, self-reported data over seven consecutive days (from Monday to Sunday). This decision was made to enable participants to follow the more consistent rhythm of a standard week (71). An alarm was programmed to emit a signal ("beep") at four precise times during the day: 11:00 a.m. (T1), 2:00 p.m. (T2), 6:00 p.m. (T3), and

TABLE 1 | Descriptive statistics and comparison analyses between family history of depression and healthy control groups.

	FHD $N = 16$	HC$N = 16$	Test t; χ^2
	Mean (S.D.) [Range]	**Mean (S.D.) [Range]**	**df = (30; 1)**
Sociodemographic information			
Sex: female, *n*	12 (75%)	12 (75%)	0, $p = 1$
Age	24.31 (4.08) [20–36]	25.19 (4.79), [20–37]	−0.56, $p = 0.582$
SES	58.19 (17.14) [23–77]	58.06 (16.69), [15–84]	−0.02, $p = 0.983$
Students: *n*	14 (87.5%)	13 (81.3%)	0.24, $p = 0.626$
Parent with MDD history			
Mother, *n*	11 (69%)		
Father, *n*	4 (25%)		
Both, *n*	1 (6%)		
Age at parental MDD onset	12.56 (7.75) [0–25]		
Having lived with MDD parent, *n*	15 (94%)		
Currently living with MDD parent, *n*	7 (44%)		
Clinical information: [range]			
MADRS [0–60]	3.81 (2.81) [0–9]	4.37 (4.42) [0–14]	−0.43, $p = 0.671$
STAI A	30.5 (9.25) [20–53]	29.19 (5.75) [20–42]	−0.48, $p = 0.7$
STAI B	31.38 (10.94) [20–60]	34.5 (10.37) [21–53]	−0.82, $p = 0.96$
BDI-II [0–63]	6.69 (6.82) [1–25]	5.8 (5.21) [1–19]	0.38, $p = 0.708$
ESM protocol: [range]			
PA [0–6]	4.22 (0.85) [2.46–5.43]	4.31 (0.84) [3.18–5.9]	−0.30, $p = 0.764$
NA [0–6]	0.87 (0.79) [0.13–2.55]	0.95 (0.71) [0.03–2.38]	−0.32, $p = 0.748$
Subjective stress [0–9]	2.29 (1.49) [0.56–6.57]	2.48 (1.29) [0.36–4.22]	−0.40, $p = 0.691$

FHD, Family history of depression; HC, Healthy control; MDD, Major depression disorder; SES, Socioeconomic status assessed with the index of socioeconomic position (1–35 lower class; 36–54 lower-middle class; 55–67 middle class; 68–80 upper-middle class; >80 upper class) IPSE; (67); MADRS, semi-structured interview Montgomery-Asberg depression rating scale (68); BDI-II, Beck Depression Inventory II (69); STAI, State Trait Anxiety Inventory (68), A, state; B, trait; ESM, Experience Sampling Method; PA, Positive affect; NA, Negative affect.

9:00 p.m. (T4). Participants self-reported their affective states and subjective stress 30 min after waking in the morning (T0). In most cases, ESM data collection started the week after the initial meeting and the scan session. A final clinical interview was conducted to ensure that participants finished without any outstanding questions or inconveniences related to their participation.

Measurements

ESM Measurements

A total of 1,062 observations were collected, which represents a 95% participant compliance rate. The lowest participation was in 25 self-reported observations (71%), which satisfied the criteria for a representative sample of data (72). Affective states were rated by participants using statements that began with: "At the moment, emotionally I feel…." These were rated on 7-point Likert scales (1 = Not true at all to 7 = Totally true). Items were selected from the PANAS-X (73) and from Wichers et al. (74). We included an additional item, "vulnerable," to reflect a negative low-dominance affective state. The were "confident" and "happy" for positive affect (PA; $\alpha = 0.74$) and "irritable," "alone," "angry," "depressed," "vulnerable," "ashamed," and "anxious" for negative affect (NA; $\alpha = 0.89$). Subjective Stress was rated by participants on a 10-point scale with the item "Now, I evaluate my stress at…" (0 = No stress to 9 = Extremely stressed) (75). Aggregated mean scores were computed as individual traits for subjective stress. Positive affect (PA) was computed as mean scores of the items "confident" and "happy," and then aggregated for a PA trait score. Negative affect (NA) was computed as mean scores of the items "irritable," "alone," "angry," "depressed," "vulnerable," and "anxious," and then aggregated for an NA trait score.

The Fribourg Reward Task

The Fribourg Reward Task is a monetary incentive delayed task, that was previously shown to elicit striatal activation (36). Participants performed a spatial delayed recall task with two levels of cognitive load (low = 3 circles and high = 7 circles) differentiated by the number of circles to be remembered (see **Figure 1**). At the onset of each trial, a visual cue showed the level of cognitive load and the monetary reward associated with performance ("blank screen" = no reward or "$$" = reward). Participants then saw a fixation cross (500 ms), followed by an array of yellow circles (3 or 7 circles) (1,500 ms). A fixation cross was then displayed (3,000 ms) before the presentation of the target blue circle, which appeared at any position on the screen during 1,500 ms. With a response box in their right hand, participants responded "yes" or "no" to the question of whether this blue circle occupied a position previously occupied by yellow circles, and did so as quickly as possible. Participants had a maximum of 1,500 ms to respond. After that, a blank screen was displayed during a variable jittered inter-stimulus-interval (ISI; 0 or 2,000 ms) and the feedback displayed (1,000 ms) "blank

screen" for no reward or "1 CHF" for reward gain. A final display (1,000 ms) showed a blank screen or the "accumulated amount of gain." Every four trials, participants rated their mood and stress levels (max. 20 s). Task-related mood and stress were rated by participants on a 10-point Likert scale (0 = Emoticon with very negative mood and 9 = Emoticon with very positive mood), as was current stress (0 = "- -" No stress and 9 = "++" Extremely stressed), all within a maximum of 20 s (see **Figure 1**).

