

Research Report

Gender difference in empathy for pain: An electrophysiological investigation

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ABSTRACT

Our recent event-related brain potential (ERP) study disentangled the neural mechanisms of empathy for pain into an early automatic emotional sharing component and a late

the investigations measuring self-report of empathy found that females scored higher than males (Eisenberg and Lennon, 1983). A recent work also found that females scored higher than males on the Empathy Quotient that measures empathizing as a drive and an ability (Wheeler et al., 2006). These results are consistent with the notion that females are more empathic than males (Baron-Cohen et al., 2005).

Nevertheless, as Lennon and Eisenberg (1987) noted, gender difference in empathy measured through subjective reports may be contaminated by social desires and a bias to confirm the sex-role stereotypes. Most importantly, such approach tells little about the cognitive and neural mechanisms underlying gender difference in empathic processes. Some early studies recording heart rate or galvanic skin response found that, relative to females, males showed stronger physiological responses associated with empathic induction (Craig and Lowery, 1969). However, modulations of such physiological activity reflect consequences of empathic responses rather than the empathic processes.

Recent neuroimaging studies have identified neural processes involved in empathy for pain. Functional magnetic resonance imaging (fMRI) studies that compared hemodynamic responses to painful versus non-painful stimuli showed increased activations in the brain areas such as the insula and anterior cingulate cortex (ACC) (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 activity in these brain areas correlates with participants' estimates of the intensity of observed pain (Jackson et al., 2006; Saarela et al., 2007) and reflects the affective component of empathy. Research employing transcranial magnetic stimulation (TMS) found that the amplitudes of motor-evoked potentials (Avenanti et al., 2005, 2006) and somatosensory-evoked potentials (Bufalari et al., 2007) were modulated by perception of others' pain, suggesting that the sensorimotor and somatosensory cortex may be also involved in empathic responses to others' pain.

However, up to date, the gender difference in cognitive and neural processes of empathy for pain remains poorly understood because previous neuroimaging studies did not directly compare the brain imaging results between male and female subjects. These studies either grouped neuroimaging data from the two sexes together in data analysis (Avenanti et al., 2005, 2006; Jackson et al., 2005, 2006, Gu and Han, 2007) or measured neural activities from only one gender (e.g., females, Singer et al., 2004). To our knowledge, there is only one fMRI study trying to examine the gender difference in neural substrates underlying empathy for pain. Singer et al. (2006) recruited male and female subjects in an economic game, in which two confederates played fairly or unfairly with the subjects. They found that empathic neural responses in ACC and insula to fair confederates' pain were comparable between male and female subjects. This is apparently different from the conclusion of previous studies measuring subjective self-reports of empathy. However, Singer et al. (2006) showed further that the empathy-related responses were reduced when male subjects watched unfair than fair confederates' pain whereas females did not show such modulation of empathy-related responses. It appears that males' empathic responses are more vulnerable than those of females to the variation of social relationship. However, because of the low temporal resolution of BOLD

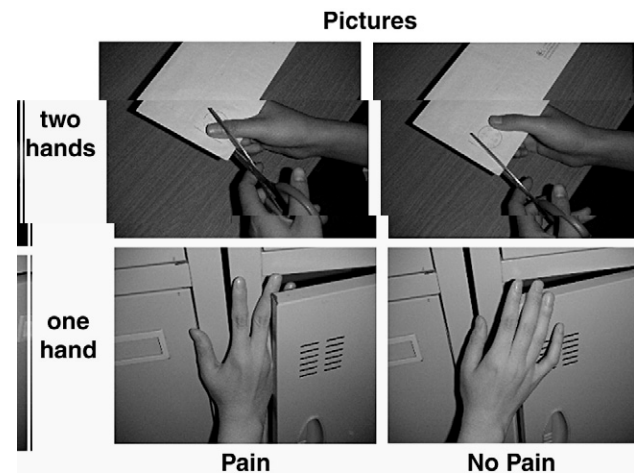


Fig. 1 – Illustration of the stimulus displays used in the current study. The left two pictures show painful stimuli and the right two pictures show no-pain stimuli.

signals recorded using fMRI, it remains unresolved when such modulation of empathy-related responses occurred.

