Neural correlates of heat-evoked pain memory in humans

Liping Wang, 1,2 Peng Gui, 1 Lei Li, 1 Yixuan Ku, 1,2 Mark Bodner, 5 Gaojie Fan, 6 Yong-Di Zhou, 2,3,4 and Xiao-Wei Dong 1,2

1 Key Laboratory of Brain Functional Genomics, MOE and STCSM, Institute of Cognitive Neuroscience, East China Normal University, Shanghai, People’s Republic of China; 2 NYU-ECNU Institute of Brain and Cognitive Science at NYU Shanghai and Collaborative Innovation Center for Brain Science, Shanghai, People’s Republic of China; 3 Department of Neurosurgery, Johns Hopkins University, Baltimore, Maryland; 4 Krieger Mind/Brain Institute, Johns Hopkins University, Baltimore, Maryland; 5 MIND Research Institute, Irvine, California; and 6 Department of Psychology, Colorado State University, Fort Collins, Colorado

Submitted 9 February 2015; accepted in final form 31 December 2015

Wang L, Gui P, Li L, Ku Y, Bodner M, Fan G, Zhou YD, Dong XW. Neural correlates of heat-evoked pain memory in humans. J Neurophysiol 115: 1596–1604, 2016. First published January 6, 2016; doi:10.1152/jn.00126.2015.—The neural processes underlying pain memory are not well understood. To explore these processes, contact heat-evoked potentials (CHEPs) were recorded in humans with electroencephalography (EEG) technique during a delayed matching-to-sample task, a working memory task involving presentations of two successive painful heat stimuli (S-1 and S-2) with different intensities separated by a 2-s interval (the memorization period). At the end of the task, the subject was required to discriminate the stimuli by indicating which (S-1 or S-2) induced more pain. A control task was used, in which no active discrimination was required between stimuli. All event-related potential (ERP) analysis was aligned to the onset of S-1. EEG activity exhibited two successive CHEPs: an N2-P2 complex (~400 ms after onset of S-1) and an ultralate component (ULC; ~900 ms). The amplitude of the N2-P2 at vertex, but not the ULC, was significantly correlated with stimulus intensity in these two tasks, suggesting that the N2-P2 represents neural coding of pain intensity. A late negative component (LNC) in the frontal recording region was observed only in the memory task during a 500-ms period before onset of S-2. LNC amplitude differed between stimulus intensities and exhibited significant correlations with the N2-P2 complex. These indicate that the frontal LNC is involved in maintenance of intensity of pain in working memory. Furthermore, alpha-band oscillations observed in parietal recording regions during the late delay displayed significant power differences between tasks. This study provides in the temporal domain previously unidentified neural evidence showing the neural processes involved in working memory of painful stimuli.

PAIN MEMORY HAS BEEN RECOGNIZED as a key element in modulation of pain perception in both physiological and pathological conditions (Apkarian 2008; Woolf and Salter 2000). It influences future pain perception (Koyama et al. 2005; Porro et al. 2002; Taddio et al. 1995) and contributes to the recognition of pain in others as well (Singer et al. 2004). Studies have also shown that pain memory underlies the clinical assessment of pain and analgesic efficacy, which often relies on the patient’s retrospective evaluation of pain experienced before and after a treatment (Breme et al. 2000; Erskine et al. 1990; Terry et al. 2008). In addition, recent studies have indicated a connection between long-term memory of pain evoked by an initial inciting injury and the development of centralized chronic pain (Apkarian 2008; Woolf and Salter 2000). However, we have a very limited understanding of the neural processes involved in pain memory (Khoshnejad et al. 2014), especially in long-term pain memory.