Correct responses were rewarded in the reward condition ("$$"), but not in the no-reward condition ("blank screen"). Each participant performed two distinct block sessions. In the second block, we added an experimental stress condition with six unpredictable mild electric shocks, previously adjusted to the participant's level of sensitivity. At the beginning of the second block, participants were informed that they would receive electrical shocks unrelated to the task and that they might receive electrical shocks at any time during the block. Before entering the scanner, every participant practiced the task to ensure a good understanding of it and answered questions. The task was implemented using E-Prime Professional (Version 2.0.10.353, Psychology Software Tools, Inc.). Stimuli were presented via goggles (VisualStimDigital MR- compatible video goggles; Resonance Technology Inc., Northridge, CA, USA) with a visual angle of 60°, a resolution of 800 × 600 pixels, and a 60 Hz refresh rate. In this current study, we considered only the reward (reward vs. no-reward) factor of the experiment in our analyses to test our a priori hypotheses.

Acute Experimental Stress Manipulation

We induced an acute stress condition in participants during the second block of our experimental design with an unpredictable mild electric shock on the external side of the left hand. The electrical shock intensity was calibrated to each participant before they entered the scanner with a standard shock workup procedure, starting at the lowest level and increasing the intensity until the participant identified an "aversive, but not painful" feeling (77). Electric shocks were induced through an electrical pain stimulator using the PsychLab© measuring system, with MRI-compatible electrodes and cables. The highest allowable shock intensity level was 5 mA (milliamperes).

MRI Data Acquisition

Magnetic resonance imagery (MRI) was performed at the Department of Diagnostic and Interventional Neuroradiology of the University Hospital of Bern, Switzerland. The functional MRI images were acquired using a Siemens (Erlangen, Germany) TrioTim syngo 3.0-Tesla whole-body scanner equipped with a radio frequency 32-channel head coil. MRI acquisition included 3D T1-weighted (Magnetization Prepared Rapid Acquisition Gradient Echo; MPRAGE) images with the following settings: sagittal slices: 176; FOV: 256 × 256 mm; matrix size: 256 × 256; voxel size: 1.0 × 1.0 × 1.0 mm^3; TR: 1,950 ms; TE: 2.2 ms; flip angle: 90°. The event-related task-based fMRI included an EPI pulse sequence with the following settings: interleaved ascending slices: 38; FOV: 230 × 230 mm^2; matrix size: 64 × 64; voxel size: 3.6 × 3.6 × 3 mm^3; TR: 2,000 ms; TE: 30 ms; flip angle: 90°.

fMRI Data Analysis

fMRI data were analyzed using Statistical Parametric Mapping software (SPM12; https://www.fil.ion.ucl.ac.uk/spm/). The echo-planar images were realigned to the 37th volume, slice timing corrected, coregistered to the structural MR image, spatially normalized to standard Montreal Neurological Institute (MNI) 152 coordinate space, resampled into 3 × 3 × 3 mm voxels, and smoothed with an isotropic 6-mm full-width half maximum Gaussian kernel. Statistical analysis was performed within the framework of the general linear model. We considered only the reward delivery phase as robust striatal differences between FHN and healthy have been evidenced in this phase in particular (27): Because the main focus of this article was on the relationship between neural activation and ESM measures, we focused our analyses on a specific contrast (reward vs. no reward during the reward feedback phase) to limit the number of analyses, in particular with respect to the small sample sizeFor this reason, we will report here only the results related to the whole brain and ROI analyses in response to reward during reward feedback and their association with the ESM measures. Other data related to this study and this sample have been reported elsewhere, in particular the results related to the anticipation phase (76). For each participant, four distinct events were modeled as separate regressors in an event-related manner for the duration of each phase: (a) trial cue (2,000 ms); (b) stimulus presentation (6,000 ms); (c) feedback (2,000 ms); and (d) mood and stress rating (20,000 ms). Subsequently, these regressors were convolved with the canonical hemodynamic response function implemented in SPM12. The six movement parameters (three translations and three rotations) obtained from the realignment procedure were also included in the model. We used a high-pass filter with a cut-off frequency of 1/128Hz. Only trials with correct responses were analyzed. Statistical analyses of single-subject fMRI data were implemented using a general linear model (GLM) with a total of 20 regressors corresponding to six movement parameters and conditions—Stress (control/Stress) × Load (high/low) × Reward (no/rewarded)—across the four events. Note that only high-reward vs. not rewarded trials were used in analysis to increase contrast. A second-level (random-effects) model analysis was performed with independent *t*-test for group analyses. Contrast maps were constructed for the main effect of Reward (high reward > not rewarded), Stress (no-stress vs. stress), and Load (high vs. low), as well as interaction effect for Reward × Stress, Reward × Load, and Stress × Load, for both anticipation and feedback delivery phases. These contrast maps were used for both region of interest (ROI)-based statistical analyses and for whole-brain main effects analysis. For ROI-based analyses, a mask was created with automated anatomical labeling (AAL2) template (78, 79) for bilateral caudate, putamen, and pallidum regions, with two added parcellations for the bilateral nucleus accumbens (Nacc) to create a mask of striatal regions typically involved in reward processing based on (16). An alpha of 0.05 was used with correction for multiple non-independent comparisons using Gaussian random