We recently recorded event-related brain potentials (ERP) to painful or no-pain (neutral) stimuli in order to examine the temporal dynamic features of empathic responses (Fan and Han, *in press*). Subjects were presented with pictures of hands that were in painful or neutral situations (Fig. 1) and were asked to perform a pain judgment task that required attention to the pain cues in the stimuli or to perform a counting task that withdrew their attention from the pain cues. We found early differentiation between painful and neutral stimuli over the frontal lobe at 140 ms after sensory stimulation. A long-latency empathic response was observed after 380 ms over the central-parietal regions and was more salient over the left than right hemispheres. The late empathic response was modulated by top-down attention to the pain cues whereas the early empathic response was not. In addition, the ERP amplitudes at 140–180 ms were correlated with subjective reports of the degree of perceived pain of others and of self-unpleasantness. These ERP findings support the proposition that empathy for pain can be decomposed into an early automatic process and a late controlled process, which respectively underpin the early emotional sharing and late cognitive evaluation of others' pain.

The present study investigated gender differences in neural mechanisms of empathy for pain by comparing empathy-related ERPs between male and female participants. To do that, we reanalyzed the ERP data of our previous experiment (Fan and Han, *in press*) by separating the subjects into male and female groups. Of particular interest was whether the early automatic or the late controlled process of empathy is different between males and females.

2. Results

2.1. Behavioral performance

The mean RTs and response accuracies in each condition from male and female participants are shown in Table 1. The ANOVAs

Table 1 – Mean RTs and response accuracy (standard deviation) in each stimulus condition

	Pain judgment	Hand counting
RTs (ms)		
Male		
Painful	627 (50.0)	479 (43.4)
Neutral	474 (43.4)	2274

performed on RTs showed significant main effects of Task [$F(1,24)=289.297, p<0.001$] and Gender [$F(1,24)=6.403, p<0.05$]. RTs were longer in the pain judgment task than in the counting task. Females responded faster than males. Because there was a significant interaction of Pain×Gender [$F(1,24)=13.614, p<0.01$], post-hoc analysis was conducted and confirmed that males responded faster to painful than to neutral stimuli [$F(1,12)=7.250, p<0.05$] whereas a reverse pattern was true for females [$F(1,12)=6.365, p<0.05$]. In addition, ANOVAs showed a reliable interaction of Pain×Task×Gender [$F(1,24)=9.961, p<0.005$]. Separate analysis showed a reliable interaction of Pain×Task for males [$F(1,12)=18.106, p<0.005$], because males responded faster to painful than neutral stimuli in the pain judgment task [$F(1,12)=13.056, p<0.005$] but not in the counting task [$F(1,12)=1.213, p>0.1$]. In contrast, the interaction of Pain×Task was not significant for females [$F(1,12)=0.876, p>0.1$], suggesting that differential behavioral responses to painful and neutral stimuli did not differ between the two tasks for females.

The ANOVAs performed on response accuracies showed a significant main effect of Pain [$F(1,24)=15.860, p<0.005$] and Task [$F(1,24)=194.146, p<0.001$]. Subjects' accuracies were higher to neutral than painful stimuli, and higher in the counting than pain judgment tasks. There were reliable interactions of Gender×Pain [$F(1,24)=8.383, p<0.01$], Task×Pain [$F(1,24)=12.337, p<0.005$] and Gender×Task×Pain [$F(1,24)=6.540, p<0.05$]. Separate analysis revealed that, for females, response accuracy was higher to neutral than to painful stimuli in the pain judgment task [$F(1,12)=15.805, p<0.005$] but not in the counting task [$F(1,12)=3.872, p>0.1$]. In contrast, response accuracies did not differ between painful and neutral stimuli in both tasks for males [$F(1,12)=1.154, p>0.1$].

