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RESEARCH****Research Report****E e t- e t e t e t****t e t e t****Yan Mu, Yan Fan, Lihua Mao, Shihui Han****Department of Psychology, Functional Imaging Center, Academy for Advanced Interdisciplinary Studies, Peking University, 5 Yiheyuan Road, Beijing 100871, People's Republic of China***ARTICLE INFO****Article history:**

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ABSTRACT

Our recent event-related potential (ERP) studies showed that phase-locked electro-physiological activities mediate both early emotional sharing and late cognitive evaluation during empathy for pain. However, whether non-phase-locked neural oscillations are involved in empathic responses remains unknown. To investigate the functional role of non-phase-locked theta (3–8 Hz) and alpha (9–14 Hz) oscillations in empathy for pain, we recorded electroencephalogram (EEG) from healthy adults who performed pain judgment of pictures of hands in painful or neutral situations. Wavelet analysis was used to calculate EEG spectral power with high time–frequency (TF) resolution. We found that, relative to neutral stimuli, painful stimuli induced increased theta event-related synchronization (ERS) at 200–500 ms but decreased alpha event-related desynchronization (ERD) at 200–400 ms, providing evidence for the engagement of theta and alpha activity in empathy for pain. In addition, subjective ratings of perceived pain and self-unpleasantness positively correlated with theta band ERS but negatively correlated with alpha band ERD related to painful stimuli, suggesting that theta and alpha oscillations are respectively involved in emotional sharing and regulation during empathy for pain. Finally, the long-latency upper theta (6–8 Hz) and alpha band TF power significantly decreased by repeated exposure to painful stimuli, indicating short-term adaptive changes of empathy-related neural activity.

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1. t t

Empathy refers to the social ability to understand and share emotional states of others. Recent functional magnetic resonance imaging (fMRI) studies investigated the neural mechanisms of empathy for pain by comparing neural activities associated with perception of others in painful and neutral situations and have shown evidence that a brain circuit including the anterior cingulate cortex (ACC) and insula is involved in empathy for pain (Singer et al., 2004; Jackson et al., 2005; Jackson et al., 2006; Botvinick et al., 2005; Saarela et al., 2007; Gu and Han, 2007). The sensory and motor cortices

are also modulated by observation of others in pain (Avenanti et al., 2005; Avenanti et al., 2006), suggesting that both the sensory and affective components of the pain matrix engage in empathic responses to perceived pain.

Our recent event-related potential (ERP) study disentangled dynamic empathic neural responses into an early process of emotional sharing and a late process of cognitive appraisal (Fan and Han, 2008; Han et al., 2008). We found that ERPs over the frontal lobe differentiated between painful and neutral stimuli as early as 140 ms after sensory stimulation. In addition, the magnitude of the early ERP components elicited by the painful stimuli negatively correlated with subjective

* Corresponding author. Fax: +86 10 6276 1081.

E-mail address: shan@pku.edu.cn (S. Han).

ratings of both perceived pain and self-unpleasantness. However, a long-latency empathy-related positivity after 380 ms over the central-parietal regions was not correlated with subjective ratings but decreased when attention was withdrawn from the pain cues in the stimuli. We proposed a two-stage model of empathy for pain consisting of early emotional sharing and late cognitive evaluation.

The current work further examined if non-phase-locked neural oscillations engage in empathic processes. Neural oscillations reflect neural rhythm changes of ongoing neural activities that are time-locked but not phase-locked to stimulus onset. Both external stimuli and internal mental events can induce event-related synchronization (ERS) or desynchronization (ERD) of neural oscillations (Pfurtscheller and Lopes da Silva, 1999). ERS/ERD can be identified by the increase/decrease of spectral power at specific frequency band in association with various cognitive processing. For example, theta rhythm (4–7 Hz) oscillations have origins in hippocampus (Buzsaki, 2002) and ACC in humans (Pizzagalli et al., 2003; Nishida et al., 2004) and are associated with affective valence discrimination of visual displays (Aftanas et al., 2001; 2003; Krause et al., 2000). Alpha (8–14 Hz) oscillations play an important role in a variety of cognitive processes and mainly serve as an inhibition mechanism (see Knyazev, 2007; Klimesch et al., 2007 for review). Sarlo et al. (2005) also reported modulation of alpha band ERD associated with watching emotional movie clips. Their findings, however, could not dissociate EEG activity associated with emotional recognition from EEG activity linked to empathy.