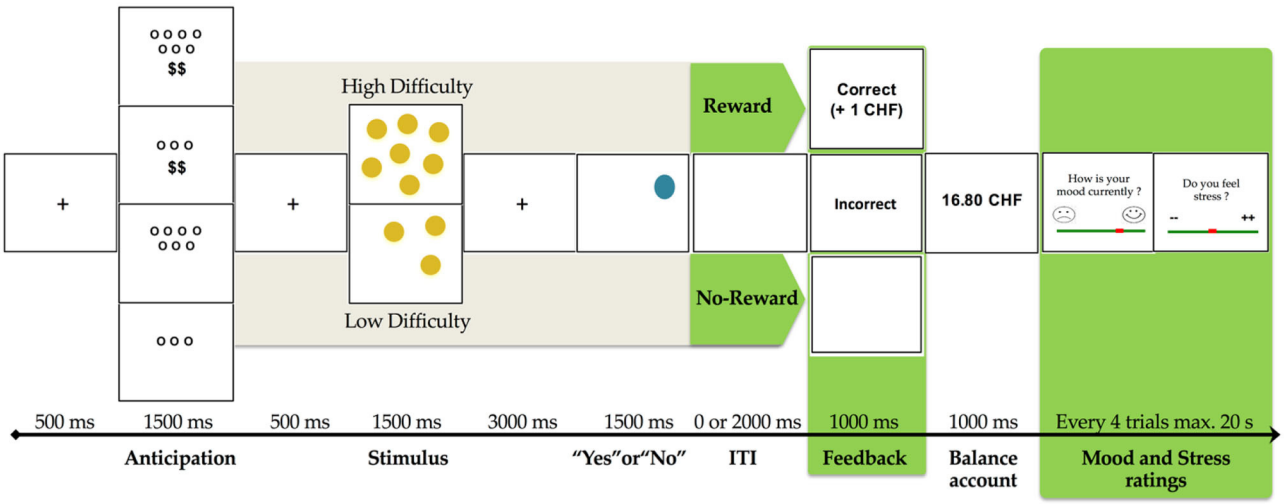

FIGURE 1 | Fribourg reward task. Illustration of trial conditions randomly distributed in both control and stress conditions (unpredictable threat of shock). Variables used in the present study are in green [adapted from Gaillard et al., (76), p. 4].

field theory (80) and suprathreshold cluster-size statistics (81). The initial voxel-level threshold for all analyses was set at $p < 0.001$, uncorrected. We used conservative whole-brain correction and kept clusters that reached significance after Family Wise Correction (FWC) at $p < 0.05$. Parameter estimates (beta weight) were extracted from coordinates that showed significant activation after FWC at $p < 0.05$, based on the average activation within the ROI using the MarsBaR toolbox (http://marsbar.sourceforge.net), and referred based on the AAL2 atlas (78, 79) for the main effect of Reward (i.e,. reward condition vs. no reward condition) during the outcome phase in the control condition and in the stress condition.

To control the effects of the reward task, we performed a 2 × 2 × 2 × 2 repeated measures ANOVA including Group (FHD vs. HC) as the between-subject factor, and Stress (no- vs. threat-of-shock), Reward (no- vs. reward), and Load (high vs. low) as within-subject factors for responses accuracy, reaction times (RT) and self-reported mood and stress scores during the task. Results were adjusted with Bonferroni correction for multiple comparisons. We expected faster RT and higher accuracy, higher mood scores during reward as well as an effect of stress on these variables. In particular, we expected higher self-reported stress scores during the stress condition.

Correlations with ESM measures were performed using the beta-weights obtained for the contrast of interest and the self-reported mean for PA, NA and subjective stress over 7 days. We used SPSS (IBM SPSS Statistics, Version 25.0, Armonk, NY, USA) for descriptive analyses of the participants, independent *t*-test and χ^2 analysis.

RESULTS

Participants

Socio-demographic and clinical description of the participants is presented in **Table 1**. The FHD did not differ significantly from the HC in terms of gender, age, or socioeconomic status. Both groups were mainly composed of students (87 and 81%, respectively). The results of semi-structured interview for depressive symptoms MADRS (68), as well as self-reports for depressive symptom severity BDI-II (69) and for state and trait anxiety (STAI) (82) did not differ significantly between FHD and HC groups. In both groups, one participant has reached BDI-II (69) scores above the clinical threshold. This was not the case for the MADRS (68) scores.

Our results showed that 44% reported currently living with the parent with the history of MDD. Nearly all participants (94%) had lived with their depressive parent. Parents with a history of MDD were mainly mothers (75%); one participant reported that both parents had a history of MDD.

Behavioral Data Analyses

Table 2 presents the detailed results for the behavioral data analyses for the task.

Reaction Time and Accuracy

For RT, we found significant main effects for the Stress [$F_{(1,30)} = 17.38$, $p < 0.001$, $\eta^2 = 0.37$], and Load conditions [$F_{(1,30)} = 130.94$, $p < 0.001$, $\eta^2 = 0.81$] as well as a statistical trend for the Stress x Load interaction [$F_{(1,30)} = 3.23$, $p = 0.08$, $\eta^2 = 0.10$]. *Post-hoc* tests indicate that FHD and HC individuals were responding faster in the stress condition ($M = 730.66$ ms, $SE = 16.60$ ms) than in the control condition ($M = 784.34$ ms, $SE = 16.36$ ms); as well as faster in the high load condition ($M = 709.35$ ms, $SE = 15.77$ ms) than in the low-load condition ($M = 805.65$ ms, $SE = 15.73$ ms). We did not consider further the statistical interaction stress × load as this is not the main focus of the current study.