2.2. Electrophysiological data

Grand-averaged ERPs recorded at the central and lateral occipital electrodes in each stimulus condition are illustrated in Fig. 2 respectively for males and females. Both painful and neutral stimuli elicited a negative component at 90–130 ms (N110) over the frontal-central area, which was followed by a positive wave at 140–200 ms (P180) and a negative wave at 200–280 ms (N240). There was another negative deflection peaking

at 340 ms (N340) followed by a long-latency positivity between 360 and 800 ms (P3). ERPs over the occipito-temporal area were characterized with a positivity wave at 80–140 ms (P1), a negative wave at 140–200 ms (N170), and a positive wave at 200–450 ms (P320). A long-latency negative deflection was also observed over the occipito-temporal electrodes. The voltage topographies in Fig. 2 illustrate the scalp distribution of each ERP component.

The ANOVAs of ERP amplitudes recorded at the frontal-central electrodes showed a significant main effect of Pain between 140 and 660 ms [$F(1,24)=14.265$ to 31.656 , all $p<0.01$]. Relative to the neutral stimuli, painful stimuli elicited a positive shift of the ERPs in these time windows. The main effect of Task was significant at 120–280 ms [$F(1,24)=14.675, p<0.01$] and at 460–700 ms [$F(1,24)=212.048, p<0.001$] over the frontal-central area, due to the fact that, relative to the counting task, pain judgment task induced a positive shift in the early time window and larger P3 amplitude. There was a reliable interaction of Pain×Task at 380–500 ms over the frontal-central area [$F(1,24)=7.894, p<0.01$], suggesting that the painful stimuli elicited larger amplitudes at the ascending phase of the P3 component than neutral stimuli during the pain judgment task [$F(1,24)=35.725, p<0.001$] but not the counting task [380–460 ms, $F(1,24)=3.735, p>0.05$].

The descending phase of the P320 at 420–660 ms at the occipito-temporal electrodes was of larger amplitude to the painful than neutral stimuli [$F(1,24)=10.690, p<0.01$]. The pain judgment task elicited a positive shift at 80–320 ms relative to the counting task [$F(1,24)=21.236, p<0.001$], whereas the counting task evoked a larger long-latency negativity at 460–780 ms [$F(1,24)=74.903, p<0.001$]. There was a significant interaction of Pain×Task at the occipito-temporal electrodes at 220–300 ms [$F(1,24)=5.222, p<0.05$] and 420–580 ms [$F(1,24)=7.673, p<0.05$], because the pain judgment task elicited larger amplitude at the ascending phase of the P320 associated with the neutral stimuli than with the painful stimuli [240–300 ms, $F(1,24)=7.639, p<0.05$] whereas a reverse pattern was observed in the descending phase of the P320 [420–580 ms, $F(1,24)=16.675, p<0.001$].

Of particular interest in the current work, we found a reliable interaction of Pain×Gender between 500 and 660 ms [$F(1,24)=5.891, p<0.05$] at the frontal-central electrodes. Separate analysis showed that, for females, the amplitudes of the P3 in this time window was of larger amplitudes to the painful than neutral stimuli [$F(1,12)=17.867, p<0.01$]. For males, however, the amplitudes at 580–660 ms did not differ between the painful and neutral stimuli [$F(1,12)=1.106, p>0.1$]. Moreover, there was a reliable three-way interaction of Pain×Task×Gender at 340–540 ms [$F(1,24)=5.584, p<0.05$] over the frontal-central area. Further analysis confirmed that, for females, the P3 amplitude in this time window was larger to the painful than neutral stimuli in the task of pain judgment [$F(1,12)=23.584, p<0.001$] but not in the counting task [$F(1,12)=0.845, p>0.5$]. However, no significant interaction of Pain×Task was observed for males [$F(1,12)=0.290, p>0.5$], although the main effect of Pain was significant in this time window [$F(1,12)=19.124, p<0.01$], suggesting that the pain effect was comparable between the two tasks.

