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Original Article

Social hierarchy modulates neural responses of empathy for pain

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Abstract

Recent evidence indicates that empathic responses to others' pain are modulated by various situational and individual factors. However, few studies have examined how empathy and underlying brain functions are modulated by social hierarchies, which permeate human society with an enormous impact on social behavior and cognition. In this study, social hierarchies were established based on incidental skill in a perceptual task in which all participants were mediumly ranked. Afterwards, participants were scanned with functional magnetic resonance imaging while watching inferior-status or superior-status targets receiving painful or non-painful stimulation. The results revealed that painful stimulation applied to inferior-status targets induced higher activations in the anterior insula (AI) and anterior medial cingulate cortex (aMCC), whereas these empathic brain activations were significantly attenuated in response to superior-status targets' pain. Further, this neural empathic bias to inferior-status targets was accompanied by stronger functional couplings of AI with brain regions important in emotional processing (i.e. thalamus) and cognitive control (i.e. middle frontal gyrus). Our findings indicate that emotional sharing with others' pain is shaped by relative positions in a social hierarchy such that underlying empathic neural responses are biased toward inferior-status compared with superior-status individuals.

Key words: social hierarchy; empathy; anterior insula (AI); anterior medial cingulate cortex (aMCC); Toronto Alexithymia Scale-20 Items (TAS-20); functional connectivity

Introduction

Empathy reflects the ability to identify and share the emotions and feelings of others (Decety and Jackson, 2004; Zaki, 2014). Numerous functional imaging studies have explored the neural signatures underlying empathy with experimental paradigms in which participants were exposed to the pain experience of others (Singer *et al.*, 2004; Jackson *et al.*, 2005; Lamm and Decety, 2008; Gu *et al.*, 2012, 2013). A recent meta-analysis has revealed that the bilateral anterior insula (AI) and anterior medial cingulate cortex (aMCC) are most consistently involved in the perception of others' pain, and thereby are identified as the core network of empathy for pain (Lamm *et al.*, 2011). Notably, these brain regions have also been implicated in representing affective-motivational aspects of the first-person physical and social pain experience (Peyron *et al.*, 2000; Rainville, 2002; Eisenberger *et al.*, 2003). Therefore, the engagement of the aMCC and AI in perceiving others' pain is thought to subserve emotional sharing with others and constitute the affective aspects of empathy (Singer *et al.*, 2004; Xu *et al.*, 2009; Lamm *et al.*, 2011).

Empathic neural responses to others' pain often occur automatically; however, they are also tremendously modulated by

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various individual and situational factors (Decety and Jackson, 2004; Goubert *et al.*, 2005; De Vignemont and Singer, 2006; Cheng *et al.*, 2007; Zaki, 2014). For instance, brain activity underlying the perception of others' pain is modulated according to perceiver's empathic ability, which is often measured by the interpersonal reactivity index (IRI) (Davis, 1980). The higher perceiver's scores on dispositional empathy, the stronger aMCC and AI responses to the pain of others (Singer *et al.*, 2004, 2006). Notably, the ability to identify one's own feelings also modulates empathic neural responses, such that people with difficulties in identifying and describing their own emotions (i.e. alexithymia) show attenuated activations in AI while introspecting their own feelings and while empathizing with others' pain (Silani *et al.*, 2008; Bird *et al.*, 2010). These findings are consistent with the 'shared representations' account of empathy, positing that neural networks engaged by the first-person pain experience also underpin the sharing of others' pain (De Vignemont and Singer, 2006; Lamm *et al.*, 2011; Rütgen *et al.*, 2015).

Regarding the context-dependent empathic responses, it has been revealed that neural responses of the aMCC and AI to the pain of others are constrained by top-down attention and cognitive reappraisal (Gu and Han, 2007; Lamm *et al.*, 2007a,b). Further, the empathic neural responses of aMCC and AI are modulated by interpersonal relations such that they are attenuated while observing disliked others or out-group members in pain (Singer *et al.*, 2006; Xu *et al.*, 2009). Likewise, Meyer *et al.* (2012, 2015) recently observed that empathy for the social exclusion (i.e. social pain) of friends as compared with strangers relied more heavily on affective pain regions including aMCC and AI. Taken together, these findings indicate that affective sharing with others' pain is modulated according to both personal and situational factors. However, specific to situational factors, few studies have examined how empathy and underlying brain functions are modulated by social hierarchies that are ubiquitous to human societies (Cheng *et al.*, 2014).

In human societies, social hierarchies can be readily established according to many dimensions, such as knowledge, skill and physical strength. For instance, Zink *et al.* (2008) created social hierarchies among experimental participants based on their performances in a simple perceptual task; and they demonstrated that people are strongly engaged in this hierarchical context. Employing similar procedures, previous studies have shown modulations of social hierarchies on human socioemotional functioning (Boksem *et al.*, 2012; Hu *et al.*, 2014, 2015) and attentional/cognitive processes (Santamaría-García *et al.*, 2013; Breton *et al.*, 2014; Feng *et al.*, 2015). More relevant to empathy modulation, the knowledge that others are superior often conflicts with positive self-views and provokes negative feelings due to upward social comparison (Smith *et al.*, 1996; Takahashi *et al.*, 2009). These negative feelings in turn may preclude empathy for superior-status individuals. Indeed, people tend to eliminate emotional sharing or even feel pleasure when imagined misfortune happens to advantaged targets (Smith *et al.*, 1996; Brigham *et al.*, 1997; van Dijk *et al.*, 2006; Takahashi *et al.*, 2009). Therefore, it is likely that empathic neural responses in the aMCC and AI are diminished in response to painful stimulation applied to superior-status compared with inferior-status targets.

To test this hypothesis, we examined empathic neural responses with functional magnetic resonance imaging (fMRI) in a hierarchical context. Prior to fMRI scanning, we followed the procedures of Zink *et al.* (2008) to create social hierarchies based on incidental skill in a game setting. Specifically, subjects performed a perceptual task and were told that all participants were ranked according to performance on the task. Covertly, all participants were told that they were medially ranked ('two-star players'). Thus, self-identities of hierarchical positions were set experimentally. During subsequent fMRI scanning, participants were asked to empathize with inferior-status ('one-star players') or superior-status ('three-star players') targets receiving painful or non-painful stimulation (Xu *et al.*, 2009). With this experimental design, we assessed modulations of social hierarchy on empathic neural responses with both a regions-of-interest (ROIs) analysis and an exploratory voxel-wise whole-brain analysis. The ROI analysis focused on the bilateral AI and aMCC for their consistent involvement in empathy for pain (Lamm *et al.*, 2011).

With these neuroimaging measurements, we first examined whether empathic brain responses were attenuated in perceiving pain of superior-status as compared with inferior-status targets. Furthermore, we investigated whether neural responses of AI and aMCC to others' pain were modulated according to behavioral measures such as empathy-related personality traits and subjective ratings to others' pain. For this purpose, personality measures reflecting participants' ability to understand their own feelings (manifested as low level of alexithymia) and others' emotions (reflected by high scores on the IRI) were examined due to their demonstrated associations with empathic neural responses (Singer *et al.*, 2004; Bird *et al.*, 2010). Taken together, our study examined both context-specific and person-specific empathic neural responses to others' pain.

Materials and methods

Subjects

Twenty-two individuals (11 females) (mean age ± s.d.: 22.23 ± 1.85) participated in this study and completed fMRI scanning for monetary compensation. All participants were right-handed, had normal or corrected-to-normal vision, and had no history of neurological or psychiatric disorder. Written informed consents were collected for all participants. The study was conducted according to the ethical guidelines and principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Beijing Normal University.

Stimuli

A set of 64 color photographs, showing faces of four targets (two females) unknown to all participants, was employed in this study. These photographs, 16 for each target, were derived from video clips used in a previous study (Xu *et al.*, 2009). Notably, Xu *et al.* (2009) have demonstrated that these stimuli are adequate to elicit empathy-related brain activity and subjective empathic feelings. For each target, eight photographs depicted faces receiving painful stimulation (needle penetration) to the left or right cheek; and the other eight photographs showed faces receiving non-painful stimulation (Q-tip touch) (Figure 1a and b). Each photograph was set to the same size of 298 × 298 pixels.

Procedure

Prior to fMRI scanning, participants' personality traits were measured by the IRI (Davis, 1980) and TAS-20 Items (Bagby *et al.*, 1994). IRI is a self-administered questionnaire measuring the empathetic ability in four aspects: (i) empathic concern, feeling of warmth and concern for others; (ii) perspective taking, adopting the perspective of other people; (iii) fantasy, identifying with fictitious characters in books or movies and (iv) personal

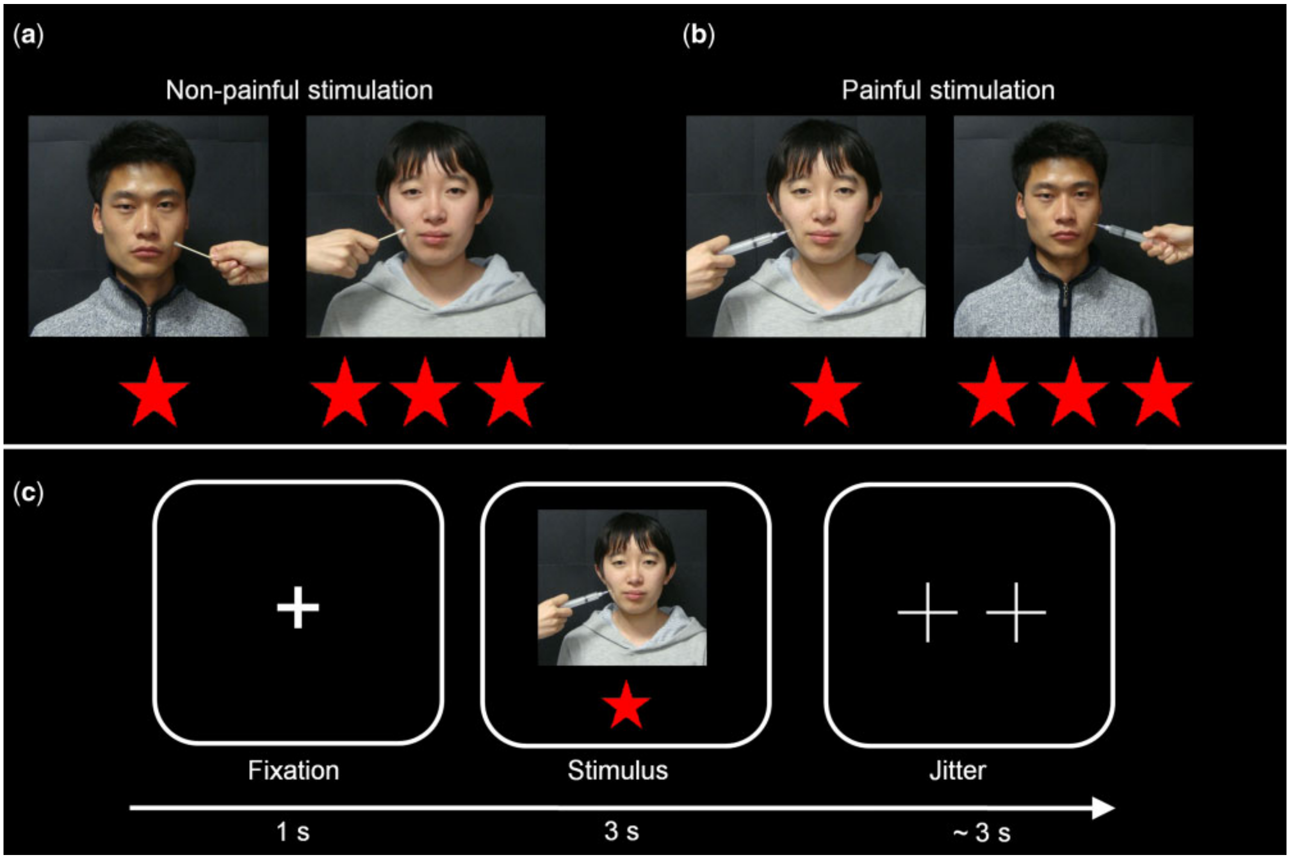

Fig. 1. Illustration of experimental stimuli and procedure. a) Non-painful stimulation to inferior-status and superior-status targets. b) Painful stimulation to inferior-status and superior-status players. c) Experimental procedure. Note: the photographs displayed in the figure were not employed in the experiment but were only used for illustration purpose.

distress, feelings of discomfort and anxiety when witnessing the negative experiences of others. TAS-20 is a self-administered questionnaire consisting of 20 items, which are scored on a 5-point scale from ‘strongly disagree’ to ‘strongly agree’, with higher scores indicating greater levels of alexithymia. TAS-20 provides an overall measure of deficiency in understanding, processing or describing emotions (Bagby *et al.*, 1994), and it consists of three subscales: difficulty identifying emotions, difficulty describing emotions and externally oriented thinking. The associations between alexithymia and empathy have been previously observed, suggesting that the awareness of one’s own emotions is a prerequisite to share emotions of others (Moriguchi *et al.*, 2007; Grynberg *et al.*, 2010).

To establish the social hierarchy, all participants were asked to perform a dot-estimation task. In this task, participants were presented with 100 red dots in a white background and asked to judge which side (left or right) of the field had more dots (Feng *et al.*, 2013). Participants were told that their performance in this task would be evaluated by both speed and accuracy and would be compared with other players for ranking purpose. They were also told that more than 650 people had already performed this task as a part of a cognitive ability test, and all of them were ranked as inferior (‘one star players’), medium (‘two star players’) or superior (‘three star players’) status according to their performance. Covertly, outcomes of this dot-estimation task were always fixed, such that all participants were told that they were mediumly ranked based on their performance. Similar procedures to establish social hierarchy were initially employed in a landmark study by Zink *et al.* (2008), and these authors demonstrated that individuals are strongly engaged in the hierarchical context in this paradigm. Accordingly, this paradigm has been widely employed in the current literature (Boksem *et al.*, 2012; Santamaría-García *et al.*, 2013; Breton *et al.*, 2014).

After the dot-estimation task, participants were told that a fraction of the aforementioned 650 players had agreed to take part in a sensory test in which they had received painful or non-painful stimulation. Participants were then told that they would view faces of four of these players in the other two social positions: two (one female) superior players and two (one female) inferior players. For the four targets employed, the combinations of targets and hierarchies were counterbalanced across subjects to control for potential confounding factors such as attractiveness. To ensure that participants believed that the four players had received both painful and non-painful stimulation, participants were asked to watch video clips that vividly depicted needle penetration or Q-tip touch applied to each target. In cases where a participant questioned about the ranking procedure or stimulation applied, the experiment was terminated and such participants (three females and two males, not included in the present sample of $N = 22$) were excluded from fMRI scanning.

On the fMRI session, each trial of the fMRI task consisted of a central fixation (1 s) followed by a photograph (3 s) of either inferior or superior player (Figure 1c). On each photograph, participants were instructed to empathize and judge how much pain the depicted target was feeling (de Greck *et al.*, 2012). No overt response was required from participants for minimizing motor-related confounds (Decety *et al.*, 2008; Akitsuki and Decety, 2009). Afterwards, an optimized jitter generated by an fMRI simulator software (http://www.cabiatl.com/CABI/resources/fmrisim/) was presented with minimum of 1 s and average of 3 s. Each scanning run consisted of 64 trials and lasted for 448 s. Each participant completed two scanning runs with each photograph being non-repetitively presented once in each run.

In the post-scan session, participants were asked with two evaluation scales for each photograph presented: (i) 'how painful do you think the target feels' (pain intensity: 1 = not at all, 9 = extremely painful) and (ii) 'how pleasant do you feel when observing the photograph' (pleasantness: 1 = extremely unpleasant, 9 = extremely pleasant). Finally, participants were asked whether they believed that their own and the four viewed targets' social positions were based on their performances in the dot-estimation task and whether the painful/non-painful stimulations applied to targets were real. The debriefing received positive confirmations from all participants that completed the fMRI scanning.

Data acquisition

Imaging data were acquired with a 3T Siemens Trio scanner equipped with a 12-channel transmit/receive head coil. A T2-weighted gradient-echo echo-planar-imaging (EPI) sequence was used to acquire functional images (TR/TE = 2000 ms/30 ms, flip angle = 90°, number of axial slices = 33, slice thickness = 3.5 mm, gap between slices = 0.7 mm, matrix size = 64 × 64, FOV = 224 × 224 mm). High-resolution anatomical images covering the entire brain were also obtained by a magnetization prepared rapid acquisition with gradient-echo (MPRAGE) sequence (TR/TE = 2530/3.39 ms, flip angle = 7°, number of sagittal slices = 144, slice thickness = 1.33 mm, matrix size = 256 × 256, FOV = 256 × 256 mm).

Data analysis

Behavioral data analysis. Behavioral data analyses were carried out using SPSS 16.0 (IBM, Somers, USA) with a significance threshold of $P < 0.05$ (two-tailed). Subjective ratings of pain intensity and pleasantness were submitted to a 2 (social hierarchy: superior status *vs* inferior status) × 2 (stimulation valence: painful stimulation *vs* non-painful stimulation) repeated measures analysis of variance (ANOVA).

fMRI data analysis. Functional neuroimaging data analyses were performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Preprocessing of functional data included slice-timing correction, realignment through rigid-body registration to correct for head motion, spatial normalization to the Montreal Neurological Institute (MNI) template, spatial smoothing (FWHM = 5 mm) and temporal high-pass filtering (removal of low frequency drift of $T > 80$ s).

A two-level general linear model (GLM) was used to analyze functional data. The first-level modeling included regressors defined for each subject. These regressors modeled blood oxygenation level-dependent (BOLD) responses to the fixation and the four task conditions of painful stimulation applied to inferior players (Inferior-Pain), non-painful stimulation applied to inferior players (Inferior-NoPain), painful stimulation applied to superior players (Superior-Pain) and non-painful stimulation applied to superior players (Superior-NoPain). The six movement parameters obtained from the realignment (three translations, three rotations) were also included in the design matrix as nuisance regressors. Each task regressor was generated by convolving the corresponding boxcar stimulus function with a canonical hemodynamic response function (HRF) (Büchel *et al.*, 1998). To improve noise estimation, the GLM also considered signal temporal autocorrelations with a first-order autoregressive model (Bullmore *et al.*, 1996). In the first-level GLM, regression coefficients (or beta values) for each regressor were computed at every voxel within the brain.

With the obtained parameter estimates, we performed a region-of-interest (ROI) analysis based on a priori hypotheses (Poldrack, 2007; Poldrack and Mumford, 2009). This ROI analysis focused on the aMCC and bilateral AI as they are most consistently implicated in perceiving others' pain, thereby constituting the core network of empathy for pain (Lamm *et al.*, 2011). To determine the ROIs independently of the present data, the regions of bilateral AI (Figure 2a) and aMCC (Figure 3a) were defined as spheres (radius = 10 mm) centered at MNI coordinates (x/y/z = −40/22/0 mm, 39/23/−4 mm and −2/23/40 mm) reported in a previous meta-analysis (Lamm *et al.*, 2011). The average parameter estimates across all voxels in each ROI were extracted from each subject for all experimental conditions using SPM REX toolbox (https://www.nitrc.org/projects/rex/). These data were then compared between conditions with a 2 (social hierarchy: superior status *vs* inferior status) × 2 (stimulation valence: painful stimulation *vs* non-painful stimulation) repeated measures ANOVA.

The ROI analysis was supplemented with an exploratory whole-brain analysis using voxel-wise repeated measures ANOVA. This analysis was employed to confirm the interaction between social hierarchy and stimulation valence in the predefined ROIs as well as to explore the same interaction in other brain regions. To correct for false positives yielded by multiple comparisons, statistical maps were clipped with a joint threshold at both the voxel level and the cluster level. The cluster threshold was determined using a Monte Carlo simulation-based estimator implemented in Matlab (Slotnick *et al.*, 2003; Slotnick and Schacter, 2004). On the basis of simulations (5000 iterations) and the estimated spatial smoothness of FWHM = 9 mm, a family-wise error (FWE) correction at $P < 0.05$ is achieved with a cluster defining threshold of $P < 0.005$ and a cluster extent of 86 contiguous resampled voxels (688 mm^3) (Janes *et al.*, 2010; Dietsche *et al.*, 2014; Abel *et al.*, 2015; Henry *et al.*, 2015; Willems *et al.*, 2015). This joint threshold was applied to all results of whole-brain analyses.

Focusing on the predefined ROIs of AI and aMCC, we also performed an analysis of psychophysiological interaction (PPI) (Friston *et al.*, 1997) to examine how social hierarchy modulates functional connectivity between the AI/aMCC and other regions of the brain. Specifically, we used the generalized PPI toolbox (http://www.nitrc.org/projects/gppi) (McLaren *et al.*, 2012) with fMRI signal time courses individually extracted from the AI and aMCC as the seeding signals. These seeding signals were then deconvolved with the canonical HRF, resulting in estimates of the underlying neuronal activity (Gitelman *et al.*, 2003). Subsequently, the interactions of these estimated neuronal time-series and vectors representing each of the onsets for the fixation and four stimulus types (Inferior-Pain, Inferior-NoPain, Superior-Pain, Superior-NoPain) were computed. Lastly, these interaction terms were re-convolved with the HRF and entered into a new GLM along with the vectors for the onsets of each stimulus type (i.e. the psychological terms), the original average time-series, and nuisance regressors (i.e. six movement parameters derived from realignment corrections). Group level analysis of the PPI data was almost identical to that of activation

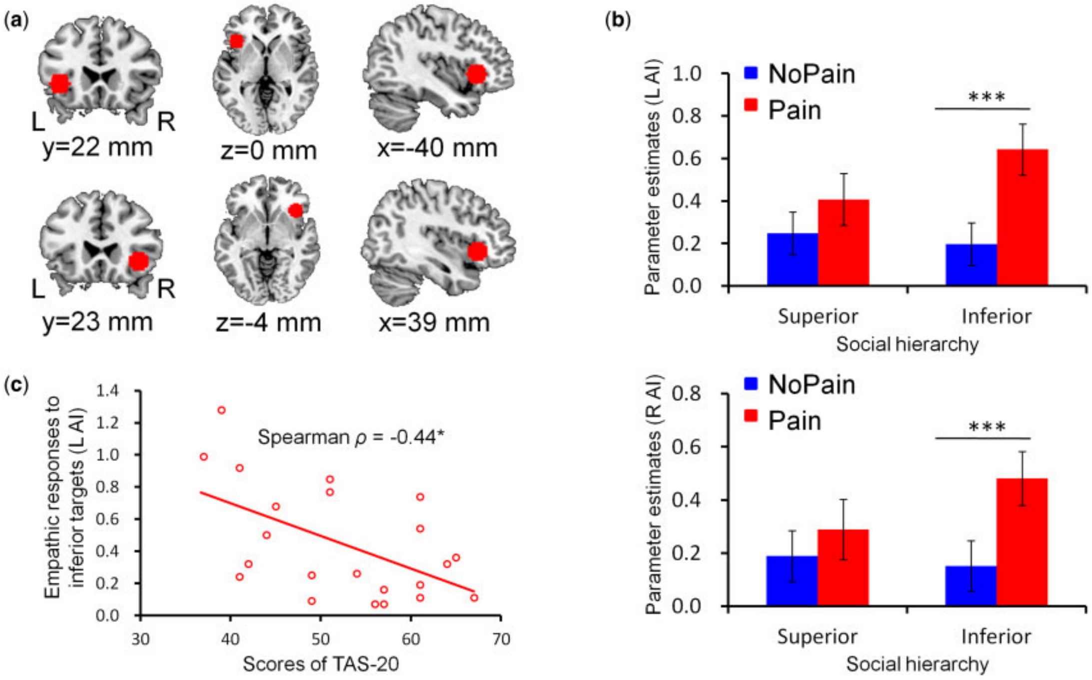

Fig. 2. fMRI ROI results of the anterior insula. a) Functional ROI in the bilateral anterior insula. b) ROI analysis of the parameter estimates of the bilateral anterior insula as a function of social hierarchy and stimulation valence. Error bars indicate one standard error. c) The correlation between scores of TAS-20 and empathic responses of the left AI in response to inferior targets (pain *vs* nopain). L, left; R, right; AI, anterior insula. ***$P < 0.0005$; *$P < 0.05$.

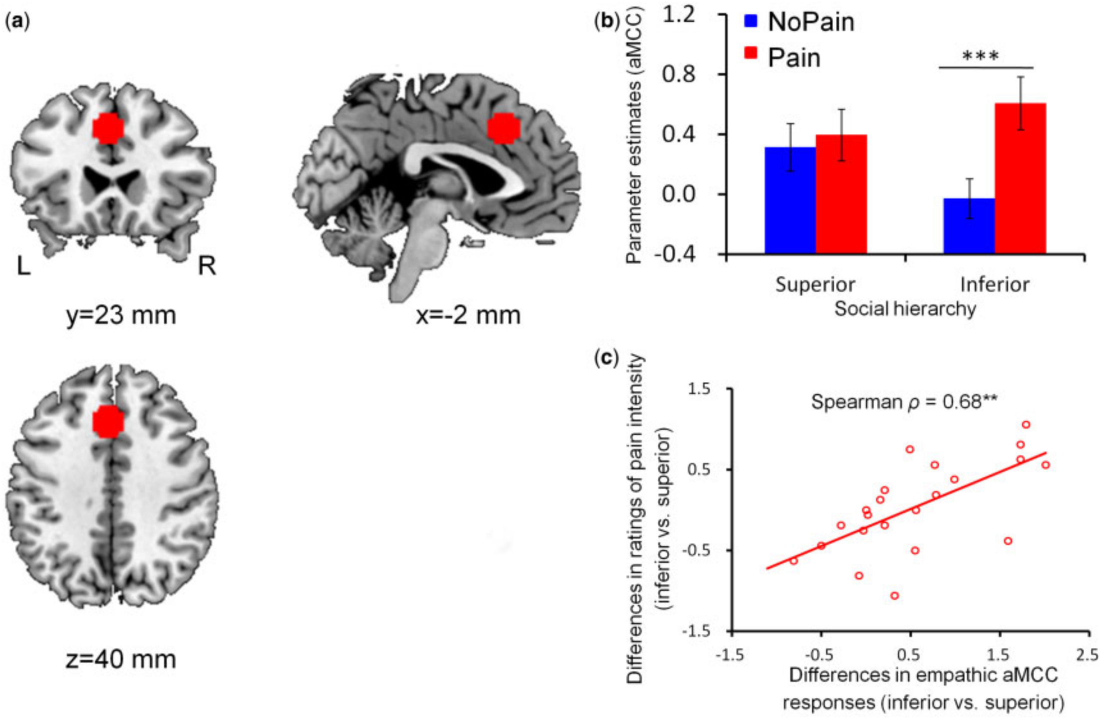

Fig. 3. fMRI ROI results of the aMCC. a) Functional ROI in the aMCC. b) ROI analysis of the parameter estimates of the aMCC as a function of social hierarchy and stimulation valence. Error bars indicate one standard error. c) The correlation between empathic aMCC responses and subjective ratings of pain intensity regarding the differences between inferior-status and superior-status targets [i.e. (Inferior-Pain − Inferior-NoPain) − (Superior-Pain − Superior-NoPain)]. L, left; R, right; aMCC, anterior medial cingulate cortex. ***$P < 0.0005$; **$P < 0.01$.

data except the beta values used were derived from the PPI regressors. In this study, we focused on connections that exhibited a significant interaction effect of social hierarchy × stimulation valence. Namely, those connections with a different painful *vs* non-painful contrast between the superior and inferior status.

Moreover, given previous reports of differential behavioral responses to superior-status men and women (Maner *et al.*, 2007; DeWall, 2008), potential effects of target gender were explored by adding it as a within-subjects factor to the GLMs described earlier. However, since we did not observe significant modulations of target gender on either subjective ratings or empathic AI and aMCC responses (Supplementary Figures S1 and S2), the current data analyses on the empathic responses were collapsed across gender of targets.

Finally, to examine potential relationships between the internal brain activation and external behavior, Spearman's Rank non-parametric (i.e. Spearman ρ) correlations that are more robust to outliers than Pearson's linear correlations (Rousselet and Pernet, 2012) were computed to determine associations among dispositional (personality scores), behavioral (subjective ratings), fMRI (BOLD signal changes) and functional connectivity (connectivity strengths) measures.

Results

Behavioral results

Relative to non-painful stimulation, painful stimulation was rated with higher scores of pain intensity ($F(1, 21) = 123.25$, $P < 0.0005$) and lower scores of pleasantness ($F(1, 21) = 9.84$, $P < 0.01$). These rating scores of painful and non-painful stimulations did not differ between superior and inferior status (all $P > 0.05$).

fMRI results: ROI analysis

The analysis of BOLD responses in the left AI ($F(1, 21) = 17.42$, $P < 0.0005$), right AI ($F(1,21) = 9.24$, $P < 0.01$) and aMCC ($F(1, 21) = 22.20$, $P < 0.0005$) confirmed the augmented activity for painful stimulation as compared with non-painful stimulation; whereas the main effect of social hierarchy was not significant (left AI: $F(1, 21) = 2.61$, $P > 0.05$; right AI: $F(1, 21) = 1.40$, $P > 0.05$; aMCC: $F(1, 21) = 0.71$, $P > 0.05$). Moreover, in supporting our hypothesis, we observed significant interactions of social hierarchy and stimulation valence in all of these three regions (left AI: $F(1, 21) = 7.27$, $P < 0.05$, Figure 2b; right AI: $F(1, 21) = 5.86$, $P < 0.05$, Figure 2b; aMCC: $F(1, 21) = 10.75$, $P < 0.005$, Figure 3b). For superior-status targets, BOLD responses in these areas did not significantly differ between painful and non-painful stimulation (left AI: $t(21) = 1.54$, $P > 0.05$; right AI: $t(21) = 1.10$, $P > 0.05$; aMCC: $t(21) = 0.73$, $P > 0.05$). For inferior-status targets, however, painful stimulation elicited higher BOLD responses than non-painful stimulation (left AI: $t(21) = 5.97$, $P < 0.0005$; right AI: $t(21) = 4.15$, $P < 0.0005$; aMCC: $t(21) = 5.45$, $P < 0.0005$). Noteworthy, to non-painful stimulation, aMCC showed stronger responses to superior-status than inferior-status targets ($t(21) = 2.54$, $P < 0.05$).

The correlation analysis revealed that empathic responses of the left AI to inferior targets (i.e. Inferior-Pain *vs* Inferior-NoPain) were negatively correlated with participants' scores of TAS-20 (Spearman $\rho = -0.44$, $P < 0.05$, Figure 2c); whereas this correlation was not significant in response to superior-status targets ($P > 0.05$). In addition, empathic aMCC responses and empathic subjective ratings of pain intensity were positively correlated with each other regarding the difference between inferior and superior status [i.e. (Inferior-Pain − Inferior-NoPain) − (Superior-Pain − Superior-NoPain)] (Spearman $\rho = -0.68$, $P < 0.005$, Figure 3c).

fMRI results: exploratory whole-brain analysis

Whole-brain analysis of neuroimaging data was detailed in the supplementary materials (Supplementary Figures S3–S5 and Tables S1–S3).

fMRI results: PPI analysis

PPI analysis was performed to assess the interaction effects of social hierarchy × stimulation valence on the functional connectivity between AI/aMCC and other brain regions. The connectivity contrast of [(Inferior-Pain *vs* Inferior-NoPain) > (Superior-Pain *vs* Superior-NoPain)] for the left AI as a seed region identified the following brain regions ($P < 0.05$ FWE corrected at the cluster level): the left thalamus (−14/−6/10 mm, cluster size = 182 voxels, $T = 5.14$) (Figure 4a and b) and the right calcarine (30/−66/8 mm, cluster size = 138 voxels, $T = 4.03$); and the reverse contrast identified the left middle occipital gyrus (−28/−92/0 mm, cluster size = 126 voxels, $T = -4.55$). Notably, empathic left AI-thalamus connectivity and empathic left AI responses were positively correlated with each other regarding the difference between inferior and superior status [i.e. (Inferior-Pain − Inferior-NoPain) − (Superior-Pain − Superior-NoPain)] (Spearman $\rho = 0.58$, $P < 0.01$, Figure 4c).

The connectivity contrast of [(Inferior-Pain *vs* Inferior-NoPain) > (Superior-Pain *vs* Superior-NoPain)] for the right AI as a seed region identified the right middle frontal gyrus (MFG) (42/−8/32 mm, cluster size = 91 voxels, $T = 4.52$) (Figure 5a and b); whereas no significant cluster was identified with the reverse contrast. The correlation analysis revealed that scores of TAS-20 were positively correlated with empathic AI-MFG connectivity changes in response to inferior-status targets (Spearman $\rho = 0.55$, $P < 0.01$, Figure 5c). Further, the strength of right AI-MFG connectivity in response to the pain of inferior targets showed a negative correlation with empathic AI responses to inferior-status targets (Spearman $\rho = -0.46$, $P < 0.05$, Figure 5d). These correlations were not significant in response to superior-status targets (all $P > 0.05$).

Finally, aMCC showed significant functional covariation with the right precuneus (38/−80/36 mm, cluster size = 91 voxels, $T = 4.43$) as revealed by the connectivity contrast of [(Inferior-Pain *vs* Inferior-NoPain) > (Superior-Pain *vs* Superior-NoPain)], whereas no significant cluster was identified with the reverse contrast.