For accuracy, we found significant main effects for the Stress [$F_{(1,30)} = 7.14$, $p < 0.01$, $\eta^2 = 0.19$], Reward [$F_{(1,30)} = 3.98$, $p < 0.05$, $\eta^2 = 0.12$] and Load [$F_{(1,30)} = 84.23$, $p < 0.001$, $\eta^2 = 0.74$]

TABLE 2 | Main and interaction effects for within- and between-subject contrasts on behavioral responses related to Fribourg reward task performance during fMRI.

				RT			Accuracy			Mood			Stress		
Within-subject contrasts	**Stress**	**Reward**	**Load**	$F_{(1,30)}$	p	η^2	$F_{(1,30)}$	p	η^2	$F_{(1,30)}$	p	η^2	$F_{(1,30)}$	p	η^2
Stress	Stress vs. control			**17.38**	**<0.001**	**0.37**	**7.14**	**0.01**	**0.19**	**3.93**	**0.06**	**0.12**	2.19	0.15	0.07
Reward		R vs. NR		0.96	0.33	0.03	**3.98**	**0.05**	**0.12**	**4.01**	**0.05**	**0.12**	0.32	0.58	0.01
Load			H vs. L	**130.94**	**<0.001**	**0.81**	**84.23**	**<0.001**	**0.74**	2.14	0.15	0.07	0.18	0.67	0.01
Stress × group	Stress vs. control			0.17	0.68	0.01	2.09	0.16	0.06	0.08	0.77	0.00	0.04	0.85	0.00
Reward × group		R vs. NR		0.14	0.71	0.00	0.90	0.35	0.03	0.18	0.67	0.01	0.22	0.64	0.01
Load × group			H vs. L	1.27	0.27	0.04	0.80	0.38	0.03	1.88	0.18	0.06	0.01	0.91	0.00
Stress × reward	Stress vs. control	R vs. NR		2.44	0.13	0.07	0.94	0.34	0.03	0.04	0.85	0.00	0.12	0.73	0.00
Stress × load	Stress vs. control		H vs. L	3.14	0.09	0.09	0.10	0.75	0.00	0.06	0.80	0.00	0.09	0.76	0.00
Reward × load		R vs. NR	H vs. L	0.44	0.51	0.01	**5.65**	**0.02**	**0.16**	0.15	0.70	0.00	0.74	0.40	0.02
Stress × reward × group	Stress vs. control	R vs. NR		0.14	0.71	0.00	1.90	0.18	0.06	0.02	0.88	0.00	0.07	0.79	0.00
Stress × load × group	Stress vs. control		H vs. L	3.23	0.08	0.10	0.43	0.52	0.01	0.64	0.43	0.02	0.16	0.69	0.00
Reward × load × group		R vs. NR	H vs. L	2.45	0.13	0.08	0.06	0.81	0.00	0.02	0.89	0.00	0.06	0.80	0.00
Stress × reward × load	Stress vs. control	R vs. NR	H vs. L	0.00	0.97	0.00	0.62	0.44	0.02	1.05	0.31	0.03	1.14	0.29	0.04
Stress × reward × load × group	Stress vs. control	R vs. NR	H vs. L	3.07	0.09	0.09	2.94	0.10	0.09	0.36	0.55	0.01	0.15	0.70	0.00
Between-subject contrasts	Group														
Group	FHD vs. HC			2.22	0.15	0.07	0.04	0.84	0.00	0.44	0.51	0.01	0.02	0.89	0.00

Results are corrected for multiple comparisons by applying a Bonferroni correction. Bold indicates two-tailed ($p < 0.05$) and one-tailed ($p < 0.05/2$) significant results. RT, Reaction time; R, Rewarded; NR, Not rewarded; H, High; L, Low. Partial eta squared (η^2) values range from 0 to 1, and represents the proportion of total variance accounted for by the factor(s), while excluding other factors from the total explained variance (i.e., non-error variation) in the repeated measures ANOVA (83).

factors as well as a significant interaction reward × load [$F_{(1,30)} = 5.65$, $p < 0.02$, $\eta^2 = 0.16$]. Both FHD and HC individuals provided more accurate responses in the stress conditions ($M = 82.6\%$, $SE = 2.1\%$) than in the control (no-stress) conditions ($M = 78\%$, $SE = 2.1\%$), in the low load condition ($M = 87.3\%$, $SE = 2\%$) than in the high load condition ($M = 73.3\%$, $SE = 2.1\%$), and in the reward condition ($M = 81.6\%$, $SE = 1.9\%$) than no-reward condition ($M = 79\%$, $SE = 2.2\%$). Both FHD and HC individuals provided more accurate responses for high load in the reward condition ($M = 76\%$, $SE = 2.3\%$) than in the no-reward condition ($M = 70.5\%$, $SE = 2.5\%$), while we found no significant increment in the low load condition between the reward ($M = 87.2\%$, $SE = 2\%$) and the no-reward conditions ($M = 87.5\%$, $SE = 2.2\%$). No significant group differences were found for RT and accuracy.

Self-Reported Mood and Stress

For the self-reported mood scores, our results show significant main effects of the Reward factor [$F_{(1,30)} = 4.01$, $p < 0.05$, $\eta^2 = 0.12$] factors; and a statistical trend for the Stress factor [$F_{(1,30)} = 3.93$, $p < 0.06$, $\eta^2 = 0.12$]. *Post-hoc* tests indicate that both FHD and HC individuals rated their mood higher in the reward condition ($M = 6.87$, $SE = 0.28$) than in the no-reward condition ($M = 6.72$, $SE = 0.28$), and in the control condition (no-stress) ($M = 6.91$, $SE = 0.29$) than in the stress condition ($M = 6.67$, $SE = 0.29$). With regard to the stress ratings, we did not find any significant results.