There was a reliable interaction of Task×Gender at 100–140 ms [$F(1,24)=5.948, p<0.05$] over the occipito-temporal area. For females, the descending phase of the P1 was of larger

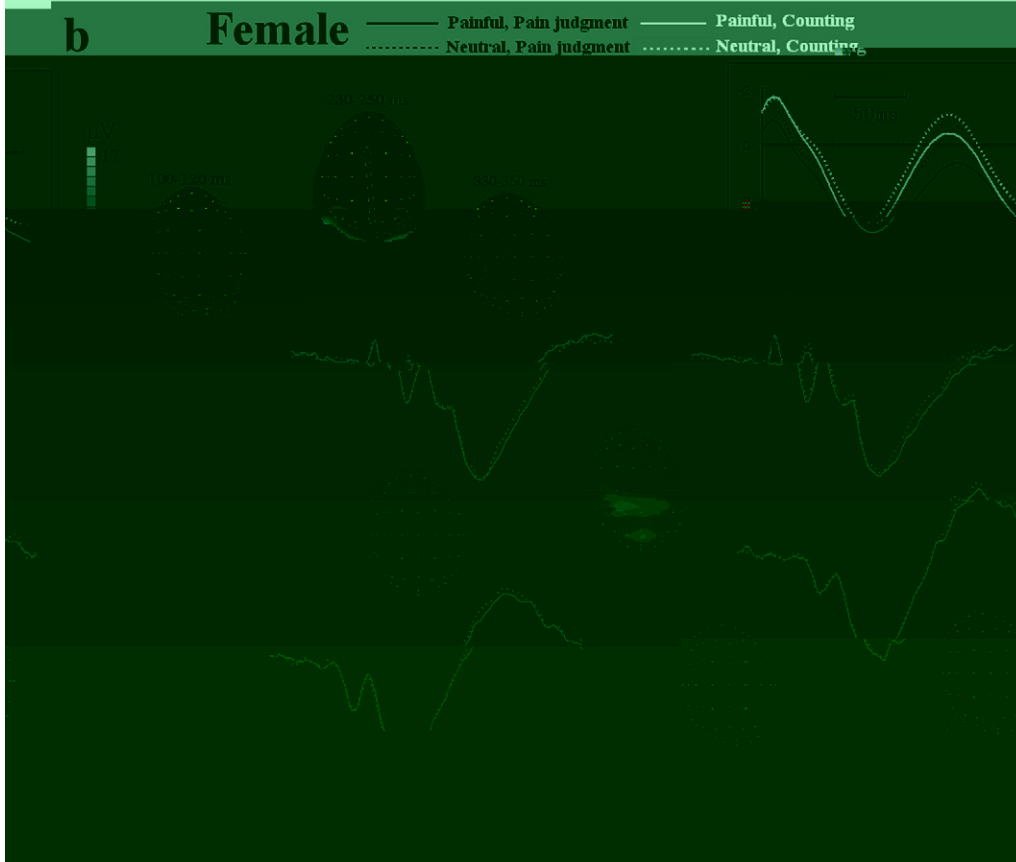
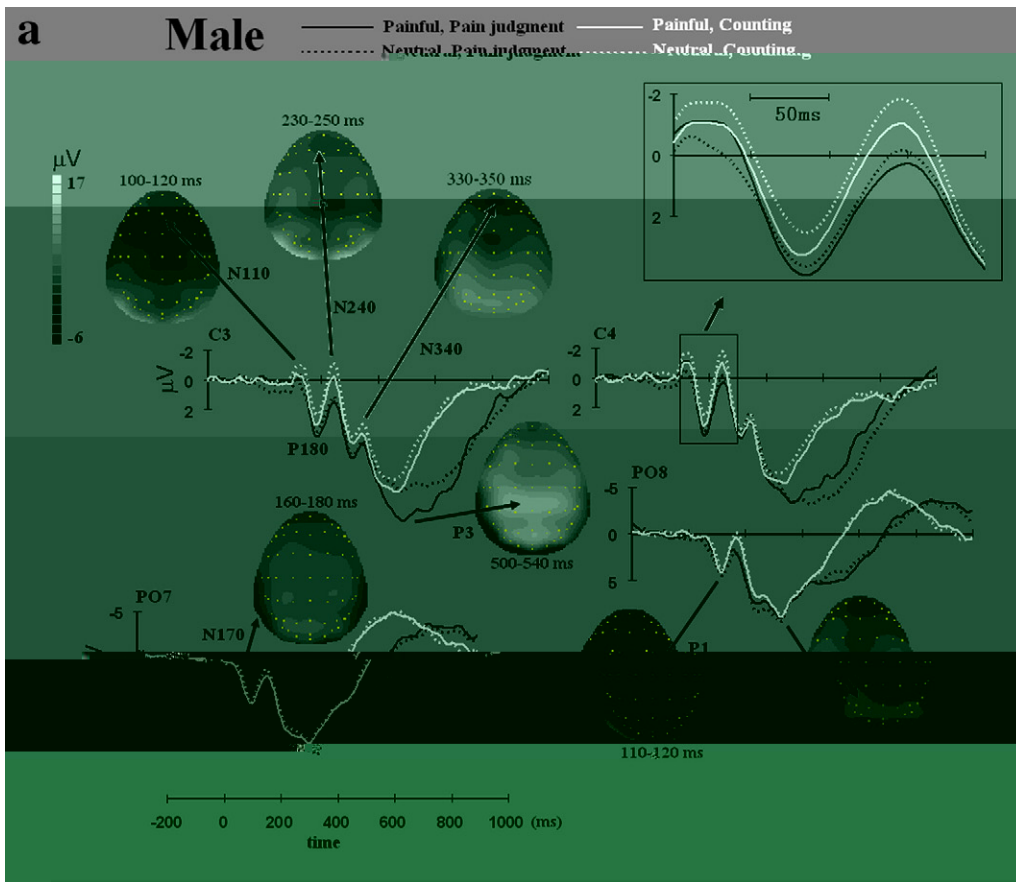