The current study investigated whether empathy for pain modulated theta and alpha oscillations induced by painful and neutral stimuli similar to those used in our previous work (Gu and Han, 2007; Fan and Han, 2008). A recent research showed that magnetoencephalographic (MEG) oscillations with a frequency of around 10 Hz induced by current pulse

stimulation over the left median nerve at the wrist was

However, the TF power showed ERD related to painful neutral stimuli at 600–900 ms over the left parietal and occipital electrodes (PO5: $t(14)=-4.208$, $p<0.001$; P5: $t(14)=-4.211$, $p<0.001$; PO3: $t(14)=-3.586$, $p<0.01$; P3: $t(14)=-3.335$, $p<0.01$), at 800–900 ms over the frontal area (F3: $t(14)=-2.478$, $p<0.05$; F7: $t(14)=-2.644$, $p<0.05$; AF3: $t(14)=-2.257$, $p<0.05$; AF4: $t(14)=-2.326$, $p<0.05$), and at 900–1000 ms over the right parietal–occipital regions (PO4: $t(14)=-2.182$, $p<0.05$; PO6: $t(14)=-2.22$, $p<0.05$; PO8: $t(14)=-2.274$, $p<0.05$; O2: $t(14)=-2.250$, $p<0.05$, Fig. 2a).

To investigate the functional role of the neural oscillations related to empathy for pain identified above, we calculated correlations between FPS-R scores and differential theta band power related to painful and neutral stimuli. We found that theta1 band differential power positively at 400–500 ms correlated with both the degree of perceived pain (PO6: $r=0.699$, $p<0.01$, Fig. 2b) and self-unpleasantness (PO6: $r=0.603$, $p<0.02$, Fig. 2c) at the posterior regions.

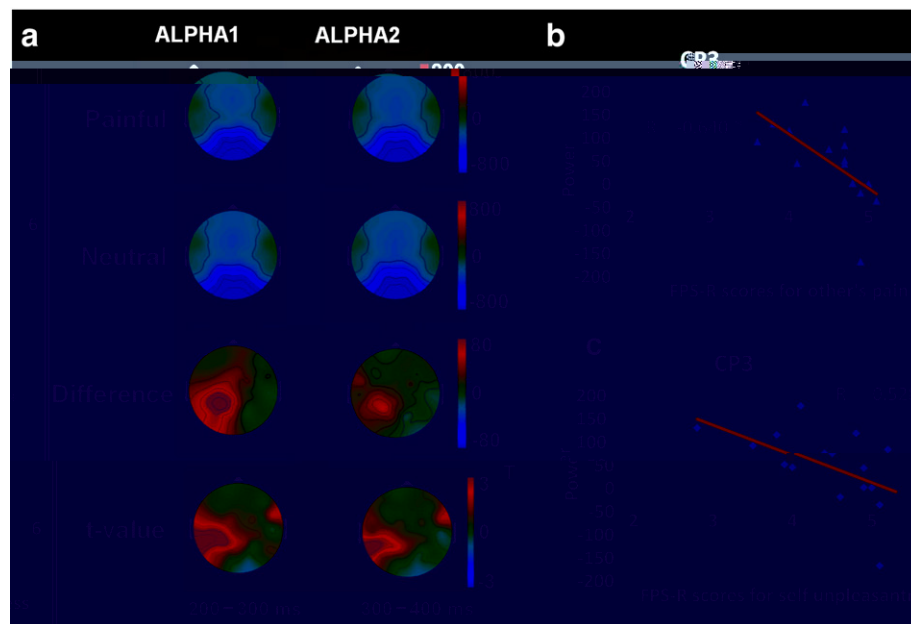
2.2.2.2. Alpha band activity. Alpha1 band activity exhibited less ERD when judging painful than neutral pictures at 200–400 ms in the left central and parietal regions (CP3: $t(14)=3.381$, $p<0.01$; P3: $t(14)=3.183$, $p<0.01$; CP5: $t(14)=3.909$, $p<0.01$; P5: $t(14)=2.538$, $p<0.05$, Fig. 3a). Alpha2 band also showed less reduction of TF power related to painful than neutral pictures at the left central and temporal–parietal electrodes at 200–400 ms (TP7: $t(14)=3.773$, $p<0.01$; P3: $t(14)=2.381$, $p<0.05$; CP3: $t(14)=2.190$, $p<0.05$; CP5: $t(14)=2.796$, $p<0.02$, Fig. 3b) and at 500–700 ms (CP5: $t(14)=2.646$, $p<0.05$; P5: $t(14)=2.238$, $p<0.05$; CP3: $t(14)=2.611$, $p<0.05$; P3: $t(14)=2.367$, $p<0.05$).