Studies of memory in various nonpainful cortical sensory (e.g., visual, auditory, and tactile) systems have indicated that global cortical networks, including both association and primary sensory cortical areas, are involved in working memory (Pasternak and Greenlee 2005). Furthermore, findings by a number of groups have suggested that working memory largely relies on the temporary activation of subsets of long-term memory networks and, intrinsically, working memory and long-term memory share the same global cortical networks (Curtis and D’Esposito 2003; Fuster 2004; Lewis-Peacock and Postle 2008; Wang et al. 2012; Zhou et al. 2007). Therefore, it is reasonable to assume that such global working memory networks and an overlap between working memory and long-term memory exist not only in the nonpainful cortical sensory systems but also in the pain cortical sensory system. It appears that elucidating the neural mechanisms underlying working memory (including pain working memory) may lead to a better understanding of the dynamics of neural networks for long-term memory (Fuster 2008).

A recent pioneer study on pain memory reported cortical locations of pain short-term memory-specific activity, which included the primary somatosensory cortex (SI)/posterior parietal cortex (PPC), anterior insular cortex (aIC), and secondary somatosensory cortex (SII) (Albanese et al. 2007). However, no study to date has explored in the temporal domain neural processes of working memory of pain. Thus, to understand the function of cortical networks for pain memory, we investigated in the present study the temporal neural processes of pain working memory by recording contact heat-evoked potentials (CHEPs) in humans with electroencephalography (EEG) technique and a delayed matching-to-sample (DMS) task similar to the task used successfully in tactile working memory studies in both monkeys (Romo and Salinas 2003) and humans (Ohara et al. 2006; Spitzer et al. 2010; Spitzer and Blankenburg 2011).
MATERIALS AND METHODS

Subjects

Fourteen right-handed healthy volunteers (5 men, 9 women; age range 19–25 yr) participated in the study. Each subject gave signed informed consent after a complete explanation of the purpose and design of the study. The study protocol was approved by the Ethics Committee on Human Experiments of East China Normal University.

Stimulator

The pain stimulus was administered by a stimulator (Pathway, Medoc, Ramat Yishai, Israel) that had a round thermode contacting a cutaneous area of 572.5 mm² (27 mm in diameter). This thermode comprised a heating thermofoil (Mincro Products, Minneapolis, MN) covered with a 25-μm layer of thermo-conductive plastic (Kapton, thermal conductivity of 0.1–0.35 W/mK at 23°C). Ten micrometers within this plastic layer, there were two embedded thermocouples providing an estimate of the temperature at the thermode surface. The thermofoil permits a heating rate of up to 70°C/s, and the Peltier device allows a cooling rate of 40°C/s (Granovsky et al. 2005).

Experimental Paradigm

All procedures were performed in a dimly lit, electromagnetically shielded, and soundproof room with an environmental temperature of ~22°C. Before EEG recording sessions, the participants were first tested to determine their heat pain thresholds. A modified method of limits algorithm (Yosipovitch and Yamnitsky 1997) was used for calculating pain thresholds. Thus the thermal stimuli consisted of continuously increasing temperatures in steps of 0.5°C from a base temperature of 35°C. Subjects were asked to manually stop the stimulation once they perceived a pain sensation. This procedure was repeated 10 times for each subject.

After the pain threshold temperature was obtained for all subjects, six temperatures (43.5, 44.5, 45.5, 46.5, 47.5, and 48.5°C; each repeated 10 times and presented randomly) were used for the subjective numerical pain rating procedure to determine the stimuli to be used for the DMS task. A validated Chinese version of the visual analog scale (VAS; scale of 0–10, with 0 corresponding to “no pain” and 10 corresponding to “the worst pain”) was used to assess the subject’s experience (Carlsson 1983; Gu and Han 2007; Meng et al. 2013). On the basis of the behavioral results, two temperatures (45.5 and 46.5°C), both above the pain threshold for all subjects, were chosen so that the subjects not only were able to successfully finish the task but also at the same time could tolerate the painful experience evoked by the stimuli. One day before the recording session instructions for performing the DMS task were fully explained to the subjects, and two practice sessions (36 trials/session) were then conducted by each subject until his/her task performance reached a correct response rate of 80%. All psychophysical tests were performed in Chinese.