Table 2 – Mean FPS-R scores (standard deviation) of others' pain and self unpleasantness

	Male	Female
Painful stimuli		
Others' pain	4.32(0.52)	4.39(0.89)
Self unpleasantness	4.29(0.67)	4.30(0.84)
Neutral stimuli		
Other's pain	1.28(0.29)	1.07(0.13)

[$F(1,12)=18.351$, $p<0.01$], whereas no such difference was observed in males [$F(1,12)=2.361$, $p>0.1$]. Furthermore, there was a significant interaction of Pain \times Task \times Gender between 420 ms and 540 ms over the occipito-temporal area [$F(1,24)=6.272$, $p<0.05$]. Separate analysis showed a reliable interaction of Pain \times Task at 420–540 ms in females [$F(1,12)=23.061$, $p<0.001$], suggesting that the descending phase of the P320 showed larger amplitude to the painful than neutral stimuli in the pain judgment task [$F(1,12)=15.887$, $p<0.01$] but not in the in counting task [$F(1,12)=0.343$, $p>0.5$]. For males, however, the interaction of Pain \times Task was not significant [$F(1,12)=0.069$, $p>0.5$], although the main effect of Pain was significant in this time window [$F(1,12)=19.124$, $p<0.01$].

We also observed an interaction of Gender \times Pain \times Hemisphere at 140–300 ms over the occipito-temporal area [$F(1,24)=9.042$, $p<0.01$]. Separate ANOVAs showed a reliable interaction of Pain \times Hemisphere at 160–300 ms for females [$F(1,12)=8.644$, $p<0.05$] but not for males [$F(1,12)=1.241$, $p>0.1$], suggesting a more salient effect of painful contents of the stimuli over the left than right hemispheres for females.

2.3. Correlation between subjective rating and ERP amplitudes

After the EEG recording procedure, subjects were asked to evaluate the pain intensity felt by the model in painful and neutral stimuli and to report subjective feeling of their own unpleasantness when watching others in pain. The mean scores and standard deviation of the subjective reports are shown in Table 2. The ratings of others' pain were subject to ANOVAs with Pain (painful vs. neutral) and Gender as main effect. There was only a significant main effect of Pain [$F(1,24)=470.330$, $p<0.001$], suggesting higher scores for painful than neutral stimuli.