ESM Protocol: Group Comparisons

Aggregated means and standard deviation of the daily life measurements are reported in **Table 1**. Results of the PA and NA mean score comparison between the FHD and HC groups showed no significant differences ($p = 0.74$ and 0.78 respectively). Similarly, no group difference was found for the reported daily life stress ($p = 0.69$).

fMRI Results

Table 3 presents the results of the whole-brain analyses in the contrast of interest. To control for the effect of the stress condition, we also report the regions activated in the main contrast comparing the stress vs. no stress condition.

Striatal Activation During Feedback: Group Comparison

The whole-brain analysis for group comparison showed a significant difference in BOLD response in part of the VS, i.e., in the left putamen region between FHD and HC group during feedback delivery for the main effect of reward (reward vs. no reward condition in the control condition, see **Table 3**) at $p < 0.005$ FWE that remains significant in the stress condition, i.e., comparison of reward vs. no reward condition in the stress condition (see **Figure 2**). Specifically, we found a stronger VS activation in the FHD group ($M = 5.53$, $SD = 4.06$) than in the HC group ($M = -0.71$, $SD = 3.58$), $t_{(30)} = 4.46$, $p = 0.024$, under stress with a very large effect size (Cohen's $d = 1.63$).

VS Reward-Response Under Stress Association With ESM

Spearman correlations were performed between beta parameter estimates extracted in the VS based on the striatal mask, whose peak activation was located in the ventral striatum around the left medial caudate (see **Table 3**) and mean scores of self-reported PA, NA and subjective stress in daily life. Considering both groups together, our results showed a significant positive correlation with PA $r_s = 0.34$, $p = 0.05$, and a significant negative correlation with NA $r_s = -0.36$, $p = 0.042$ and no significant correlations with reported stress $r_s = -0.21$, $p = 0.22$. Considering the groups separately, the positive correlation between VS activation and PA was significant in both groups (FHD: rs = 0.49, $p = 0.05$; HC: rs = 0.49, $p = 0.05$), while the negative correlation with NA was significant only in the HC group (rs = −0.55, $p = 0.02$) and not in the FHD group (rs = −0.31, $p = 0.23$); and the correlation with reported stress remained not significant (FHD: rs = −0.29, $p = 0.27$; HC: rs = −0.13, $p = 0.62$), (see **Figure 3**).

Additional Regions Activated During Feedback

The whole-brain analysis for the main effect of reward showed significant differences in BOLD response in the comparison of the reward condition vs. the no-reward condition bilaterally in the occipital cortex, the anterior cingulate cortex, and the inferior frontal gyrus as well as in the right parietal cortex, right middle cingulate gyrus, right middle and superior frontal gyrus, right periaquaductal area, right thalamus, right hippocampus and in the left insula, left orbitofrontal cortex, and left cerebellum in the HC participants. In the FHD group, we found significant differences in BOLD response bilaterally in the anterior cingulate gyrus, the insula, and the parietal cortex as well as the right orbitofrontal cortex, right middle frontal gyrus and left occipital cortex (see **Table 3**).

Regions Activated in Response to Stress

The whole-brain analysis for the main effect of reward showed significant differences in BOLD response in the comparison of the stress condition vs. the no stress condition in the right superior parietal cortex, right lateral occipital cortex, right precuneus, right caudate as well as in the left superior frontal cortex and left insula in the healthy controls. In the FHV group, our results evidenced bilateral significant differences in BOLD responses in the parietal cortex that were also significantly more activated in the group comparison.

DISCUSSION

To our knowledge, this may be the first study to report a significantly increased ventral striatal neural response to reward delivery received during stress exposure in individuals with FHD compared to healthy controls. These results are counter to our hypothesis and previous findings on the blunting effect of stress on the hedonic capacity (84–86). Another remarkable finding is the association between the observed ventral striatal activation with daily life measures of PA in FHD participants and healthy participants as well as a significant negative correlation with

TABLE 3 | Significant BOLD responses to reward delivery in the reward vs. in participants with family history of depression (FHD) and in healthy control (HC).