Previous EEG and MEG studies with laser devices have shown that the time window of first pain has a duration of 100 ms, centered around 300–500 ms after the onset of laser stimulus, and that of second pain has a duration of 1,000 ms, ranging from 500 to 1,500 ms (Hu et al. 2014; Magerl et al. 1999; Ploner et al. 2002). Therefore, to ensure that the delay period was able to accommodate the neural processes of first and second pain, the DMS task was designed with a 2-s delay. The subjects were required to keep their eyes fixated on a white cross (2 × 2 cm in size) at the center of the monitor in front of them (1 m away) throughout an entire trial. A trial (Fig. 1A) began with a colored cue (a red or green cross of the same size as the white cross, appearing for 1,000 ms, randomly chosen to replace the white cross at the center of the monitor) indicating the task type (memory or control). For half of the participants, red indicated a memory trial and green denoted a control trial. For the other half, the color cues were reversed.

The DMS task, a working memory task, consists of two heat pulses separated by a 2,000-ms delay period (onset to onset) that were delivered to the subject’s right forearm (dorsal aspect) after a 1,000-ms baseline period. The first stimulus (S-1) was pseudorandomly chosen between two temperatures (45.5 and 46.5°C). The second stimulus (S-2) was either 1.2°C higher or lower than S-1. For example, if S-1 was 45.5°C, then S-2 would be 44.3°C in half of the trials and 46.7°C in the other half. The temperature of S-2 was also randomly assigned. The duration of both S-1 and S-2 was 480 ms (Fig. 1A, inset). The baseline temperature of the thermode was set as 37°C.

Fig. 1: A: experimental paradigm. A trial begins with a colored cue (a red/green cross appearing for 1,000 ms at the center of the monitor, assigned randomly trial by trial) indicating the task type (memory or control). After a 1,000-ms foreperiod, there are 2 heat pulses separated by a 2,000-ms delay period. The first stimulus (S-1) is 45.5 or 46.5°C and is randomly chosen. The second stimulus (S-2) is either 1.2°C higher or lower than S-1, also randomly assigned. The duration of the S-1 or S-2 is 480 ms, and the baseline temperature of the thermode is set as 37°C (inset). The subject’s response is a button press chosen out of 2 buttons to indicate which stimulus (the S-1 or the S-2) is more painful. The intertrial interval (ITI) is 5,500 ms. B: 24 central-medial electrodes are used and grouped into 9 regions of interest (ROIs) for statistical analysis: frontal left: AF3, F1, F3; frontal medial: Fz; frontal right: AF4, F2, F4; central left: FC1, FC3, C1, C3; central medial: Cz; central right: FC2, FC4, C2, C4; parietal left: CP1, CP3, P1; parietal medial: CPz, Pz; and parietal right: CP2, CP4, P2.
For the memory trials, the subject was instructed to memorize S-1 and compare it with S-2 after the 2-s delay. Immediately after S-2, the subjects were presented the questions “Is S-1 more painful?” and “Is S-2 more painful?” on the screen. They responded by pressing a button (1 or 2) with the left index or middle finger. In the control trials, the subjects were not required to compare S-1 with S-2. Instead, after S-2 two numbers appeared on the screen, “1” and “2,” corresponding to the two buttons. The subjects were asked to press the button corresponding to the number that had a higher luminosity. In both tasks, a trial was terminated by the subjects’ response made within a 3-s period (between onset of S-2 and onset of button press). A trial was ended and logged as an error if no response was received within that 3-s period. The intertrial interval (between end of a trial and onset of visual cue in next trial) was 5.5 s.

Each subject performed 90 memory and 90 control trials, pseudo-randomly arranged. The trials were assigned to five sessions (36 trials per session). The visual cues, pain stimuli, and response questions were counterbalanced among the subjects and sessions. During EEG recordings, a rest period (3–5 min) was inserted between sessions. To avoid pain sensitization, the position of the thermode was changed slightly during the rest period. The heat stimuli by the heat stimulator was observed in any subject. Visual displays and response recordings were achieved with the E-Prime system (Schneider et al. 2002).