Discussion

Our study examined the influence of social hierarchy on the neural responses to others' pain. We identified brain activation to the pain of others in the AI and aMCC that are implicated in affective aspects of empathy for pain (Lamm *et al.*, 2011). The empathic neural responses in the left AI inversely correlated with the alexithymia traits, and neural responses in the aMCC were positively associated with subjective sensitivity to others' pain. Notably, we observed significant modulations of social hierarchy on these empathic neural responses, such that they were evident in the perception of pain of inferior-status targets but were significantly attenuated in response to the pain of superior-status targets. Finally, we observed stronger functional couplings of AI with brain regions implicated in emotional processing (i.e. thalamus) and cognitive control (i.e. MFG) in response to the pain of inferior-status than superior-status targets. Our findings indicate that brain functions underlying empathy are modulated by the relative positions in a social

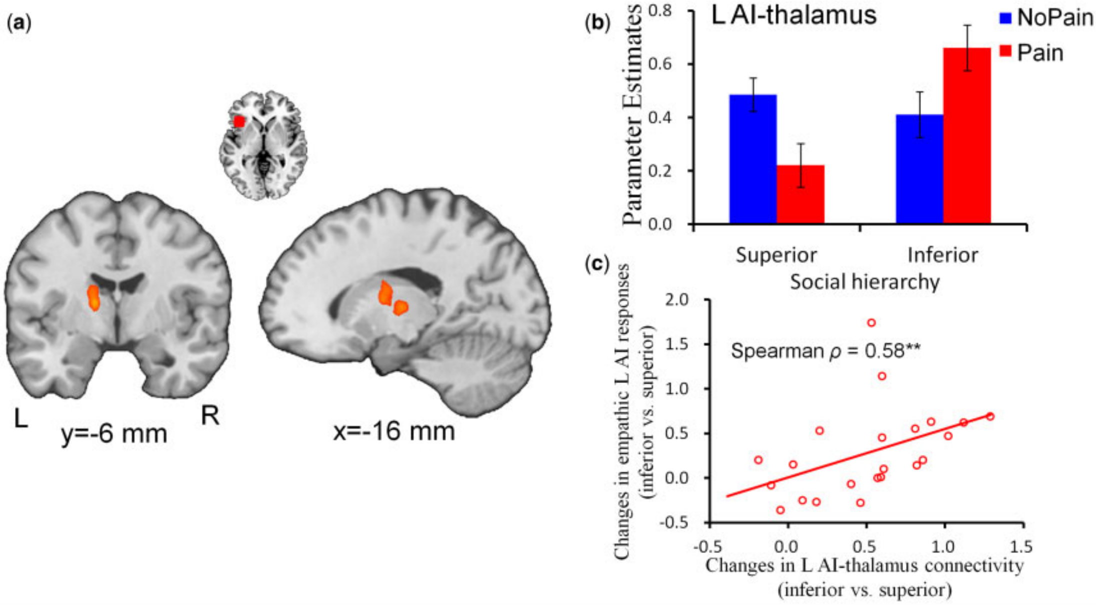

Fig. 4. Interactive effects of social hierarchy and stimulation valence on functional coupling between left anterior insula and thalamus. a) Illustration of the left thalamus showing significant changes in functional coupling with the left anterior insula as revealed by the interaction of social hierarchy and stimulation valence. Images are thresholded at $P < 0.05$ corrected for multiple comparisons at the cluster level. b) Parameter estimates of the left AI-thalamus connectivity as a function of social hierarchy and stimulation valence. Error bars indicate standard error. c) The correlation between strength of left AI-thalamus connectivity and empathic AI responses regarding the differences between inferior-status and superior-status targets [i.e. (Inferior-Pain − Inferior-NoPain) − (Superior-Pain − Superior-NoPain)]. L, left; R, right; AI, anterior insula. **$P < 0.01$.

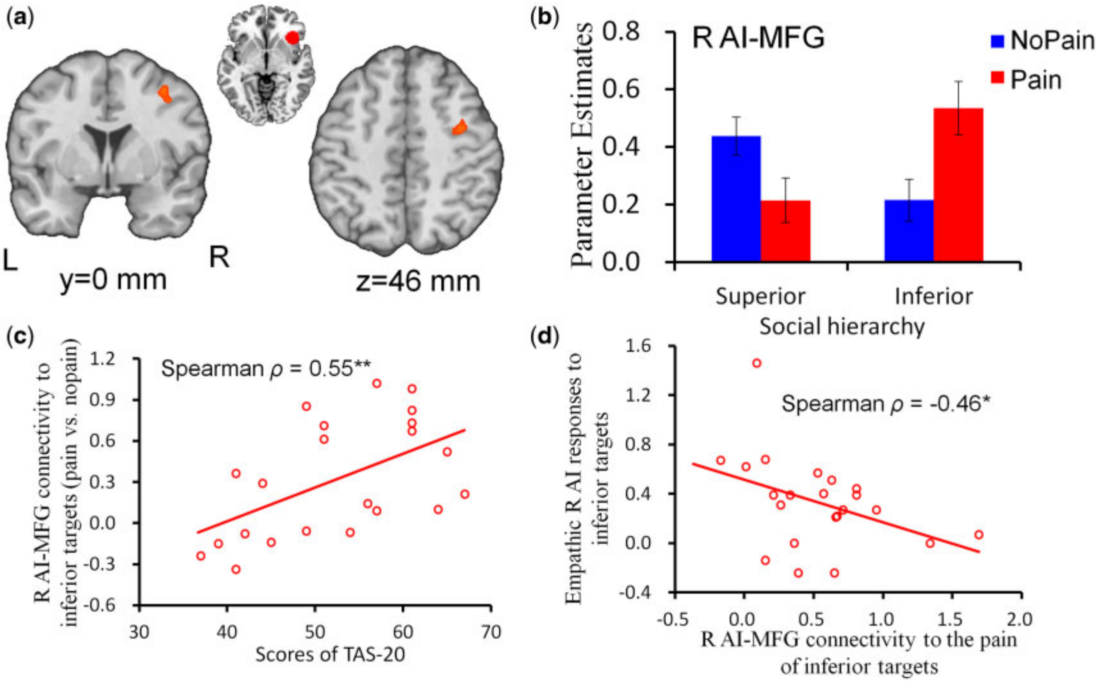

Fig. 5. Interactive effects of social hierarchy and stimulation valence on functional coupling between right anterior insula and MFG. a) Illustration of the right MFG showing significant changes in functional coupling with the right anterior insula as revealed by the interaction of social hierarchy and stimulation valence. Images are thresholded at $P < 0.05$ corrected for multiple comparisons at the cluster level. b) Parameter estimates of the right AI-MFG connectivity as a function of social hierarchy and stimulation valence. Error bars indicate standard error. c) The correlation between scores of TAS-20 and strength of right AI-MFG connectivity in response to inferior targets. d) The correlation between strength of right AI-MFG connectivity in response to the pain of inferior targets and empathic AI responses to inferior-status targets. L, left; R, right; AI, anterior insula; MFG, middle frontal gyrus. **$P < 0.01$; *$P < 0.05$.

hierarchy such that empathic neural responses are biased toward inferior-status compared with superior-status targets.

We first replicated previous findings on the neural signatures underlying empathy for others' pain. Among other brain regions, the AI and aMCC showed stronger responses to the painful than non-painful stimulation applied to others. The AI and aMCC responses to others' pain are thought to represent feeling states of others (Lamm *et al.*, 2011; Bernhardt and Singer, 2012). This assertion has support from the present and previous observations that empathic aMCC responses were associated with subjective sensitivity to the pain of others (Lamm and Decety, 2008). Furthermore, the AI and aMCC are also engaged in affective and motivational aspects of first-person pain experience (Peyron *et al.*, 2000; Rainville, 2002), leading to the notion that emotional sharing with others' pain is based on shared neural representations for first-person and vicarious experiences of emotion (Singer *et al.*, 2004; Lamm *et al.*, 2011; Bernhardt and Singer, 2012; Rütgen *et al.*, 2015). This hypothesis is confirmed by our findings that neural responses of AI to the pain of inferior-status targets correlated inversely with alexithymia traits that involve difficulties in understanding one's own emotions (Silani *et al.*, 2008; Bird *et al.*, 2010). Noteworthy, correlations of the AI and aMCC activations with behavioral measures were different. The AI responses were correlated with alexithymia scores, whereas the aMCC responses with pain intensity ratings. Whether these findings imply different roles of the AI and aMCC remains to be elucidated, since much of the research has focused on the commonality of AI and aMCC (see also Gu *et al.*, 2010; Bernhardt and Singer, 2012). Recent attempts to dissociate functions of these brain regions have not yet provided straightforward predictions on the distinct correlations of their activations with behavioral measures (Gu *et al.*, 2010, 2012, 2013).

We next studied the modulations of social hierarchy on empathic neural activity in the bilateral AI and aMCC. Our findings revealed that empathy-related activations in these brain regions were significantly attenuated in response to the pain of superior-status targets. These results concur with previous observations that empathic neural responses in the aMCC and AI are modulated by interpersonal relationship such that they are remarkably decreased by the knowledge that out-group members or disliked others are in pain (Singer *et al.*, 2006; Xu *et al.*, 2009). The evidence that empathic neural responses are modulated by interpersonal relations supports the context-dependent account of empathy (De Vignemont and Singer, 2006).

Modulations of social hierarchy on empathic neural responses might be mediated by the social comparison processes. For instance, the knowledge that others are better threatens positive self-views and induces negative affect due to upward social comparison (Major *et al.*, 1993). This negative affective link with superior-status targets in turn may dampen empathy (Singer *et al.*, 2006). This is supported by the stronger aMCC responses to superior than inferior targets at baseline in the context of non-painful stimuli. Such an aMCC activation pattern echoes previous observation that upward social comparison with advantaged targets induced enhanced activations in the aMCC, which was thought to reflect painful feelings or conflicts of positive self-concepts (Takahashi *et al.*, 2009). In Takahashi *et al.*'s (2009) study, negative affective link predicts experienced pleasure and associated brain activations (e.g. ventral striatum) in response to imagined misfortunes on advantaged individuals. We did not identify the involvement of reward neural circuit in response to the pain of superior-status targets. This might be due to the reason that participants were asked to intentionally empathize with the pain of others. Noteworthy, this affective account is very tentative given that we did not collect participants' attitudes toward superior-status and inferior-status targets. Alternatively, differential empathic neural responses to inferior and superior targets might be attributed to attentional/cognitive processes (Gu and Han, 2007; Lamm *et al.*, 2007b). It has been demonstrated both by previous data (Zink *et al.*, 2008) and by the main effect of social status in the present whole-brain analyses that greater attentional resources are directed to the superior than inferior targets. As such, when viewing superior targets in pain, the status itself may deter attention from allocating to pain so that empathic neural response are dampened (Gu and Han, 2007).

Despite the observed effects of social status on the fMRI responses to others' pain, social status had no effect on participants' self-reported ratings of pain intensity. This divergence could be due to attention redirection in the self-paced rating task, which presumably allowed more time for evaluation as well as increased attention to the pain-related features. Another possible account is that subjective ratings of pain intensity for superior-status targets might be based on cognitive evaluations or sensory perception (cf. Xu *et al.*, 2009). It is not without precedent that differential neuropsychological processes are involved in empathizing with different targets. Indeed, Meyer *et al.* (2012, 2015) have demonstrated that empathy for strangers' social suffering relies more heavily on mentalizing networks, whereas empathy for friends' social suffering relies on networks implicated in emotional sharing and self-processing. In line with this account, our whole-brain analysis revealed that empathy for the pain of superior-status relative to inferior-status targets induced stronger responses in the precuneus, which is implicated in mentalizing (Lieberman, 2010).

The neural empathic bias to inferior-status targets was accompanied by enhanced functional connectivity of AI and aMCC with other brain regions including thalamus and MFG. On the one hand, the thalamus plays a critical role in affective aspects of empathy (Nummenmaa *et al.*, 2008; Hillis, 2014). Patients with thalamus lesion have shown lower ability in emotional empathy as measured by the 'Reading the mind in the Eyes Test' (Wilkos *et al.*, 2015). The thalamus might contribute to emotional empathy by relaying sensory information about affective experience of others to the insula to shape the representation of others' emotion (Craig, 2002; Hillis, 2014). In line with this viewpoint, our results revealed that stronger AI-thalamus connectivity strengths predicted higher empathic neural responses of the AI. On the other hand, the MFG is often involved in cognitive control and presumably contributes to emotion regulation of empathy (Decety and Jackson, 2004; Gu and Han, 2007). This is also consistent with our findings that the stronger right AI-MFG connectivity strengths predicted lower empathic AI responses to inferior-status targets. In addition to emotional sharing, emotion regulation constitutes another crucial component of empathy to manage intersubjective transactions between self and other (Decety and Jackson, 2004; Lamm *et al.*, 2010).

Several limitations warrant consideration. First, our study did not consider gender of perceivers as a potential moderators as many previous studies did (Chiao *et al.*, 2008; Zink *et al.*, 2008; de Greck *et al.*, 2012). It is possible that genders of perceivers and targets interact with each other to modulate the processing of social hierarchy and its effects on socio-emotional functioning (Maner *et al.*, 2007; DeWall, 2008). Replication in larger groups of men and women will help to clarify sex differences in the modulation of social hierarchy on empathic neural responses. Second, we deliberately used faces of neutral expressions for both painful and non-painful stimulations to avoid confounding effects of emotional contexts on empathic responses (cf. Han *et al.*, 2009). One may argue that neural responses to painful stimulation were attributed to conflict resolution. This argument is not consistent with our results that empathic neural responses of the AI/aMCC were modulated according to empathy-related personality traits (i.e. alexithymia) and subjective sensitivity to others' pain. Finally, our design did not include a same-status condition that could help to identify the directions of effects of social hierarchy on empathic responses. For instance, it is possible that empathic responses to inferior targets reflect general affective sharing as in the neutral (e.g. same-status) condition rather than increased empathy for the pain of inferior targets.

In summary, our findings confirmed the hypothesis that empathic neural responses are modulated by relative positions in a social hierarchy. We showed evidence that the affective neuronal network consisting of the aMCC and AI is engaged in empathic responses to the pain of inferior-status but not superior-status individuals. In addition, the AI showed stronger functional couplings with thalamus and MFG that are respectively associated with emotional processing and cognitive control in response to the pain of inferior-status than superior-status targets. These findings indicate a bias of emotional sharing with inferior-status compared with superior-status others and complement previous observations on the effects of social hierarchy on human social behaviors and cognitive functions (Koski *et al.*, 2015).

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Supplementary data

Supplementary data are available at SCAN online.

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Dissociable early attentional control mechanisms underlying cognitive and affective conflicts

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It has been well documented that cognitive conflict is sensitive to the relative proportion of congruent and incongruent trials. However, few studies have examined whether affective conflict processing is modulated as a function of proportion congruency (PC). To address this question we recorded event-related potentials (ERP) while subjects performed both cognitive and affective face-word Stroop tasks. By varying the proportion of congruent and incongruent trials in each block, we examined the extent to which PC impacts both cognitive and affective conflict control at different temporal stages. Results showed that in the cognitive task an anteriorly localized early N2 component occurred predominantly in the low proportion congruency context, whereas in the affective task it was found to occur in the high proportion congruency one. The N2 effects across the two tasks were localized to the dorsolateral prefrontal cortex, where responses were increased in the cognitive task but decreased in the affective one. Furthermore, high proportions of congruent items produced both larger amplitude of a posteriorly localized sustained potential component and a larger behavioral Stroop effect in cognitive and affective tasks. Our findings suggest that cognitive and affective conflicts engage early dissociable attentional control mechanisms and a later common conflict response system.

Attentional control refers to the ability to select and maintain actions in accordance with ultimate goals by ignoring task-irrelevant information[1], and is typically probed in tasks wherein different incompatible response tendencies are simultaneously induced[2,3]. For instance, participants in the traditional Stroop task are asked to name the color of the printed words that possess congruent (e.g., RED printed in red) or incongruent (RED printed in green) semantic meanings. Incongruent stimuli consistently induce increased response times (RT) and error rates relative to congruent stimuli (i.e., interference effects), reflecting enhanced competition for attentional resources in response to incongruent compared to congruent stimuli[4]. In other words, more attentional control (i.e., attentional selection or adjustment) is needed for appropriate responses to incongruent stimuli. The attentional control mechanism underling cognitive conflict is modulated by the relative proportion of congruent and incongruent trials, with high proportions of congruent trials leading to large interference effects, i.e., a proportion congruency (PC) effect[5,6]. The PC effect may reflect a high-level strategic adjustment, manifested as a proactive top-down attentional control in the low proportion congruency (LPC) context and a reduced engagement of reactive control in the high proportion congruency (HPC) context[7,8].

The PC effect on cognitive conflict can be detected by scalp event-related potentials (ERP) brain recording methods which allow a high temporal resolution. Previous findings have identified an early conflict-related component (i.e., N2) that exhibits a similar PC effect as at the behavioral level. In particular, the amplitude of the

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conflict-related N2 is augmented in the LPC context[9,10] (but see also ref. 11), and this is associated with reduced interference effects. These effects echo the conflict-monitoring theory which maintains that infrequent incongruent trials in the HPC context decrease the level of control, producing a stronger interference effect; in contrast, frequent incongruent trials in the LPC context presumably lead to a steady maintenance of a high level of control, producing a weaker interference effect[12]. Furthermore, the sustained potential (SP), a late conflict-related component, is also modulated by the PC, such that its amplitude is augmented and associated with a larger interference effect in the HPC context compared to the LPC one[9,11,13,14]. Regarding the localization of these conflict-relevant components, accumulating evidence indicates that the N2 component is generated in the dorsal anterior cingulate (dACC)[15,16] or the dorsolateral prefrontal cortex (DLPFC)[17,18], reflecting the detection of conflict or conflict maintenance, while the SP component is generated in the lateral frontal and extrastriate cortices and thought to reflect conflict resolution[4,19].

Affective conflict constitutes another important type of conflict that involves emotional stimuli and may engage different mechanisms of attentional control to those of cognitive conflict[20,21]. In view of the importance of affective conflict in the context of emotion regulation and affective disorders[22–24], the past decade has witnessed an increasing interest in studying the psychological and neural signatures underlying its resolution[25–28]. Early studies on affective conflict often assessed the influence of emotional distractors on individual performance on target stimuli, i.e., naming the color of aversive words (e.g., "disgust" printed in red)[29]. However, emotional distractors and target stimuli employed in these tasks are neither semantically incongruent nor do they induce incompatible response tendencies. Accordingly, these tasks are unable to induce affective conflict that is comparable to cognitive conflict induced by the classical Stroop task[25,30]. Ektin *et al.* (2006) have developed a new word-face paradigm that allows for direct comparisons to be made between affective and cognitive conflicts. Specifically, participants are presented with facial expressions (e.g., fearful or happy) overlaid with congruent or incongruent emotional labels (e.g., "fearful" or "happy"), and asked to judge the facial expressions while ignoring the distractor of emotional word labels across the face[25]. As such, the affective conflict is derived from incompatible response tendencies between emotional expressions and word labels[8,25]. To compare the affective and cognitive conflicts, participants often perform another comparable cognitive conflict task, wherein they are asked to judge the gender of the faces while ignoring the distractor of gender word labels across the faces[26,31,32].

Recent functional magnetic resonance imaging (fMRI) studies have compared the PC effect on conflict-related brain activations in affective and cognitive word-face Stroop tasks[31,33], and identified similar actions on the dACC but different ones on the dorsal striatum and anterior insula[33], suggesting both overlapping and distinct attentional control mechanisms underlying cognitive and affective tasks. Utilizing the high temporal resolution afforded by the ERP technique, we recently compared the modulation of PC on cognitive and affective conflict processing at distinct temporal stages in a flanker task using word stimuli[34]. The PC effect on a central N450, as an extension of the early central N2, was enhanced in the LPC context during cognitive tasks, whereas it was reduced during affective tasks. This differential PC effect on the N450 was localized in the DLPFC, with activity being increased in the cognitive task and reduced in the affective one. Furthermore equivalent PC effects were found on a parietal SP component during cognitive and affective tasks[34]. These findings generally echo observations of a recent study comparing cognitive and affective interference effects[35]. In particular, the authors identified greater N2 amplitude in the affective than the cognitive task regardless of stimulus congruency. In addition, they observed a stronger interference effect on N450 amplitude in the cognitive than the affective task, whereas the interference effect on the SP component was comparable in both tasks[34]. Taken together, previous ERP findings indicate that cognitive and affective conflict processing engage an early dissociable attentional control mechanism but a later common conflict response system.

Building on previous findings, here we further compared the PC effects on cognitive and affective conflicts with cognitive and affective versions of a commonly-used face-word Stroop task[26,31,33,36], where the relative proportion of congruent and incongruent trials were varied in each block. We postulated that comparisons between the impact of cognitive and affective conflicts would allow us to assess the extent to which current models of attentional control based primarily on evidence on cognitive conflict effects would also be applicable to affective conflict. Although our previous ERP study has shed light on the modulation of the temporal dynamics of both cognitive and affective conflict processing by PC, it remains unclear whether the effects were specific to the revised flanker task using word stimuli, given that complex semantic processing may influence the time course of the conflict-related ERP components[37,38]. This potential confound was addressed in the current study by employing faces as stimuli[26,31,32]. In line with previous findings[34], we hypothesized the early conflict-sensitive N2 component originating in the DLPFC would be augmented in the LPC context during the cognitive conflict task whereas the opposite would occur during the affective conflict task. We further hypothesized equivalent PC effects on the later parietal SP component during the cognitive and affective tasks.

Results

Behavioral performance. A 2 (Task: cognitive, affective) × 2 (Proportion congruent: high, low) × 2 (Congruency: congruent, incongruent) repeated measures ANOVA was conducted on the RTs (Fig. 1C) and error rates (Fig. 1D). There was no main effect of Task for either RTs or error rates, suggesting that the two tasks were comparable in difficulty. A main effect of Congruency was identified for both RTs ($F_{1,21} = 100.81$, $p < 0.001$, $\eta^2 = 0.83$) and error rates ($F_{1,21} = 15.09$, $p < 0.005$, $\eta^2 = 0.42$), revealing slower responses (657 ms vs. 613 ms) and more error rates (0.04 vs. 0.02) in response to incongruent than to congruent trials (i.e., the interference effect). Furthermore, significant interactions of Congruency × Task ($F_{1,21} = 5.12$, $p < 0.05$, $\eta^2 = 0.20$) and Congruency × Proportion congruent ($F_{1,21} = 28.33$, $p < 0.001$, $\eta^2 = 0.57$) were observed for RT. Follow-up analyses showed that the interference effect was found in both cognitive ($F_{1,21} = 80.44$, $p < 0.001$, Congruent vs. Incongruent: 616 ms vs. 666 ms) and affective ($F_{1,21} = 57.39$, $p < 0.001$, Congruent vs. Incongruent: 610 ms vs. 647 ms) tasks, with no significant difference between the magnitude of this interference effect in the two

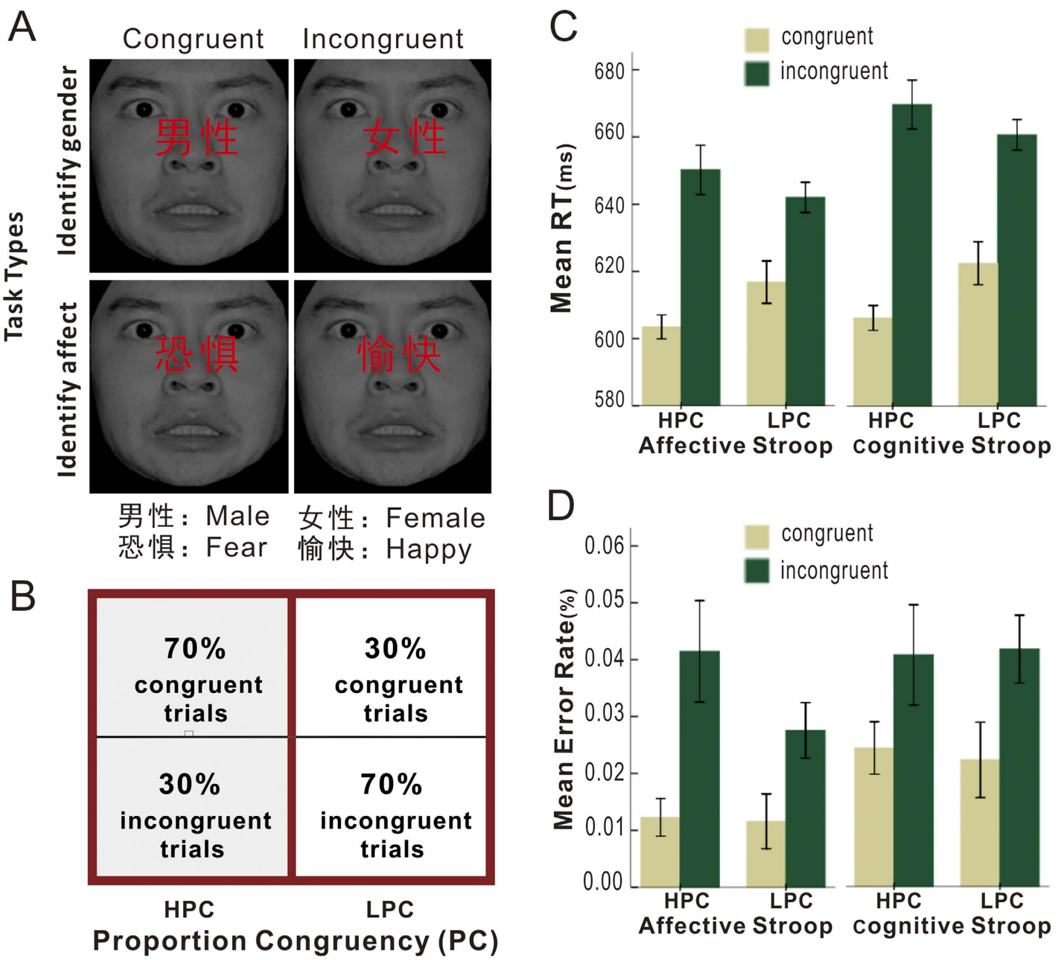

Figure 1. Experimental protocol and behavioral results. (**A**) The experimental design regarding Task types (cognitive task, affective task) and Stimulus congruence (congruence, incongruence). (**B**) Left panels: the high proportion congruency (HPC) block including 70% congruent trials and 30% incongruent trials; Right panels: the low proportion congruency (LPC) block including 30% congruent trials and 70% incongruent trials. (**C,D**) Left panels: mean RTs and mean error rates for congruent (yellow) and incongruent (green) trials in the HPC and the LPC contexts during affective task. Right panels: mean RTs and mean error rates for congruent (yellow) and incongruent (green) trials in the HPC and the LPC contexts during the cognitive task. The error bars represents one standard error.

tasks ($p > 0.05$). The interference effect was also found in both HPC ($F_{1,21} = 103.23$, $p < 0.001$, Congruent vs. Incongruent: 606 ms vs. 661 ms) and LPC contexts ($F_{1,21} = 56.11$, $p < 0.001$, Congruent vs. Incongruent: 620 ms vs. 652 ms) in the two tasks. In addition, a significantly larger interference effect was induced in the HPC context than the LPC one ($t_{1,21} = 3.45$, $p < 0.001$, 55 ms vs. 32 ms). No other significant main effects or interactions were found ($p > 0.05$) for RTs or error rates. These results showed that both the cognitive and affective tasks had robust interference effects which were modulated by the PC, as indexed by attenuated interference effects in the LPC context compared with the HPC one.

ERP Results. *N1.* There were no significant effects on N1 latency over the parieto-occipital areas ($p > 0.05$). For N1 amplitude, there was a significant interaction between Task, Proportion congruency, and Congruency ($F_{1,21} = 4.38$, $p < 0.05$, $\eta^2 = 0.17$). As shown in Table 1 and Fig. 2, larger negative deflections were elicited by congruent compared with incongruent trials only in the HPC context during the affective task ($F_{1,21} = 8.18$, $p < 0.01$), while there was no interference effect on N1 amplitude in other conditions ($p > 0.05$). No other significant main effects or interactions involving N1 amplitude were observed ($p > 0.05$).

N2. The latency of N2 over the fronto-central areas did not differ significantly across factors ($p > 0.05$). However, as shown in Table 1 and Fig. 2, N2 amplitude showed a marginally significant main effect of Congruency ($F_{1,21} = 3.19$, $p = 0.09$, $\eta^2 = 0.13$), such that larger negative deflections were elicited by incongruent (0.93 μV) than by congruent stimuli (1.19 μV). In addition, a significant interaction between Task, Proportion congruency, and Congruency was identified ($F_{1,21} = 8.62$, $p < 0.01$, $\eta^2 = 0.29$). Follow-up analyses revealed that larger negative deflections were elicited by incongruent than by congruent trials in the LPC context during the cognitive task ($F_{1,21} = 4.35$, $p < 0.05$) and in the HPC context during the affective task ($F_{1,21} = 6.58$, $p < 0.05$). In contrast, there

		Cognitive Stroop task				Affective Stroop task			
		HPC		LPC		HPC		LPC	
		Latency	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
N1	Congruent	106 (9)	−2.31 (2.09)	103 (11)	−2.39 (2.15)	103 (9)	−2.36 (2.17)	103 (11)	−2.38 (1.83)
(80–150 ms)	Incongruent	104 (10)	−2.43 (2.44)	102 (10)	−2.13 (2.08)	101 (12)	−1.91 (1.98)	103 (9)	−2.32 (2.03)
N2	Congruent	245 (20)	0.96 (3.60)	241 (17)	1.41 (4.06)	239 (17)	1.38 (3.81)	241 (19)	1.03 (3.91)
(220–280 ms)	Incongruent	244 (19)	1.25 (3.64)	242 (17)	0.81 (3.63)	241 (17)	0.79 (3.98)	241 (18)	0.85 (4.09)
SP	Congruent		3.15 (3.46)		3.61 (3.32)		3.45 (2.29)		3.77 (2.72)
(650–700 ms)	Incongruent		5.08 (4.02)		4.85 (3.39)		4.95 (3.35)		4.52 (2.90)

Table 1. Mean latencies (ms) and amplitude (μV) of N1, N2 and SP components elicited by the congruent and incongruent stimuli in the high and low proportion congruency contexts during cognitive and affective Stroop tasks. Standard deviations are shown in brackets. Note: high proportion congruency, HPC; low proportion congruency, LPC.