Group contrasts	Regions	L/R	MNI coordinates			Cluster size	*T*-value	pFWE
			X	Y	Z			
Main effect of reward: reward condition > no reward condition								
HC > FHD	No significant activation							
HD > HC	Putamen	L	−15	9	0	24	4.77	<0.005
		L	−24	6	−3			
		L	−15	9	6			
ROI								
HC	Caudate	L	−9	−6	0	37	6.21	$P < 0.001$
			−6	0	9		4.80	
FHD	Caudate	L	−15	−6	15	12	6.34	$P < 0.01$
HC	Inferior occipital gyrus	L	−36	−87	−12	3,343	11.52	<0.001
	Inferior occipital gyrus	R	33	−93	−3		10.01	
	Middle occipital gyrus	R	36	−93	6		10.16	
	Superior parietal gyrus	R	36	60	57	470	9.35	<0.001
	Inferior parietal gyrus	R	48	−45	48		8.66	
			30	−54	45		7.89	
	Anterior cingulate cortex	L	−3	33	30	380	7.63	<0.001
			−3	39	15		7.00	
		R	6	39	9		7.34	
	Middle cingulate cortex	R	6	−12	27	77	6.53	<0.001
		R	6	−27	36		5.72	
	Precentral gyrus	L	−51	12	33	192	8.19	<0.001
			−54	6	39		6.17	
	Inferior frontal gyrus	L	−51	33	21		7.22	
	Inferior frontal gyrus	R	54	12	21	189	6.95	<0.001
		R	51	30	18		6.33	
	Middle frontal gyrus	R	45	39	15		5.93	
		R	39	60	−6		6.18	
	Middle frontal gyrus	R	36	54	9	83	6.18	<0.001
		R	45	51	−3		5.89	
	Superior frontal gyrus, dorsolateral	R	36	54	9		6.00	
	Insula	L	−36	9	−12	104	6.8	<0.001
			−42	18	−9		5.48	
	Orbitofrontal cortex	L	−54	27	−6		5.13	
	Ventral tegmental area		0	−15	−9	76	6.06	<0.001
	Periaquaductal area	R	6	−30	−6		5.41	
	Thalamus	R	6	−24	0		5.36	
	Hippocampus	R	21	−27	−9	38	5.63	<0.005
			18	−39	6		5.44	
	Cerebellum	L	−3	−54	−42	53	5.23	<0.001
		L	−15	−57	−36		5.15	
FHD	Fusiform gyrus	L	−33	−57	15	4,640	17.46	<0.001
	Inferior occipital gyrus	L	−30	−90	−9		14.79	
		L	−42	−69	−12		14.54	
	Anterior cingulate gyrus	R	9	33	27	1,010	8.49	< 0.001
		L	−3	36	12		8.46	
		L	−3	27	27		7.47	
	Insula	L	−36	18	6	655	9.44	<0.001
		L	−39	9	−12		7.67	
	Orbitofrontal cortex	R	39	33	−3	758	7.74	<0.001
	Insula	R	30	21	−12		7.4	
	Inferior frontal gyrus	R	39	12	30		7.36	

(Continued)

TABLE 3 | Continued

Group contrasts	Regions	L/R	MNI coordinates			Cluster size	*T*-value	pFWE
			X	Y	Z			
	Inferior parietal gyrus	R	54	−42	48	218	7.6	<0.001
	Superior parietal gyrus	R	54	−33	57		6.43	
	Inferior parietal gyrus	L	−48	−45	45	86	7.02	<0.001
	Post-central gyrus	L	−42	−33	51		5.13	
	Angular gyrus	R	30	−69	48	39	5.37	<0.001
	Superior parietal gyrus	R	33	−60	54		4.80	
	Middle frontal gyrus	R	48	51	12	25	4.93	<0.001

daily life measures of NA that was significant only in the healthy control group.

Unexpectedly there was no significant difference in the striatal activation during reward delivery between FHD and HC in the condition without stress. This differs from previous findings on blunted striatal responses to reward in high-risk individuals (24–27). This could be related to the lack of power; the sample may have been too small to detect difference between FHD and HC groups. However, McCabe et al. (22) did not report any striatal response to reward difference between groups with high and low risk of MDD. A common factor, shared by our study and McCabe et al.'s (22) previous research, is related to the mean age of the sample, which is older in our study (above 20 years). Striatal development studies have shown an important change between childhood and early adulthood in healthy individuals (87), and individuals with FHD (27). In addition, evidence demonstrates that neural response sensitivity to monetary and social reward changes across developmental stages (88). A further explanation could be related to the design, since participants might have been expecting the stress condition, and the condition without stress cannot be considered without taking into account the stress condition.

The increased sensitivity to reward outcomes during stress exposure for the FHD group compared to the HC group is consistent with a heuristic model of depression and the specific influence of stress on reward processing (9), as well as with psychobiological mechanisms of resilience and vulnerability (89). In our sample, the increased sensitivity to reward in the stress condition could be interpreted as a sign of a specific resilience marker in a brain region (i.e, the putamen) previously related to vulnerability to family risk of MDD (27). Putamen activation has been suggested to play a unique role in the intergenerational risk of depression, with evidence of an association between maternal and daughter putamen responses to anticipation of loss (90). Since we excluded participants with a previous history of mental disorder and since our sample was composed of young adults and not of adolescents, we might have included resilient individual, i.e., individuals who had passed through the high risk phase of adolescence without developing MDD or another psychopathology. This hypothesis is supported by the finding that the groups did not differ with regard to their subjective stress ratings, PA and NA measures in everyday life. Thus, in our results the increased VS response to reward delivery under stress could be a marker of a resilient profile. This interpretation should be however be taken with caution due to the small sample of participants, and because we did not use a longitudinal setting.

In line with that hypothesis, our significant association between increased ventral striatal reward reactivity and PA in daily life could be interpreted as a protective factor. Previous findings showed that the VS response to reward was associated to PA in daily life (35, 91). A higher VS response to winning has been reported as a resilience marker in adolescent girls with unknown parental mental health histories (92). High sensitivity to reward experiences in daily life has been shown to increase resilience after environmental adversity (57). More PA after stress events has been shown to mediate the relation between sensitivity to reward and trait resilience (93). More broadly, increased reward response could buffer and blunt stress responses more quickly in a less predictable environment [for a review of a reward pathway buffering stress; (94) #132]. In that context, our unexpected finding that there was not reduced self-reported reward sensitivity (measured as PA) in the FHD group, could be associated with the hypothesis that we might have included resilient individual, i.e., individuals who did not develop psychopathological problems during the high-risk period of adolescence. An addition to the existing literature comes from our finding of a significant negative correlation between daily life NA and ventral striatal activation to reward that was specific to the HC group. To our knowledge, no study has investigated the correlation between neural reward reaction and NA.