**EEG Recording and Analysis**

CHEPs were recorded with EEG. The recording system was from Brain Products (Munich, Germany). Sixty-five Ag-AgCl scalp electrodes were arranged in a standard 10-20 system (American Clinical Neurophysiology Society 2006). EEG signals were referenced to FCz and grounded at AFz. Electrooculogram (EOG) signals were recorded to detect horizontal and vertical eye movements. Impedance of each electrode was kept below 5 kΩ. EEG and EOG signals were filtered (0.01–250 Hz band pass), amplified, digitized (500-Hz sample rate), and stored for off-line analysis.

Off-line EEG data were preprocessed with Brain Vision Analyzer (version 2.0.1, Brain Products) and custom MATLAB (MathWorks, Natick, MA) scripts. EEG and EOG signals were filtered (0.01–40 Hz band pass) with slopes of 24 dB. EOG-contaminated elements among the EEG signals were removed by an independent component analysis (ICA) method (Makeig et al. 1996). The EEG data were then referenced with a common average reference. Extreme signals with slopes > 50 μV/ms or maximal differences > 120 μV within 200 ms were excluded from further analysis.

A time period from 200 ms before to 2,000 ms after the S-1 onset was selected for event-related potential (ERP) analysis. ERPs were calculated by averaging correctly performed trials. The average value of the voltage during the 200-ms period preceding the onset of S-1 served as the baseline, which was used for subsequent subtraction of the ERPs. All ERP analysis was aligned to the onset of S-1. To identify significant CHEPs, we first examined the whole delay period by contrasting the waves between memory and control conditions. On the basis of the interested time windows indicated by the mapping results, we primarily focused on differences in oscillatory power between memory and control trials.

Twenty-four central-medial electrodes were used and grouped into nine regions of interest (ROIs; Fig. 1B) for statistical analysis: frontal left: AF3, F1, F3; frontal medial: Fz; frontal right: AF4, F2, F4; central left: FC1, FC3, C1, C3; central medial: Cz; central right: FC2, FC4, C2, C4; parietal left: CP1, CP3, P1; parietal medial: CPz, Pz; and parietal right: CP2, CP4, P2. Four-way repeated-measures analysis of variance (ANOVA) was used to compare the amplitude of ERP components and oscillatory powers. The within-subject factors were FP (frontal, central, and parietal), LR (left, medial, and right), Condition (memory and control), and Intensity (high and low). Post hoc Bonferroni’s test was used for pairwise comparisons. All statistical analyses were performed with STATISTICA 6.1 (StatSoft, Tulsa, OK) and SPSS 20 (SPSS, Chicago, IL).

**RESULTS**

**Behavioral Results**

Thermal pain thresholds for each subject are shown in Fig. 2A; note that the temperature used for pain stimulation (45.5 or 46.5°C) was higher than all thresholds. Discriminative accuracy was 88 ± 5% (mean ± SD) under the memory condition and 99 ± 2% under the control condition. In the memory
Table 1. Four-way repeated-measures ANOVA for N2, P2, N2-P2 complex, ULC, and LNC