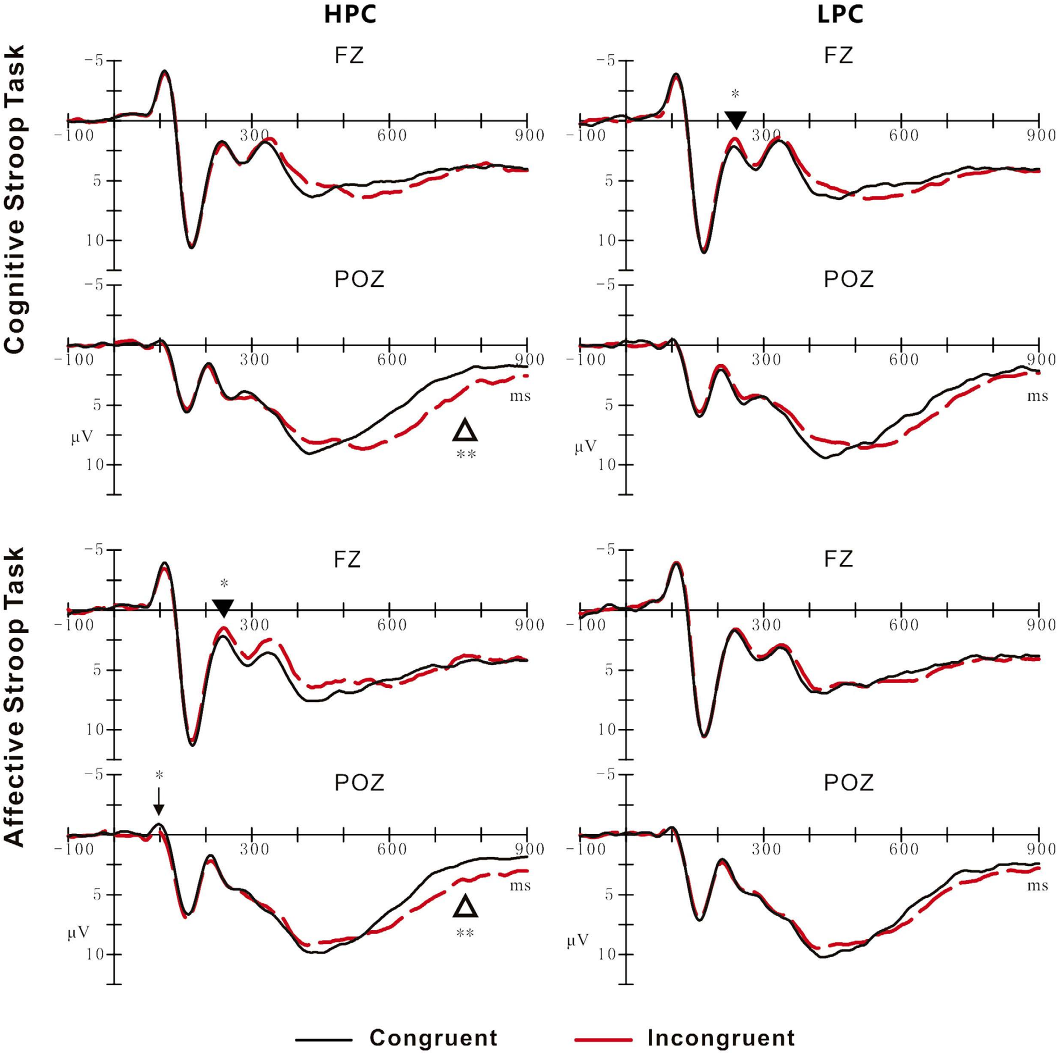

Figure 2. Grand average ERP waveforms at Fz and POz for congruent (black solid lines) and incongruent (red dot lines) trials in the high proportion congruency (HPC) (Left panels) and the low proportion congruency (LPC) (Right panels) contexts during the cognitive task (two top panels) and affective task (two bottom panels). Arrow = N1, Solid triangle = N2, open triangle = SP. $^{*}P < 0.05$; $^{**}P < 0.01$.

was no interference effect in the HPC context during the cognitive task ($F_{1,21} = 1.00$, $p = 0.33$) or in the LPC context during the affective task ($F_{1,21} = 0.64$, $p = 0.43$). Most importantly, a follow-up analysis computing the interference effect using incongruent minus congruent trials as the dependent variable revealed that the effect

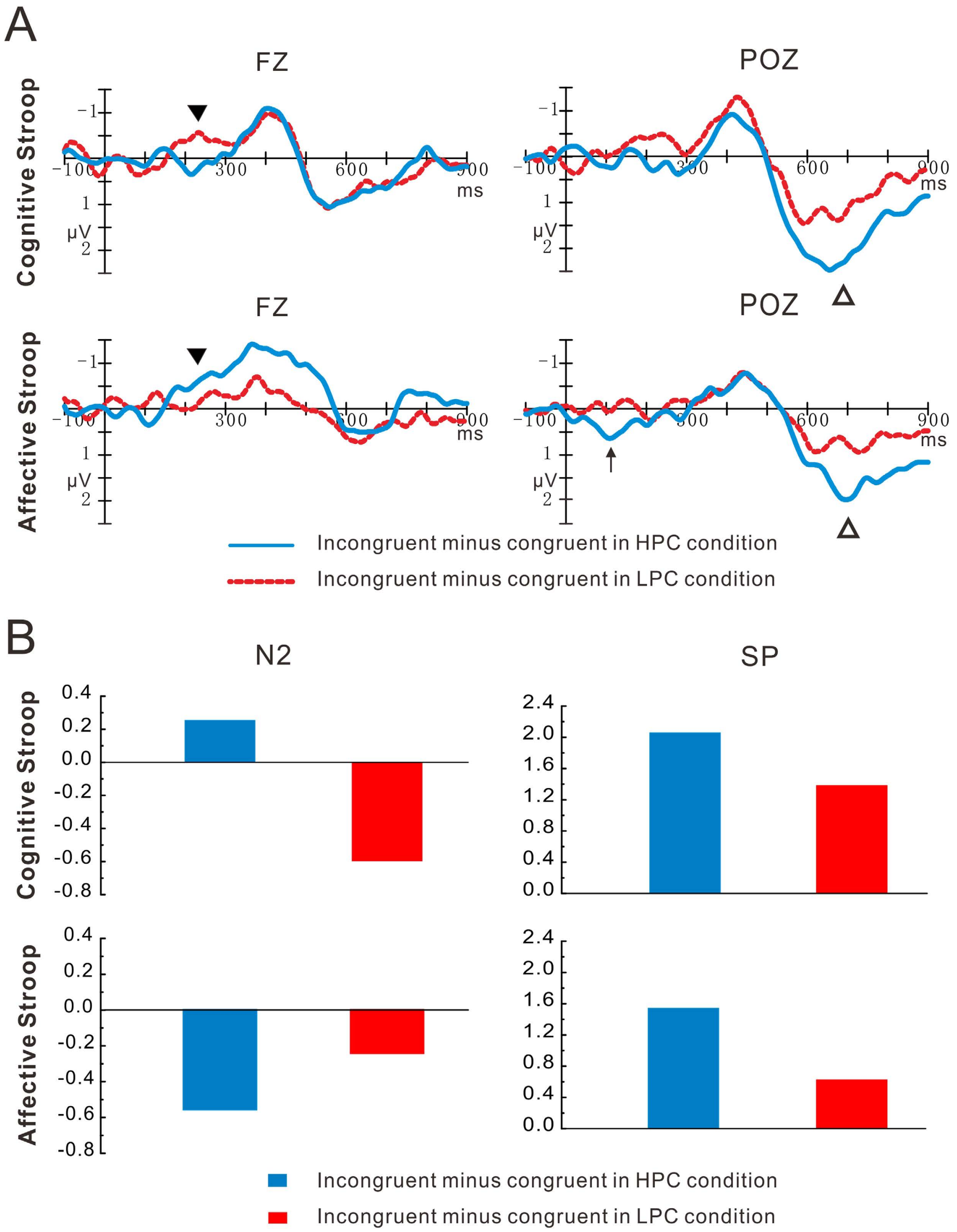

Figure 3. Dissociated effects of congruency context on N2 and SP during cognitive and affective tasks. (**A**) Difference waves at Fz and POz between incongruent and congruent stimuli in the high proportion congruency (HPC) (blue solid lines) and the low proportion congruency (LPC) (red dot lines) context during the cognitive (top panels) and affective tasks (bottom panels). Solid triangle for N2, open triangle for SP. (**B**) Histogram shows the effect of stimulus congruency (i.e., incongruency vs. congruency) on N2 amplitude (μV) (Left panels) and SP amplitude (μV) (Right panels) in the HPC (blue columns) and the LPC (red columns) contexts during the cognitive (top panels) and affective (bottom panels) tasks.

was larger in the LPC context ($-0.60\,\mu V$) than the HPC one ($0.30\,\mu V$) during the cognitive task, $F(1, 21) = 5.62$, $p < 0.05$, but was smaller in LPC context ($-0.18\,\mu V$) than HPC one ($-0.59\,\mu V$) during the affective task, $F(1, 21) = 4.72$, $p < 0.05$. Thus, the N2 showed an opposite modulation of the PC effect during the cognitive and affective tasks (Fig. 3). As illustrated in Supplementary Fig. 2A, the opposite pattern of the PC effect was also revealed clearly in the N2 voltage maps from the central brain area during the cognitive and affective tasks. No other significant main effects or interactions involving the N2 amplitude were observed ($p > 0.05$).

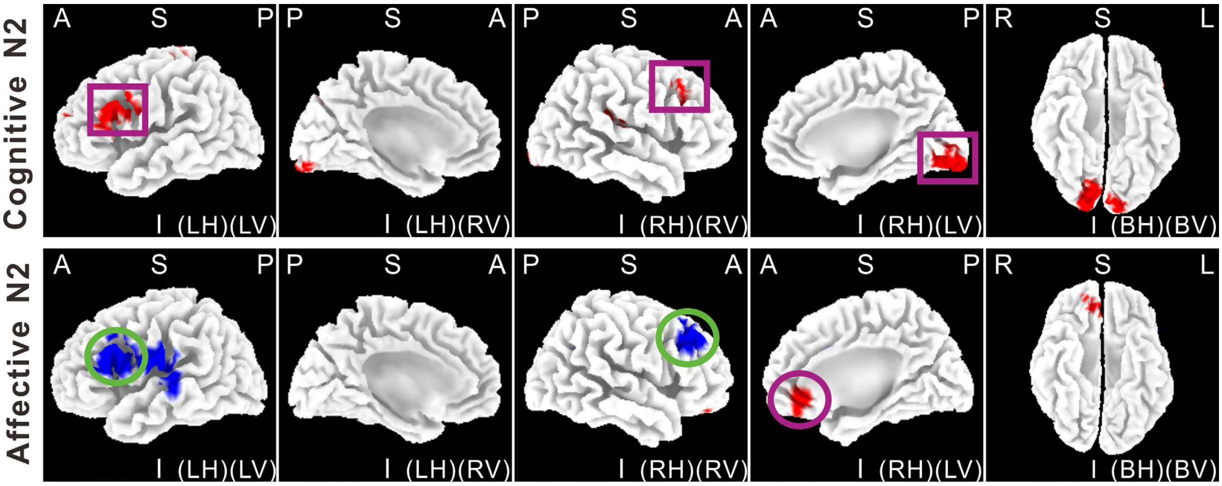

Figure 4. The sLORETA source localization for the difference waves (incongruency minus congruency) of the N2 component between the low and high proportion congruency contexts during cognitive task (top panels) and affective tasks (bottom panels). The image of N2 corresponds to 220 – 280 ms post-stimulus latency. A = anterior. P = posterior. S = superior. I = inferior. LH = left hemisphere. RH = right hemisphere. BH = both hemispheres. LV= left view. RV = right view. BV = bottom view. Red: the maximum activation, Blue: the minimum activation. Square: cognitive task, Circle: affective task.

SP. As shown in Table 1 and Fig. 2, SP amplitude exhibited a significant main effect of Congruency ($F_{1,21} = 43.90$, $p < 0.001$, $\eta^2 = 0.68$), with a larger amplitude being elicited by incongruent trials (4.50 μV) than by congruent ones (3.50 μV). Furthermore, a significant interaction between Congruency and Proportion congruency ($F_{1,21} = 4.55$, $p < 0.05$, $\eta^2 = 0.18$) was identified. Planned comparisons indicated that a larger SP amplitude was elicited by incongruent trials than by congruent ones in both the HPC context ($F_{1,21} = 28.52$, $p < 0.001$, 5.01 μV vs. 3.30 μV) and the LPC one ($F_{1,21} = 26.81$, $p < 0.001$, 4.68 μV vs. 3.69 μV). In addition, as shown in Fig. 3, the interference effect on the SP was larger in HPC context than in LPC one ($F_{1,21} = 4.55$, $p < 0.05$, $\eta^2 = 0.18$; 1.71 μV vs. 1.00 μV). No other significant main effects or interactions on SP amplitude were observed ($p > 0.05$). Supplementary Fig. 2A shows that the positive voltage distributed over the parieto-occipital surface of the skull in the HPC context was stronger than that in the LPC context during both cognitive and affective tasks.

Correlational analyses. To verify whether ERP components were associated with performance on the conflict tasks, we conducted Pearson's correlation analyses between conflict-related ERP amplitude and the behavioral response interference in each context. The interference effects of RT were not correlated with N1 or N2 amplitude ($p > 0.05$). However, interference effects of RT were significantly correlated with the conflict-related SP amplitude in the HPC context during both the cognitive ($r = 0.562$, $p = 0.006$) and affective conflict tasks ($r = 0.555$, $p = 0.007$).

LORETA Results. Figure 4 shows the LORETA solution of the N2 difference wave between the LPC and HPC contexts during cognitive and affective conflict processing. During the cognitive task, the maximum activation was localized at the inferior frontal gyrus (X = 15, Y = −93, Z = −8, BA 9 and 45), and lingual gyrus (BA 17 and 18). Its minimum activation was localized at the superior temporal gyrus (X = 54, Y = −62, Z = 26, BA39). During the affective conflict task, the maximum activation was localized at the anterior cingulate gyrus (X = 15, Y = 43, Z = −6, BA 32) and medial frontal gyrus (BA 10). Its minimum activation was localized at the middle frontal gyrus (X = 35, Y = 31, Z = 31, BA9).

Discussion

The primary purpose of the current study was to investigate the influence of PC (i.e., the relative proportion of congruent and incongruent trials) on temporal processing dynamics during cognitive and affective control tasks. Behavior and EEG data were recorded when participants performed cognitive and affective face-word Stroop tasks. We observed comparable interference effects in these two tasks, such that performance of participants was impaired by the incongruent compared to congruent stimuli. Furthermore, our study identified PC modulation of interference effects, in that the behavioral Stroop effect was attenuated in the LPC context compared to the HPC one. HPC context might induce increased global attention for irrelevant words, as well as the predictability of context congruency, leading to enhanced interference effects. In contrast, LPC context might increase focal attention on the task-relevant stimuli (i.e., gender or expressions of faces)[1], leading to attenuated conflicts.

The PC effect on different stages of cognitive and affective conflict processing was examined with conflict-related ERP components. Firstly, the amplitudes of early N2 and the late SP components were modulated by the PC; secondly, the modulatory effect of PC exhibited opposite patterns on both N2 potentials and their activity generation (i.e., DLPFC) for cognitive and affective tasks. In contrast, similar PC effects were identified at late SP components in the cognitive and affective tasks. These results are consistent with our recent findings[34] using cognitive and affective flanker tasks, thereby providing two independent demonstrations for the existence of both different and similar temporal dynamics between cognitive and affective conflict processing.

Dissociable Early Attentional Control Mechanisms Underlying Cognitive and Affective Conflict Processing. In the cognitive word-face Stroop task, a stronger conflict-related N2 effect was observed in the LPC than HPC context, which is consistent with previous studies using similar cognitive conflict tasks[9,10,34]. The patterns of N2 amplitude in cognitive conflict processing may be attributed to broad attentional and habitual responses to the word and the face components when subjects are expected to process frequent congruent stimuli. Thus, an infrequent incongruent stimulus in the HPC context might elicit sudden and rapid attentional shifts leading to faster responses and an attenuated N2 component. However, when subjects are required to process frequent incongruent stimuli they will predictably and strategically increase their attentional focus on face identification in order to reduce the amount of conflict that they experience. Thus the potential inclination to read the word could be persistently overcome in early conflict processing and this proactive processing eventually benefits response generation, resulting in an enhanced N2 effect in the LPC context[7,34].

However, in the affective Stroop task, the attentional control mechanism may be different due to the prioritizing and permanence of emotional information[22,39–42]. In the HPC context, the facilitation of irrelevant emotional words in frequent congruent trials may reduce the attentional requirement for target responses resulting in enhanced emotional engagement, because more residual attentional resources are focused upon irrelevant the emotional words as well as the relevant emotional faces. Thus, the top-down attentional selection of the target face expression from the ignoring distractor of emotional words in rare incongruent trials may be in competition with ongoing emotional engagement[25,26], resulting in an enhanced N2. This may reflect an increasing attentional demand to resolve the competition between distractor inhibition and affective processing[25,26,31]. In contrast, in the LPC context during the affective task, most attention resources are initially focused upon the inhibition of the emotional distractor words, and this inhibition persists throughout the entire processing period, even in the congruent trials, resulting in an attenuated N2 effect. Overall, these affective findings suggested the presence of an interaction between emotional processing and top-down attentional selection under the modulation of PC in conflict processing[20,43].

Consistent with previous studies[17,18], the cognitive N2 effects were generated at both DLPFC and sensory cortex. A previous fMRI study has also reported sustained activity of the DLPFC modulated by PC context in a cognitive conflict task[44]. This suggests that conflict with non-emotional stimuli is resolved by the enhancement of a relevant stimulus representation in the sensory cortex followed by top-down control from DLPFC[26,45,46]. This conclusion is supported by the findings of larger N170 and N300 ERP components in the cognitive conflict task (see more details in Supporting Materials), suggesting that increased attentional resources were engaged in face perception and categorization during the face gender identification task[47–49]. In contrast, during the affective conflict task N2 effects were generated at DLPFC and rACC suggesting that increased attentional resources were engaged in inhibition of face expression identification during the task[50,51]. Importantly, the opposite PC effects on N2 amplitude in cognitive and affective tasks were localized in the DLPFC, with activity increased in the cognitive task but reduced in the affective one. Overall, these findings cannot be explained by the dominant conflict control theory[12] which proposes that dACC is activated first and drives DLPFC in cognitive control and that dACC drives rACC in affective control[26] when conflict is increased. A novel and more integrated hypothesis which can incorporate both the similarities and differences between neural processing of cognitive and affective conflict is therefore needed.

Notably, a more negative N1 component was evoked by congruent than incongruent trials in the HPC context during the affective task, which is consistent with our previous study[34]. This is an interesting finding which may reflect variable attentional engagement in relation to emotional information in the HPC context. The most likely interpretation of the attentional mechanism is that there are effects of perceptual or attentional additivity involved when individuals pay attention to facial affect, see congruent information, and have many congruent trials to learn this congruency and respond to it visually. This supports our proposal that emotionally-induced additivity may compete with conflict detection for the rare incongruent trials which produce larger N2 effects in the HPC context in the affective task. Alternatively, such changes might reflect the complexity of attentional selection for emotional information under low attentional focus, a possibility that needs to be clarified in future studies using different manipulations of attentional anticipation.

Similar Late Response System Associated With Cognitive and Affective Control. In the present study, the SP component showed similar patterns of modulation by the PC effect during cognitive and affective tasks, which is also consistent with observations in our previous study[34]. Moreover, the SP effect correlated positively with response interference only in the HPC context during both tasks, suggesting that the SP may represent the response stage of conflict processing[13,19,34,52]. This conjecture echoes topographical findings showing a positive voltage distributed over the parieto-occipital surface of the skull since the SP was positively activated in the inferior parietal lobe during the two tasks (see more details of the discussion on SP localization in Supporting Materials). The inferior parietal lobe may be involved in controlling goal-directed behaviors and execution of action[53–55]. Our current experimental findings therefore directly support the widely held view that the SP reflects conflict resolution in cognitive[13,14,19,56] and affective[34,57] conflict tasks.

Conclusion

In summary, in addition to the PC effects on behavior demonstrated using Stroop tasks, the current study also found different early attentional processing but similar late response processing for cognitive and affective conflict tasks involving N2 and SP evoked potential components respectively. These results suggest that cognitive and affective controls share a similar conflict response system but dissociable early attentional control mechanisms.

Material and Methods

Participants. Twenty-two young healthy adults (10 females, mean age = 21.80 years, SD = 1.91 years, range 19–25 years) were paid to participate in this study. All subjects were right handed and had normal or corrected to normal vision by self-report. None had any reported history of neurological or psychiatric diseases. The research protocol was approved by the ethics committee of Beijing Normal University. Written informed consent was obtained from all participants prior to the study, which was approved by the Institutional Review Board of Beijing Normal University Imaging Center for Brain Research. The methods were conducted in accordance with approved guidelines.

Stimulus material and experimental task. A total of 32 human face pictures, including 16 (8 females and 8 males) depicting a happy expression and 16 (8 females and 8 males) depicting a fear expression, were selected from the Chinese Affective Picture System[58]. Participants performed two modified versions of face-word Stroop tasks. In the cognitive face-word Stroop task, faces were presented with either the Chinese word "男性" ("nanxing", means male) or "女性" ("nǚxing", means female) superimposed across the face (Fig. 1A, top panels), producing gender-congruent and -incongruent stimuli[26]. In the affective face-word Stroop task, faces were presented with the Chinese word "恐惧" ("kongju", means fear) or "愉快" ("yukuai", means happy) superimposed across the face (Fig. 1A, bottom panels), such that the word and facial expression were either congruent or incongruent[26,59]. Participants were required to categorize the gender or expression of faces while trying to ignore the task-irrelevant word stimuli. The words were in red and projected approximately across the center of the faces (i.e. across the nose region). The size of the Chinese characters in bold was about 1° (horizontal) × 1° (vertical).

Experimental procedure. All participants performed both the cognitive and affective Stroop tasks, with the order of tasks being counterbalanced across subjects. Each task consisted of three sessions, and each session included four blocks with two kinds of PC: two blocks with a HPC context consisting of 70% congruent and 30% incongruent trials; and two blocks with a LPC context consisting of 70% incongruent and 30% congruent trials (Fig. 1B). Each block consisted of 52 randomly presented trials. The two PC contexts were presented in an ABBA or BAAB order which was counterbalanced across subjects. Half of the participants responded to the fearful or male faces with the index finger and to the happy or female faces with the middle finger of their right hand, and the opposite mapping was used for the other half of the participants. Consistent with our previous study[34], each trial began with a 1500 ms fixation (white cross) followed by a 1500 ms photographic stimulus (3.5° wide and 5° high) on the center of the black screen. During the presentation of stimuli, participants were instructed to respond as quickly and accurately as possible. The stimulus disappeared once a subject's response was made. All participants achieved above 85% accuracy on the 20 practice trials prior to the formal experiment. The tasks were programmed in E-Prime (Psychology Software Tools, Inc.) and run using a Hewlett-Packard (HP) Pavilion f523 computer with a 17- inch color CRT monitor.

We controlled for: (i) stimulus repetition[60] by using alternative target stimuli across trials (i.e., a face picture would not be repeated in the following trial), (ii) response repetitions[26] by employing alternate responses to target stimuli across trials (i.e., a response to a face picture would not be repeated in the following trial) and keep the same proportion (50%) of response alternations to target faces for all congruency trial types, and (iii) negative priming[61] by avoiding direct repetitions of the same face with varying word distracters (i.e., the distractor word in the present trial would be different with the response to a target face judgment in the following trial). Furthermore, there was no category switch cost[62] on the time course of cognitive and affective conflict processing (see also Supplemental Methods and Discussion for more details about the control analysis)

Electrophysiological data recording and processing. The electroencephalogram (EEG) was recorded from 64 scalp sites using tin electrodes mounted in an elastic cap (NeuroScan Inc., Herndon, Virginia, USA) according to the international 10/20 system. The left mastoid was used as reference electrode. All electrode impedances were below 5 kΩ. The EEG was online sampled at an A/D rate of 500 Hz/channel and a band-pass of 0.05–100 Hz. A 30 Hz low-pass filter was used offline. Trials with signals exceeding ± 80 μV were automatically excluded from the average. See Supplemental Methods for more details about the recording procedure.

Data analysis. Error trials, post-error trials and the first trial of each block were excluded from analyses of both the RTs and ERP data. This cut-off procedure excluded 9.8% of all the trials. The number of epochs included in the ERP averages was above 75 for each condition.

We selected the time window and electrode sites for different components on the basis of (i) previous relevant studies[11,34], (ii) visual inspection of the topographical distribution of grand averaged ERPs, and (iii) difference waves for each subject. The following components were analyzed: N1 (80–150 ms) at CP3, CPz, CP4, P3, Pz and P4 electrode sites, N2 (220–280 ms) at F3, Fz, F4, FC3, FCz and FC4 electrode sites, as well as the conflict SP (650–750 ms) at P3, Pz, P4, PO3, POz and PO4 electrode sites. In light of previous studies, the peak latencies (time duration from stimulus onset to the peak of each component) and baseline-to-peak amplitude were measured and analyzed for N1 and N2 components, while mean amplitude was measured and analyzed for SP to make current results comparable to previous findings[11,34]. To compare the time course of cognitive and affective conflict processing, we also analyzed N170, P1, N300 and P300, the main task specific ERP components[47–49] (see Supplemental Methods and Discussion for more details about the analysis of task specific components). Segments of 100 ms before and 900 ms after the onsets of stimuli were extracted for each component from the continuous EEG, and the pre-stimulus baseline was removed.

A 3-way repeated measures analysis of variance (ANOVA) on the amplitude and latency of each component was conducted with following independent variables: Task (cognitive, affective), Proportion congruency (high, low), Congruency (congruent, incongruent). The dependent variables were the average values of all electrode sites selected for each ERP component. Bonferroni correction for the p-values was used to control for multiple comparisons, and p values were corrected by Greenhouse–Geisser if necessary. Differences were considered significant at $p < 0.05$, and partial-eta^2 (η^2) is reported as a measure of effect size. All statistical analyses were carried out with SPSS (Version 17.0, Chicago, SPSS Inc.).

LORETA source localization method. In order to investigate the localization of the generators of PC effects during conflict processing, we carried out an sLORETA analysis using differences in the ERP components[63]. This method has no localization bias and provides a genuine inverse solution with exact, zero error localization. It is capable of imaging standardized current density with nearly zero localization error. The electrical potential lead field was calculated using the boundary element method[64]. Electrode coordinates were registered to the digitized Montreal Neurological Institute (MNI) standard brain[65]. Talairach space was used to represent the electrical activity of each voxel[66]. The cortical surface was based on Van Essen average cortex[67]. For details of the sLORETA analysis, see also[34] and Supplemental Methods.

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Author Contributions

T.C., Q.G. and Y.L. designed the study. T.C., S.S. and S.Y. performed the data collection. T.C., C.F., S.S. and P.V. analyzed the data. T.C., X.Y., X.W. and W.B. prepared figures. T.C., K.K., C.F., Y.L. J.F., X.H. and Q.G. wrote the manuscript. All authors participated in the revising of the manuscript.

Additional Information

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Moral judgment modulates neural responses to the perception of other's pain: an ERP study

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Morality and empathy are both crucial in building human society. Yet the relationship between them has been merely explored. The present study revealed how the morality influenced empathy for pain by comparing the ERPs elicited by pictures showing the targets' in pain primed by different moral information about the targets. We found that when the target was a moral one or a neutral one, the painful pictures elicited significantly larger amplitude in N2 than the non-painful pictures, but when the target was an immoral one, the difference between the amplitudes of N2 component elicited by painful and non-painful pictures became insignificant. We proposed that this effect was induced by the decreased affective arousal when observing an immoral person in pain. The reduced neural response towards the immoral one's pain can keep us alert when we face the potentially dangerous people thereby increasing our chance of survival. SLORTEA results showed the source of this difference in N2 localized in the ventral medial prefrontal cortex (vmPFC) and the rostral anterior cingulate cortex (rACC) areas.

Morality is a code of values and customs that guide social conduct, which is innate to the human brain[1]. Morality is a fundamental component of human cultures and has been defined as prescriptive norms regarding how people should treat one another, including concepts such as justice, fairness, and rights[2]. It seems that human beings always perceive and evaluate others intuitively as morally laden[3,4]. Studies have shown that when people form the first impression of a person or a group, they are more interested in their traits concerning morality than traits concerning competence and sociality[5]. Neuroimaging studies found two regions were critical in moral judgment: the amygdala and the ventral medial prefrontal cortex (vmPFC). The former one is mainly engaged in guiding behaviors based on bottom-up, stimulus-based information which is emotionally salient and the role of the latter one is more integrative and modulated by present goals[6,7].One study found that viewing scenes that evoked moral emotions (e.g. physical assaults, poor abandoned children) activated the vmPFC[8]. And study comparing patients with bilateral damage of the vmPFC with neurologically normal control group found that for personal moral dilemmas, the patients with vmPFC damage were more likely to endorse the proposed action[9].

Empathy is defined as the ability to vicariously share the affective states of others, thereby facilitating our comprehension of the affections, motivations and actions of others[10,11]. Neuroimaging evidence suggests that there are two components of empathy which are subserved by distinct brain networks[12]. The affective component of empathy has been framed as reflecting rapid bottom–up activation of subcortical/cortical circuitries with neural underpinnings in the mirror neuron system (i.e. intra-parietal lobule, inferior frontal gyrus (IFG) and dorsal premotor cortex) and the limbic system (i.e. amygdala, ACC, anterior insula and ventral striatum[13–16]. The cognitive component of empathy, on the other hand, has been shown to be influenced by higher-level, top–down, signals originating in prefrontal cortical circuitries[12,14]. ERP studies found that both early (N1, N2) and later (P3) ERP components were revealed from the comparison of observing others receiving painful stimuli to non-painful stimuli[17–19]. N2 component has been consistently reported in observing other's physical pain and has been suggested as a biomarker of the affective component of empathy for pain[20]. The gender difference in empathy for pain was found on N2 component, where the females who were more empathic show enhanced amplitudes on N2 than males[43]. The amplitude of N2 was also significantly correlated with subjective rating of affective empathy and scores in Empathic Concern Scale[21,22].

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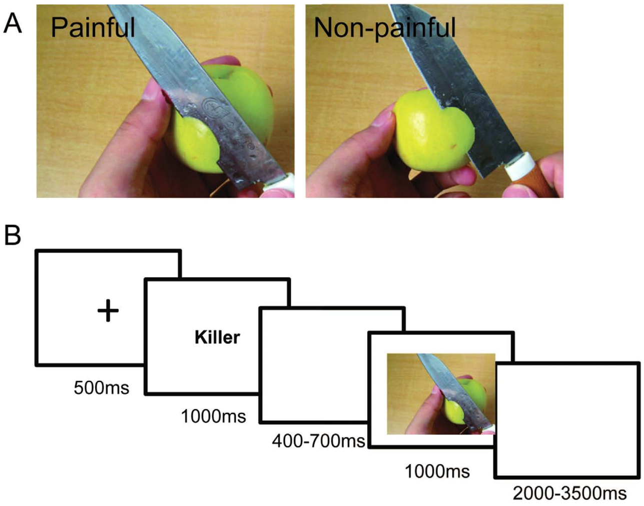

Figure 1. Experimental design (**A**) an example of the picture stimuli used in the experiment. The Left side shows a painful picture and the right side shows a non-painful picture. (**B**) an example of a single trial.

There is a complex relation between morality and empathy based on the literature from developmental, behavioral psychology, and social neuroscience[23]. Empathy plays an important role in morality by two ways: first, empathy allows humans to understand how others are emotionally affected by given actions, which can directly inform people to make moral decisions in the next step; secondly, empathy can motivate people to behave in accordance with moral principles such as maximizing the well-being of others or not inflicting harm to others[23–25]. Meanwhile, it is reasonable to suppose that morality also has a strong effect on empathy. When facing immoral persons, we would try not to get involved with their emotions and feelings since the immoral persons are more likely to be dangerous. Keeping alert and emotionless to immoral ones would be better for our own safety. This assumption was supported by the evidence that reduced empathic responses were observed when viewing unfair person's pain, compared to viewing the pain of a fair one[26]. However, how morality modulates empathy has not been explored from the temporal aspect yet, as far as we know.

To address this question, the present study used a word-priming paradigm, where the participants were primed with words describing different moral information about the characters preceding pictures depicting people's hand/forearm/foot under painful or non-painful conditions. There were three kinds of characters: the 'moral' one (Blood donor), the 'immoral' one (Killer) and the 'neutral' one (Unidentified). To explore the influence of morality on empathy, we compared the differences between the ERP components of different conditions during the presentation of the pictures. We hypothesized that if there was a reduced empathic responses when observing immoral person's pain then a reduced N2 would be observed in the presentation of painful pictures primed by immoral cue (i.e. Killer) comparing to the presentation of painful pictures primed by moral and neutral cues (i.e. Blood Donor and Unidentified).

Methods

Participants. Twenty-eight right-handed participants (14 male, 21.54 ± 2.25y (mean ± S.E.)) with no history of neurological disorders, brain injury or developmental disabilities participated in the experiment. All of them have normal or corrected to normal vision. All participants signed an informed consent form before the experiment. The experiment was conducted in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194) and was approved by the Medical Ethical Committee of the Medical School of Shenzhen University, China.

Stimuli. The stimuli used in the experiment were pictures showing a person's hands/forearms/feet in painful or non-painful situations, which have been used in previous ERP studies. All the situations depicted in these pictures were ordinary events in daily life (Fig. 1A, Left). All the events showing in the non-painful pictures were corresponding to these in the painful ones just without the nociceptive component (Fig. 1A, Right). There were 60 painful pictures and 60 non-painful pictures in total. All of them had the same size of 9 × 6.76 cm (width × height) and 100 pixels per inch. 9-point Likert scales were used to evaluate the pain intensity, emotional valence and arousal level of each picture, the results of the evaluation can be accessed from the original papers[17,19].

Experimental procedures. Participants sat in a dark and quiet room alone during the recording. A 15-inch color monitor was placed in front of him/her. During the task, the pictures were presented in the center of a white background. Each stimulus was presented with a size of 22.5 × 16.9 cm (width × height), subtending a visual angle of 12.8° × 7.7°at a viewing distance of 100 cm.

It was a 3 × 2 within-subjects design. The first factor was moral information, which was manipulated by the priming words at three levels: the "Killer", the "Blood Donor" and the "Unidentified". The second factor was the pictures: "Painful" pictures and "Non-painful" pictures. During the recording the participants observed the pictures appearing randomly. Before the appearance of the pictures, participants would see a priming word informing them the moral information of the person in the following picture. The participants were instructed to image the person in the picture was the same character they were informed by the priming word. In order to help the participants imagine, before the recording, they were given two news reports to read: one describing the terrorists killing innocent passengers in a train station; the other one describing college students voluntarily donate their blood to help people.

In each trial, a fixation was presented for 500 ms, followed by the priming word lasting for 1000 ms. Then a blank interval was presented for 400 ms to 700 ms randomly. Subsequently, the picture was presented for 1000 ms. There was an interval of 2000 to 3500 ms between trials (Fig. 1B). In order to avoid the lack of attention due to the passive observation task, the participants were required to answer questions about the priming word or the picture randomly (12.5% of the trials were followed by a question). The participants were instructed to answer them by pressing the button "1" or "2" on a keyboard placed in front of them. For example, the question could be "What is the identity of the person?" Two choices appeared below the question: "Killer" and "Unidentified". If they believed "Killer" was the correct answer, they would press button "1" otherwise they would press button "2". There were 360 trials separated into 3 sessions evenly. Each single picture was repeated 3 times. There was a 30 seconds rest between sessions.

The participants were given a written instruction of the task and enough practice before the EEG recording to ensure the task was fully understood. The pictures appeared during the practice were excluded from the task. After the EEG sessions the participants were asked to subjectively evaluate the moral level of the three characters (Killer; Blood Donor; Unidentified) on a 9-point Likert scale (1: the most immoral; 9: the most moral; 5: neither immoral nor moral).

EEG acquisition and analysis. Electroencephalography (EEG) data were recorded from a 64-electrodes scalp cap using the 10–20 system (Brain Products, Munich, Germany). Left side of mastoid was used as reference and the electrode on the medial-frontal site was used as ground. Three electrodes were used to measure the electrooculogram (EOG) (for horizontal EOG, electrode was placed on the outer canthus of the left eye; for vertical EOG, the electrode was placed below the left eye). EEG and EOG activity was amplified at 0.01 Hz ~ 100 Hz band-passes and sampled at 250 Hz. All electrode impedances were maintained below 5 kΩ.

EEG data were pre-processed and analyzed using Matlab R2011b (MathWorks, US) and EEGLAB toolbox[27]. EEG data at each electrode were re-referenced to the average of the left and right mastoids before further analysis. Then the signal passed with 0.01–30 Hz band-pass filter. Time windows of 200 ms before and 1000 after onset of picture stimuli were segmented from EEG. And the time window of 200 ms before and 1000 after the onset of the priming word stimuli were also segmented. EOG artifacts were corrected using an independent component analysis (ICA)[28]. Epochs with amplitude values exceeding $\pm 50\,\mu V$ at any electrode were excluded from the average. These epochs constituted $5 \pm 2.7\%$ of the total number of epochs.

Further statistical analysis was conducted in IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). For ERP data, based on previous ERP studies using the same stimuli and voltage scalp maps in the current results the following electrodes were included for further analysis: F4, FC4, C4,CP4, and P4 (five right sites); Fz, FCz, Cz, CPz, and Pz (five midline sites); F3, FC3, C3, CP3, and P3 (five left sites)[17,19,29]. Repeated measures ANOVA (2 (Picture: Painful/Non-Painful) × 3 (Moral information: Unidentified/Killer/Blood Donor) × 3 (regions: left/midline/right) × 5 (electrodes)) were performed for each component of the picture stimuli epochs and for each component of the priming word stimuli epochs separately. Mean amplitudes were obtained from each grand-averaged peak. Degrees of freedom for F-ratios were corrected according to the Greenhouse–Geisser method. Statistical differences were considered significant at $p < 0.05$; post-hoc comparisons were Bonferroni-corrected at $p < 0.05$.