In addition to the results observed in striatal regions, we also found in both groups significant reward-related activations in regions, which have been typically associated with the cerebral reward system (12), including the orbitofrontal and medio-prefrontal cortex and the anterior cingulate gyrus in both groups of participants. Interestingly, our results also evidenced significant reward-related BOLD responses in the occipital and the parietal cortex. This is in line with previous studies showing for instance increased responses in the occipital cortex to rewarded tasks, especially in tasks involving visual attention (95). Activation in the parietal cortex was reported in response to reward tasks, in particular in tasks involving several levels of reward (96) as this is the case in our task. However, we found no significant group difference in any of these regions, but regions of the parietal cortex were also significantly more activated in the stress condition and this activation was also more

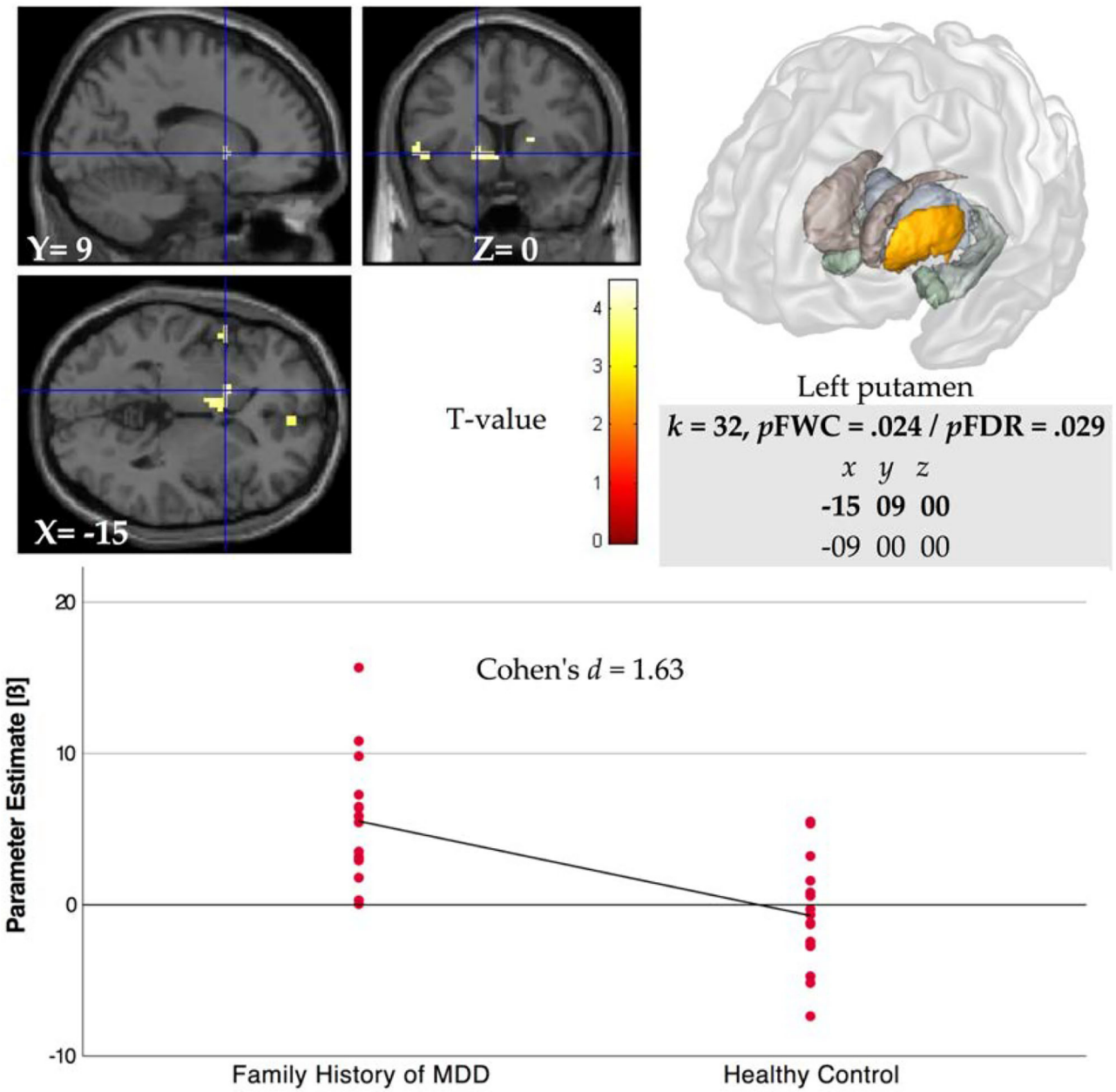

FIGURE 2 | Left ventral striatal (VS, i.e., putamen) region BOLD activation for comparison of FHD and HC groups during reward feedback in stress condition for contrast rewarded > not rewarded ($p < 0.005$ FWE). Parameter estimates (beta weight) were extracted from coordinates that showed significant activation after FWE at $p < 0.05$ in the ROI analyses for the main effect of reward.

accentuated in the FHD group than in the HC group. Increased activation in parietal regions in response to acute experimental stress has been documented in previous studies [for instance (97)] and interpreted as an augmented cognitive control under stress conditions. This increased activation in regions associated with cognitive controls could therefore also be associated with the observed better performance during the task (e.g., faster reaction times and increased accuracy) in the stress condition.