We calculated the correlation between the mean amplitudes of ERPs elicited by painful stimuli in each time window and the FPS-R scores (see Fig. 3). The mean ERP amplitudes at 140–180 ms associated with the painful stimuli was significantly negatively correlated with both the score of other's pain [F3: $r(1,13)=-0.748$, $p<0.01$; FC3: $r(1,13)=-0.715$, $p<0.01$; C3: $r(1,13)=-0.616$, $p<0.05$; F4: $r(1,13)=-0.723$, $p<0.01$; FC4: $r(1,13)=-0.623$, $p<0.05$; C4: $r(1,13)=-0.689$, $p<0.01$] and the score of self unpleasantness [F3: $r(1,13)=-0.810$, $p<0.01$; FC3: $r(1,13)=-0.816$, $p<0.01$; C3: $r(1,13)=-0.736$, $p<0.01$; F4: $r(1,13)=-0.804$,

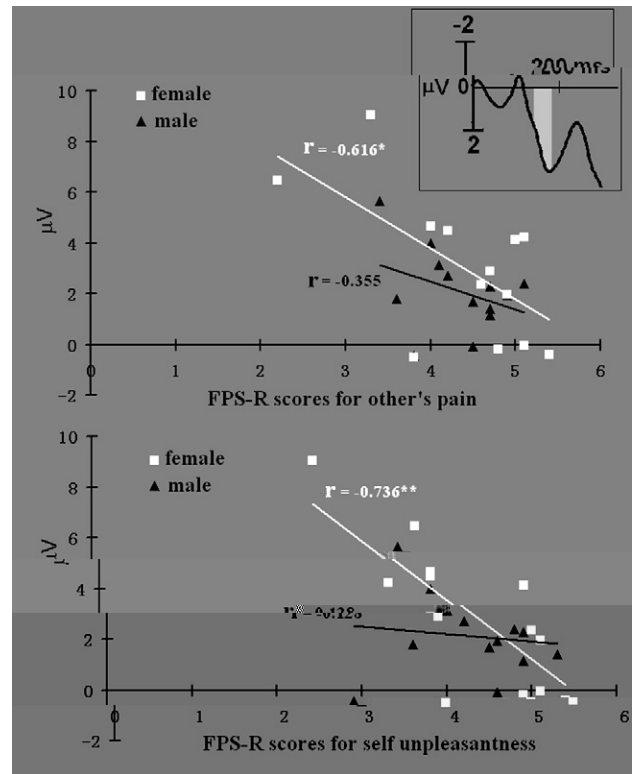


Fig. 3 – Correlation between the amplitudes of ERPs evoked by painful pictures and the FPS-R scores of both other's pain (upper panel) and self-unpleasantness (lower panel). The up-right panel shows the ERPs before 300 ms and the white area shows the time window (140–180 ms) during which the ERP amplitudes showed significant correlation with subjecting ratings. The p -values equivalent of * and ** are 0.05 and 0.01, respectively.

$p<0.01$; FC4: $r(1,13)=-0.803$, $p<0.01$] for females. The larger the ERP amplitudes in this time window, the lower perceived pain intensity and the weaker subjective feeling of unpleasantness induced by the perception of others' pain. However no reliable correlation was observed for males between the mean ERP amplitudes at this time window and the subjective reports score of other's pain [all $p>0.5$] and score of self unpleasantness [all $p>0.5$].

3. Discussion

Previous studies investigated gender difference of empathy by measuring subjective reports and found evidence favored females (Eisenberg and Lennon, 1983; Wheelwright et al., 2006). The current work extends the previous research by examining gender difference in the neural processes underlying empathy for pain by recording ERPs from male and female

Fig. 2 – (a) ERPs to picture stimuli recorded at the frontal-central and occipito-temporal electrodes (C3–C4, PO7–PO8) from males. The up-right panel illustrates the early pain effect between 100 and 300 ms after stimulus delivery. (b) ERPs to picture stimuli recorded at the frontal-central and occipito-temporal electrodes (C3–C4, PO7–PO8) from females. The up-right panel illustrates the early pain effect between 100 and 300 ms after stimulus delivery.

healthy adults. In particular, we investigated gender difference in the early automatic and late controlled processes of empathy for pain that were indexed by differential neural activity elicited by painful and neutral stimuli (Fan and Han, *in press*).