Based on the scalp-recorded electric potential distribution, the standardized low resolution brain electromagnetic tomography (sLORETA) software was used to compute the cortical three-dimensional distribution of current density. The sLORETA method is a properly standardized discrete, three-dimensional (3D) distributed, linear, minimum norm inverse solution[30,31]. In order to visualize the likely neural generators of scalp voltages within these temporal windows where the significant effect were found, the grand average was imported into sLORETA and the source estimation during these time windows were generated.

Results

Behavioral data. In order to keep the participants attended, we randomly inserted questions in trials during the task. The percentage of trials with questions was 12.5%. The accuracy of all participants was $96.270 \pm 2.81\%$ (mean ± SE). The rating of moral information of "Blood Donor" was significantly higher than "Killer" (Blood Donor: 8.067 ± 0.214; Killer: 2.333 ± 0.237 (mean ± S.E.); $t_{(87)} = 7.99$, $p < 0.001$). We didn't report the subjective rating of the "Unidentified" here because all of the first 9 participants raised the question about how to rate an unidentified character therefore we didn't ask the latter 19 participants to rate it.

ERPs. The grand averaged ERPs to pictures and priming words were computed separately for each condition. There are six conditions in total: "Unidentified" followed by painful picture (U_P); "Unidentified" followed by non-painful picture (U_NP); "Killer" followed by painful picture (K_P); "Killer" followed by non-painful picture (K_NP); "Blood Donor" followed by painful picture (B_P); "Blood Donor" followed by non-painful picture (B_NP).

ERPs to picture stimuli. ERPs for picture stimuli displayed a negative component from 120 ms to 170 ms (N1) over the frontal and central regions, a positive component from 180 ms to 230 ms (P2) over the central region, a negative deflection from 240 ms to 290 ms (N2) over the frontal and central regions, a positive component from 350 ms to 450 ms (P3) over the parietal area and a late positive deflection from 500 ms to 700 ms (LPC) over the central and parietal regions.

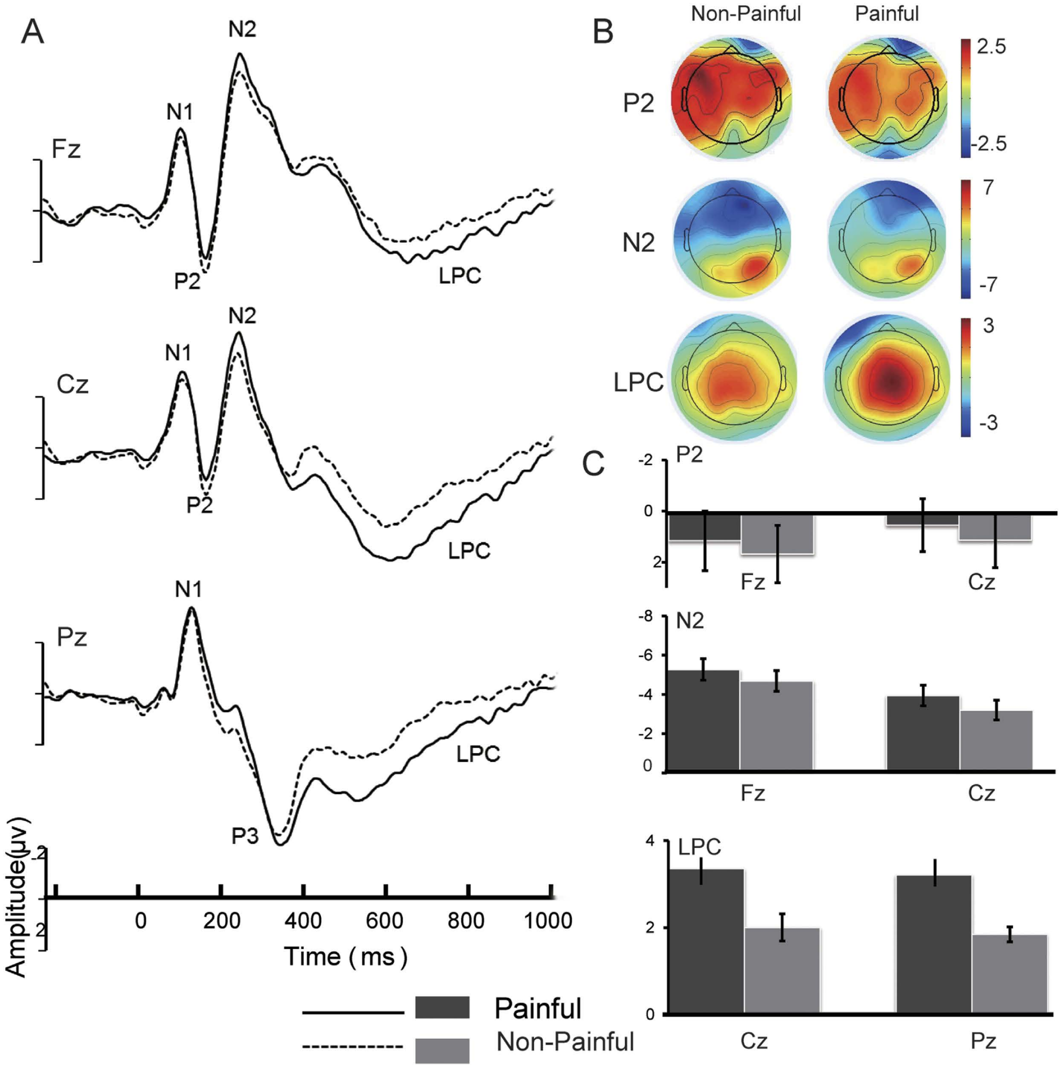

Figure 2. Cortical responses to painful and non-painful stimuli. (**A**) ERPs elicited by the painful stimuli were significantly decreased relative to those elicited by non-painful stimuli in the P2 window. ERPs elicited by the painful stimuli were significantly increased relative to those elicited by non-painful stimuli in N2 and LPC windows. (**B**) The Voltage scalp maps for P2, N2 and LPC in non-painful and painful conditions; (**C**) The averaged amplitudes within the P2, N2 and LPC time window in each conditions.

The main effect for pictures was significant in three components: P2, N2 and LPC. For P2 components, the non-painful pictures elicited a more positive deflection than painful pictures ($F_{(1,\,27)} = 10.273$, $p = 0.003$). For region ($F_{(2,\,54)} = 4.279$, $p = 0.019$) demonstrated P2 component, larger amplitudes were observed over the left than the right brain region ($p = 0.020$), but not the central region ($p = 0.295$). For N2 component, the painful pictures elicited a larger negative waveform than the non-painful pictures ($F_{(1,\,27)} = 19.263$, $p < 0.001$). For region ($F_{(2,\,54)} = 8.077$, $p = 0.001$) shown N2 component, the most negative deflection was found in the midline region than in the left and right region ($p = 0.001$, $p = 0.012$). For electrode ($F_{(4,\,108)} = 54.592$, $p < 0.001$) in N2 component reveals the presence of N2 component over the frontal and central areas. For LPC component, the painful pictures elicited a larger positive deflection than the non-painful pictures ($F_{(1,\,27)} = 16.745$, $p < 0.001$). For region ($F_{(2,\,54)} = 10.353$, $p < 0.001$) shown LPC component, the largest positive deflection was found in the midline region than the left and right region ($p < 0.001$, $p = 0.001$). For electrode ($F_{(4,108)} = 17.011$, $p < 0.001$) reveals the presence of LPC in the central and parietal areas, but not in the frontal area (Fig. 2).

Critically, the effect for morality on empathy was found in the N2 component. The Morality × Picture interaction ($F_{(2,\,54)} = 3.502$, $p = 0.044$) indicated that the amplitude of N2 on pictures varied by moral information. By using pairwise comparisons, we found that when the priming word was “Unidentified” and “Blood Donor”, the painful pictures elicited a significantly more negative waveform than the non-painful pictures ($p = 0.017$, $p < 0.001$). However, the same comparison failed to reveal any significant differences between the two kinds of pictures on N2 when the priming word was ‘Killer’ ($p = 0.244$) (Fig. 3A).

In order to identify whether the change of difference between painful and non-painful pictures in different moral levels is due to the change in the painful stimuli or non-painful stimuli, or both, we separated the painful

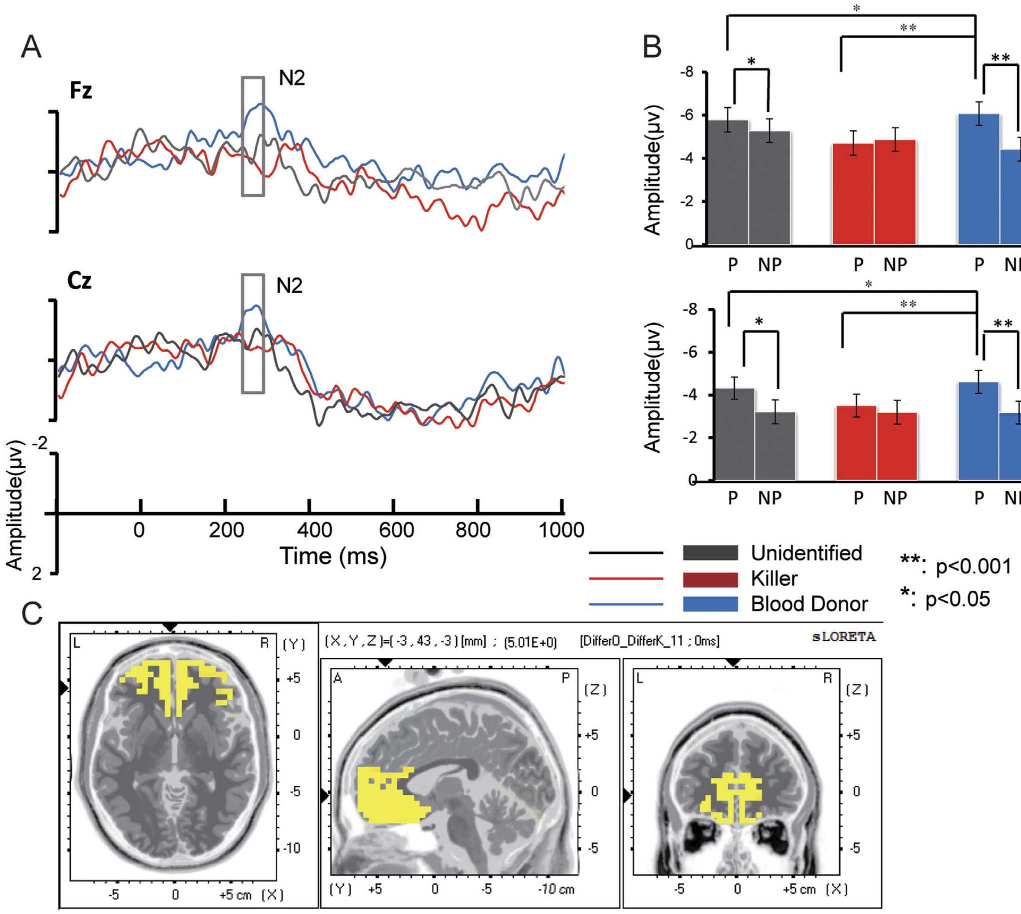

Figure 3. Difference waves to picture stimuli primed by different words (Grey: Unidentified; Red: Killer; Blue: Blood Donor). (**A**) The difference wave of (Painful – Non-painful) stimuli under three conditions at Fz and Cz sites. The Grey window illustrated the time window of N2. (**B**) The averaged amplitude under each condition (P: painful picture; NP: non-painful picture) at Fz and Cz sites. (**C**) sLORETA analyses revealed that the differences (Log of ratio of average),of dorsal ACC (BA32) and vmPFC (BA10) activation within the N2 window in response to painful picture and to non-painful picture was greater when the pictures were primed by "Blood Donor" than When the pictures were primed by " Killer".

trials from the non-painful trials and ran two repeated measures ANOVAs (3 (Moral information: Unidentified/Killer/Blood Donor) × 3 (regions: left/midline/right) × 5 (electrodes)) for painful trials and non-painful trials separately on the N2 component. We found that there are no significant difference in non-painful trials on moral level but only in the painful trials, the main effect of moral information was significant ($F_{(2, 54)} = 6.006$, $p = 0.005$). The "Blood Donor" primed painful picture stimuli elicited a stronger negative amplitude than the "Unidentified" primed ones ($F_{(1, 27)} = 12.475$, $p = 0.002$) and the "Unidentified" primed ones elicited a stronger negative amplitude than the "Killer" primed ones ($F_{(1, 27)} = 5.155$, $p = 0.031$) (Fig. 3B).

It was worth noting that the stimuli associated by the priming label contain many attributes. The current design did not totally exclude the effects of the context rendered by the attributes other than morality (e.g., emotional valence and intensity). In order to clarify the influence of the priming's valence and intensity has on the observed significant Morality × Picture interaction on N2, we re-contacted the 28 college students who had participated in the ERP study. We first refreshed them about the study then asked them to rate the intensity and valence of each priming word. To be more specifically, for the intensity, we asked them to rate from 1 to 7 (1: least intensive; 4: quite intensive, 7: very intensive); for the valence, they were also asked to rate from 1 to 7(1: very negative, 4: neutral, 7: very positive). We run repeated measures ANOVA with the subjective rating of intensity and valence of the priming words, separately. We found that the subjective rating of intensity and valence were significantly different among the three priming words (intensity: $F(2, 27) = 1221.61$, $p < 0.001$; Valence: $F(2, 27) = 2262.26$, $p < 0.001$). Pairwise comparison show that the rating of intensity of "Killer" and "Blood Donor" are significantly higher than the rating of intensity of "Unidentified" (Unidentified: 1.679 ± 0.146; Killer: 4.5 ± 0.227; Blood Donor: 4.892 ± 0.165 (mean ± s.e), $p < 0.001$, $p < 0.001$). The difference between the intensity of "Killer" and "Blood Donor" was not significant ($p = 0.610$). And the rating of valence of the "Killer" was significantly smaller (more negative) than the rating of "Blood Donor" and "Unidentified" (Unidentified: 3.75 ± 0.122; Killer:

2 ± 0.136; Blood Donor: 4.929 ± 0.162 (mean ± s.e), $p < 0.001$, $p < 0.001$). The rating of valence of "Unidentified" was significantly smaller than the rating of "Blood Donor" ($p < 0.001$).

Furthermore, in order to rule out the potential impact of the intensity and valence of the priming words on the amplitude of N2, we tried to run an ANCOVA to test whether the subjective rating of intensity and valence of the priming words were covariated with the amplitudes of N2. However, before the ANCOVA analysis, we found that the intensity and valence variables were not linearly related with amplitudes of N2 as the dependent variable, which did not meet the important assumption of ANCOVA. This indicated that the intensity and valence of the priming word did not impact on the observed N2.

Standardized low resolution tomography analysis (sLORETA). Since the significant effect was found in the time window of N2 component (240 to 290 ms after the onset of stimuli), source estimation was conducted within this time window. We computed the cortical three-dimensional distribution of current densities of the two different waves between the Painful and Non-painful conditions primed by "Blood donor" and "Killer" (B_P>B_NP and K_P>K_NP), separately for all 28 subjects. Then we ran a paired t-test to compare the current density map generated by B_P>B_NP and K_P>K_NP and a number of brain areas in frontal lobe were revealed, including the vmPFC, orbitofrontal cortex (OFC), ACC and lateral PFC. The maximum sources were found in the ventral end of the pregenual cingulate cortex (pgACC, belong to the rostral ACC (rACC))[32]. (BA32, (MNI coordinates (x, y, z) = 3, 43, −3; Log of ratio of average = 1.051, p = 0.047) and vmPFC[33] (BA10, MNI coordinates (x, y, z) = 9, 57, −8; Log of ratio of average = 1.047, p = 0.049) (Fig. 3C).

Discussion

The present study utilized ERPs to investigate the modulation of morality on the perception of other's pain. A word priming paradigm was applied by showing word to prime the moral information of the character in the following picture. There were three priming words, indicating three moral characters: the neutral one (Unidentified), the immoral one (Killer) and the moral one (Blood Donor) and two kinds of pictures: the painful ones and the non-painful ones. The significant effect of morality on empathy was found on the N2 component. We found an interaction effect of moral information × picture: when the priming word was the "Killer", there was no significant difference between the painful and the non-painful pictures; when the priming words were "Unidentified" and "Blood Donor", the amplitudes elicited by painful pictures on N2 was significantly larger than non-painful pictures.

Morality is a major component that forms the social norm and social expectancy[1]. Usually, moral judgments concern actions where one party harms or helps another, or treats a person or group fairly or unfairly[34,35]. What distinguish moral judgments from other items such as preference, aesthetics or non-moral good and bad is that moral judgments entail a belief that someone should be rewarded or punished[36]. Moral information may decrease the affective arousal and emotional contagion when observing the pain of the immoral targets. From an evolutionary point of view, if we reduce our emotional involvement with the immoral persons, we can be more alert when facing them. N2 component has consistently been found when participants observe other's physical pain and it may index an early automatic component related to the sensitivity to other's pain[20,37]. One ERP study found that the N2 component was enhanced when facing the pain of the participants' own-race compared to other race. The reduced N2 possibly reflected suppressed affective responses towards other-races' pain in the early stage and more sensitivity to own race member's feelings[22]. In the current study, the source generators of the difference in N2 include the pgACC and vmPFC. This region was found to be consistently activated by negative affect and pain[32]. And the activity of pgACC has been reported to be significantly correlated with both the Balanced Emotional Empathy Scale (BEES)[38] score and the Empathic Concern score of the Interpersonal Reactivity Index (IRI)[39] in observing other's pain[40]. It seems that the decreased activation of pgACC possibly indicated a reduced affective response to other's pain. In addition, a series of neuroimaging evidence suggested that the vmPFC is involved in the emotional aspect of empathy[42,43]. Notice that in the current experimental settings we cannot ensure the participants actually "empathized" with the virtual characters. But when the participants were presented with emotionally salient pictures showing other's pain, the affective arousal and the early emotional contagion process would be activated to facilitate the encoding of the stimuli. Therefore, we proposed that the reduced difference in N2 amplitude, as well as weaker activation of rACC and vmPFC reflect the decreased affective arousal and emotional contagion towards the immoral persons' pain. However, due to the limitation of the spatial resolution of source localization in ERP studies. Future studies may need to replicate the present findings with fMRI and investigate the neural localization and functional connectivity of the effect of moral modulation on empathy.

In summary, our ERP findings highlight the neural mechanisms underlying the modulation effects of morality on the perception of other's pain by finding that when the person in pain is immoral, the difference in brain responses to painful and non-painful stimuli would decrease compared to when the person is moral or neutral. This effect may be induced by less affective arousal and emotional contagion towards immoral person's pain. The brain regions that are responsible for this effect would be the vmPFC and the pgACC. The differences in facing moral or immoral persons' pain can keep us alert when facing people who are potentially dangerous and might harm us.

The present study has some important limitations. The results indicated a decreased affective arousal of other's pain primed with the immoral information, however, the current study did not explore the neural correlates of the priming moral information, and this may raise concerns on whether the findings reflect modulation effects of morality only or combining with other effects, such as the lasting effect of the priming. Future study would be better to put effort on excluding the effects of the context and priming of moral information during empathy.

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Author Contributions

C.F. designed the experiment, collected and analyzed the data. C.F., N.M. and Y.J.L. wrote the main manuscript. All authors reviewed the manuscript.

Additional Information

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When your pain signifies my gain: neural activity while evaluating outcomes based on another person's pain

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The overlap between pain and reward processing pathways leds researchers to hypothesize that there are interactions between them in the human brain. Two hypotheses have been proposed. The "competition hypothesis" posits that reward can reduce pain-related neural activity and *vice versa*. The "salience hypothesis" suggests that the motivational salience of pain and reward can be mutually reinforced. However, no study has tested these two hypotheses from temporal perspective as we know. In the present study, pictures depicted other people in painful or non-painful situations were used to indicate the valence of outcomes in a gambling task. The event-related potential results revealed an interaction between another person's pain and outcome valence in multiple time stages. Specifically, the amplitudes of the N1 and P3 were enhanced in the win condition compared with the loss condition when the outcome was indicated by painful picture. This interactions between pain and reward support the salience hypothesis but not the competition hypothesis. The present results provide evidence from human subjects that support the salience hypothesis, which claims that observing other people's pain can enhance the salience of reward.

Pain and reward are both powerful motivators for human behavior. Noxious stimuli that trigger painful experiences induce avoidance behavior, whereas stimuli that predict reward induce approach behavior[2]. These behavioral tendencies have historically been considered opposite to each other[3]. Partly due to this reason, the neural mechanism of reward processing and that of pain processing have been investigated largely independently[4]. However, emerging brain-imaging evidence suggests that overlapping brain regions are recruited in the processing of both painful and rewarding stimuli, including the lateral prefrontal cortex, anterior insula (AI), posterior insula, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex (ACC), ventral striatum, and amygdala, among others[3]. The extensive similarities in the neural substrates of pain and reward systems encourages investigators to discuss the interactions between the two[5].

Two competing theories have been proposed to describe interactions between the reward and pain systems. The "competition hypothesis" proposes that reward can reduce pain-related neural activity and *vice versa*[6]. According to this theory, reward and threat (mostly referring to physical pain) compete against each other. In situations that involve both reward and threat, responses to reward are reduced by threat-related processing and *vice versa*. In previous functional magnetic resonance imaging (fMRI) studies, participants were exposed to pictures of their significant others (i.e., highly rewarding stimuli) while experiencing physical pain (i.e., highly salient but negative stimuli). A reduction of neural activity was detected in regions that are related to the affective component of pain (ACC, AI) compared with participants who were exposed to pictures of neutral objects while experiencing physical pain[7,8]. In another study, participants underwent a task in which they were simultaneously told about the chance of winning money (reward) and the chance of receiving a shock (pain). The study found that the effect of reward was reduced by threat and *vice versa*[9]. The "salience hypothesis" suggested that rewarding and painful stimuli are represented in terms of their motivational salience. In situations that involve both reward and threat (pain), neural activation would be enhanced compared to the "single" condition because of aggregated

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motivational salience[9]. Interestingly, although the salience hypothesis has been extensively discussed, little empirical evidence has been provided by human studies to support this theory[9].

In experimental paradigms that were used in most previous studies that devoted to investigate the interaction between reward and pain, rewarding stimuli were task-relevant and painful stimuli were used as distractors, or the reverse was true. This might lead to competitions on limited attentional and cognitive resources, which may provide experimental results in favor of the competition hypothesis[6]. Additionally, most studies in this field used a cue paradigm, in which a cue that indicates subsequent pain or reward experiences was presented to the participant. After a time delay, the actual painful or rewarding stimulus was presented. This paradigm allowed the participants to weigh between pain and reward during the time delay, which may trigger a competition between the subsequent processing of pain and that of reward[9]. However, what remains largely unknown is whether the processing of these two attributes would be weakened when the same stimulus contains both painful and rewarding information (according to the competition hypothesis) or whether the salience of this stimulus is enhanced as a whole (according to the salience hypothesis). Clarifying this issue is crucial because it would exclude the possibility that participants make a "trade-off" between pain and reward. In the present study, participants performed a gambling task, in which pictures that showed other people in painful or non-painful situations were used to indicate the valence of their monetary outcome (i.e., win or loss). Specifically, in half of the trials, a picture that showed another person's pain indicated monetary gain in the current trial. In the other half of the trials, a picture that showed another person's pain indicated monetary loss. In this task design, rewarding information could be directly conveyed by painful information, thus excluding the possibility of competition on attentional resources between reward processing and pain processing.

It is worth noting that the salience hypothesis and competition hypothesis are not antagonistic to each other. One possibility is that they are both true, but manifest in different temporal stages of processing. To our knowledge, the literature lacks high-temporal-resolution data that could directly address this possibility. In the present study, the event-related potentials (ERPs) were recorded to investigate the interaction between pain and reward from a temporal perspective. Using ERPs with millisecond temporal resolution is beneficial for detecting dynamic changes in the interaction between pain and reward, thus may provide novel knowledge about the debate[10].

Painful stimuli are herein referred to as pictures that show another person's pain. Seeing another person suffering pain has been consistently reported to be an aversive and unpleasant experience[11,12]. Results from fMRI studies regarding the perception of another person's pain found that when observing such pain, brain regions that are involved in self-pain experience (e.g., the AI and ACC) were activated, which means when observing other's pain, we partly experienced pain oursevleve[13–15]. This ability to feel and understand how other peoples feel when observe other's experience the same feelings (e.g, pain) was named "empathy"[16,17]. Neuroimaging evidence suggests that two components (i.e., affective and cognitive) are involved in perceiving another person's pain, which are subserved by distinct brain networks[18]. The affective component of empathy has been framed as reflecting rapid, bottom-up activation of subcortical/cortical circuitries[19–22]. The cognitive component of empathy has been shown to be influenced by higher-level, top-down signals that originate in prefrontal cortical circuitries[18,21]. Event-related potential studies support this two-system model, in which both early (N1, N2) and late (P3) ERP components are involved when a subject observes another person receiving painful stimuli compared with non-painful stimuli. These findings indicate that the perception of another person's pain generally involves three key processes: an early, automatic, bottom-up process that is related to perception-action coupling (indexed by the N1 component[23]); an early affective arousal and sharing process (reflected by the N2 component); and a later, cognitively controlled, top-down process (indexed by the P3 component[24–26].

Rewarding stimuli are herein referred to as monetary outcomes that are indicated by pictures. The fast and accurate representation of outcome feedback is crucial for reward processing[27].Human brain has been shaped by evolutionary adaptation into developing specific mechanisms to assess the valence, magnitude, and other aspects of outcomes, thus linking outcome information with subjective and motivational significance[28]. Event-related potential studies have found that a centro-parietal located P3 component encodes the salience of stimuli[29–31]. Positive outcomes evoke a larger P3 than negative outcomes, and outcomes with a larger magnitude elicit a larger P3 than outcomes with a smaller magnitude[32,33].

We compared ERPs when the participants observed pictures that showed another person's pain or no pain, which indicated different kinds of monetary consequences of gambling. Our hypothesis was that when a positive outcome (reward) was represented as another person's pain, the competition hypothesis would be supported if the reward value reduces neural response to painful stimuli. Conversely, the salience hypothesis would be supported if the reward value enhances neural response to painful stimuli. More specifically, if the "Pain-Win" (painful picture indicates monetary win) condition elicits larger amplitudes of ERP components compared with other conditions, particularly the "No Pain-Win" condition, then the interaction between pain and reward during this stage fits the salience hypothesis. Otherwise the interaction during this stage fits the competition hypothesis. Furthermore, if the experimental effect described above occurs in the early visual discrimination and/or attentional process, then the effect should be observed on the N1 component; if this effect mainly modulate the affective arousal of painful stimuli, then we would observe the effect on the N2 component; finally, if the effect influences the later cognitive evaluation process, we would expect to find the effect on the P3 component as well.

Materials and Methods

Participants. Twenty-three right-handed university students with no history of neurological disorders, brain injury or developmental disabilities were recruited through advertisement to participate in the experiment. The handedness of participants was tested using the Chinese translation of Edinburgh Handedness Inventory[34]. All of them have normal or corrected to normal vision. The histories of neurological disorders of the participants were assessed through a self-report version of questionnaires. In the questionnaire, the participants need to answer YES or NO to report if they have ever been diagnosed as following conditions: stroke, seizure, anxiety, depression,

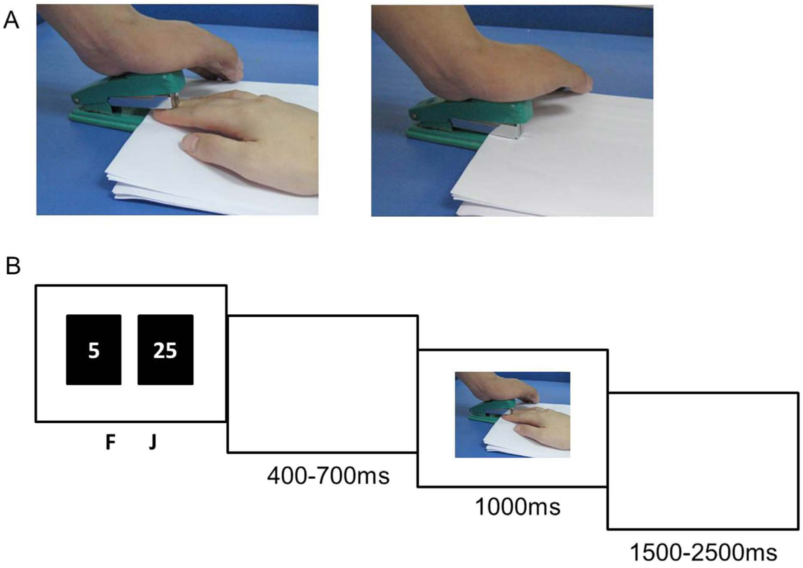

Figure 1. Experimental design. (**A**) an example of the pictures used in the experiment. The Left side shows a painful picture and the right side shows a non-painful picture. (**B**) An example of a single trial.

other neurologic disorder (nerve, spinal cord or brain disorder), significant vision or hearing disorders. We only recruited participants who gave no YES to any condition. All participants signed an informed consent form before the experiment. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee of the Medical School of Shenzhen University, China. The data of three subjects were excluded; two of them were excluded because too few epochs survived after artifact correction (less than 50%) and one was due to extremely biased behaviors in the game (consistently choosing the large value option in all trials). As a result, the final sample consisted of twenty participants (11 male, 22.95 ± 0.44 years (mean ± S.E)).

Stimuli. The stimuli used in the experiment were pictures showing a person's hands/forearms/feet in painful or non-painful situations, which have been used in previous ERP studies[1,35]. All the situations depicted in these pictures were ordinary events in daily life. All the events showing in the non-painful pictures were corresponding to those in the painful pictures, but without the nociceptive component (Fig. 1A). There were 60 painful pictures and 60 non-painful pictures in total. All of them had the same size of 9 × 6.76 cm (width × height) and 100 pixels per inch. Luminance, contrast ratio and color were matched between painful and non-painful pictures. Previous studies have confirmed that painful and non-painful pictures were significantly different on the dimensions of pain intensity and arousal level, but not emotional valence, according to self-reported rating[35].

Experimental procedures. Stimulus display and behavioral data acquisition were conducted using E-Prime software (Version 2.0, Psychology Software Tools, Inc, Boston, USA). During the task, participants sat comfortably in an electrically-shielded room approximately 100 cm from a 15 inch LCD color computer screen. Each trial began with the presentation of two grey rectangles (2.3° × 3.2° of visual angle) on the left and right sides of a fixation point in which two numbers ("25" and "5", indicating the gambling points) were individually presented to indicate two alternative options. The positions of the two numbers were counterbalanced across trials. The participants were asked to make a selection by pressing the "F" or "J" key on a keyboard with their index fingers. The rectangles remained on the screen until a response was given. Then a blank interval would present for 400 to 700 ms randomly. After that, the outcome of the participants' choice was presented as pictures showing a person's hands/forearms/feet in painful or non-painful situations. The picture would last for 1000 ms on the screen. In two of all four blocks a picture showing others in painful situations indicated monetary loss in the current trial, while pictures showing others in non-painful situations indicated monetary gain (other's pain = self's loss). For example, if participants chose "5" and received a painful picture, that means they had loss 5 points in this trial. In the other two blocks pictures showing others in pain indicated monetary gain while pictures showing others in non-painful situations indicated monetary loss (other's pain = self's gain). In this condition, a painful picture after selecting "5" means the participants had loss 5 points in this trial. There was an interval of 1500 to 2500 ms between trials (Fig. 1B). There were 120 trials in each block. The order of the blocks was counterbalanced using an ABBA.

The experiment was a 2 × 2 × 2 within-subjects design. The first factor was the content of pictures: painful or non-painful. The second factor was the magnitude of the choices: small (5) or large (25). The third factor was the valence of the outcome: win or lose. Thus, there were 8 conditions in total (Table 1).

Before the experiment, participants were instructed about the rules and the meaning of the pictures in the task. In addition, they were told that the higher the score they earned, the more bonus money they would receive at the

Conditions	Picture	Outcome	Condition name
1	Painful	Win	P_W
2	Non-Painful	Lose	NP_L
3	Painful	Lose	P_L
4	Non-Painful	Win	NP_W

Table 1. Conditions. There were three factors (the chosen Value, Picture and Outcome), each including 2 levels resulting 8 conditions in total. However, since the factor "Value" was not included in later analysis, only two other factors were considered resulting 4 conditions as listed.

	Small bet (5)		Larger bet (25)	
	Pain = Win	Pain = Lose	Pain = Win	Pain = Lose
RTs (ms)	876.93 ± 45.22	902.61 ± 65.02	899.23 ± 39.12	881.33 ± 67.53
Number of trials	110.2 ± 14.22	112.54 ± 21.22	124.95 ± 25.22	124.31 ± 15.10

Table 2. Behavioral data. Mean RTs (ms) and choice. There were four conditions here: choosing small bet when painful picture representing win; choosing small bet when painful picture representing lose; choosing large bet when painful picture representing win and choosing large bet when painful picture representing win.

end of the experiment. However, after the participants finished the task, they were briefed that their total gains and losses were predetermined, and all participants received 150 RMB (~25 US dollars) for their participation.

EEG acquisition and analysis. Electroencephalography (EEG) data were recorded from a 63-electrode scalp cap using the 10–20 system (Brain Products, Munich, Germany). The channel at the middle site between FPz and Fz (i.e., the location of FCz) was used as reference. Two electrodes were used to measure the electrooculogram (EOG). EEG and EOG activity was amplified at 0.01 Hz~100 Hz band-passes and sampled at 500 Hz. All electrode impedances were maintained below 5 kΩ.