Alpha1 band activity at 200–300 ms over the left central–parietal regions negatively correlated with both the degree of

perceived pain (CP3: $r=-0.593$, $p<0.05$) and self-unpleasantness (CP3: $r=-0.544$, $p<0.05$). Alpha2 band activity at 200–300 ms and 550–600 ms over the left central–parietal electrodes also correlated negatively with the degree of perceived pain (CP3: $r=-0.640$, $p<0.01$, and $r=-0.648$, $p<0.01$, respectively) and self-unpleasantness (CP3: $r=-0.528$ and -0.581 , both $p<0.05$, respectively, Figs. 3c and d).

2.2.3. Adaptive changes of pain effects

Analysis of theta2 band power to painful and neutral stimuli showed a significant interaction of Stimulus Valence×Block at 600–800 ms over the left temporal–parietal electrode (T7: $F(1, 14)=11.303$, $p<0.005$; TP7: $F(1, 14)=11.883$, $p<0.01$; P7: $F(1, 14)=7.272$, $p<0.05$, Fig. 4a). Post-hoc t-test confirmed that theta2 band power to painful pictures significantly decreased in the late than early blocks (T7: $t(14)=2.443$, $p<0.05$; TP7: $t(14)=2.647$, $p<0.02$), whereas no such effect was observed for neutral stimuli. Similarly, alpha1 showed a reliable interaction of Stimulus Valence×Block over the left frontal electrodes at 500–600 ms (FC3: $F(1, 14)=5.475$, $p<0.05$; F3: $F(1, 14)=8.362$, $p<0.05$; F5: $F(1, 14)=17.018$, $p<0.001$; AF7: $F(1, 14)=19.300$, $p<0.001$) and at 800–900 ms (FC3: $F(1, 14)=15.81$, $p<0.001$; F3: $F(1, 14)=12.051$, $p<0.002$; F5: $F(1, 14)=19.504$, $p<0.001$; AF7: $F(1, 14)=13.490$, $p<0.01$, Fig. 4b). Post-hoc analysis for the alpha1 band validated a robust reduction of alpha1 power related to painful stimuli in the late than early blocks at 500–600 ms (FC3: $t(14)=3.316$, $p<0.005$) and at 800–900 ms (FC3: $t(14)=2.385$, $p<0.05$), whereas no such effect was observed for neutral stimuli. Alpha2 band power exhibited similar adaptation effect at 600–800 ms over the right parietal–occipital areas (PO6: $F(1, 14)=5.979$, $p<0.05$; PO8: $F(1, 14)=6.290$, $p<0.05$; O2: $F(1, 14)=10.761$, $p<0.01$, Fig. 4c).