Our study has some limitations. First, the small sample size of this preliminary study did not allow us to investigate participants' age in relation to parental onset of MDD, or to use years lived with depressed parents to predict striatal activation. Secondly, our design did not include a counterbalanced condition in the no-stress (control) and stress (unpredictable threat of shock) conditions. In that context, the observed stress main effect in reaction times and accuracy could reflect a learning effect

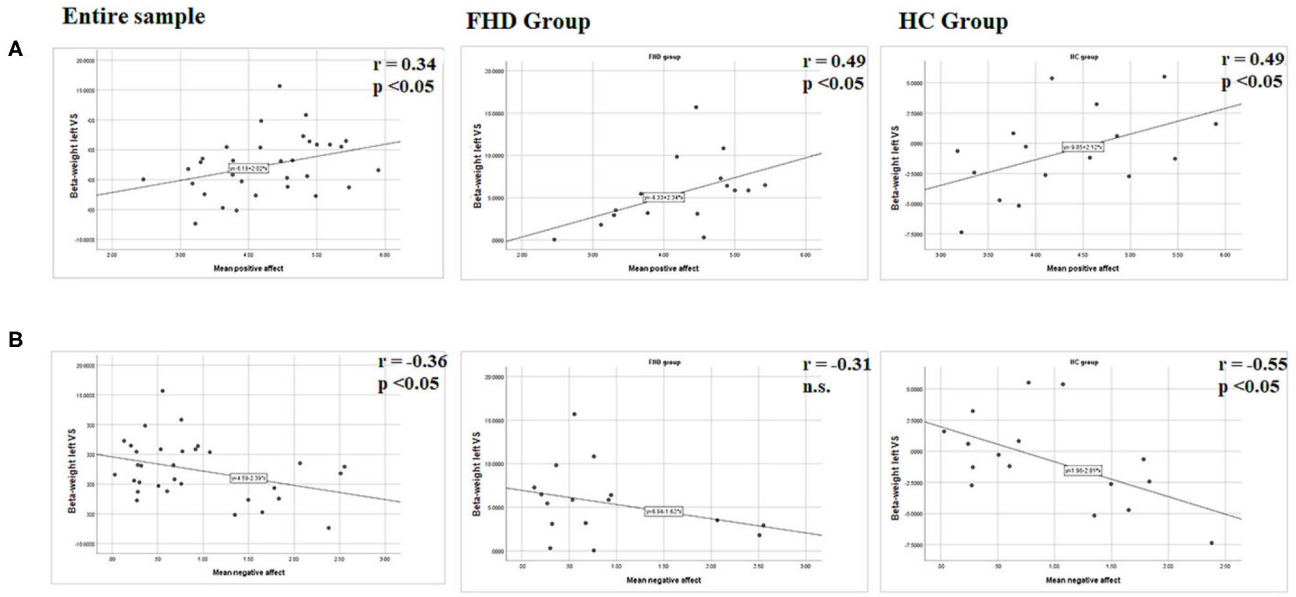

FIGURE 3 | Graphical presentation of the statistical relationships between **(A)** mean positive affect resp. **(B)** Mean negative affect and left ventral striatal (VS) region BOLD activation during reward feedback in stress condition for contrast rewarded > not rewarded. Parameter estimates (beta weight) were extracted from coordinates that showed significant activation after FWC at $p < 0.05$ in the ROI analyses with peak activation in the caudate. Results are presented for the entire group, the FHD group and the HC group. r, Spearmann correlation coefficient, n.s., not significant.

rather than a stress effect. The lack of counter-balancing cannot however explain the lack of group difference in the condition without stress, since the same potential flaw was balanced out in the group comparison. Thirdly, our results did not evidence differences in stress ratings between the control and the stress conditions. This could be related to the small sample size as the results obtained in a larger associated sample could evidence significant stress ratings differences between the conditions (36). In addition, the different levels of cognitive load could have induced stress and be a confounding factor. Fourthly, in both groups of participants, one participant evidenced BDI scores above the clinical threshold. This could indicate that we included participants with increased depressive symptomatology in both groups or this could be related to a misunderstanding of some questions of the BDI-II, since no participant had MADRS scores above the clinical threshold and no participant fulfilled the depression criteria as determined by the MINI (61). Self-report questionnaires tend to overreport and clinician-based measures are thus the gold standard. Fifthly, the fact that a blank screen was presented in the no-reward condition in the feedback phase did not allow us to control for the brain activation related to the processing of the salience, visual attention and reading processes. Sixthly, the observed activation differences between the groups in the putamen were significant at a reduced thershold ($p < 0.005$). Seventhly, using average scores for the ESM data analysis might have obscured some important features of the experience sampling data. Measure of variability might have taken better advantage of the rich dataset and provided a better measure of emotional lability in everyday life. Finally, our results showed only associations, and a prospective design would be needed to enable the accumulation of causal and predictive evidence. Altogether, our results should be taken as preliminary and as a first step toward thinking about new pathways for studying the psychophysiological dynamics of reward processes within the laboratory and daily life environments.

CONCLUSION

Our results indicate that an increased family risk of depression was associated with specific striatum reactivity to reward in a stress condition. This is in line with previous studies showing atypical responses to reward in individuals at risk of depression. This finding extends the literature by investigating the stress-reward interaction in these individuals. Our results support previous findings that ventral striatal reward-related response is associated with PA in daily life, (46). A new finding is the negative association between NA in daily life and reward-related ventral striatal activation that was observed in the HC group but not in the FHD participants. Due to the small sample size, these results must be considered preliminary. We suggest that our integrative approach might be a promising way to tackle subtle processes and differences in the field of vulnerability research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by commission d'éthique du Canton de Vaud. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM-S, AH, PG, DS, CM-P, and GH contributed to the design of the study. MG, CG, and RR performed the study and the data analysis. CG wrote parts of the manuscript. AF was instrumental for the fMRI set up and data preparation. PH provided the electro shock methodology and stress application. CM-S and MG wrote conjointly the manuscript. All authors contributed to the manuscript revision, and read and approved the submitted version.

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