EEG data were pre-processed and analyzed using Matlab R2011b (MathWorks, Natick, USA) and EEGLAB toolbox (EEGLAB v13.4.3b)[36]. EEG data at each electrode were down-sampled to 250 Hz. Then the EEG signals were-referenced to the grand average and the electrode FCz was reinstated. After that the signals were filtered with 0.01–30 Hz band-pass. The time windows from 200 ms before to 1000 ms after the onset of picture were segmented. All epochs were baseline-corrected with respect to the mean voltage over the 200 ms preceding the onset of stimulus. EOG artifacts were corrected using an independent component analysis (ICA)[37]. Epochs with amplitude values exceeding ±50 μV at any electrode were excluded from the averaging.

Further statistical analysis was conducted in IBM SPSS Statistics 22 (IBM Corp., Armonk, USA). Statistical analysis was conducted at electrodes selected from the frontal (Fz, FCz, F3-F4, FC3-FC4), central (Cz, CPz, C3-C4, CP3-CP4), parietal (Pz, P3-P4), temporal (T7-T8, TP7-TP8, P7-P8) and occipito-temporal (POz, Oz, PO3-PO4, PO7-PO8)[24]. The main concern of the current research is the interaction between the "Picture" factor and the "Outcome" factor. We did not include the factor "Value" (small/large) in the Repeated measures ANOVA. Instead, the repeated measures ANOVA (2 (Picture: Painful/Non-Painful) × 2 (Outcome: Win/Lose) × 5 (Regions: frontal/central/ parietal/temporal/occipito-temporal) was performed for each component. Mean amplitudes were obtained from the grand-averaged waveforms. The time windows for ERP amplitude analysis were set as below: from 90 to 140 ms for the N1 component;; from 200 to 240 ms for the N2 component and from 480 to 680 ms for the P3 component. Degrees of freedom for F-ratios were corrected according to the Greenhouse–Geisser method. Statistical differences were considered significant at $p < 0.05$; post-hoc comparisons were Bonferroni-corrected at $p < 0.05$. Only significant effects were reported for the sake of brevity.

Results

Behavioral data.

The percentage of trials in which participants selected the large option (25) and small option (5) were 53 ± 6.1% and 46 ± 7.1%, respectively. The average reaction time was 890.03 ± 56.45 ms. The mean RTs and choices in different condition are shown in Table 2. ANOVAs of RTs and number of trials show no significance between conditions.

ERPs. The grand averaged ERPs elicited by pictures were computed separately for each condition. The grand averaged ERPs for the pictures displayed a negative component from 90 to 140 ms (N1) over the frontal and central regions, a negative deflection from 200 to 240 ms (N2) over the central and parietal region and a late positive component from 480 to 680 ms (P3) over the central and parietal regions.

For the N1 component, we observed a significant main effect of the region (F (4, 76) = 35.618, $p < 0.001$, $\eta_p^2 = 0.625$). The N1 component was larger in the frontal and central regions than in the parietal, temporal, and occipito-temporal regions. We also observed a significant interaction of picture × outcome interaction (F (1, 19) = 7.173, $p = 0.015$, $\eta_p^2 = 0.274$). By using pairwise comparisons, we found that only when the picture was a painful one, "win" elicited a more negative peak than "loss" ($p = 0.048$); however, when the picture was a non-painful one, the difference between win and loss was insignificant ($p = 0.156$) (Fig. 2). The mean amplitudes in different condition are shown in Table 3.

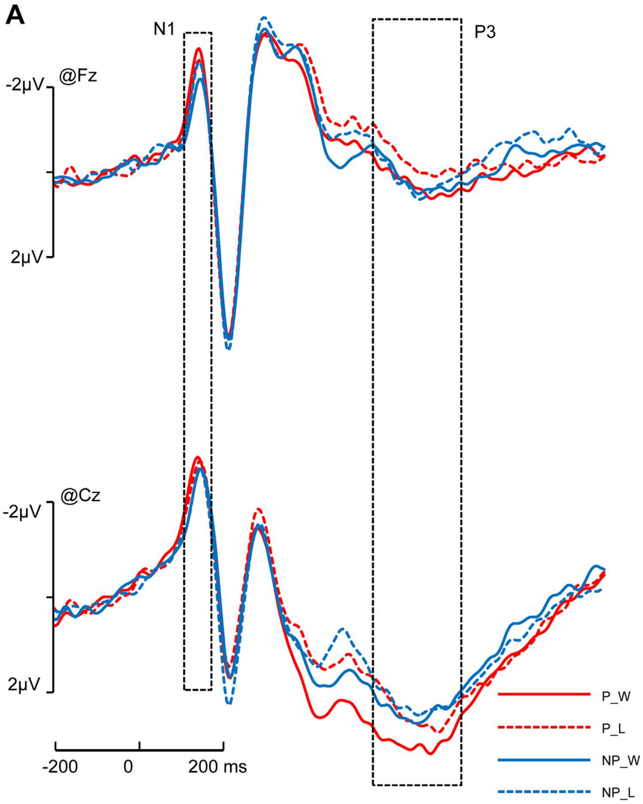

Figure 2. Interaction on N1 and P3. ERPs under 4 conditions (P_W: Painful picture and Win; P_L: Painful picture and Lose; NP_W: Non-painful picture and Win; NP_L: Non-painful picture and Lose).

Condition	Region	Amplitudes of N1 (mean ± SD); (μV)	Amplitudes of P3 (mean ± SD), (μV)
P_W	Frontal	−1.93 ± 1.14	1.02 ± 1.59
	Central	−1.17 ± 0.97	2.72 ± 1.13
	parietal	0.99 ± 1.24	1.63 ± 2.16
	temporal	1.30 ± 1.03	−1.34 ± 0.90
	occipito-temporal	2.77 ± 1.64	−0.67 ± 2.24
P_L	Frontal	−1.79 ± 1.22	0.61 ± 1.59
	Central	−1.25 ± 0.87	2.35 ± 1.09
	parietal	0.67 ± 1.76	1.71 ± 1.94
	temporal	1.38 ± 1.00	−1.02 ± 1.08
	occipito-temporal	2.51 ± 1.61	−0.29 ± 1.68
NP_W	Frontal	−1.61 ± 1.08	0.92 ± 1.46
	Central	−1.21 ± 0.88	2.32 ± 1.02
	parietal	0.70 ± 1.80	1.06 ± 1.84
	temporal	1.17 ± 0.96	−1.12 ± 0.96
	occipito-temporal	2.52 ± 1.67	−0.74 ± 1.13
NP_L	Frontal	−1.80 ± 1.16	0.95 ± 1.08
	Central	−1.08 ± 1.02	2.19 ± 1.06
	parietal	1.05 ± 1.72	1.97 ± 0.85
	temporal	1.20 ± 1.27	−1.01 ± 0.94
	occipito-temporal	2.76 ± 1.61	−0.86 ± 1,09

Table 3. ERP data. The means and SDs of N1 and P3 amplitudes in all conditions.

For the N2 component, we observed a significant main effect of the region ($F(4, 76) = 14.100$, $p < 0.001$, $\eta_p^2 = 0.426$). The N2 component was most prominent in the central and parietal regions. We also observed a significant main effect of the picture ($F(1, 19) = 9.061$, $p = 0.007$, $\eta_p^2 = 0.323$); painful pictures elicited a more negative peak than non-painful pictures on this component. A significant interaction of picture × region was

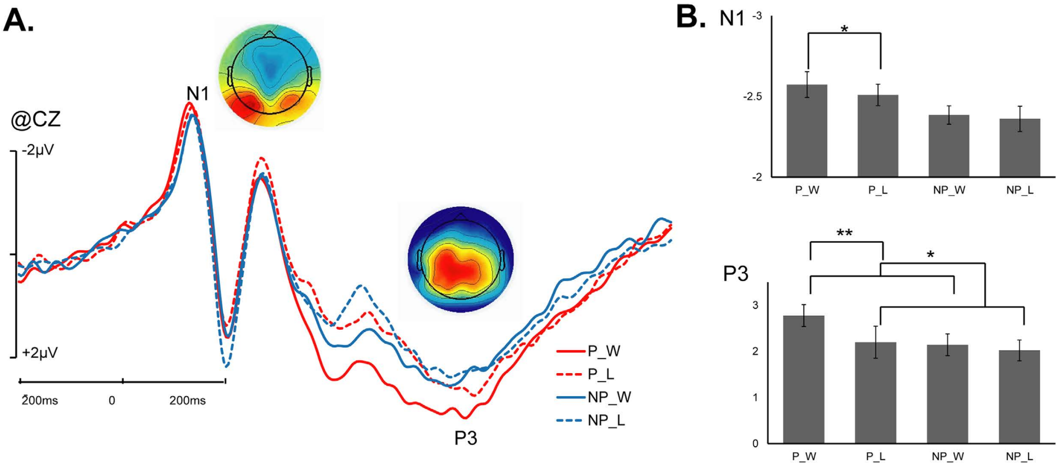

Figure 3. Cortical responses to picture stimuli. (**A**) ERPs elicited by the painful and non-painful pictures indicating win and lose at CZ site. The voltage topographies illustrate the scalp distribution of each component; (**B**) the averaged amplitudes within the N1 and P3 time Window in each conditions (P_W: Painful picture and Win; P_L: Painful picture and Lose; NP_W: Non-painful picture and Win; NP_L: Non-painful picture and Lose) (**p < 0.01; *p < 0.05).

also detected ($F(4, 76) = 9.026$, $p < 0.001$, $\eta_p^2 = 0.322$). Pairwise comparisons showed that the difference between painful and non-painful pictures on this component were significant in the central, parietal, and temporal regions ($p = 0.02$, $p < 0.001$, $p = 0.08$, respectively).

On the P3, we observed a significant main effect of the region ($F(4, 76) = 16.642$, $p < 0.001$, $\eta_p^2 = 0.467$); the P3 component was demonstrated in the central and partial areas. We observed a significant main effect of the picture ($F(1, 19) = 43.792$, $p < 0.001$, $\eta_p^2 = 0.697$). We also found a significant three-way interaction of picture × outcome × region ($F(4, 76) = 3.828$, $p = 0.026$, $\eta_p^2 = 0.168$) (Fig. 3A,B). Pairwise comparisons showed that only when the picture was painful the difference between win and loss were significant in the frontal, central, temporal, and occipito-temporal regions (Fig. 2); in these regions, only when the picture was a painful one, win elicited significant larger amplitudes of the P3 than loss ($p = 0.002$ for frontal, $p = 0.002$ for central, $p = 0.006$ for temporal, $p = 0.030$ for occipito-temporal, respectively (Fig. 3C,D)).

There was no other significant main effect or interaction ($p > 0.066$). The mean amplitudes in different condition are shown in Table 3.

Discussion

To temporally explore interactions between viewing another person's pain and monetary outcome evaluation, the present study utilized the ERPs. Our design allowed us to measure ERP responses to both painful and rewarding stimuli, thus is suitable to probe stimulus-dependent processes that are immune to the trade-off between each other. Analysis of the ERPs during the presentation of painful and non-painful pictures in win and loss conditions revealed a significant interaction between another person's pain and the outcome valence, which was reflected by a larger N1 component in the win condition than in the loss condition when the reward was indicated by painful pictures. For the P3 component, the interaction between the two factors was also significant, reflected by larger amplitude in the win condition than in the loss condition when the outcome was indicated by a painful picture. Overall, our findings support the salience hypothesis but not the competition hypothesis. In brief, when reward and pain were jointly presented, reward processing was enhanced by painful information.

The N1 is an early sensory component that is involved in selective attention and motivational processing[38], which are both sensitive to the processing of reward and another person's pain. For example, positive emotional words evoke larger N1 amplitudes than negative words. Stimuli with high motivational salience have also been reported to evoke larger N1 amplitudes, such as game rewards for pathological computer game players compared with healthy players[39] and immediate rewards for hypomania patients compared with controls[40]. Additionally, the processing of another person's pain can also modulate the N1 component, indicating that pain processing occurs during this stage[24,41,42]. The engagement of the N1 in the processing of both reward and another person's pain provides a basis for the interaction between them. For the N1 component, we observed a significant interaction between the picture and outcome. Specifically, only when the picture was painful, the win condition elicited a more negative peak than the loss condition. This data pattern indicates that participants were more sensitive to outcome valence when a painful picture was used as the outcome indicator, which clearly supports the salience hypothesis but not the competition hypothesis. This result is also consistent with previous findings in animal studies, that is, when animals confronted a reward in a conflict situation (i.e., a reward followed by an electric shock), they tended to be more sensitive to the reward[43]. In our opinion, the theoretical significance of the interaction on the N1 can be twofold. This phenomenon indicates that the interaction between pain and reward occurs at an early processing stage, which provides valuable temporal information to the field of studies.

The N2 component has been consistently reported in observing other's physical pain and it was suggested to index an early automatic component related to the sensitivity to other's pain[44], as well as a biomarker of the affective component of empathy for pain[44]. In the current experiment, we have found a main effect of picture on the N2, such that painful pictures elicited significant larger amplitudes of the N2 than non-painful pictures. This result is consistent with the literature that painful stimuli trigger higher level of affective arousal in the observers than the non-painful stimuli[45].

As mentioned in the Introduction above, the P3 component is related to the processing of both reward and another person's pain. Generally, "win" conditions evoke a larger P3 than "loss" conditions (for a review, see[46]). Viewing a picture of another person in pain also evokes a larger P3 than viewing a picture of another person who is not in pain[1,24,35,35,47]. The engagement of the P3 in both kinds of information processing provides a basis for the interaction between them. For the P3 component, the main effects of picture and outcome were both significant. In addition, we found a significant picture × outcome interaction similar with the N1, in which the "win" condition evoked a larger P3 than the "lose" condition only when the picture was painful. Together with the N1 results, this result supports the salience hypothesis but not the competition hypothesis during the later cognitive processing stage. That is, the processing of monetary win was enhanced by the processing of pain. The P3 is widely regarded as a measure of motivational significance[32,48–50]. Therefore, the P3 pattern supports the main point of the salience hypothesis that neural activations in conditions that involve both reward and pain significantly enhance because of aggregated motivational salience.

Notably, both the early N1 and late P3 showed significant interactions between pain and reward. For both the N1 and P3, when positive outcome was indicated by a painful picture, their amplitudes were enhanced, which supports the salience hypothesis. However, the present results appear to be inconsistent with previous fMRI studies that generally supported the competition hypothesis. Differences between the present experimental design and that in previous studies may explain this inconsistency. In task designs of many previous studies, painful information and rewarding information were allocated to separate stimuli, only one of which was set to be task-relevant. Thus to finish the task, participants have to focus on one attribute while suppress the processing of the other. It is not surprising that this kind of task design leads to experimental results in favor of the competition hypothesis. In contrast, the rewarding information and painful information in the present study were combined into one stimulus, and both attributes are set to be task-relevant. The present results reveal that when there is no competition for cognitive resources, stimuli that have both painful and rewarding attributes have the highest level of motivational salience, which support the salience hypothesis rather than the competition hypothesis.

Limitations. In our opinion, there were two major limitations of the present study. First, in the present study, we used painful pictures to present the "pain" concept. Although numerous studies support that observing other people in pain could elicited both somatosensory and affective components of the subjective pain experience[19,51–53], further research is still necessary to examine the reliability of current findings with first-hand painful stimuli instead of the "observed pain".

Second, painful pictures were paired with either win (i.e., reward) or loss (punishment) outcomes in the present study, but we did not contain a condition in which joyful pictures were paired with win or loss outcomes. However, to provide a full and appropriate test of competing hypotheses of interactions between reward and pain processing, the usage of positive emotional rather than neutral images paired with win or loss outcomes is needed. Instead, the present study only partially evaluates the competing hypotheses.

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Author Contributions

C.F. designed the experiment. C.F. and X.Z. collected the data. C.F. analyzed the data. C.F., R.G. and Y.-j.L. wrote the main manuscript. All authors reviewed the manuscript.

Additional Information

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Deficits in attentional processing of fearful facial expressions in schizophrenic patients

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Impaired attentional processing of negative facial expressions is prominent in schizophrenia and has been shown to be associated with patients' social dysfunctions. However, little is known about when and which specific attention deficits influence social functions. Given the dynamic feature of attention, it is necessary to investigate the attention deficits in negative emotional processing unfolding in time. The current study used event-related potentials (ERPs) to investigate the temporal dynamics of attention deficits in emotion perception and their potential relationship with emotional/social impairments in neuroleptic naive schizophrenic patients. Two specific attention deficits were identified and were found to be associated with emotional/social impairments. More specifically, the deficit in orienting attention (evidenced with the reduced P1 amplitude) was correlated with expressive deficits, while the deficit in executive control of attention (evidenced with the reduced P3 amplitude) was correlated with avolition/asociality. Together, these findings may provide novel insights into the core pathophysiological processes and offer objective biomarkers for specific emotional/social impairments in schizophrenia. It is also hoped that this study helps to bridge the gap between basic cognitive deficits and relative high-level social dysfunctions in schizophrenic patients.

Impaired attention is often observed among schizophrenic patients and their relatives[1]. A growing body of research suggests that attention dysfunction is one of the most critical determinants of quality of life in schizophrenic patients[2]. Impaired attention is detectable even before illness onset and it tends to deteriorate when patients dealing with emotional, especially negative, information[3,4]. Given the important role of negative emotion in survival[5,6], lack of appropriate attention to negative social stimuli would no doubt jeopardize patients' social skills[7,8]. The degree of social dysfunction in schizophrenia is closely associated with the severity of negative symptoms[9–11], especially those characterized by diminished expression and amotivation (i.e. avolition)[12,13]. However, little is known about whether attention deficits are associated with social dysfunction and relevant negative symptoms in schizophrenic patients.

Attention is a dynamic process, which comprises several functional constructs, including alerting, orienting and executive networks[14]. Numerous studies have demonstrated that the neural bases for different attention networks are largely independent[15–17]. Therefore, dissociation between specific domains of attention is advisable in neuroscience/clinical studies[14,18]. Researchers usually employ the attentional network test (ANT) to simultaneously examine the efficiency of alerting, orienting and executive attention[15–17]. One previous ANT study with a large sample size of schizophrenic patients has found a highly profound deficit in the executive network, a smaller but significant deficit in the orienting network and no deficit in the alerting network[19]. However, there is little knowledge about when and which specific deficits in attentional processing of negative stimuli influence social functions[20,21].

Evidences in cognitive psychology have shown that orientating and executive control of attention are involved, to a large extent, sequentially in time for negative emotional processing[21–23]. Given the dynamic feature of attention, it would be more informative to investigate the attentional deficits in negative emotional processing unfolding in time. Understanding the relationship between the sequentially involved attention networks and emotional/social impairments is an urgent task of schizophrenic neuroscience, the answer to which would provide novel insights into the core pathophysiological processes and offer objective biomarkers for specific social impairments in schizophrenia[24].

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The event-related potential (ERP) technique was employed in this study given its high time resolution[25]. Regarding orienting network, previous ERP studies in healthy subjects have indicated that the attention orienting towards negative emotional stimuli reliably enhances the occipital P1 and the parietal P3 components, representing an early increased visual perception[26] and a later voluntary attention allocation towards or re-orienting from negative emotions[21], known as "negativity bias"[5,6]. Regarding executive control network, healthy individuals typically devote more effort to resolve cognitive conflict, which is characterized by larger P3 amplitudes. However, schizophrenic patients show difficulties in allocating attention resources when encountering conflict, accompanied by a diminished P3 component[27]. Given the acknowledged emotion deficits in patients with schizophrenia[28,29], it is expected that the above mentioned ERP findings of orienting/executive function would be further deteriorated when patients process negative emotional stimuli.

Social dysfunctions in schizophrenia have received growing attention in recent years[30,31]. At the same time, a large body of work has explored the neural basis of basic cognitive processing in schizophrenic patients[32]. However, it is unclear whether the complicated social dysfunctions prominent in schizophrenia are related to basic cognitive deficits such as attention network. Therefore, the present study aimed to investigate the deficits in attentional processing of negative social stimuli (fearful faces here) unfolding in time, and their potential relationship with emotional/social impairments in schizophrenic patients. Studies focusing on this issue could help to bridge the gap between basic cognitive deficits and relative high-level social dysfunctions in schizophrenia[12,13]. Clinically, the severity of emotional/social impairments is often assessed using the Positive and Negative Syndrome Scale (PANSS)[33]. Previous studies have shown that negative rather than positive symptoms of schizophrenia consistently have two factors linked to emotional/social dysfunction[11,12], which were therefore our major concerns in this study. The two factors were diminished expression (typically involving symptoms of reduced facial and vocal expressivity and reduced verbal output) and anhedonia and asociality (composed of symptoms of anhedonia, diminished interest, and decreased social engagement)[13]. We hypothesized that schizophrenic patients are characterized by sequential deficits of orienting attention and exective attention in fearful face processing. More specifically, we expect diminished amplitudes of P1 and P3 when patients orient or disengage their attentions to or from fearful faces, and reduced P3 component when patients try to inhibit task-irrelevant emotional information, compared with healthy controls. It is further expected that the ERP abnormity found in the orienting/executive attentional process of negative facial expressions would correlate with specific negative symptom factors. This study only included neuroleptic naive patients, which helped to clarify that the observed behavioral and ERP deviations in patients were free from medication influence.

Methods

Participants.

Twenty-seven outpatients (13 females) of Beijing Huilongguan Hospital and twenty-six normal controls (12 females) in surrounding community were recruited as paid participants.

Patients were diagnosed according to the criteria for Schizophrenia in Diagnostic and Statistical Manual (DSM-IV). Patients with schizoaffective disorder, schizotypal or schizoid personality disorder were excluded. None of the patients were in a major depressive or manic episode at the time of testing. Additional exclusion criteria for patients included: 1) history of significant brain trauma, 2) neurological disorder, 3) substance abuse or dependence in the past six months, 4) mental retardation ($IQ < 70$), and 5) who had received electroconvulsive therapy in the past six months. At the time of experiment, all patients were untreated with medication. Indeed, they are all first episode patients, never treated with neuroleptics.

Healthy control participants were screened with the SCID[34] and SCID-II[35]. Exclusion criteria for control participants were 1) any lifetime Axis I psychotic or mood disorders, 2) recurrent depression, 3) paranoid, schizotypal or schizoid personality disorder, 4) seizure disorder, 5) history of head injury with possible neurological sequela, 6) the presence of one or more first-degree relatives with schizophrenia, and 7) substance abuse or dependence in the past six months.

The interview and clinical symptom rating were based on consensus of two senior psychiatrists who were trained in the Center for Psychiatric Research of Beijing Huilongguan Hospital with a high reliability ($\kappa = 0.83$). There was no significant difference between the two groups with respect to age, handedness, IQ, and education (Table 1). Written informed consent was obtained prior to the experiment. The experimental protocol was approved by the Ethics Committee of Beijing Huilongguan Hospital and was in compliance with the ethical guidelines of the American Psychological Association.

Stimuli.

The cues used in the experiment were fearful and neutral faces. Facial pictures were black and white photographs selected from the native Chinese Facial Affective Picture System[36], with equal number of facial pictures between males and females. A total of 40 faces were used (20 fearful and 20 neutral faces). Each picture had been assessed for its valence and arousal on a 9-point scale with a large sample of Chinese participants in a previous survey. Independent t-test showed that the two categories of faces have significantly different emotional valence scores ($t(38) = -9.47$, $p < 0.001$; fear $= 2.68 \pm 0.10$, neutral $= 4.27 \pm 0.14$) as well as arousal scores ($t(38) = 12.3$, $p < 0.001$; fear $= 6.73 \pm 0.23$, neutral $= 3.60 \pm 0.11$). Facial pictures ($2.5° \times 3°$) were presented with the same contrast and brightness on the black background.

The target stimuli consisted of a row of five leftward or rightward arrows. The target arrow was surrounded by four flankers, which had either the same (congruent condition) or the opposite direction (incongruent condition). The five white arrows (3.5°) were presented to the top or bottom of a central fixation.

Procedure.

In order to assess the interactions between emotion and orienting/executive attention, the experimental procedure was modified from Fan *et al.*[17] and Cohen *et al.*[37]. As shown in Fig. 1, each trial started with a fixation, followed by a cue that was presented to the top (50%) or the bottom (50%) of the fixation. Participants

Characteristics	Patient (n = 27)	Control (n = 26)	Statistics
Mean age, y	21.6 (18–26)	23.2 (17–27)	$t(51) = -1.64$, $p = 0.107$
Education time, y	13.3 (9–16)	14.2 (9–16)	$t(51) = 1.42$, $p = 0.161$
Handedness, right/left	27/0	26/0	
IQ[a]	101 (78–123)	103 (79–125)	$t(51) = -0.68$, $p = 0.498$
PANSS score[b]			
Positive scale	14.4 (12–34)	9.2 (7–17)	$p < 0.001$
Negative scale	16.2 (10–30)	10.4 (8–20)	$p < 0.001$
General Psychopathology scale	31.5 (26–50)	27.4 (25–31)	$p < 0.001$

Table 1. Demographic and clinical data of patients and control groups. Descriptive data are presented as mean (range) or mean ± standard deviation. [a]The Wechsler Adult Intelligence Scale (fourth edition)[74–76]. [b]Positive and Negative Syndrome Scale[33].

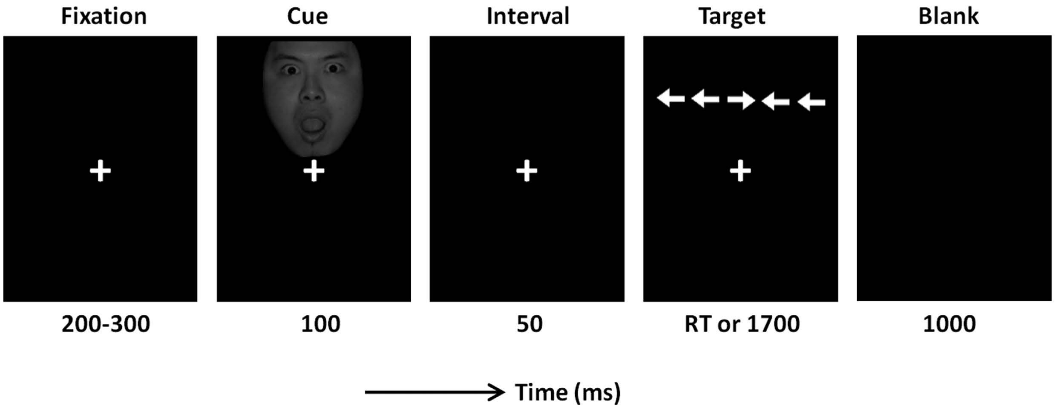

Figure 1. Illustration of one experimental trial in this study. RT, reaction time.

were required to respond as quickly and as accurately as possible regarding the direction of the target arrow by pressing the "left" or "right" button, respectively, on the joystick with their left or right thumb.

The experimental design was factorial, with three within-subject factors: emotion (fear *vs*. neutral), cue type (valid *vs*. invalid) and flanker type (congruent *vs*. incongruent). In valid and in invalid trials, the target stimuli appeared at the same and opposite location previously occupied by the emotional face. The total experiment consisted of 320 trials (40 trials per condition × two emotions × two cue types × two flanker types).

EEG recording and analysis. Brain electrical activity was recorded referentially against left mastoid and off-line re-referenced to average activities over the scalp. The data were collected by a 64-channel amplifier with a sampling frequency of 250 Hz (NeuroScan Inc., Herndon, USA). Electrodes were placed on the scalp via an elastic cap according to the standard 10–20 system. Ocular artifacts were removed from EEGs using a regression procedure. The recorded EEG data were filtered (0.01–30 Hz) and segmented beginning 200 ms prior to the onset of cues and lasting for 1200 ms, followed by baseline correction and averaging. Trials contaminated with large artifacts (peak-to-peak deflection exceeded 100 μV) were excluded from the averaging. This procedure rejected 4.8 ± 0.9 trials per condition per individual (no significant difference was found between conditions and groups).

The averaged data were derived from all electrodes, but only the electrodes at which the components reached their peak values were entered into statistical analysis. Time windows for mean amplitude calculation were centered at the peak latencies of ERP components in grand-mean waveforms, with a shorter window length for early components and a longer length for late components. The mean amplitude of the P1 was calculated at the electrode sites of O1, O2, PO3, PO4 (time window = 310–360 ms after cue onset, i.e., 160–210 ms after target onset). The mean amplitude of the P3 was calculated at the electrode sites of P1, P2, Pz and CPz (time window = 450–700 ms after cue onset, i.e., 300–550 ms after target onset).

Statistics. Descriptive data were presented as mean ± standard error. To conveniently investigate the emotion-modulation effect on orienting attention and executive attention, this study used *attention bias score* to measure the behavioral data and used *attention bias amplitude* to measure the ERP data. In particular, the attention bias scores of accuracy rate and reaction time (RT) were defined as the variable difference between validly and invalidly cued conditions, or between congruent and incongruent flanker conditions. Accordingly,

Subject number	Factor 1	Score of PANSS items and factor loadings				Factor 2	Score of PANSS items and factor loadings		
		N1 0.85	N3 0.81	N6 0.83	G7 0.58		N2 0.94	N4 0.82	G16 0.60
1	9	3	3	3	3	6	3	2	2
2	5	2	1	1	3	6	3	2	3
3	7	3	2	1	3	5	1	3	3
4	6	1	3	1	3	4	3	1	1
5	7	3	2	2	2	7	3	4	2
6	8	3	3	2	2	6	3	3	1
7	5	2	1	1	3	6	3	3	1
8	7	3	3	1	2	7	3	3	3
9	6	3	3	1	1	11	5	4	5
10	6	3	3	1	1	9	4	3	4
11	8	3	3	1	3	6	3	2	2
12	11	5	5	1	3	12	5	5	5
13	4	1	1	1	3	5	2	2	2
14	3	1	1	1	1	3	2	1	1
15	9	3	3	3	3	4	2	2	1
16	8	2	3	2	3	5	1	3	2
17	6	3	2	1	2	3	1	2	1
18	11	5	4	2	3	7	3	3	3
19	8	4	3	1	2	10	4	5	4
20	13	5	5	4	2	11	5	5	4
21	8	4	3	1	2	9	4	4	3
22	8	4	3	1	2	10	5	4	3
23	7	4	3	1	1	9	4	4	4
24	5	3	1	1	1	5	2	3	1
25	5	2	1	2	1	4	1	1	3
26	8	3	2	3	3	2	1	1	1
27	8	3	2	2	3	5	3	2	1

Table 2. The two negative symptom factors of PANSS. The factor loadings were based on the study of Jang *et al.*[39]. Factor 1- expressive deficits, Factor 2-avolition/asociality. N1-blunted affect, N2-emotional withdrawal, N3-poor rapport, N4-passive/apathetic social withdrawal, N6-lack of spontaneity and flow of conversation, G7-motor retardation, G16-active social avoidance.

two-way repeated-measures ANOVAs were performed on behavioral and ERP measurements, with emotion as the within-subject factor, and group as the between-subject factor.

According to the study of Liemburg *et al.*[38] and Jang *et al.*[39], the two negative symptom domains of PANSS could be calculated as follows. The Factor 1 (expressive deficits) consists of PANSS items of blunted affect (factor loading = 0.85), poor rapport (0.81), lack of spontaneity (0.83), and motor retardation (0.58). The Factor 2 (avolition/asociality) consists of PANSS items of emotional withdrawal (0.94), passive social withdrawal (0.82), and active social avoidance (0.60)[39]. In this study, two-tailed Pearson's r correlation was performed between the two PANSS negative factors (Table 2) and the ERP measurements of patients. Correction for multiple comparisons was based on Holm's stepwise method. Partial correlation was used to test correlation between negative symptoms and the ERP data while controlling for positive symptoms.

Results

To demonstrate the independency of orienting attention and executive attention, repeated-measures ANOVAs were first performed on measurements of the accuracy rate, the RT and the P1/P3 amplitudes, with cue validity (valid vs. invalid cues) and flanker congruence (congruent vs. incongruent flankers) as within-subject factors. No significant interaction was found (the largest F values: $F(1, 25) = 1.17$ for the controls, $F(1, 26) = 0.92$ for the patients, and $F(1, 52) = 1.11$ for all the subjects). These results indicated the independency of the two attention networks in this study.

Emotion effect on orienting attention.

Behavioral data. The attention bias score of the reaction time (RT) was defined as the differential RT between invalidly and validly cued conditions.

The interaction effect of emotion by group on the attention bias score of the RT was significant ($F(1, 51) = 8.96$; $p = 0.004$; $\eta_p^2 = 0.149$). The attention bias score in controls ($F(1, 25) = 6.42$; $p = 0.014$) was higher in the fearful cue condition (59.2 ± 6.22 ms) compared with the neutral cue condition (44.5 ± 7.12 ms). However, the emotion effect on the attention bias score did not achieve significant level in patients ($F(1, 26) = 2.46$; $p = 0.123$).

The RT in the valid cue condition (804 ± 16.1 ms) was significantly shorter than that in the invalid cue condition (858 ± 14.9 ms; $p < 0.001$).