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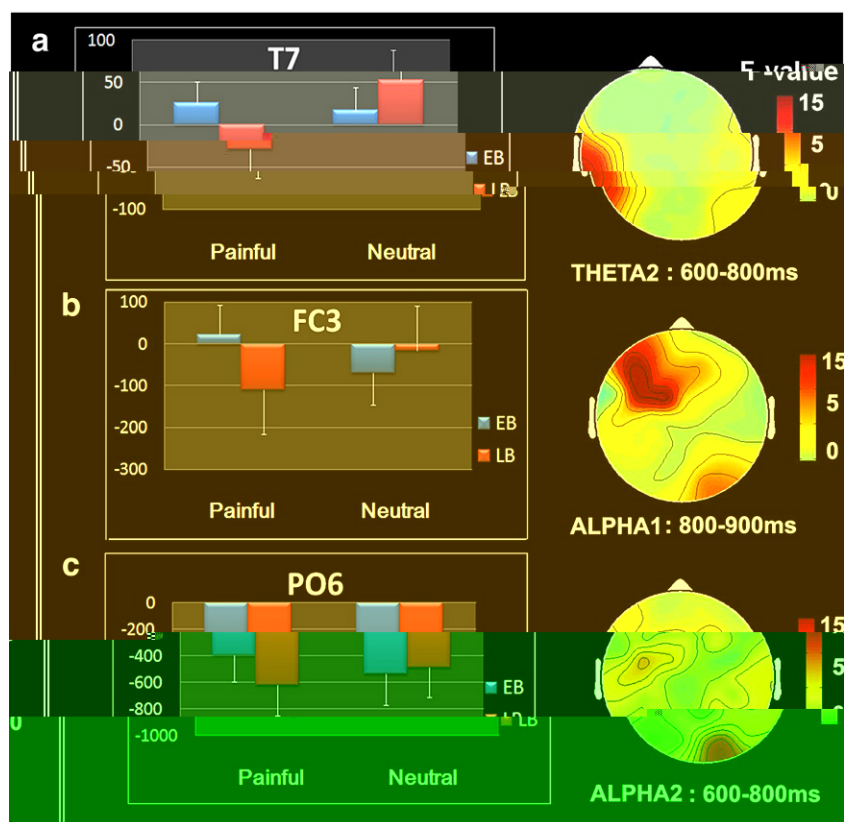


Fig. 4. (a) T7. (b) FC3. (c) PO6. Bar charts show the difference in power (Painful minus Neutral) for the two groups (EB and LB). Topographic maps show the spatial distribution of the effects. F-value scale is shown on the right of each map.

Post-hoc analysis validated the decrease of alpha2 power related to painful stimuli (PO6: $t(14)=3.269$, $p<0.01$).

3. D

The current work assessed the functional significance of non-phase-locked neural activity in understanding and sharing others' feeling of pain by examining how theta and alpha band oscillations were modulated by perceived pain in others. Behavioral data showed that behavioral responses were slower to the neutral than painful stimuli during pain judgment, suggesting a cost of time in searching for pain cues in the neutral stimuli. Our EEG data showed that both painful and neutral stimuli induced theta band ERS over the frontal-central area and alpha band ERD over the parietal-occipital areas relative to the neural rhythms during the pre-stimuli interval. More importantly, we found evidence that both theta band ERS and alpha band ERD were modulated by perceived pain in others.

We first showed that, in an earlier time window (200–500 ms) both lower theta (3–5 Hz) and upper theta (6–8 Hz) band ERS recorded from the frontal and central areas increased to the stimuli containing hands in painful situations relative to the stimuli lacking painful cues. In addition, we

found that the difference in lower theta band activity could predict subjective feelings of both perceived pain and self-unpleasantness. The larger the difference in lower theta band activity between painful and neutral stimuli, the higher the subjective ratings of perceived pain and self-unpleasantness. These results provide evidence for a link between theta oscillations and subjective feelings of others' emotional states, suggesting that theta band ERS elicited by painful stimuli may be involved in the affective processing of empathy for pain. In addition, the theta band ERS may also contribute to emotional sharing—one of the most important components of empathy for pain (Decety and Jackson, 2004), since the theta band ERS also correlated with self-unpleasantness. Previous studies found similar theta band ERS as early as 200 ms after stimulus presentation that was in association with visual stimuli containing positive or negative emotional contents (Aftanas et al., 2001; 2003). Our results compliment previous observations by showing that the time-locked synchronized theta activity also engages in discrimination of others' emotional states such as pain. As a limited number of electrodes were used in this work, it was difficult to localize the origin of the theta band ERS. However, given that previous research identified origins of theta oscillations in the hippocampus (Buzsaki, 2002) and ACC in humans (Pizzagalli et al., 2003; Nishida et al., 2004), it may be speculated that the ERS related

to perceived pain observed in our study might originate from either hippocampus and ACC, reflecting either memory retrieval of emotional experience or affective responses to others' emotional states.