Our ERP results indicate that the painful and neutral stimuli were differentiated as early as 140 ms after sensory stimulation over the frontal-central areas. In addition, the tasks of pain judgment or counting did not influence the differentiation between the painful and neutral stimuli until 380 ms over the frontal-central area and 220 ms over the occipito-temporal sites. These ERP results provide evidence for an early neural response at 140–340 ms over the frontal-central area that was elicited by observation of others in pain and independent of the task demand, suggesting an early automatic component of empathy for pain (Fan and Han, *in press*). In contrast, the later stage of the processing of others' pain depended upon the task demands. The differentiation between the painful and neutral stimuli indexed by the P3 was evident in the task of pain judgment but not in the counting task, suggesting that a controlled process of empathy for pain over the posterior parietal region occurred later than the automatic process of empathy for pain that focused over the anterior frontal-central areas. Our ERP results appear to parallel previous ERP studies that also observed an early fronto-central modulation of ERPs elicited by facial expressions at 120 ms (e.g., Eimer and Holmes, 2002) and a late positive potential at 350–750 ms that is involved in the processing of affective components of stimuli (e.g., Schupp et al., 2000). Based on their ERP findings, Fan and Han (*in press*) proposed a two-stage model of empathic responses consisting of early emotional sharing and late cognitive evaluation. This model may be applied to the processing other types of visual stimuli with emotional contents. However, both the ERP empathy effects observed in the current work and the ERP emotion effects observed in other research (e.g., Eimer and Holmes, 2002; Schupp et al., 2000) occurred much earlier than the ERP correlates of understanding others' belief, i.e., the theory-of-mind ability, which was linked to the modulation of a late slow wave ERP component over the frontal cortex that could start as early as 300 ms after sensory stimulation (Liu et al., 2004; Sabbagh and Taylor, 2000). These ERP results indicate dissociation in time course between the processing of emotion and belief contents in others' mind.

Of particular interests, we found that the early ERP pain effect (i.e., the positive shift at 140–320 ms elicited by the painful relative to neutral stimuli at the fronto-central electrodes) did not differ between male and female participants. As the pain effect in this time window was independent of the task demands, the results indicate that the early automatic process of empathy for pain is comparable for males and females. However, although the early ERP pain effect indexing the automatic process of empathy for pain did not show significant gender difference, subjective ratings were correlated with the ERP amplitudes in an early time window (140–180 ms) for females whereas no such correlation was observed for males. These results first imply that subjective feelings of both others' pain and self-unpleasantness are determined by the early automatic process of empathy. In addition, it may be further proposed that subjective feelings of both others' pain and self-unpleasant-

ness are more strongly determined by the early automatic process of empathy in females than in males. The correlation between the early ERP amplitudes and subjective ratings, which reflected conscious awareness of others' pain and one's own unpleasantness, suggest that there might be a linkage between the early ERP component and subjective experience of affective contents of awareness or the "affective consciousness" in terms of Panksepp (2005), although further evidence is required for these propositions.