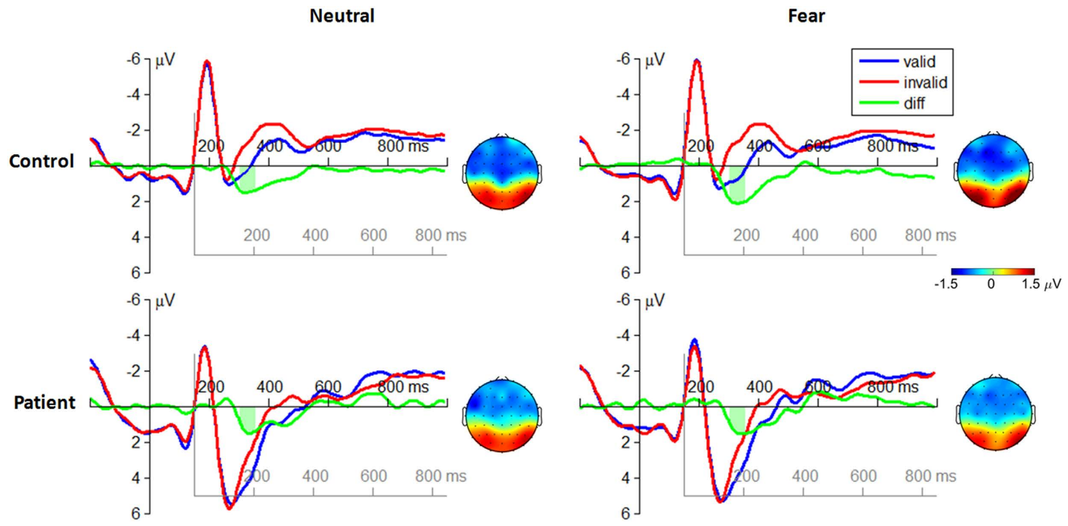

Figure 2. The grand-mean ERP waveforms in the valid cue and the invalid cue conditions at the electrode site of O1, O2, PO3, and PO4 (averaged data). The attention bias amplitude of the target-locked P1 component was defined as the mean differential amplitude between the valid cue and the invalid cue conditions within the time window of 160–210 ms after target onset (see the light green region in the figure). The black axes are locked to the cue; the grey axes are locked to the target. EEG topographies display the scalp distribution of the attention bias amplitudes of the P1 in different conditions.

The results of accuracy rate in the valid cue and the invalid cue conditions were 0.953 ± 0.009 and 0.950 ± 0.009 ($p = 0.278$). No significant effect was found in the attention bias score of the accuracy rate.

The P1 amplitude. The attention bias amplitude of the target-locked P1 component was defined as the differential amplitudes between validly and invalidly cued conditions (Fig. 2).

The interaction effect of emotion by group was significant ($F(1, 51) = 5.22$; $p = 0.027$; $\eta_p^2 = 0.093$). The attention bias amplitude of the P1 in controls ($F(1, 25) = 11.2$; $p = 0.002$) was higher in the fearful condition ($2.47 \pm 0.31\,\mu V$) compared with the neutral condition ($1.13 \pm 0.35\,\mu V$) while the emotion effect was not significant in patients ($F(1, 26) < 1$; fear $= 1.61 \pm 0.31\,\mu V$, neutral $= 1.56 \pm 0.34\,\mu V$).

The main effect of emotion was significant ($F(1, 51) = 5.99$; $p = 0.018$; $\eta_p^2 = 0.105$). The attention bias amplitude in the fearful cue condition ($2.04 \pm 0.22\,\mu V$) was larger than that in the neutral cue condition ($1.35 \pm 0.24\,\mu V$).

The P3 amplitude. The attention bias amplitude of the target-locked P3 component was defined as the differential amplitude between invalidly and validly cued condition (Fig. 3).

The interaction effect of emotion by group was significant ($F(1, 51) = 6.66$; $p = 0.013$; $\eta_p^2 = 0.115$). The attention bias amplitude of the P3 in patients ($F(1, 26) = 12.9$; $p = 0.001$) was smaller in the fearful cue condition ($0.01 \pm 0.18\,\mu V$) compared with the neutral cue condition ($0.65 \pm 0.15\,\mu V$) while the emotion effect was not significant in controls ($F(1, 25) < 1$; fear $= 0.65 \pm 0.16\,\mu V$, neutral $= 0.68 \pm 0.18\,\mu V$).

The main effect of group was significant ($F(1, 51) = 5.76$; $p = 0.020$; $\eta_p^2 = 0.101$). The attention bias amplitude evoked in the patients ($0.34 \pm 0.13\,\mu V$) was smaller than that evoked in the controls ($0.65 \pm 0.11\,\mu V$).

Correlations. Correlations were performed between the two negative symptom factors of PANSS and the attention bias amplitudes of the P1 and the P3 in fearful- and neutral-cued conditions. Totally 8 correlations ($2 \times 2 \times 2$) were performed in this section.

Results showed only one significant correlation after correction for multiple comparisons. The Factor 1 (expressive deficits) correlated significantly with the attention bias amplitude of the P1 in the fearful cue condition ($r = -0.57$, $p = 0.002$, corrected $p = 0.016$; Fig. 4). After controlling for the score of Positive scale in the PANSS, the partial correlation coefficients between Factor 1 and the attention bias amplitude of the P1 did not change greatly ($r = -0.54$, $p = 0.005$).

Emotion effect on executive attention. *Behavioral data.* The attention bias score of the RT was defined as the differential RT between the incongruent flanker condition and the congruent flanker conditions.

The interaction effect of emotion by group on the attention bias score of the RT was significant ($F(1, 51) = 5.14$; $p = 0.028$; $\eta_p^2 = 0.092$). The attention bias score in controls ($F(1, 25) = 8.41$; $p = 0.005$) was higher in the fearful cue condition (31.4 ± 4.70 ms) compared with the neutral cue condition (16.4 ± 4.88 ms). However, the emotion effect on the attention bias score did not achieve significant level in patients ($F(1, 26) < 1$).

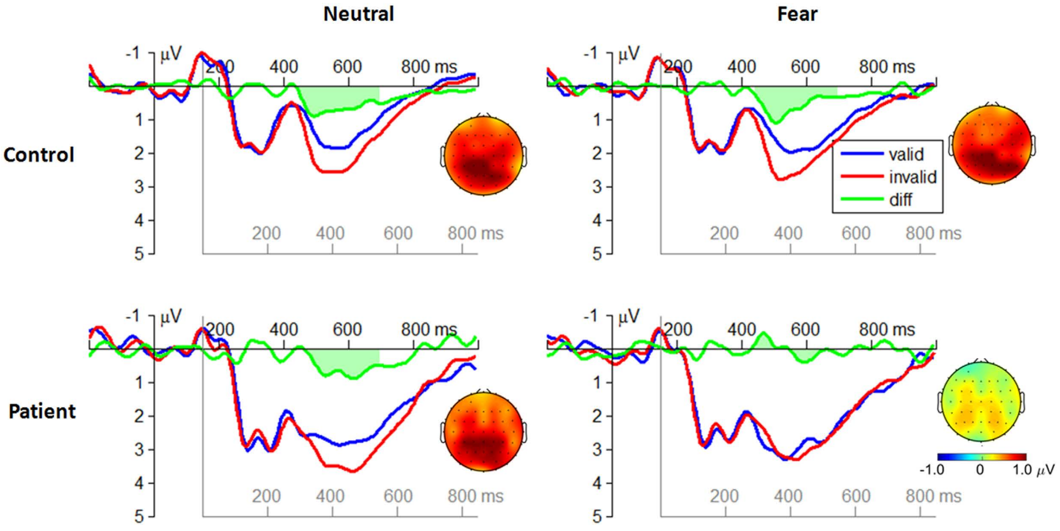

Figure 3. The grand-mean ERP waveforms in the valid cue and the invalid cue conditions at the electrode site of P1, P2, Pz, and CPz (averaged data). The attention bias amplitude of the target-locked P3 component was defined as the mean differential amplitude between the invalid cue and the valid cue conditions within the time window of 300–550 ms after target onset. EEG topographies display the scalp distribution of the attention bias amplitudes of the P3 in different conditions.

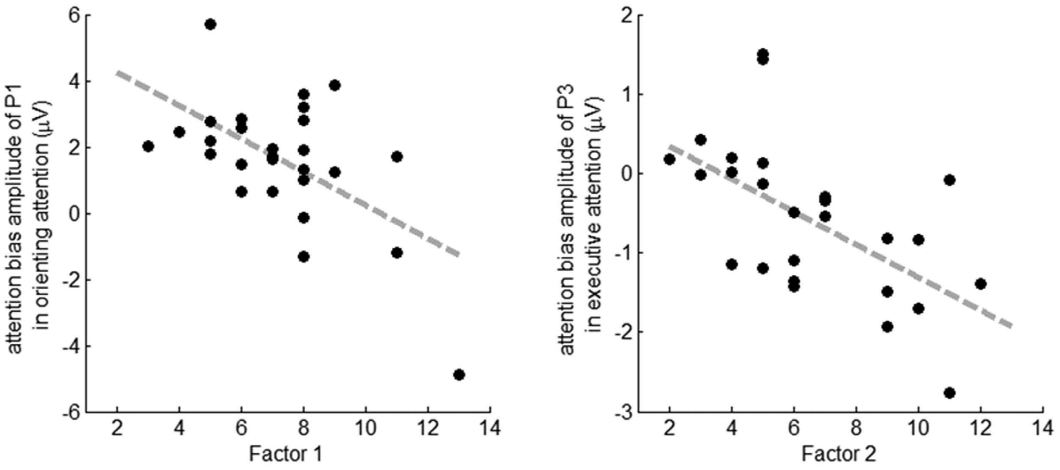

Figure 4. Correlations between the two negative symptom factors of PANSS and the attention bias amplitudes of the P1 and the P3 in orienting and executive attention networks. The x-axis is the factor score of the patients and the y-axis is the ERP amplitude. Factor 1-expressive deficits, Factor 2-avolition/asociality.

The RT in the congruent flanker condition (820 ± 14.9 ms) was significantly shorter than that in the incongruent flanker condition (841 ± 16.0 ms; $p < 0.001$).

The accuracy rate in the congruent flanker condition (0.957 ± 0.009) was significantly higher than that in the incongruent flanker condition (0.946 ± 0.010; $p < 0.001$). No significant effect was found in the attention bias score of the accuracy rate.

The P1 amplitude. The attention bias amplitude of the target-locked P1 component was defined as the differential amplitude between the incongruent flanker condition and the congruent flanker condition. No significant effect was found in the data.

The P3 amplitude. The attention bias amplitude of the target-locked P3 component was defined as the differential amplitude between the incongruent flanker condition and the congruent flanker condition (Fig. 5).

The interaction effect of emotion by group was significant ($F(1, 51) = 7.57$; $p = 0.008$; $\eta_p^2 = 0.129$). The attention bias amplitude of the P3 in patients ($F(1, 26) = 7.38$; $p = 0.009$) was smaller in the fearful cue condition (−0.60 ± 0.18 µV) compared with the neutral cue condition (−0.10 ± 0.17 µV) while the emotion effect was not significant in controls ($F(1, 25) = 1.24$, $p = 0.271$; fear = 0.73 ± 0.18 µV, neutral = 0.51 ± 0.17 µV).

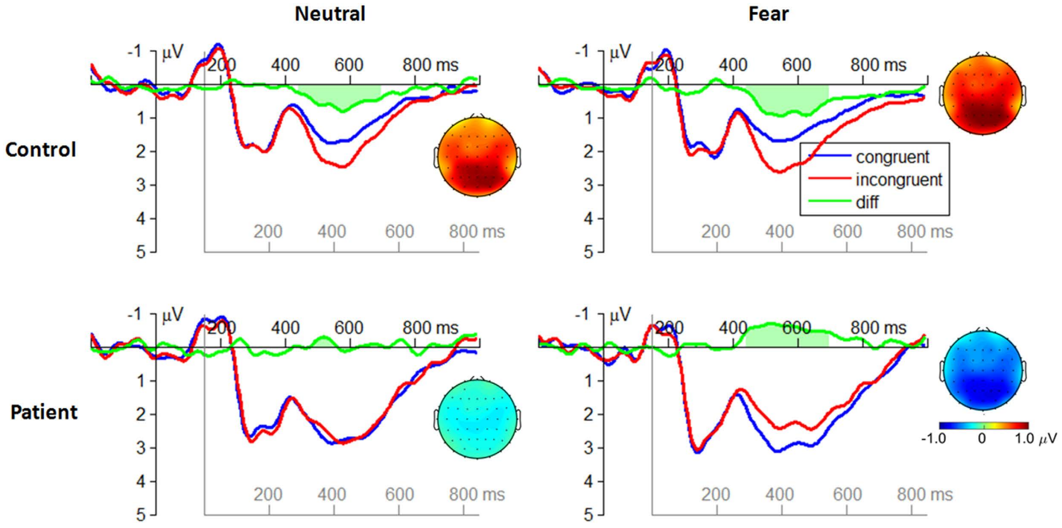

Figure 5. The grand-mean ERP waveforms in the congruent flanker and the incongruent flanker conditions at the electrode site of P1, P2, Pz, and CPz (averaged data). The attention bias amplitude of the target-locked P3 component was defined as the mean differential amplitude between the incongruent flanker and the congruent flanker conditions within the time window of 300–550 ms after target onset. EEG topographies display the scalp distribution of the attention bias amplitudes of the P3 in different conditions.

The main effect of group was significant ($F(1, 51) = 21.3$; $p < 0.001$; $\eta_p^2 = 0.294$). The attention bias amplitude evoked in the patients ($-0.35 \pm 0.15\,\mu V$) was smaller than that evoked in the controls ($0.62 \pm 0.15\,\mu V$).

Correlations. Correlations were performed between the two negative symptom factors of PANSS and the attention bias amplitudes of the P3 in fearful- and neutral-cued conditions (totally $2 \times 2 = 4$ correlations).

Results showed only one significant correlation after correction for multiple comparisons. The Factor 2 (avolition/asociality, $r = -0.58$; $p = 0.002$; corrected $p = 0.006$) correlated significantly with the attention bias amplitude of the P3 in the fearful cue condition (Fig. 4). After controlling for the score of Positive scale in the PANSS, the partial correlation coefficients between Factor 2 and the attention bias amplitude of the P3 did not change greatly ($r = -0.57$, $p = 0.002$).

Discussion

The present results identified two separate mechanisms that link specific attention deficits to different emotional/social impairments in schizophrenia. While deficits in orienting attention were correlated with the first factor of negative symptoms in patients (expressive deficits), deficits in executive control of attention were associated with the second factor of negative symptoms (avolition/asociality).

In the orienting attention network, our result revealed that schizophrenic patients were able to allocate their attention towards valid cues, evidenced with the enhanced amplitudes of the target-locked P1 component. However, the attention bias to negative stimuli was not observed in the patients, who showed similar attention bias amplitudes of the P1 between neutral and fearful conditions (Fig. 2), and even attenuated attention bias amplitudes of the P3 in fearful condition compared with neutral condition (Fig. 3). The diminished orienting attention to negative facial expressions (i.e., disappearance of "negativity bias") in schizophrenia is well in line with previous studies[40]. For instance, schizophrenic patients were found to have attenuated P1 amplitudes compared with normal subjects when they attended to negative emotional stimuli[20]; and patients displayed reduced amygdala activity, compared with controls, when they perceived fearful faces in both conscious and nonconscious conditions[41]. The "negativity bias" refers to a general tendency to process negative emotional information with priority to positive and neutral information[5]. It has been demonstrated that such quick response mainly depends on a visual pathway preferentially tuned to coarse-magnocellular inputs (i.e. low spatial-frequency information[42,43]). Our result suggests that the lack of "negativity bias" in involuntary orienting may be due to a bottom-up dysfunction within the early visual pathway in schizophrenia[40,44]. While the P1 serves as a biomarker of involuntary attention orientation, the later P3 may function as an indicator of voluntary regulation of attention[21,45]. More specifically, when the cue is invalid, participants had to re-orientate their attention to the location of the target in the dot-probe task. According to the principle of least effort[46,47], this procedure would require more cognitive resources and a larger effort of top-down regulation compared to the attention processing in the validly cued condition. Therefore the increased P3 amplitude in the invalid condition may reflect the degree of effort involved in the top-down regulation of attention, as also suggested by previous studies[21,45,48–50]. The result in Fig. 3 showed that the P3 displayed higher amplitudes in invalid condition compared with valid condition in the controls[21]; however, this pattern did not exist for the fearful cued condition in the patients. This result indicates that patients cannot appropriate re-orient his/her attention from negative emotion to goal-related direction.

More interestingly, the diminished orienting attention towards fearful faces (indexed by the attention bias amplitude of the P1) was significantly correlated with Factor 1 of the negative symptoms (i.e., expressive deficits) in schizophrenic patients (Fig. 4). Expressive deficits, which means reduced emotional expressions in social interactions, has been proved to be associated with impaired performances of affect perception tasks (e.g. facial expression recognition and discrimination)[51,52]. In addition, it has been reported that the severity of blunted affect can independently predict the performance of emotional intensity differentiation[53]. By disassociating attention constructs in the current study, it is suggested that the diminished expression in the patients is specifically associated with a failure in automatic orienting to salient signals. Though the exact causal mechanism remains unclear, one possible explanation might be that a failure in automatic orienting to salient signals may lead to patients' failure in identifying facial expressions of others[20]. Patients are thus less likely to express their own feelings, resulting in diminished expression[54].

In the executive attention network, schizophrenic patients failed to recruit enough attentional resources to resolve the flanker conflict, evidenced by the diminished amplitudes of the target-locked P3 component in incongruent condition compared to congruent one. Furthermore, such deficit became even worse when the patients were interfered by negative emotion (Fig. 5). The impaired ability to inhibit emotional information allows negative affective stimuli to exert inappropriate influence on conflict-resolving function. This result is consistent with previous studies indicating that schizophrenic patients have an impaired ability to regulate the influence of irrelevant negative affective information on cognitive processes[55,56]. Furthermore, the deficits in executive attention may be specific to social-related information, since it has been reported that patients showed no inhibitory deficit in the Stroop task when social-unrelated negative words were used[57], while they exhibited impairments of executive control when dealing with social emotional information (e.g. negative emotional faces)[18,58]. Both frontal and limbic dysfunctions (e.g. the hypo-activation of anterior cingulate cortex[59] and dorsolateral prefrontal cortex (DLPFC)[60,61]) are responsible for the deficit of executive control of attention in schizophrenia[62]. This deficit may in turn prevent the brain from inhibiting irrelevant emotional information and disturb goal-directed behaviors[63,64].

In addition, it is found that patients' abolished executive control of attention to fearful faces (indexed by the attention bias amplitude of the P3) was significantly correlated with the severity of avolition/asociality (Fig. 4). Asociality is defined as a state with diminished inspiration to participate in social activities. It is proposed that without appropriate executive control of attention to negative emotion, schizophrenic patients are unable to inhibit negative affective information when it is irrelevant to the goal-directed behavior, thus resulting in a withdrawal of any unnecessary unpleasant experiences[58], which in turn makes patients have little interest in socializing[3]. Social skill training, such as an explicit instruction on how to deal with negative social information, is likely to improve such social impairments in schizophrenic patients[65,66]. Psychopharmacological approaches are also used for effective relief of the amotivation-induced social impairments. For example, after taking apomorphine (a non-selective dopamine agonist which activates both D1-like and D2-like receptors), schizophrenic patients display enhanced activation of anterior cingulate cortex and improved willing to participate in social interaction[67,68].

It was also interesting to note that in the current study, the P3 amplitude was overall larger in the patients compared with the controls (Figs 2 and 5), which was distinct to most previous findings[27,69,70]. Actually, both hyper- and hypo-activity of ERP-measured P3 component and BOLD-measured prefrontal cortex have been identified in schizophrenic patients[71]. For instance, it was found in working memory task that patients have larger P3 amplitudes[72] and enhanced DLPFC activity[73] along with poorer behavioral performances, compared with healthy controls. A recent meta-analysis[71] further revealed that the DLPFC inefficiency might be manifested in either direction depending on task demands; when cognitive load is minimal to moderate (which is likely to be the case in our study), the DLPFC engagement is greater in the schizophrenic subjects than in controls. However, it is currently unknown whether the observed inefficiency in attention control is a general deficit or more specific to emotion perception.

Finally, readers may notice an atypical use of the component term in the present analysis. The typical peak latency for the P1component is 100–130 ms (Luck, 2005). However, we used the term P1 to name the relatively blunt component (rather than a sharp one) with the peak latency of approximately 185 ms post target onset (Fig. 2). We made this designation mainly because the scalp topography of this component was consistent with the expectation for lateral occipital P1 (Luck, 2005). The latency delay observed for the P1 component is likely attributable to its calculation method, i.e., this component was examined based on the differential waveforms between valid and invalid conditions (the P1 peaked earlier in the original ERP waveforms before waveform subtraction).

In summary, we find two separate mechanisms that link specific attention deficits to different emotional/social impairments. While deficits in orienting attention correlate with diminished expression, deficits in executive control of attention are found to be associated with avolition/asociality. Moreover, the inclusion of neuroleptic naive patients helped clarify the behavioral and ERP deviations found in this study. Though the exact causal mechanism remains unclear, we propose that the failure in orienting to salient social information may be responsible for the diminished expression in patients. The deficits in executive control of attention prevent patients to appropriately resolve social conflicts, resulting in avolition and less socializing. Together, these findings may shed some light on resolving the heterogeneity of schizophrenia, particularly with respect to the variety of impairments in social functions found in this disorder.

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Author Contributions

Y. Liu and D.Z. conceived the experiments. Y.Z. and S.T. conducted the experiments. D.Z. performed the data analysis. Y. Liu, D.Z. and Y. Luo wrote the manuscript.

Additional Information

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RESEARCH ARTICLE

The Impact of Perceptual Load on the Non-Conscious Processing of Fearful Faces

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Abstract

Emotional stimuli can be processed without consciousness. In the current study, we used event-related potentials (ERPs) to assess whether perceptual load influences non-conscious processing of fearful facial expressions. Perceptual load was manipulated using a letter search task with the target letter presented at the fixation point, while facial expressions were presented peripherally and masked to prevent conscious awareness. The letter string comprised six letters (X or N) that were identical (low load) or different (high load). Participants were instructed to discriminate the letters at fixation or the facial expression (fearful or neutral) in the periphery. Participants were faster and more accurate at detecting letters in the low load condition than in the high load condition. Fearful faces elicited a sustained positivity from 250 ms to 700 ms post-stimulus over fronto-central areas during the face discrimination and low-load letter discrimination conditions, but this effect was completely eliminated during high-load letter discrimination. Our findings imply that non-conscious processing of fearful faces depends on perceptual load, and attentional resources are necessary for non-conscious processing.

Introduction

Facial expressions are an important component of social communication. For example, fearful expressions are powerful signals of danger in the environment. Being aware of imminent danger is essential to survival of most animals [1]. For this reason, rapid detection of fearful expressions has an obvious adaptive advantage, and fearful expressions may therefore be more likely than other stimuli to capture attention.

Because of the adaptive advantage, it is often assumed that fearful expressions can be processed without attention or consciousness. Neuroimaging studies have demonstrated that the amygdala responds to fearful faces when this information is not accessible to consciousness, suggesting that fearful stimuli can be processed automatically [2–5]. Event-related potential (ERP) measures have also provided evidence for the automatic processing of subliminal fearful

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faces. Previous studies have found five main ERP components modulated by subliminal fearful faces: anterior N1, N170, vertex positive potential (VPP), N2 and P300. The study by Liddell et al. (2004) was one of the early studies to investigate the ERP responses to subliminal fearful faces and found that subliminal fear increased the amplitude of N2, while supraliminal fear enhanced P3 [6, 7]. The authors considered N2 to be an index of the automatic processing of subliminal fearful stimuli. Kiss and Eimer (2008) reported the similar findings of an N2 enhancement to fearful faces presented subliminally, but not supraliminally [8]. Not all studies have shown a pattern of enhanced N2 to subliminal fearful faces, however. Very recently, one group found the opposite effect, showing increased N2 amplitude to supraliminal and enhanced P3 to subliminal fearful faces [9]. Another study found that, compared to neutral faces, fearful faces reduced N2 amplitude in both subliminal and supraliminal conditions[10]. In addition, subliminal fearful faces can be processed at an early stage, as indicated by an N170/VPP enhancement [8, 11]. Moreover, Eimer et al. (2008) found anterior N1 enhancement in response to masked fearful faces only in trials in which participants successfully detected the fearful faces[12]. In all of these studies, the consistent finding was that the neural response to subliminal fearful faces was different from the response to neutral faces, providing evidence that the subliminal fearful faces can be processed by the brain.

Some researchers have proposed that although fearful stimuli can be processed in the absence of consciousness, such processing may not occur automatically, unconstrained by the availability of attentional resources [13]. Since attentional resources are limited, the extent to which irrelevant distractors are processed depends on the perceptual load of the main task [14]. According to perceptual load theory, perceptual load constitutes a necessary condition for selective attention. Specifically, a high perceptual load for relevant information processing exhausts attentional resources and prevents processing of irrelevant information. However, a low perceptual load does not exhaust attentional resources, thus attention can be spared to process task-irrelevant stimuli. This framework explains why emotion may be processed without attention in tasks with low perceptual load. In support of this theory, several fMRI studies have demonstrated are sponse of the amygdala to unattended fearful expressions in low but not high perceptual load conditions [15–20].

The aim of this study was to test whether the non-conscious processing of fearful faces is constrained by the availability of attentional resources. In most non-conscious processing studies, task-related fearful stimuli are presented at the focal point of attention without any competing stimuli. According to perceptual load theory [14], both task-relevant and task-irrelevant stimuli compete for limited attentional resources, and this competition does not rely on the conscious awareness of task-irrelevant stimuli. Recent studies using binocular rivalry have suggested that subliminal perception can be modulated by the perceptual load [21, 22]. For example, Bahramiet al. (2007) found that the processing of subliminal stimuli in human primary visual cortex (V1) depends on perceptual load. V1 activity to subliminal tool images was reduced in a high load condition compared to a low load condition. However, it remains unclear whether processing of subliminal fearful faces can be influenced by perceptual load.

In the present study, we measured ERPs to determine the effects of perceptual load on the non-conscious processing of fearful faces. Perceptual load was manipulated using a letter search task with letters presented at fixation, and facial expressions (fearful or neutral) were presented peripherally and masked by scrambled faces. Participants were instructed to discriminate the letters at fixation or the facial expression in the periphery. To further examine fear-specific ERP effects in response to subliminal faces, we included a face task, in which participants had to indicate whether masked facial expressions were fearful or neutral. We focused on five main ERP components (anterior N1, N170, VPP, N2 and P3). Our hypothesis was that if the non-conscious processing of fearful faces can be modulated by perceptual load, enhanced responses to fearful faces would be attenuated in the high load condition, which consumes greater attentional resources. In contrast, spill-over of spare attentional capacity in the low load condition should result in larger amplitudes for fearful faces than neutral faces. Alternately, similar ERP effects under low and high load conditions would indicate that non-conscious processing of fearful stimuli may be independent of perceptual load.

Materials and Methods

Participants

Twenty-six subjects (13 females, 13 males, right-handed, 18–27 years of age) were recruited from Beijing Normal University in China as paid participants. According to self-report, all participants had normal or corrected-to-normal vision and no history of brain injury. The study was approved by Institutional Review Boards of Beijing Normal University. Written informed consents were obtained from all participants.

Stimuli

A letter string (3.43°× 0.85° visual angle) was presented at fixation with two identical faces (1.84°× 2.14° each) in the left and right periphery (5.95° eccentricity). Faces were black and white photographs taken from the native Chinese Facial Affective Picture System [23]. A total of 60 grayscale pictures of different individual faces were used. Target face stimuli consisted of 20 fearful faces and 20 neutral faces. Another different 20 neutral faces were used to generate scrambled face masks by dividing each image into a 6×6 matrix of tiles and then randomly rearranging the tiles. Males and females were represented equally among the pictures. The letter strings comprised of six upper-case letters and included target (N or X) and nontarget letters (H, K, M, W, or Z). Low-load letter strings were made of 6 Xs or 6 Ns, whereas high load strings consisted of one of the target letters and five nontarget letters in random order (e.g. 'NHKWZM'). There was a 50% chance for the target letter to be either an 'X' or an 'N'. Such letter strings have been used in previous studies [17, 24, 25], and are considered to be valid in the manipulation of perceptual load.

Procedure

E-Prime software (Psychology Software Tools, Pittsburgh, PA) was used for stimulus presentation and behavioral response collection. The present study consisted of 6 blocks, each containing 100 trials. In each trial (see Fig 1), an initial fixation was presented for 500 ms. After an interstimulus interval (ISI) between 400 and 600 ms, two identical faces were presented together with a letter string for 16.7 ms. The faces were then masked by scrambled faces (200 ms duration), followed by a blank screen which would not disappear until a button-press or until 1500 ms elapsed. The intertrial interval was 500 ms. Participants were required to indicate whether the target letter was an 'X' or an 'N' in 4 of the blocks (letter task) or whether the masked facial expression was fearful or neutral in the other 2 blocks (face task) by pressing "F" or "J" on the keyboard with their left or right index fingers, respectively. Participants were instructed to respond to the targets as quickly and accurately as possible. At the beginning of each block, an instruction display was presented to instruct participants as to whether they would be performing the face task or the letter task. Therefore, the focus of their attention (on letters or faces) changed between blocks. The sequence of six blocks was randomized for each participant. In each block, high- and low-load letter strings appeared randomly and with equal probability, and half of the faces were fearful, the other half were neutral.

Participants were seated in a dimly lit and sound-attenuated room, with their eyes approximately 100 cm away from the screen. Stimuli were presented on a 21-inch CRT monitor (60

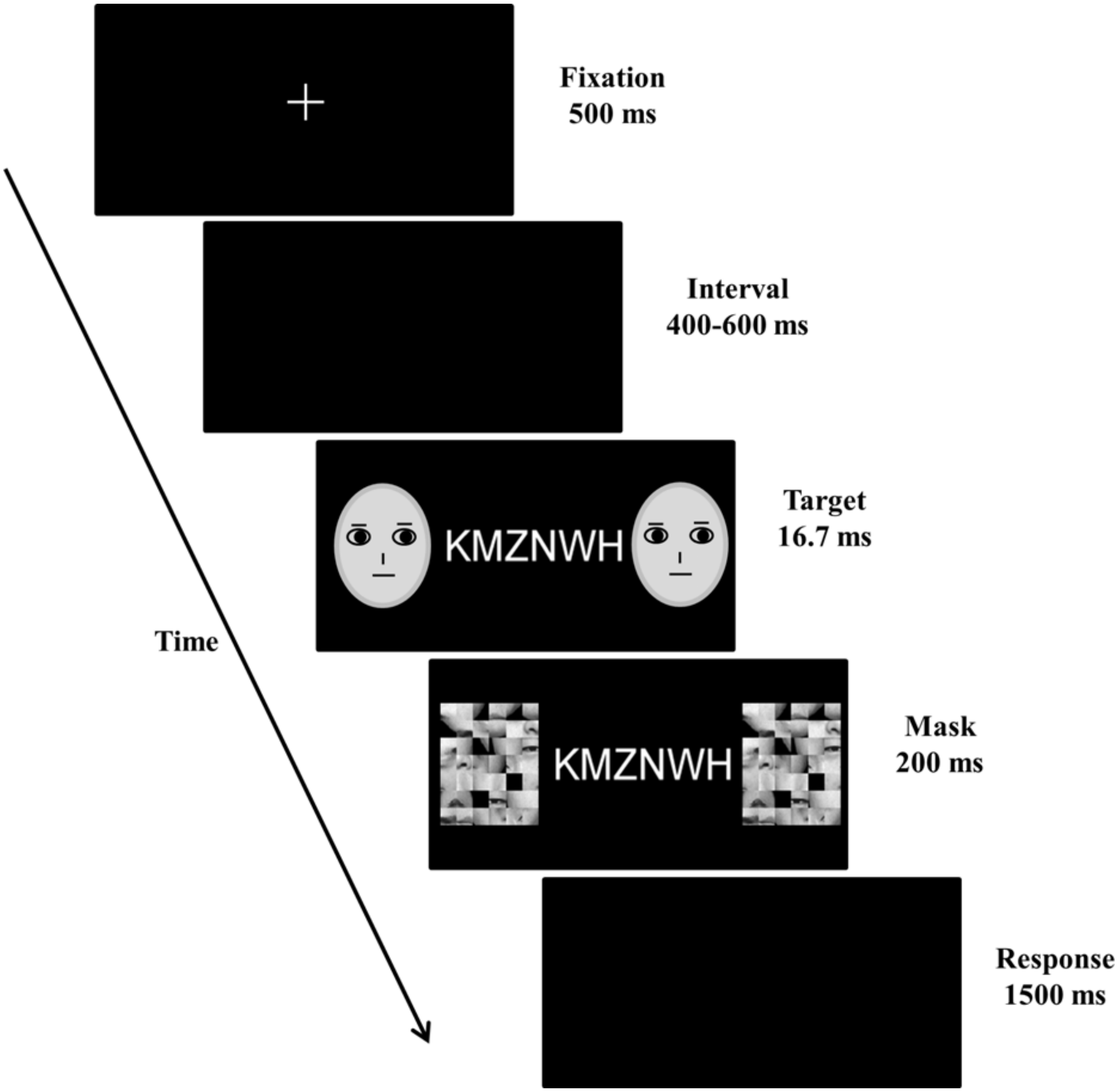

Fig 1. Example of stimulus sequence. On each trial, subjects fixated and viewed a string of 6 letters presented in the centre of the screen, and facial expressions were presented peripherally for 16.7 ms and masked by scrambled faces. The letter string comprised six identical (low load) or six different letters (high load). Participants were instructed to discriminate the letters (X or N) at fixation or the facial expression (fearful or neutral) in the periphery. Please note that schematic faces displayed in the figure were not employed in the experiment but were only used for illustration purpose due to issues of copyrights. Real facial expressions were employed as stimuli in the experiment.

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Hz refresh rate).To ensure the participants maintained vigilance for the face task, it was emphasized that although the masked face would be difficult to see, they had to attend to faces in preparation for post-testing briefings. We actually did not have briefings after the test. This method was often used in the subliminal studies [6, 7].

EEG recording

Electroencephalogram (EEG) was recorded from 64 scalp sites using Ag/AgCl electrodes mounted in an elastic cap (NeuroScan Inc., Herndon, Virginia, USA), with the reference on the left mastoid. Vertical electrooculogram (VEOG) was recorded from electrodes above and below the left eye, and horizontal electrooculogram (HEOG) was recorded from electrodes placed at the outer canthi of both eyes. All interelectrode impedance was maintained below 5kΩ. The EEG and EOG were amplified using a 0.05–100 Hz bandpass filter and continuously sampled at 500 Hz/channel. The EEG data was low-pass filtered offline below 30 Hz and re-referenced to the global average reference. Trials containing blinks, eye movements, or other artifacts (EEG sweeps with amplitudes exceeding ±80μV) were excluded.