We also found long-latency effects of perceived pain on both the lower and upper theta band ERS. The theta ERS decreased to painful relative to neural stimuli over the frontal, central and posterior occipital areas at 500–1000 ms. One possible account for the reduced theta band oscillation is that emotion-related empathic responses, such as emotional sharing, were weakened and meanwhile the process of cognitive appraisal was enhanced in this time window. This interpretation is consistent with the fact that theta oscillations make a sizable contribution to the long-latency ERP component such as P300 (Basar, 1998; Basar, 1999) and our previous ERP study found that the P300 is involved in cognitive evaluation of pain in others (Fan and Han, 2008; Han et al., 2008). Given the similar time course of P300 and the long-latency ERS modulation by perceived pain observed here, it may be proposed that the long-latency theta ERS contributed at least partially to the cognitive component of empathy for pain.

The results of alpha band oscillations provide further evidence for the role of non-phase-locked neural activity in understanding and sharing others' emotional states. We found that both lower and upper alpha band ERD varied as a function of perceived pain of others in an early time window (200–400 ms). Perceived pain weakened alpha band ERD in both the lower and upper alpha bands over the left central and parietal regions. Recent EEG research has shown evidence that alpha oscillations may support varieties of cognitive functions. For example, Klimesch et al. (1999) found that alpha band ERS increased with memory sets of items to be remembered in a memory retaining state. Alpha band ERS has also been observed over the sensorimotor areas in association with volitional inhibition of acquired motor programs (Hummel et al., 2002). Because the alpha band oscillations related to the painful and neutral stimuli in our work were characterized with ERD, the modulation of ERD by perceived pain could not be explained simply by memory retrieval or inhibition of activity in the motor cortex. Of relevance to the current work are findings of alpha band activity induced by emotional movie clips (Sarlo et al., 2005). The authors showed subjects with movie clips of 132 s depicting a thoracic operation or a cockroach invasion and found that, relative to viewing a movie clip of landscape documentary, movie clips with emotional contents resulted in greater alpha band ERD that was more salient over the right than left hemispheres. Although the current study found evidence for modulation of alpha band ERD by perceived pain in others, our findings are different from the results of Sarlo et al. (2005) in three aspects. First, our EEG results showed evidence for short-latency transient effect of perceived pain on alpha band ERD rather than long-latency sustained effect of emotional contents. Second, the alpha band ERD observed in our work was weakened by painful than neural stimuli. Third, the modulation of alpha band ERD by perceived pain was more salient over the left rather than right hemisphere in our work. These differences indicate that the modulation of event-related alpha oscillations involved in empathy is

essentially different from that of long-lasting alpha oscillations related to the processing of emotional stimuli.

More importantly, we found that the empathy-related modulations of alpha oscillations induced by painful stimuli at 200–300 ms negatively correlated with subjective feeling of pain in others and self-unpleasantness. The larger difference in alpha band TF power between painful stimuli and neutral stimuli, the less intense the perceived pain and self-unpleasantness. While being consistent with our previous ERP findings that the amplitudes of phase-locked neural activity at 140–180 ms related to the painful pictures negatively correlated with both subjective rating of other's pain and self-unpleasantness (Fan and Han, 2008), the results of the current work provide direct evidence for the link between alpha oscillations and subjective feelings of other emotional states. Using a memory search paradigm consisting of three stages of encoding, retaining, retrieval, Klimesch et al. (1999) found that alpha synchronization increased with memory sets of the items to be remembered in the memory retaining stage. The findings support the hypothesis that alpha band ERS reflects a specific top-down controlled inhibitory mechanism (Klimesch et al., 2007). In many cases people may unconsciously and automatically regulate their emotions when being in a negative emotion condition (Mauss et al., 2007). Painful stimuli used in the current work depicting painful and uncomfortable situations would evoke more emotional responses, such as personal stress and anxiety than neutral stimuli. Emotion regulation, together with emotion sharing and perspective tasking, has been supposed to play a vital role in the modulation of subjective experience of anxiety and pain reactivity during empathy (Decety and Jackson, 2006). The negative correlation between the empathy-related modulations of alpha oscillations and subjective feeling of pain in others and self-unpleasantness may be involved in such emotion regulation. Similar to the current work, an fMRI study found negative correlation between the degree of distress induced by social exclusion and the magnitude of the ventral prefrontal activity (Eisenberger et al., 2003), suggesting that the ventral prefrontal activity is engaged in the regulation or inhibition of negative emotion.