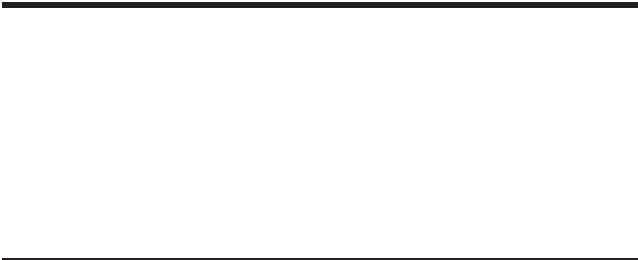
Our ERP data also showed evidence for gender difference in pain effects on neural responses in the time window of the controlled process. While the larger P3 amplitude at 340–540 ms to the painful than neutral stimuli was observed in both sexes, this pain effect was stronger for females than males. In addition, this differential pain effect was evident when participants performed the pain judgment task but not when they performed the counting task. Another way to analyze the gender difference in this time window suggests that task demands modulated the differentiation between the painful and neutral stimuli in females but not in males, because the pain effect in this time window was smaller in the counting task than in the pain judgment task only in females. Such gender difference could not simply arise from differential low-level sensory/perceptual processing of the painful and neutral stimuli. Potential differences in stimulus novelty and salience existed between the painful and neutral stimuli, which may result in distinct attentional involvement in the early sensory-perceptual processing and thus modulate the visual extrastriate activity (e.g., Martinez et al., 2001). However, the absence of differences in the occipital P1 and N1 amplitudes between painful and neutral stimuli suggests comparable effects of stimulus novelty and salience on the early sensory-perceptual processing of painful and neutral stimuli.

Nevertheless, the long-latency P3 results suggest a stronger top-down influence on the long-latency controlled process of empathy for pain in females than in males. There has been evidence that the P3 component reflects the process of stimulus evaluation and classification (Duncan-Johnson, 1981; Duncan-Johnson and Kopell, 1981; McCarthy and Donchin, 1981). Stimulus novelty also modulates the P3 amplitudes (Friedman et al., 2001). While our recent fMRI work (Gu and Han, 2007) showed that empathy-related activity in the ACC and insula decreased when top-down attention was withdrawn away from the emotional content of painful stimuli, the P3 empathy effect observed in the current work showed further ERP evidence for the dynamics of the top-down modulation of empathic responses to others' pain. Based on the cognitive functional roles of the P3 identified in the previous work (Duncan-Johnson, 1981; Duncan-Johnson and Kopell, 1981; McCarthy and Donchin, 1981; Friedman et al., 2001), Fan and Han (*in press*) suggested that the long-latency processes of empathy may function to provide extensive evaluation of painful stimuli because of their high stimulus novelty. Because the ERP results in the current work showed greater pain effect in the descending phase of the P3 component for females than males, it is likely that, relative to males, females intended to undergo more intensive evaluation of painful stimuli, as suggested by longer RTs to the painful than neutral stimuli in females. This is in agreement with females' social role of taking care of the

offspring (Vogel et al., 2003), which requires greater sensitivity to danger signals such as painful stimuli. While previous studies measuring subjective reports favored females in empathy (Eisenberg and Lennon, 1983; Wheelwright et al., 2006; Baron-Cohen et al., 2005), fMRI studies did not report such gender difference in empathy for pain (Jackson et al., 2005; 2006; Singer et al., 2004; Botvinick et al., 2005; Saarela et al., 2007; Gu and Han, 2007). The current work provided the first piece of ERP evidence for gender difference in the process of empathy for pain. Together with Singer et al.'s (2006) observation that males' empathic responses were more strongly influenced by social relationship, our current ERP results lend further support that males' and females' empathic responses are differentially modulated by top-down attention and social relationship.

Gender difference in neural activities elicited by the painful and neutral stimuli was also observed in ERP components recorded at the occipital electrodes. The early visual activity (i.e., the descending phase of the P1) at 100–140 ms varied as a function of task demands, being enhanced by the task of pain judgment relative to that observed in the counting task. However, this modulation of the visual activity was observed in females but not in males. One possibility is that, because females are more empathic or sympathetic than males (Eisenberg and Lennon, 1983; Wheelwright et al., 2006; Baron-Cohen et al., 2005), the pain judgment task generated enhanced attention to the stimuli in females than in males and thus induced stronger visual activity. This is consistent

Each subject participated in eight blocks of trials. In four blocks of trials subjects were required to judge pain vs. no-pain for hands in painful and neutral pictures. They were asked to count the number of hands in painful and neutral pictures in the other blocks of trials. Each block of trials started with the presentation of instructions for 3 s, which defined the task (i.e., pain judgment or counting the number of hands) for each block. There were 80 trials in each block. On each trial



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