Data analysis

The ERPs for the target stimuli were analyzed in the present study. The ERP waveforms were time-locked to the onset of the target stimuli. Separate EEG epochs of 1000 ms (200 ms baseline) were extracted offline for the stimuli. In the letter task, only trials with correct behavioral responses were included in the average. In the face task, because the discrimination performance of the target faces was at chance level, ERPs were collapsed across trials in which participants responded correctly or incorrectly [8]. The mean number of trials contributing to ERP averages for fearful faces in face, low-load, and high-load conditions was 98, 94, and 71, respectively, and for neutral faces was also 98, 94, and 71, respectively.

Based on the results of previous ERP studies [6–8, 11], anterior N1, N170, VPP, N2, and P3 components were measured. Through visual inspection of the grand-average and previous studies [8, 9], the baseline-to-peak amplitudes of anterior N1 (80–140 ms) and VPP (140–190 ms) and the mean amplitudes of N2 (250–330 ms) were computed at the following 9 electrode sites: F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4; the mean amplitude of P3 (450–700 ms) was computed at FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, P3, Pz, and P4. Four-way repeated measures analysis of variance (ANOVA) were conducted for these components with Task (face *vs*. low load *vs*. high load), Expression (fearful *vs*. neutral), Hemisphere (left *vs*. midline *vs*. right), and Electrode as within-subject factors. In addition, the baseline-to-peak amplitude of N170 component was measured at occipito-temporal sites (P7, P8, PO7, and PO8) as the maximal negative peak in the time window of 150–190 ms. The N170 amplitude was then analyzed using a 3 × 2 × 2 × 2 four-way repeated measures analysis of variance with Task (face *vs*. low load *vs*. high load), Expression (fearful *vs*. neutral), Hemisphere (left *vs*. right), and Electrode (parietal: P7 and P8 *vs*. parieto-occipital: PO7 and PO8) as within-subject factors. Greenhouse-Geisser corrected degrees of freedom were used whenever appropriate[26]. Post-hoc testing of significant main effects was conducted using Bonferroni method.

Results

Behavioral results

In the letter detection task, mean reaction times (RTs) and accuracy data were submitted to a 2 × 2 two-way repeated measures ANOVA with factors of Load (low load *vs*. high load) and Expression (fearful *vs*. neutral). Analysis of RTs revealed a significant main effect of Load, $F\,(1, 25) = 295.03$, $p < 0.001$, $\eta_p^2 = 922$, participants responded faster in the low-load task (M ± SE, 308.18 ± 15.46 ms) than in the high-load task (620.03 ± 25.24 ms). The results revealed no effect of Expression ($F\,(1, 25) = 0.15$, $p > 0.69$), and no interaction on RTs ($p > 0.87$). Analysis of accuracy revealed a significant main effect of Load, $F\,(1, 25) = 730.23$, $p < 0.001$, $\eta_p^2 = 0.967$. The accuracy was higher in the low-load task (96.10 ± 0.68%) compared to the high-load task (72.65 ± 1.06%). We did not find the significant main effect of Expression ($F\,(1, 25) = 0.001$, $p > 0.97$), or interaction ($p > 0.62$).

In the face task, mean RTs for trials with correctly reported fearful faces and neutral faces were 412.22 ± 37.64 ms and 417.30 ± 39.19 ms, and the difference between facial expressions

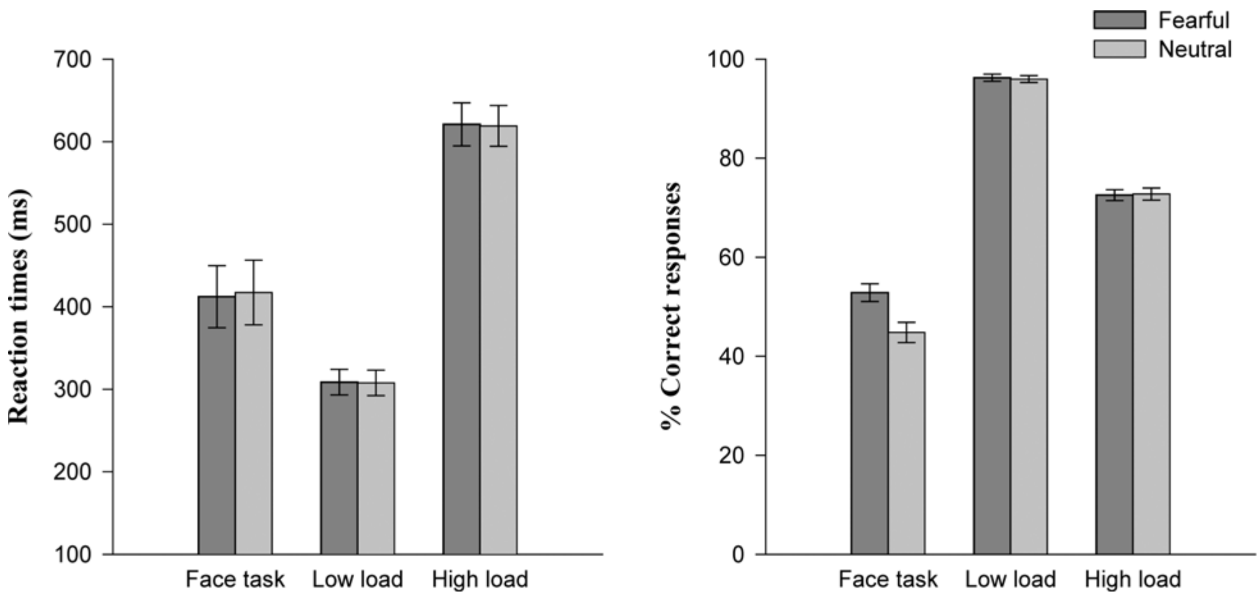

Fig 2. Reaction times and percentages of correct responses in the face task and letter task across low or high perceptual load and fearful or neutral peripheral facial expressions. Error bars show one standard error (S.E).

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was not significant, t (25) = -0.76, $p > 0.45$. The accuracy was higher for fearful faces (52.85 ± 9.10%) than neutral faces (44.81 ± 10.49%), t (25) = 2.43, $p = 0.023$. See Fig 2 for behavioral results.

To obtain an objective estimate of participants' ability to detect masked fearful faces in the face task, d' values (Macmillan and Creelman, 1991) were measured on the basis of hits (correct responses on trials with fearful targets) and false alarms (incorrect responses on trials with neutral targets). The mean d' (-0.05) did not significantly differ from zero (t (25) = -1.25, $p > 0.22$), suggesting that participants' performance of face discrimination was at the level of chance. These data suggest that participants were not able to categorize the subliminal facial expressions above chance. Response bias c (Macmillan and Creelman, 1991) was also computed and showed that participants were more likely to report fearful faces ($c = -0.11$; t (25) = -2.45, $p = 0.022$). The result of accuracy analysis showed a high accuracy for fearful faces (fearful: 52.85%; neutral: 44.81%), which may be due to participants having a higher tendency to answer "fear" when in doubt.

ERP results

Anterior N1. Anterior N1 is an early anterior negativity (80-140ms) and the anterior part of the visual P1. Four-way repeated measures ANOVA of Task (face *vs*. low load *vs*. high load) by Expression (fearful *vs*. neutral) by Hemisphere (left *vs*. midline *vs*. right) by Electrode (frontal: F3, Fz, and F4 *vs*.fronto-central: FC3, FCz, and FC4 *vs*. central: C3, Cz, and C4) on anterior N1 amplitudes yielded a significant main effect at Electrode, F (1.17, 29.17) = 8.03, $p = 0.006$, $\eta_p^2 = 0.243$. Post-hoc tests showed that the anterior N1 amplitude was significantly more negative for fronto-central sites (-2.44 ± 0.22 μV) relative to central sites (-1.95 ± 0.18 μV; $p < 0.001$), but there was no differences between frontal (-2.36 ± 0.26 μV) and fronto-central sites, or between frontal and central sites (all ps > 0.05). The main effect of Hemisphere also reached significance (F (2, 50) = 40.91, $p < 0.001$, $\eta_p^2 = 0.621$), and post hoc tests showed that the amplitude was enhanced for midline (-2.87 ± 0.26 μV) compared to the left (-1.89 ± 0.19 μV) and right

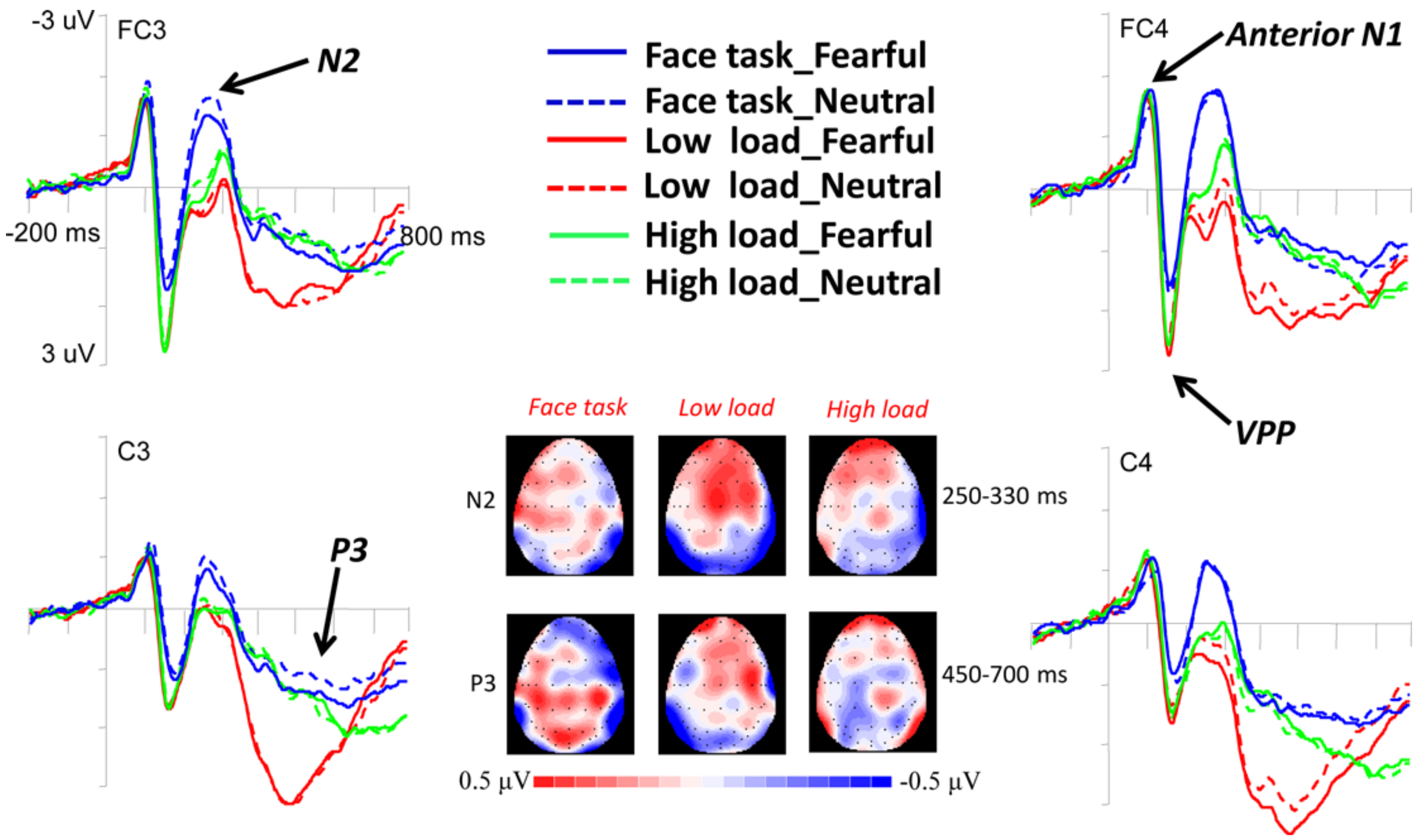

Fig 3. Grand average ERP waveforms elicited by masked fearful faces and masked neutral faces in the face task and letter task across low or high perceptual load at fronto-central and central electrodes. The topographic maps at the bottom display differences between the ERPs for fearful and neutral stimuli in the time window of 250-330ms and 450–700 ms.

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(-1.99 ± 0.20μV) hemispheres (all $ps < 0.05$). The Electrode × Hemisphere interaction reached significance, $F(2.40, 59.94) = 17.01$, $p < 0.001$, $\eta_p^2 = 0.405$, showing that frontal and fronto-central sites elicited larger amplitudes than central sites over both the left and right hemisphere (all $ps < 0.05$), but no difference between frontal and fronto-central sites was observed (all $ps > 0.05$); over the midline, the amplitudes were higher for FCz than Fz and Cz (all $ps < 0.05$) with no difference between Fz and Cz ($p > 0.05$). There was no significant effect involving task and expression (see Fig 3).

N170. Four-way repeated measures ANOVA of Task (face *vs*. low load *vs*. high load) by Expression (fearful *vs*. neutral) by Hemisphere (left *vs*. right) by Electrode (parietal: P7 and P8 *vs*.parieto-occipital: PO7 and PO8) on N170 amplitudes yielded a main effect of Task ($F(1.20, 29.91) = 60.16$, $p < 0.001$, $\eta_p^2 = 0.706$), indicating that both low load (-5.23 ± 0.54 μV) and high load (-5.14 ± 0.53 μV) elicited larger negativity than the face task (-3.18 ± 0.52 μV). The main effect of Electrode also reached significance, $F(1, 25) = 24.13$, $p < 0.001$, $\eta_p^2 = 0.491$, showing that the amplitudes were more negative for parieto-occipital electrodes (-5.37 ± 0.66 μV) than parietal electrodes (-3.67 ± 0.40 μV). Moreover, the interaction of Expression by Hemisphere by Electrode was significant, $F(1, 25) = 7.84$, $p = 0.01$, $\eta_p^2 = 0.239$, indicating that the N170 amplitude was marginally larger for fearful faces (-3.53 ± 0.37 μV) compared to neutral faces (-3.35 ± 0.39 μV) at electrode P8 ($p = 0.07$), but no difference between fearful faces and neutral faces was found at electrode P7, PO7 and PO8 (all $ps > 0.11$) (see Fig 4).

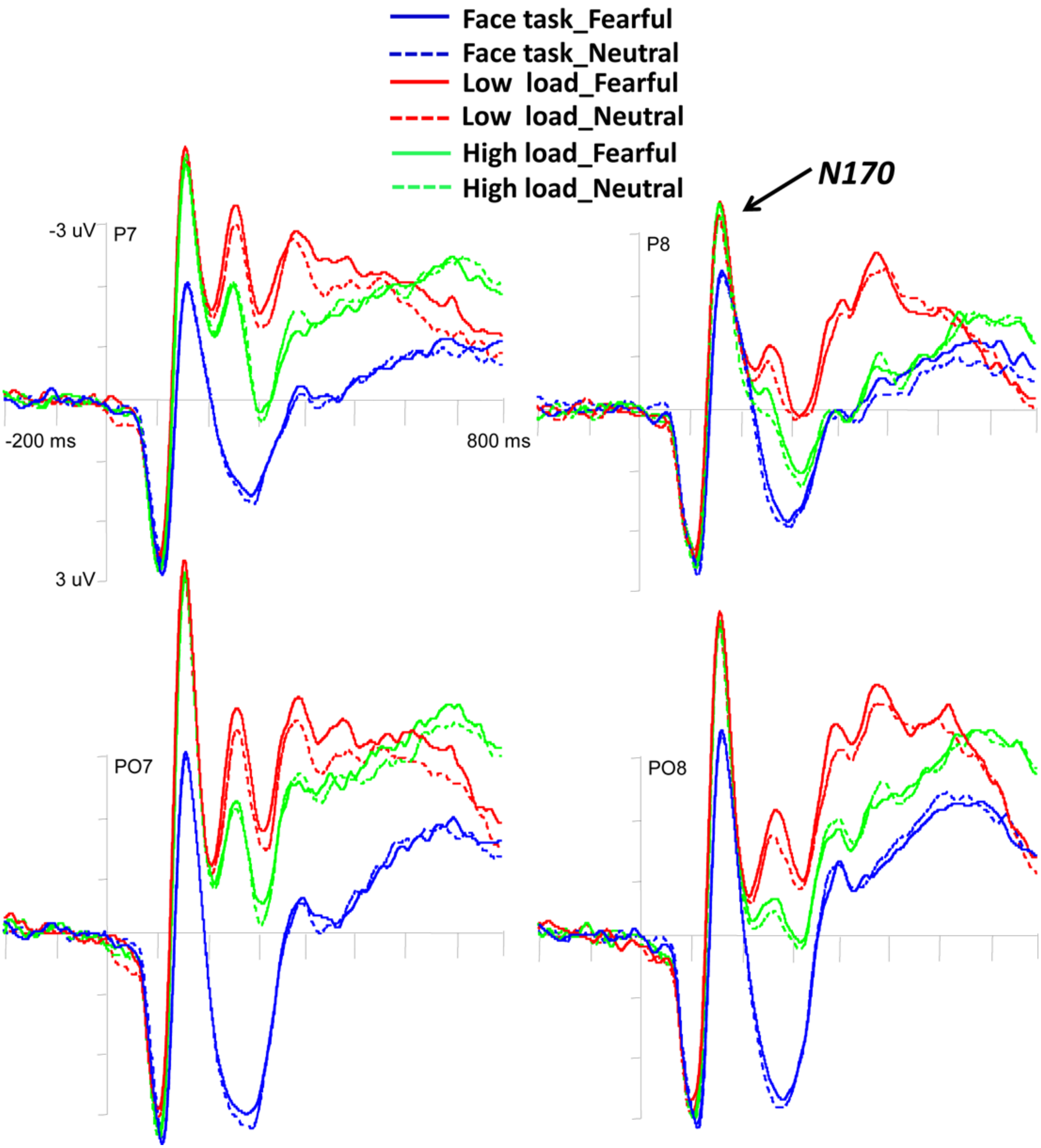

Fig 4. Grand average ERP waveforms elicited by masked fearful faces and masked neutral faces in the face task and letter task across low or high perceptual load at lateral occipito-temporal electrodes.

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VPP. Four-way repeated measures ANOVA of Task (face *vs*. low load *vs*. high load) by Expression (fearful *vs*. neutral) by Hemisphere (left *vs*. midline *vs*. right) by Electrode (frontal: F3, Fz, and F4 *vs*.fronto-central: FC3, FCz, and FC4 *vs*. central: C3, Cz, and C4) on VPP amplitudes yielded a significant effect of Task (F (1.30, 32.45) = 38.59, $p < 0.001$, $\eta_p^2 = 0.607$), indicating that the amplitudes were smaller for the face task (2.03 ± 0.33 μV) than low-load (2.97 ± 0.33 μV) and high-load (3.02 ± 0.35 μV) tasks (all ps < 0.001), and no difference between low and high load tasks was observed ($p > 0.47$). The main effect of Electrode also reached significance (F (1.14, 28.58) = 27.88, $p < 0.001$, $\eta_p^2 = 0.527$), and post hoc tests demonstrated larger amplitudes at frontal sites (3.32 ± 0.39 μV) than fronto-central (2.77 ± 0.36 μV) and central (1.92 ± 0.29 μV) sites, and the difference between the latter two sites also reached significance (all ps < 0.01) (see Fig 3).

N2 (250-330ms). Four-way repeated measures ANOVA of Task (face *vs*. low load *vs*. high load) by Expression (fearful *vs*. neutral) by Hemisphere (left *vs*. midline *vs*. right) by Electrode (frontal: F3, Fz, and F4 *vs*.fronto-central: FC3, FCz, and FC4 *vs*. central: C3, Cz, and C4) on N2 amplitudes yielded main effects of Task, Expression, and Hemisphere (F (2, 50) = 35.20, $p < 0.001$, $\eta_p^2 = 0.585$; F (1, 25) = 7.74, $p = 0.01$, $\eta_p^2 = 0.236$; F (2, 50) = 15.39, $p < 0.001$, $\eta_p^2 = 0.381$). The face task (-1.44 ± 0.29 μV) elicited larger negativity than low load (0.20 ± 0.31 μV) and high load (-0.63 ± 0.30 μV), and the difference between the latter two tasks also reached significance (all ps < 0.01). In addition, the amplitudes were more negative for neutral faces (-0.69 ± 0.27 μV) compared with fearful faces (-0.55 ± 0.29 μV). Increased amplitudes were observed over midline (-1.25 ± 0.36 μV) compared to left (-0.29 ± 0.25 μV) and right (-0.33 ± 0.28 μV) hemisphere (all ps < 0.001), and no difference was found between the left and right hemisphere ($p > 0.99$).Importantly, there was also a Task × Expression × Hemisphere interaction (F (4, 100) = 2.68, $p = 0.036$, $\eta_p^2 = 0.097$). Further analysis revealed that the N2 amplitudes were more positive for fearful than neutral faces in the face and low-load tasks (all ps < 0.05), but no difference in N2was observed between facial expressions in the high-load task (all ps > 0.05). In the face task, the N2 difference between facial expressions was observed over the left hemisphere (fearful, -0.97 ± 0.28 μV; neutral, -1.13 ± 0.29 μV; $p = 0.039$), but not observed over the midline (fearful, -1.92 ± 0.37 μV; neutral, -2.02 ± 0.38 μV; $p > 0.38$) or right hemisphere (fearful, -1.31 ± 0.29 μV; neutral, -1.29 ± 0.24 μV; $p > 0.73$). In the low load condition, the N2 difference between facial expressions was observed over both the midline (fearful, -0.05 ± 0.41 μV; neutral, -0.42 ± 0.37 μV; $p = 0.004$) and right hemisphere (fearful, 0.68 ± 0.33 μV; neutral, 0.36 ± 0.34 μV; $p = 0.013$), but not over the left hemisphere (fearful, 0.36 ± 0.29 μV; neutral, 0.28 ± 0.29 μV; $p > 0.45$) (see Fig 3).

P3 (450-700ms). Four-way repeated measures ANOVA of Task (face *vs*. low load *vs*. high load) by Expression (fearful *vs*. neutral) by Hemisphere (left *vs*. midline *vs*. right) by Electrode (fronto-central: FC3, FCz, and FC4 *vs*. central: C3, Cz, and C4 *vs*. centro-parietal: CP3, CPz, and CP4 *vs*. parietal: P3, Pz, and P4) on P3 amplitudes revealed a main effect of Task, F (2, 50) = 23.72, $p < 0.001$, $\eta_p^2 = 0.487$. As shown in Fig 3, Post-hoc tests indicated that P3 amplitude was greater in the low load task (1.84 ± 0.13 μV) than in face (0.80 ± 0.14 μV) and high load tasks (1.22 ± 0.17 μV; all ps < 0.01), while the latter two tasks did not show significant differences ($p > 0.068$). Also the main effect of Electrode was observed (F (1.23, 30.68) = 10.58, $p = 0.002$, $\eta_p^2 = 0.297$). Post-hoc tests indicated that P3 amplitude was greater at the central sites (2.00 ± 0.19 μV) than fronto-central sites (1.35 ± 0.24 μV; $p = 0.001$) and parietal sites (0.33 ± 0.27 μV; $p = 0.001$), while there was no difference between central sites and centro-parietal (1.47 ± 0.18 μV, $p > 0.15$). Moreover, a significant Task × Expression × Hemisphere interaction was observed, F (4, 100) = 2.64, $p = 0.038$, $\eta_p^2 = 0.095$. Post-hoc tests showed that fearful faces elicited larger P3 amplitudes than neutral faces in the face and low-load tasks, but this effect was only observed over the left hemisphere in the face task (fearful, 0.86 ± 0.15 μV;

neutral, 0.60 ± 0.13 μV; $p = 0.013$) and over the right hemisphere in the low-load task (fearful, 1. 72 ± 0.17 μV; neutral, 1.51 ± 0.17 μV; $p = 0.016$). The effect was completely eliminated in the high-load task (all $ps > 0.26$).

Discussion

To examine whether processing of subliminal fearful faces is constrained by attentional resources, we manipulated perceptual load by having participants perform simple and difficult letter search tasks. Two identical faces (either neutral or fearful) were presented peripherally and masked by scrambled faces. Participants were unable to categorize the faces by emotional expression. ERP results in the face task showed that fearful faces were associated with reduced N2 amplitude and increased P3 amplitude relative to neutral faces. The perceptual-load manipulation was highly effective in both behavioral and ERP responses, as participants were consistently faster and more accurate at detecting letters in the low-load task than in the high-load task. Similar to the face task, the low-load task was associated with reduced N2 and increased P3 amplitudes in response to fearful faces relative to neutral faces. However, no changes in ERP components were observed during high perceptual load. Our results suggest that processing of subliminal fearful faces depends on perceptual load.

Based on ERP findings in the face task and low-load task, N2 and P3 appear to be sensitive to the influence of perceptual load upon non-conscious processing of fearful faces. Previous studies have found these two components to be modulated by subliminal or supraliminal conditions with a great deal of variability across studies. Most reports have shown that enhanced N2 to fearful faces in subliminal but not supraliminal conditions, and the N2 effect was therefore interpreted as an index of a non-conscious attention-orienting response to fearful faces [6–8]. Some researchers also reported that a P3 enhancement to fearful faces was found in supraliminal but not subliminal conditions, suggesting that P3 might be related to conscious processing of emotional stimuli [6, 8, 11]. However, other studies observed no difference in N2 between subliminal fearful and neutral faces [9, 11], or enhanced P3 to fearful faces on subliminal trials [9]. In contrast to previous investigations, our study showed an enhanced positivity for fearful faces relative to neutral faces from about 250 ms to 700 ms after stimulus onset. That is, reduced N2 and enhanced P3 to fearful faces were revealed in the face task and low-load task. In line with our findings, a recent study by Smith (2012) revealed that N2 amplitude was reduced for fearful faces relative to neutral faces, regardless of whether the faces were subliminal or supraliminal[10]. Enhanced positivity for fearful faces has often been observed under supraliminal conditions [27–31]. Such modulation may reflect the elaboration and context evaluation of the incoming emotional signals [31, 32]. Our findings suggest that such emotional positivity may not be consciousness-specific, but can also be elicited by non-conscious stimuli. Balconi and Mazza (2009) also reported that P3 amplitudes were increased for subliminal facial expressions with high arousal (e.g., fear, happiness, surprise) compared to faces with low arousal (e.g., neutral, sadness) [9]. These ERP effects imply that the brain can detect subliminal threat information, which is adaptive for human survival.

An unexpected finding was the distinct topographic differences between fearful and neutral faces in different tasks. For the face task, the emotional positivity effects of fearful faces (N2, P3) were greater in the left hemisphere; for the low-load task, these effects were greater in the right hemisphere. For decades, many researchers have investigated brain lateralization of emotional processing, and the dominance of the right hemisphere has been emphasized in negative facial expression processing, while some studies have also supported left brain activity [33, 34]. The specific pattern of brain activation observed during face and low-load tasks in the current study may have been due to the task demands, which determined whether facial expressions were processed in the focus of attention or the periphery. In the face task, participants were required to discriminate facial expressions in the periphery, and the faces were processed with sufficient attentional resources. In the low-load task, participants performed a letter discrimination task at the focal point, and fewer attentional resources remained for processing peripheral faces. In other words, task demands influenced the degree of attentional resources allocated to process faces, and might have affected brain activation. Research by Hardee et al. (2008) has suggested that the left and right amygdala play different roles in emotional processing [35]. The right amygdala may act as a course detector of overall change, focusing automatically and non-selectively on potential threat signals [3], while the left amygdala is sensitive to detailed information of emotional expression (e.g., gaze direction, eye white area) and differentiates between emotional expressions, demonstrating a higher level of discrimination [35]. The emotional positivity for fearful faces in our study might reflect a contribution of subcortical (e.g. amygdala) modulation of cortical activity [36]. In the face task, plenty of available attentional resources made the details of emotional expressions (e.g., eyes, mouth) available for processing and the left amygdala may have been more involved in processing than the right amygdala. In contrast, the right amygdala might be activated in low load conditions with less attentional resources to process fearful faces, and this process might be coarse and automatic. Our ERP effect in low load condition was consistent with a previous fMRI study [20], which found that unattended fearful faces activated the right but not left amygdala in the low-load task. Furthermore, the left frontal regions (e.g., anterior cingulated, inferior frontal, medial frontal), used for alerting one to significant and novel stimuli, can be activated in response to non-conscious emotional faces presented inside the attentional focus [37, 38]. However, the anatomical level of the specific ERP effects cannot be inferred from the present study. Further source analyses and fMRI studies are needed to determine the role of the left and right hemisphere in emotional processing.

A fundamental question in the study of emotion is its relationship to attention and awareness. Previous reports have shown that processing of emotional stimuli could be affected by perceptual load when stimuli were presented under supraliminal conditions [15–17, 19, 20]. In the present study, we focused on the relationship between non-conscious processing of fear and perceptual load. From an evolutionary perspective, detecting fearful faces might provide important social cues that enhanced the survival of the individual, thus increasing the chances of survival of the species. Therefore, fearful faces may have a special ability to reduce the effect of perceptual load on non-conscious processing. However, all of these ERP effects found within the face and low-load tasks were completely eliminated in the high-load task. ERP modulation by perceptual load may suggest that attentional capacity constitutes a necessary condition for the perception of emotional information, even when this information is not consciously perceived. The automatic processing of emotional stimuli depends on the extent to which the main task depletes attentional resources. ERP effects in the low-load task may be triggered by spare attentional capacity, that allows masked fearful faces to be processed. Our results suggest that the effects of perceptual load are not restricted to the neural representation of emotional stimuli that have reached conscious awareness and extend load theory to non-conscious processing.

In addition, our study did not find an early ERP effect (anterior N1, N170, VPP) related to the subliminal emotional processing. Recent studies have indicated that the electrophysiological differences between fearful and neutral faces occur early (within 200 ms). For example, subliminal fearful faces elicited larger N1 amplitudes than neutral faces, but only on correct trials [12], and enhanced VPP amplitudes were also observed for subliminal fearful faces [8]. Modulation of N170 by fearful faces was also observed in the subliminal condition, meaning that fearful faces elicited larger amplitudes than neutral faces [11], even when the faces were presented outside the attentional focus [39]. However, some researchers found that modulation of N170 by emotional valence was only observed when participants could reliably detect the fearful stimulus [10, 40]. Compared to previous subliminal studies, the task demands and the location of the faces in the present study were distinct. Esslen et al. (2004) proposed that minor difference in experimental design might cause different results [36]. Thus, the reason for this discrepancy between the current study and previous studies needs to be explored in future experiments.

Conclusions

The present study investigated whether non-conscious processing of emotional stimuli depends on perceptual load. An emotional positivity was observed over the frontal and central areas from about 250 ms to 700 ms after stimulus onset in the face task and low-load tasks, but not in the high-load task. Our findings suggest that attentional resources are needed for the non-conscious processing of fearful faces. This provides initial evidence that perceptual load may affect the mechanisms underlying non-conscious processing of emotional stimuli.

Author Contributions

Conceived and designed the experiments: LW XM YL. Performed the experiments: CF. Analyzed the data: LW. Contributed reagents/materials/analysis tools: LJ XZ WL YL. Wrote the paper: LW XM.

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To Know or Not to Know? Theta and Delta Reflect Complementary Information about an Advanced Cue before Feedback in Decision-Making

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To investigate brain activity during the reinforcement learning process in social contexts is a topic of increasing research interest. Previous studies have mainly focused on using electroencephalograms (EEGs) for feedback evaluation in reinforcement learning tasks by measuring event-related potentials. Few studies have investigated the time–frequency (TF) profiles of a cue that manifested whether a following feedback is available or not after decision-making. Moreover, it remains unclear whether the TF profiles of the cue interact with different agents to whom the feedback related. In this study we used the TF approach to test EEG oscillations of the cue stimuli in three agents ('Self', 'Other', and 'Computer') conditions separately. The results showed that the increased central-posterior delta power was elicited by the feedback unavailable cues more so than with the feedback available cue within 200–350 ms after the onset of the cue, but only in the self-condition. Moreover, a frontal-central theta oscillation had enhanced power when following the feedback unavailable cue as opposed to the feedback available cue across three agencies. These findings demonstrated that the cue for knowing an outcome produced reward prediction error-like signals, which were mirrored by the delta and theta oscillations during decision-making. More importantly, the present study demonstrated that the theta and delta oscillations reflected separable components of the advanced cue processing before the feedback in decision-making.

Keywords: delta, theta, reinforcement learning, agent, time–frequency.

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INTRODUCTION

It is important for human beings to learn from external feedback after making a decision for maximizing reward. In the past two decades, many researchers have adopted varied decision-making tasks, in which feedback was available to facilitate participant behaviors (for reviews, see Walsh and Anderson, 2012; Ullsperger et al., 2014). Nevertheless, it is quite common that a person cannot get access to the feedback of his/her own decision-making in reality. Therefore, it would be interesting to investigate how the brain response to a cue that informs whether the decision-makers' feedback will be shown or not. Despite plenty of literatures discussing the neural bases of feedback learning, however, few studies have focused on the brain activity changes in human subjects when they receive a cue which indicated feedback information will either be available, or not.

Given that the feedback information plays a key role in a trial-and-error learning task, participant curiosity about feedback will be evoked when feedback information is unavailable, according to the information-gap theory (Loewenstein, 1994). Loewenstein (1994) proposed an information-gap theory that epistemic curiosity is aroused when an individual realizes a difference between "what one wants to know" and "what one knows". Kang et al. (2009) have found that epistemic curiosity activates reward circuitry in a functional magnetic resonance imaging (fMRI) study. One of our previous studies shows that the participants preferred to know others' results in a gambling task, even when to know this information was costly (Han et al., 2012). Thus, it is plausible that curiosity will not be satisfied when feedback information is unavailable. According to reinforcement learning theories, the reward prediction error (RPE), *i.e.* differences between expected and obtained reinforcements, can be used to adjust associations between actions and corresponding reward in decision-making (Schultz, 1997; Holroyd and Coles, 2002). In a broader sense, RPE could be elicited in many situations in which a mismatch between expected and actual outcomes occurs (Kuss et al., 2011) and predict the "goodness" of on-going events (Holroyd and Coles, 2002). Taking these two lines of research together, we hypothesized that the cue of missing feedback will generate RPE during reinforcement learning task and this signal can be detected by electroencephalograph (EEG) activities in the brain.