Previous fMRI studies reported empathy-related activity in the midline brain structure such as the ACC and bilateral insula (Singer et al., 2004; Jackson et al., 2005; Saarela et al., 2007). However, our recent ERP study (Fan and Han, 2008) found greater difference in ERP amplitudes between the painful and neutral stimuli over the left than the right hemispheres. Consistent with the ERP findings, the current paper reports correlations between subjective ratings of perceived pain/self-unpleasantness and the non-phase-locked alpha activity recorded at the left central-parietal electrodes. Relative to BOLD signals that peak at 4–6 s after stimulus delivery, the EEG/ERP results reflect short-latency (several hundred milliseconds) neural activity associated with empathy. It is possible that BOLD signals manifest accumulation of neural activity in a long period of time that failed to reveal hemispheric asymmetry in empathic responses.

Finally, we found that both theta and alpha oscillations induced by painful stimuli decreased in the late than early EEG recording sessions. These adaptive changes of empathy-related non-phase-locked activity occurred at a relatively

long latency (i.e., after 500 ms). Given that the theta band ERS observed here reflected emotion-related processing involved in empathy, our results suggest that repeated exposure to painful stimuli may weaken the emotional responses during empathy. Consistent with this, as alpha band ERD reflects release of inhibition of top-down controlled cognitive processes (Pfurtscheller and Andrew, 1999; Klimesch et al., 2007), the adaptive changes of the alpha band ERS imply that, in contrast to the emotional responses involved in empathy, the cognitive engagement for evaluation of the painful situation may be enhanced after being repeatedly exposed to perceived pain. Emotional regulation may also be augmented to overcome negative emotion during empathy such as self-stress and other uncomfortable feelings (Decety and Jackson, 2006). Our EEG results compliment the fMRI study, in which neural activity in ACC and insula underlying empathy for pain was eliminated in physicians who practice acupuncture for years (Cheng et al., 2007b), by showing that short-term adaptation may influence both the emotional and cognitive components of neural activity underlying empathy for pain.

In summary, our EEG results provide evidence that, similar to the phase-locked ERPs, non-phase-locked neural activities were also modulated by perceived pain in others. Such modulation could take place as early as 200 ms after sensory stimulation. In addition, the power of theta and alpha oscillations correlated with subjective evaluations of intensity of perceived pain and self-unpleasantness. The EEG results are consistent with our previous ERP findings (Fan and Han, 2008; Han et al., 2008), supporting that both emotional sharing and emotion regulation are involved in empathy for pain. Moreover, our EEG results suggest that empathy-related neural activities may undergo short-term adaptive changes.

4. E e e t e e

4.1. Subjects

Fifteen healthy adults (aged between 18 and 24 years, 11 males, 4 females, mean age \pm SD = 20.8 \pm 1.82) participated in the study as paid volunteers. All subjects were right-handed, had normal or corrected-to-normal vision, and were not color blind. Informed consent was obtained from each subject before the study. This study was approved by a local ethic committee at the Department of Psychology, Peking University.

4.2. Stimuli and procedure

Visual stimuli consisted of 40 digital color pictures showing one hand or two hands in painful and neutral situations that were identical to those in our previous work (Gu and Han, 2007; Fan and Han, 2008). Painful pictures included situations such as a hand trapped in a door or cut by scissors. Twenty pictures showed hands in painful situation. Each painful picture matched with a neutral one in which one or two hands situated in similar contexts but did not imply any pain. The stimuli were presented in the center of a gray background of a 21-in. color monitor, subtending a visual angle of $4^\circ \times 3.15^\circ$ at a viewing distance of 100 cm.

Each subject participated in four blocks of trials, judging pain vs. no pain for hands in painful and neutral pictures. Each block of trials started with the presentation of instructions for 3 s followed by 80 trials. On each trial the stimulus display was presented for 200 ms in the center of the screen, which was followed by a fixation cross with a duration varying randomly between 800 and 1600 ms. The stimuli in each block of trials were presented in a random order. Subject responded to each stimulus by a button pressing using the left or right index finger.

4.3. Measurement of subjective reports

After the EEG recording session, subjects were asked to evaluate the intensity of pain supposedly felt by the model in the stimuli and their own unpleasantness when they perceived the painful stimuli. The evaluations were measured using a 6-point scale (1=no pain, 6=very much painful, or 1=no unpleasantness, 6=very much unpleasant) with the Face Pain Scale-Revised (FPS-R) adapted from the Faces Pain Scale (Bieri et al., 1990), which contained six photocopied faces showing neutral to extremely painful expression.

4.4. EEG data recording and analysis

EEG was continuously recorded from 62 scalp electrodes that were mounted on an elastic cap according to the extended 10–20 system, with the addition of two mastoid electrodes. The reference electrode was at the right mastoid. The electrode impedance was kept less than 5 k Ω . Eye blinks and vertical eye movement were monitored with electrodes located above and below the left eye. The horizontal electro-oculogram was recorded from electrodes placed 1.5 cm lateral to the left and right external canthi. The EEG was amplified (band pass 0.01–100 Hz) and digitized at a sampling rate of 250 Hz.

ERPs were first calculated in each stimulus condition (pain judgment of painful vs. neutral pictures) with averaging epochs beginning 200 ms before stimulus onset and continuing for 1200 ms. Trials contaminated by eye blinks, eye movements, or muscle potentials exceeding ± 50 mv at any electrode were excluded from the average. ERPs in each stimulus condition were then subtracted from each corresponding EEG epoch to remove the phase-locked EEG activity from the EEG data.

Theta and alpha oscillations were quantified based on a time–frequency (TF) wavelet decomposition of the signal between 3 and 14 Hz. The power of each single trial was averaged to obtain non-phase-locked components. The signal was convoluted by complex Morlet's wavelet $w(t, f_0)$ (Kronland-Martinet et al., 1987) with a Gaussian shape in time (SD σ_t) and frequency (SD σ_f) domains around its central frequency f_0 :

$$w(t, f_0) = A \exp(-t^2/2\sigma_t^2) \exp(2i\pi f_0 t)$$

with $\sigma_f = 1/2\pi\sigma_t$. Wavelets are normalized so that their total energy is 1, the normalization factor A being equal to: $(\sigma_t\sqrt{\pi})^{-1/2}$. A wavelet family is characterized by a constant ratio (f_0/σ_f), which should be chosen in practice greater than ~ 5 (Grossmann et al., 1989). The wavelet family was defined by $f_0/\sigma_f = 5$ (wavelet duration $2\sigma_t$ of about 1.6 periods of

oscillatory activity at f_0), with f_0 ranging from 3 to 14 Hz in 1 Hz steps. The time-varying energy $E(t, f_0)$ was defined as the square norm of the result of the convolution of a complex wavelet $w(t, f_0)$ with the signal $s(t)$: $E(t, f_0) = |w(t, f_0) \times s(t)|^2$. Convolution of the signal by a family of wavelets provides a TF representation of the signal. The mean TF energy in a pre-stimulus window (–200 to 0 ms) calculated as the baseline power was subtracted from the pre- and post-stimulus TF power in each frequency band and was then subjected for further statistically analysis.

4.5. Statistical analysis of EEG

Similar to the previous research (Pfurtscheller and Lopes da Silva, 1999), we calculated the percentage increase/decrease of TF power in the following way: $ERS/ERD = [(A - R)/R] \times 100\%$, where A refers to the spectrum power at a specific time window after stimulus onset and R refers to the spectrum power in the pre-stimulus 200 ms window. ERD and ERS were computed in four sub bands (theta1: 3–5 Hz; theta2: 6–8 Hz; alpha1: 9–11 Hz; alpha2: 12–14 Hz) by aggregating the signal of power in 200 ms periods, resulting in five consecutive time windows of 200 ms from 0 to 1000 ms after stimulus onset. The TF power values in specific time window and frequency band in different situations (painful vs. neutral stimuli) were then subjected to paired t-tests to test the pain effect. To investigate possible adaptive changes of the neural activities associated with empathy for pain, the TF power was calculated respectively for the first two blocks of trials (early blocks) and the last two blocks of trials (late blocks) in each stimulus condition, which were then analyzed by the repeated measure analysis (ANOVAs) with the factors being Stimulus Valence (painful vs. neutral) and Block (early-block vs. late-block).

A e e t

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