By recording EEG activity on the scalps of human participants, previous event-related brain potentials (ERP) and time–frequency (TF) studies have linked the feedback-related negativity (FRN) component, frontal midline theta, and delta oscillations with reward predication error signals originating from the mid-brain dopamine system (Bernat et al., 2011, 2015; Foti et al., 2014; Li et al., 2016; Pornpattananangkul and Nusslock, 2016). The FRN was observed in the frontal-central region in a 200–350 ms time window after feedback stimulus presented and showed larger amplitude following negative feedback than following positive feedback (Miltner et al., 1997; Holroyd and Coles, 2002). Due to the component overlapping issue in traditional ERP studies, the FRN has been considered to be affected by the P300 component (or later positive component) which arises right after the former FRN (Sambrook and Goslin, 2015).

In our previous paper, we exploited a gambling task with three agencies (Self, Other, and PC) involving, and manipulating, a cue which indicated whether the results of three agencies' gambling were unavailable or not (Han et al., 2013). We observed that larger later positivity component (LPC) was associated with unavailable cues compared to available cues. Moreover, the LPC in the Other condition was correlated with the interpersonal curiosity trait in participants (Han et al., 2013). In fact, we hypothesized that the FRN component could be the component of interest in that study (Han et al., 2013, p. 46). One possibility behind the vanished FRN component might be the overlapping from other late component as mentioned above.

The TF method which focused on spectral characteristics should help to separate the FRN from P300 (Bernat et al., 2011). Earlier studies revealed that the P300 is composed mainly of activity in the delta (<3 Hz) band (Bernat et al., 2007; Gilmore et al., 2010) while the FRN is composed largely of activity in the theta (4–8 Hz) range (Cohen et al., 2011). In addition to these issues in FRN studies in particular, traditional ERP approaches also lack the ability to detect the rich, complex information, about oscillatory activity that varies in phase from trial-to-trial (Cohen et al., 2007, 2011). Hence, we used the TF method to explore the multi-dimensional neural dynamics of feedback information cue processing. Recent studies have linked the theta and delta frequencies with RPE in decision-making tasks (Foti et al., 2014; Bernat et al., 2015). Therefore, we mainly focused on theta and delta power in the present study.

Studies focused on feedback-guided learning have consistently found that increasing theta power (4–8 Hz) was associated with feedback that was worse than expected, i.e., negative RPE (Cohen et al., 2007; Marco-Pallares et al., 2008; Hajihosseini et al., 2012). Although these finding have often been replicated, there were also inconsistent findings around whether the theta power was sensitive to RPE in particular or unexpected events in general (Cohen et al., 2007; Doñamayor et al., 2012; Hajihosseini and Holroyd, 2013). With a dynamic reward-learning task and associated computational model, Cavanagh et al. (2011) found that medial-frontal theta was correlated with unsigned prediction error but has an asymmetrical sensitivity to negative events. Interestingly, the same group has found that the medial and lateral frontal theta corresponded to the degree of negative RPE and positive RPE in the service of behavioral adjustment (Cavanagh et al., 2010). Taken these together, medial frontal theta oscillation seems to be a good candidate index for the processing of negative RPE in our study, in which, the two types of cue occurred with equal probability.

The converged evidence showed that both waking and sleep delta waves mainly originate from the medial frontal cortical regions (for a review, see Knyazev, 2012), however, delta activity was shown to be concentrated in more posterior regions on the scalp (for a review, see Güntekin and Başar, 2015). Delta oscillations have been implicated in the motivational relevance of the task and the salience of the target stimulus (Knyazev, 2007, 2012) and appear to be associated with reward processing (Knyazev, 2007; Cavanagh, 2015). In a dynamic reinforcement learning task, Cavanagh found that delta activity at different times reflected RPE and state prediction error separately (Cavanagh, 2015). More specifically, early delta activity, which constitutes reward positivity, may correspond to a surprising reward signal, while later delta activity, which contributed to the P300 component, appeared to associate with behavioral adjustments. The finding that delta frequency was sensitive to positive RPEs was also reported in a recent study, which used principal components analysis (Sambrook and Goslin, 2016).

Based on the aforementioned literature, we reanalyzed the data from our previous paper (Han et al., 2013) using the TF approach and focused on the oscillation profiles of cues which indicated whether the feedback will be available or not. We also compared the TF distributions in three agents' conditions in order to show whether the cue effect is only self-relevant or related to any agent in general. We hypothesized that the cue for showing feedback will elicit positive RPE, while that for no feedback will generate negative RPE. Moreover, these RPEs could be reflected by the medial frontal theta and delta oscillation. In addition, a recent study, in which the researcher applied the TF method to a classical gambling task, has demonstrated that the theta and delta frequencies reflected different functional significances in the outcome evaluation (Bernat et al., 2015). According to this finding, we also hypothesized that the theta and delta measures may have different sensitivities to agent and cue-type.

MATERIALS AND METHODS

Previous non-overlapping results from this dataset are reported elsewhere (Han et al., 2013). For more detailed information about the experimental design, see Han et al. (2013).

Participants

Nineteen subjects participated in the experiment as volunteers. One participant's data was excluded because of excessive movement artifacts. Thus, the data from 18 participants (eight males) with ages ranging from 20 to 25 ($M = 22.1$ and $SD = 1.4$) were taken for TF analysis. All participants were healthy and right-handed. They all had normal, or corrected-to-normal, vision and gave informed written consent before participation. This study was approved by the local Ethics Committee.

Experimental Procedure

The participants were informed that they would participate in a three-agent (Self, another participant called "Other", and a computer, called "PC") on-line gambling game. Unknown to the real participants, the "Other" participant was pretended by a research assistant and his/her behavior was simulated by computer. The "Other" participant was a stranger with the same gender to the real participant and they were introduced to each other before the experiment. Each trial began with a 500 ms white fixation cross against a black background, followed by a picture of two golden eggs which was displayed for 800 ms on the screen. Then a phrase appeared on the two eggs to indicate which agent's turn it was next. "Your turn" means it was the participants' turn to make a decision between these two eggs, while "A's turn" and "PC's turn" represented the other person's turn and the PC's turn to make a selection, correspondingly. Three agents could press either "F" or "J" to select the left or right egg. Thereafter, a 500 ms confirmatory cue appeared with a red circle to confirm the selection, followed by a blank screen, which lasted randomly from 600 to 1000 ms. Then, a yellow circle without a cross (available cue), or with a cross inside (unavailable cue), was presented on the screen to indicate whether the participant would see the feedback from this trial or not. Participants were told that whether feedback was given or not did not affect their cumulative monetary gain. For trials with an unavailable cue, a "?" mark would appear instead of the outcome.

There were 360 critical trials in total. The experiment was conducted with two (available, unavailable) by three (Self, Other, and PC) within-subject design and each condition was repeated 60 times. The order of the three agents' actions was randomized at the trial level. The participants had a 1-min break after each group of 72 trials. All stimuli were presented by E-Prime Version 1.1 software on a computer.

Data Acquisition

Brain electrical activity was recorded at 64 scalp sites using tin electrodes mounted in an elastic cap (Brain Product, Munich, Germany), with a ground electrode placed on the frontal midline and references placed on the left and right mastoids. Vertical electrooculograms (EOGs) were recorded supra-orbitally and infra-orbitally relative to the left eye. The horizontal EOG was recorded as the difference in activity from the right vs. the left orbital rim. The impedances of all of the electrodes were less than 10 kΩ. The EEG and EOG were amplified using a 0.05–100 Hz band pass and continuously digitized at 500 Hz/channel for off-line analysis. Note that the following ERP and TF analysis were time-locked to the onset of the cue stimuli before the final feedback.

Data Analysis

Electroencephalograph data were imported and processed using EEGLAB (Delorme and Makeig, 2004). Continuous EEG data were band-pass filtered at between 1 and 40 Hz. EEG epochs were extracted using a window analysis time of 2000 ms (1000 ms pre-stimulus and 1000 ms post-stimulus) and baseline corrected using the pre-stimulus time interval. Trials contaminated by eye-blinks and movements were corrected using an independent component analysis (ICA) algorithm (Delorme and Makeig, 2004). In all datasets, individual eye movements, showing a large EOG channel contribution and a frontal scalp distribution, were clearly observed in the removed independent components. After pre-processing, these data were submitted to further TF analysis.

We were interested in the identification and characterization of oscillatory activities induced by each stimulus. A wavelet transform was used for the TF analysis in this study. The EEG data from each single trial were convoluted by complex Morlet wavelets $W(t, f_0)$ (Kronland-Martinet et al., 1987) having a Gaussian shape both in the time domain $SD\,\sigma_t$ and in the frequency domain $SD\,\sigma_f$ around its central frequency $f_0 : W(t, f_0) = A \cdot \exp\left(-t^2/2\sigma_t^2\right) \cdot \exp(2i\pi f_0 t)$, with $\sigma_f = 1/2\sigma_t$. A wavelet family is characterized by a constant ratio $\left(f_0/\sigma_f\right)$, which should be chosen in practice to be greater than five (Grossmann et al., 1989). The wavelet family used here was defined by $f_0/\sigma_f = 7$, with f_0 ranging from 1 to 30 Hz. The time resolution of this method, therefore, increases with frequency, whereas the frequency resolution decreases. After that, the TF representations (absolute value of the wavelet transform) of single-trial EEG data were averaged over single-trials given each channel, each subject, and each stimulus. Subsequently, the data from −200 to 800 ms were taken for further analysis to avoid the edge effect of in the wavelet transform used here. The baseline was then corrected for each frequency bin.

For the statistical analysis, the FRN-like amplitude, the theta power within 200–350 ms and 400–700 ms was measured at FCz where these activities peak (Holroyd and Coles, 2002; Li et al., 2010, 2015, 2016), whereas the delta power within 200–350 ms was measured at Cz and the delta power within 400–700 ms was calculated at Pz based on the present scalp distributions of the delta activity.

RESULTS

ERP Results

Note that we have reported the ERP results in a previous study (Han et al., 2013); however, we used a narrow frequency band (0.01–16 Hz) to filter the original data. To facilitate the appropriate TF analysis using a wavelet transform in this study, the continuous EEG data were filtered by the 1–40 Hz bandpass filter during pre-processing.

As showed in **Figure 1**, the ERP data were measured as the mean value of the difference wave between available and unavailable conditions within the 200–350 ms time window at FCz. These data were submitted to one way ANOVA with agent (Self, Other, and PC) as within-subject variables. The results showed that the main effect of agent was significant, $F(2,34) = 14.91$, $p < 0.001$, and $\eta^2 = 0.47$. The pair-wise comparison suggested that the difference wave in the Self condition (-2.58 ± 0.46 μV) was significantly larger than that in the Other condition (-0.75 ± 0.5 μV and $p < 0.001$), and PC condition (-0.26 ± 0.3 μV and $p < 0.001$). However, there was no significant difference between the difference wave in the Other condition and PC condition ($p = 0.2$).

TF Results within the 200–350 ms Time Window

The TF representations and corresponding scalp distributions are shown in **Figures 2** and **3**. A three-way ANOVA analysis was carried out on the theta power at FCz with agent (Self, Other, and PC), and cue-type (unavailable and available) as within-subject variables. The results showed that the main effect of cue-type was significant, $F(1, 17) = 11.24$, $p < 0.005$, and $\eta^2 = 0.40$. Pair-wise comparisons revealed that the theta power in the unavailable cue condition ($M = 7.74 \times 10^4$ and $SEM = 1.14 \times 10^4$) was significantly stronger than that in the available cue condition ($M = 5.42 \times 10^4$, $SEM = 7.6 \times 10^3$, and $p < 0.005$).The main effect of agent was not significant, $F(1.6,28.5) = 1.36$, $p = 0.27$, and $\eta^2 = 0.07$. The interaction effect between cue-type and agent did not reach a significant level, $F(2,34) = 2.66$, $p = 0.09$, and $\eta^2 = 0.14$. The main statistical results were shown in **Table 1**.

The TF representations and corresponding scalp distributions are shown in **Figures 4** and **5**. A three-way ANOVA analysis was also conducted on the delta power at Cz with agent (Self, Other, and PC) and cue-type (unavailable and available) as independent variables. As shown in **Figure 3**, the main effect of agent reached a significant level, $F(1.2,20) = 11.03$, $p = 0.002$, and $\eta^2 = 0.39$. The following test suggested that the delta power in the Self-condition ($M = 1.13 \times 10^5$ and $SEM = 2.33 \times 10^4$) was significantly larger than that in the Other condition ($M = 3.98 \times 10^4$, $SEM = 7.24 \times 10^3$, and $p < 0.003$), and PC condition ($M = 4.27 \times 10^4$, $SEM = 9.78 \times 10^3$, and $p < 0.005$). However, the delta power was not significantly different between the Other, and the PC, conditions ($p = 0.7$). The main effect of cue-type also reached a significant level, $F(1,17) = 4.96$, $p < 0.05$, and $\eta^2 = 0.23$. Pair-wise comparison showed that the available cue induced a larger delta power ($M = 8.06 \times 10^4$ and $SEM = 1.48 \times 10^4$) than the unavailable cue ($M = 4.99 \times 10^4$ and $SEM = 1.13 \times 10^4$), $p < 0.05$. More importantly, the interaction effect between agent and cue-type was significant, $F(1.4,23.2) = 6.04$, $p < 0.02$, and $\eta^2 = 0.26$. The following analysis suggested that the delta power following an available cue ($M = 1.6 \times 10^5$ and $SEM = 3.38 \times 10^4$) was significantly larger than for an unavailable cue ($M = 9.23 \times 10^4$, $SEM = 2.5 \times 10^4$, and

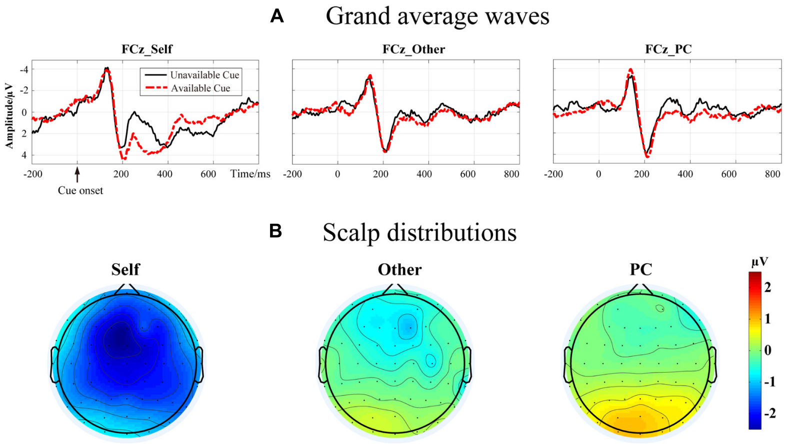

FIGURE 1 | (A) The grand average waves elicited by a unavailable cue (red) and an available cue (green) in Self, Other, and PC conditions at FCz. **(B)** The corresponding scalp distribution of three difference waves between the event-related potential elicited by unavailable cue and available cue in three conditions separately.

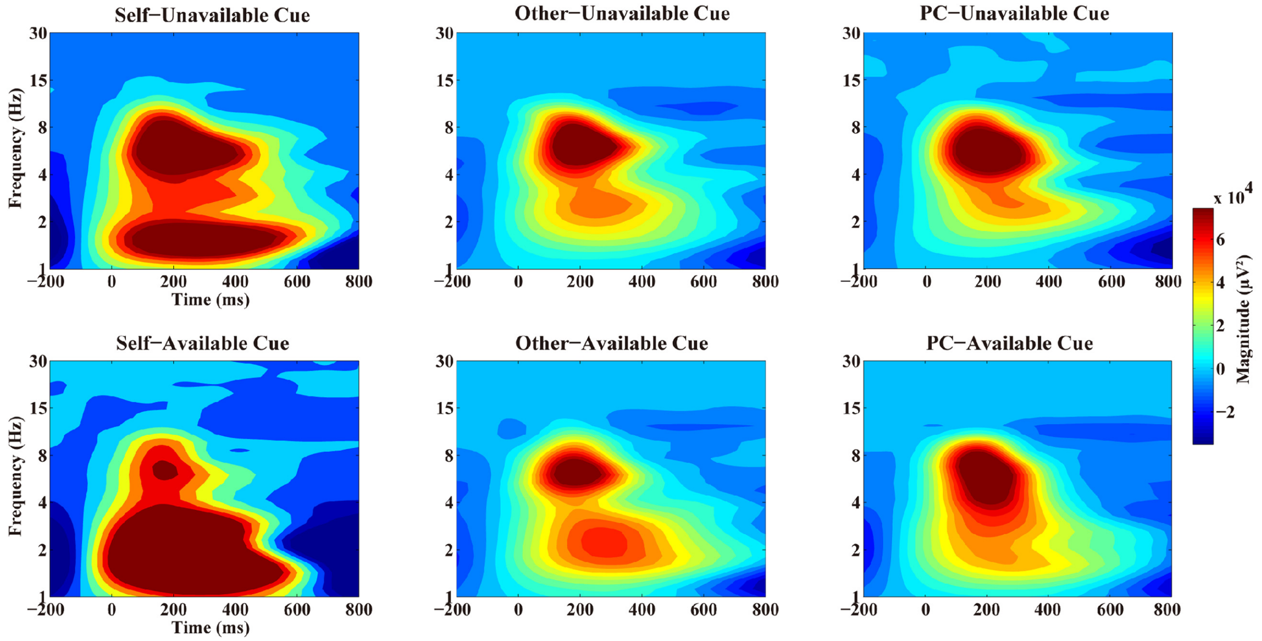

FIGURE 2 | Time–frequency representation of two types of cues in three agents' conditions at FCz. The upper panel showed the time–frequency representation of Unavailable cue in three agents' condition while the lower panel showed the time–frequency representation of Available cue in three conditions separately.

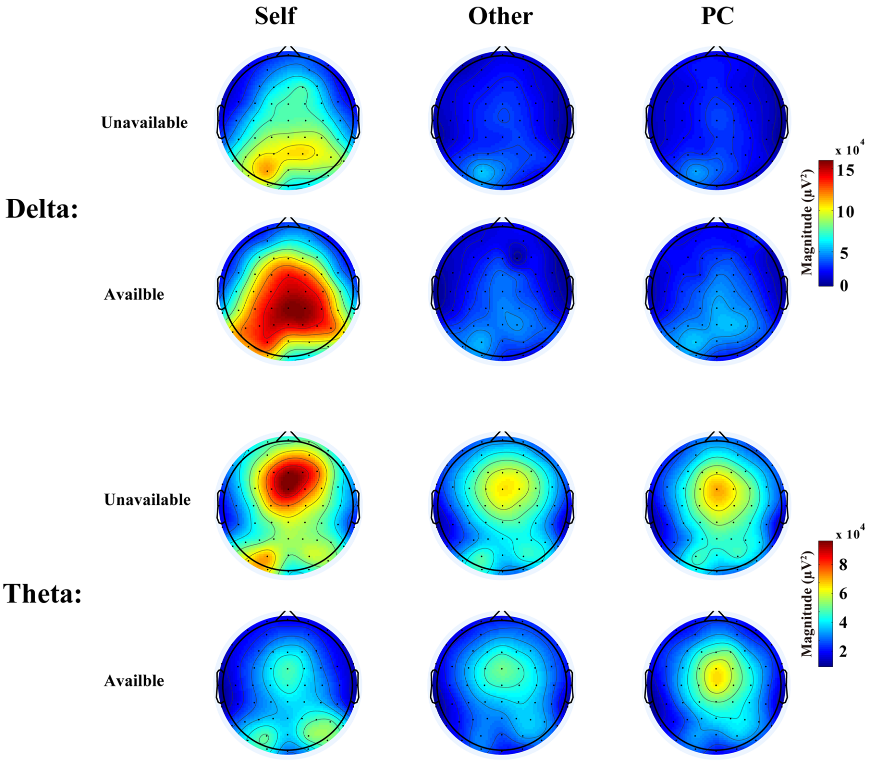

FIGURE 3 | Scalp distributions of delta and theta elicited by the two types of cues in three agents' conditions in the 200–350 ms time window.

TABLE 1 | Statistical results: theta and delta power in two time-windows.

	200–350 ms		400–700 ms	
	Theta	**Delta**	**Theta**	**Delta**
Agent	$F = 1.36$	$F = 11.03^{**}$	$F = 3.4$	$F = 8.73^{**}$
Cue-type	$F = 11.24^{**}$	$F = 4.96^{*}$	$F = 11.45^{**}$	$F < 1$
Agent × Cue-type	$F = 2.66$	$F = 6.04^{*}$	$F = 3.09$	$F = 2.15$

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

$p < 0.02$) only in the Self-condition, however, there was no notable difference between the delta power elicited by an available cue and an unavailable cue in the Other condition ($p = 0.46$), and PC condition ($p = 0.45$).

TF Results within the 400–700 ms Time Window

Based on the ERP results in Han et al. (2013) and the ERP waves as shown in **Figure 1**, we have also analyzed the theta and delta profiles within the 400–700 ms time window. As mentioned above, a three-way ANOVA was carried out on the theta power at FCz with agent (Self vs. Other vs. PC) and cue-type (unavailable vs. available) as independent variables. Results revealed that the main effect of agent was not significant, $F(1.4,24.2) = 3.4$, $p = 0.07$, and $\eta^2 = 0.17$. However, the main effect of cue-type reached a significant level, $F(1,17) = 11.45$, $p = 0.004$, and $\eta^2 = 0.4$. Pair-wise comparison showed that a larger theta power was observed following an unavailable cue ($M = 1.05 \times 10^4$ and $SEM = 3.65 \times 10^3$) than after an available cue ($M = 1.21 \times 10^3$ and $SEM = 2.37 \times 10^3$). There was no other significant interaction effect found ($p =$ ns).

The statistical results for delta at Pz showed that the main effect of agent was significant, $F(1.3,22.7) = 8.73$, $p = 0.004$, and $\eta^2 = 0.34$. Pair-wise comparison revealed that the delta power in the Self-condition ($M = 6.35 \times 10^4$ and $SEM = 1.97 \times 10^4$) was notably larger than that in the Other condition ($M = 1.53 \times 10^4$ and $SEM = 9.9 \times 10^3$, $p = 0.003$), and PC condition ($M = 1.37 \times 10^4$, $SEM = 6.58 \times 10^3$, and $p = 0.01$), while there was no significant difference between the latter two conditions ($p = 0.85$). However, the main effect of cue-type was not significant, $F(1,17) < 1$, $p = 0.9$, and $\eta^2 = 0.001$. The interaction effect did not reach a significant level, $F(1.2,20.4) = 2.15$, $p = 0.16$, and $\eta^2 = 0.11$.

DISCUSSION

In the present work, we have reanalyzed the data from our previous ERP study using a TF approach. Basically, the present work has extended our findings from the ERP results of a cue which manifested whether the outcome of a decision will be presented or not. In the previous study, we found that the LPC amplitude was notably different between the "unavailable" and the "available" conditions and linearly reduced from "Self", to "Other", to "PC" conditions (Han et al., 2013). Here, we showed that the main difference of ERP between the "unavailable" and the "available" conditions appeared from about 200 ms following cue presentation. The feature of these difference waves, and their scalp distributions, suggested that the "unavailable" cue elicited an FRN-like effect after 1 Hz high-pass filtering. These results confirmed the current concerns that the FRN effect might have been superimposed by the LPC component which is mainly driven by the power of low-frequency activities (Sambrook and Goslin, 2016). Moreover, the decomposition of EEG activity by TF method allowed us to understand better how the experimental manipulation affected the brain activities when processing these advanced cues.

The present findings firstly expanded current understanding of reinforcement learning processes in such a trial and error task. A large number of studies have focused on the outcome evaluation by time-domain and frequency domain (for reviews, see Ullsperger et al., 2014). Much evidence converges to show that FRN component, delta activity, and medial frontal theta power, reflected the RPE signals in reinforcement learning (Cohen et al., 2011; Cavanagh, 2015; Sambrook and Goslin, 2016). Our design and data reanalysis, to our knowledge, is the first to have shown that the advanced cue before outcome elicited similar RPE signals, which was reflected on frontal central theta frequency and central posterior delta activity within the traditional FRN time window. In fact, Bromberg-Martin and Hikosaka (2009) found that macaque monkeys preferred to seek advance information about the size of a water reward. More importantly, their results showed that the same mid-brain dopamine neurons response to primitive, and the desire for advance, information about upcoming rewards, which they termed as 'cognitive reward', was present. In line with this study, another functional MRI study also found that cognitive feedback activated similar dopaminergic regions as monetary reward in an information-integration category learning task (Daniel and Pollmann, 2010). Therefore, we speculated that an advanced cue that indicated the information availability of upcoming monetary reward may have also been processed as a cognitive reward in human learning.

The theta oscillation profiles elicited by the advanced cue replicated current TF studies which focused on negative and positive feedback evaluation in a reinforcement learning task (Marco-Pallares et al., 2008; Cavanagh et al., 2010; Foti et al., 2014; Mas-Herrero and Marco-Pallarés, 2014; Bernat et al., 2015). The enhanced theta band power has been associated with negative RPE compared to positive RPE in reinforcement learning tasks (Marco-Pallares et al., 2008; Cavanagh et al., 2010). Notably, the theta power was divergent between the unavailable cue condition and available cue condition within both of the two time windows analyzed, however, the theta frequency was not sensitive to the agent in the present context. This finding suggested that the theta activity was related to the processing of missing "cognitive reward" information in general. In our design, three agencies have conducted the same gambling task in the laboratory. Therefore, our participants could learn from their own feedback directly, and from Other's and PC's feedbacks, by observational learning (Bandura et al., 1966). Additionally, Holroyd and Coles (2002) suggested that the RPE was conveyed from the mid-brain dopamine system to ACC and is used as a "teaching signal" to other regions for the purpose of improving performance

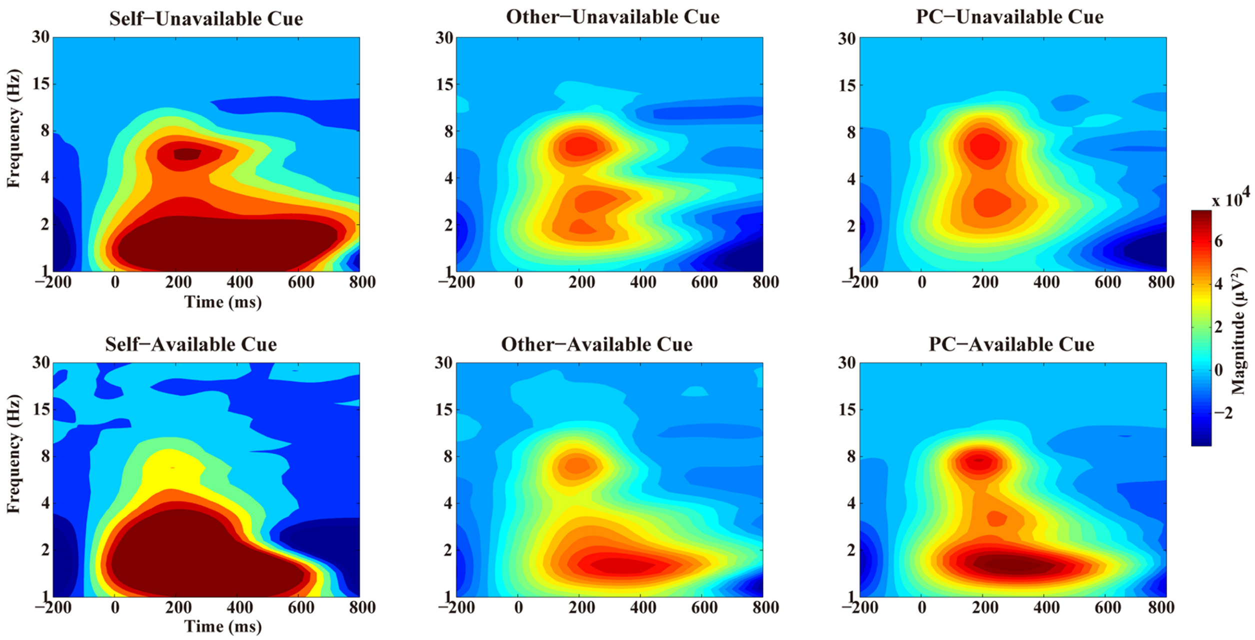

FIGURE 4 | Time–frequency representation of two types of cues in three agents' conditions at Pz. The **Upper panel** showed the time–frequency representation of Unavailable cue in three agents' condition while the **Lower panel** showed the time–frequency representation of Available cue in three conditions separately.

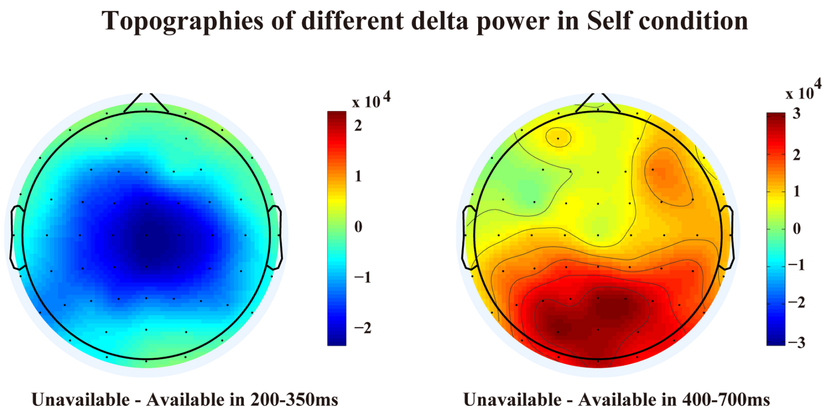

FIGURE 5 | Scalp distributions of different delta power between unavailable cue and available cue in the Self condition.

(Sambrook and Goslin, 2015). Based on this background, we proposed that the theta oscillation might be associated with an RPE signal which was used to improve learning, including self-relevant and observational learning. Another possibility is that the theta oscillation is sensitive to general negative events, such as the blocking of curiosity and satisfaction for Self, Other's, and the PC's results here, and social rejection, in a previous study (Cristofori et al., 2013).

In contrast to the theta frequency, the delta activities revealed different patterns in the 200–350 ms and 400–700 ms time windows. Larger delta power was observed following available cue than after unavailable cue mainly at central electrodes, however, this effect was mainly observed in the Self-condition and only in the 200–350 ms period, which is the classical FRN time window. The central delta activity in the first phase replicated previous findings which demonstrated that enhanced delta power was observed in positive feedback condition than in negative feedback condition (Bernat et al., 2015; Cavanagh, 2015; Li et al., 2016). These results might support the statement that the early central delta oscillation is related to positive RPE signal, which generated from the dopamine system (Cavanagh, 2015).

Interestingly, the delta frequency in the late time window (400–700 ms) reached maximum at posterior sites and only affected by the agent factor. These results firstly demonstrated that the late posterior delta oscillation reflected a different process compared to the early delta. The delta activities in the 400–700 ms could mainly contribute the LPC amplitude which was reported in our previous paper (Han et al., 2013). According to an influential theory, late large positive deflection, such as P3 reflected the activity of the neuromodulatory locus coeruleus–norepinephrine system, which enhance the response to motivationally significant events (Nieuwenhuis et al., 2005; Nieuwenhuis, 2011). Based on this theory, we inferred that the late posterior delta activity also reflected motivational significance of self-relevant information and corresponding attentional involvement. In specific, although the probabilities of cue stimuli are equal among three agents, self-relevant cues are more salient compared to Other's cue and PC's cue in such a context. The higher motivational significance of self-relevant information may be driven by 'engaged curiosity' as suggested by Panksepp (1998).

Note that Bernat et al. (2015) recently suggested that theta reflects most salient primary feedback while delta is sensitive to both primary and second feedback attributes. Although both their data, and our data, suggested that theta and delta reflect different separable components in reinforcement learning tasks, our study demonstrated that the delta, rather than theta, reflected more salient and self-relevant stimuli. On the other hand, theta power showed sensitivity to all of the negative events across agencies over two time windows (200–350 ms and 400–700 ms). These inconsistent findings may have been due to the different paradigms and phases of interest in the two studies. Additionally, several recent TF studies have found that frontal theta was related to the unsigned RPE rather than negative RPE (Hajihosseini and Holroyd, 2013). Given that the probabilities of the two types of cues were equal in the present study, we could not provide evidence to support this argument, leaving an open question for future study: whether the theta power observed here would be modulated by probability of cognitive reward, or not.

Limitations and Future Directions

Bromberg-Martin and Hikosaka (2009) suggested that modern reinforcement learning theory should take 'cognitive reward' into consideration. Our study further provided electrophysiological evidence from human subjects that 'cognitive reward' can generate similar RPE signals, which were indexed here by theta and early delta power, as the primary and second rewards. The processing of the cue information may alarm the system into preparing for future feedback information with the aim of optimizing reinforcement learning. As proposed by Holroyd and Yeung (2012), humans need to learn context-specific sequences of behavior to achieve a final goal through hierarchical reinforcement learning. When a cue was established between decision-making and feedback, the brain may have to adjust the connection between response and reward during reinforcement learning. The processing of an advanced cue may be part of hierarchical reinforcement learning in a special context. The lack of trials undertaken in the final feedback phase in the present study, meant that this hypothesis could not be tested directly by comparing the processing of cue and feedback. Future studies are, therefore, required to test this hypothesis.

AUTHOR CONTRIBUTIONS

PL and JW designed the study, JW and XP collected the data, FC, TY, and ZC analyzed the data, and PL and HL wrote the paper.

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