<table>
<thead>
<tr>
<th></th>
<th>N2</th>
<th>P2</th>
<th>N2-P2</th>
<th>ULC</th>
<th>LNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>$F_{2,26} = \frac{5.409}{\eta} = 0.011$</td>
<td>$F_{2,26} = \frac{17.154}{\eta} &lt; 0.001$</td>
<td>$F_{2,26} = \frac{3.32 \times 10^{-4}}{\eta} = 0.001$</td>
<td>$F_{2,26} = \frac{3.93}{\eta} &lt; 0.001$</td>
<td>$F_{2,26} = \frac{1.10 P = 0.346}{\eta} = 0.078$</td>
</tr>
<tr>
<td>LR</td>
<td>$F_{2,26} = \frac{7.07 \times 10^{-3}}{\eta} = 0.004$</td>
<td>$F_{2,26} = \frac{41.377}{\eta} &lt; 0.001$</td>
<td>$F_{2,26} = \frac{8.94 P = 0.001}{\eta} = 0.001$</td>
<td>$F_{2,26} = \frac{8.94}{\eta} = 0.001$</td>
<td>$F_{2,26} = \frac{8.406}{\eta} = 0.005$</td>
</tr>
<tr>
<td>Condition</td>
<td>$F_{2,26} = \frac{0.262}{\eta} = 0.017$</td>
<td>$F_{2,26} = \frac{0.254}{\eta} = 0.062$</td>
<td>$F_{2,26} = \frac{0.02}{\eta} = 0.083$</td>
<td>$F_{2,26} = \frac{0.017}{\eta} = 0.060$</td>
<td>$F_{2,26} = \frac{0.02}{\eta} = 0.092$</td>
</tr>
<tr>
<td>Intensity</td>
<td>$F_{2,26} = \frac{1.379}{\eta} = 0.098$</td>
<td>$F_{2,26} = \frac{12.654}{\eta} = 0.004$</td>
<td>$F_{2,26} = \frac{0.825}{\eta} = 0.003$</td>
<td>$F_{2,26} = \frac{0.24}{\eta} = 0.067$</td>
<td>$F_{2,26} = \frac{0.22}{\eta} = 0.067$</td>
</tr>
</tbody>
</table>

Significant $P$ values are in boldface. ULC, ultralate component; LNC, late negative component; FP, frontal, central, and parietal; LR, left, medial, and right.

condition, 2.2% of trials on average received no responses from subjects. The reaction time (Fig. 2B) under the memory condition was 1.096 ± 1.82 ms, which was significantly longer than that under the control condition (662.9 ± 107.7 ms, paired $t$-test, $P < 0.001$). This longer reaction time was probably due to the additional processes of the memory task, which required the subjects to respond as accurately as possible after comparing the intensity of pain following the delivery of two stimuli. VAS scores for the two pain stimuli (45.5 and 46.5°C) were 3.29 ± 0.16 and 4.11 ± 0.17, respectively, and were significantly different from each other (paired $t$-test, $P < 0.001$; Fig. 2C).

**CHEPs**

All ERPs are time-locked to the onset of S-1. The repeated-measures ANOVA results for the amplitude of the three main components (N2-P2, ULC, and LNC) are shown in Table 1.

**N2-P2 complex.** The N2-P2 amplitude elicited main effects for FP [$F_{2,26} = \frac{32.3}{\eta} < 0.001$], $\eta^2 = 0.713$, LR [$F_{2,26} = 61.4 P < 0.001$, $\eta^2 = 0.825$], and Intensity [$F_{2,26} = 12.8 P < 0.001$, $\eta^2 = 0.558$]. Post hoc analysis of the main effects revealed that there was a differential response of the N2-P2 complex to the stimulus intensities in the central (high: 4.53 ± 0.41 μV, low: 3.99 ± 0.42 μV, $P < 0.05$) and frontal (high: 0.28 ± 0.46 μV, low: -0.16 ± 0.37 μV, $P < 0.05$) regions (Fig. 3, Fig. 4, top). These indicated that the high-intensity stimulus yielded a larger N2-P2 response than the low-intensity stimulus under both memory and control conditions.

Additionally, two-way interactions, FP × Condition [$F_{2,26} = 7.46 P = 0.002$, $\eta^2 = 0.365$], LR × Intensity [$F_{2,26} = 3.96 P = 0.031$, $\eta^2 = 0.234$], and FP × LR [$F_{2,26} = 16.4 P < 0.001$, $\eta^2 = 0.558$] were observed. Post hoc analysis of the FP × Condition interaction revealed a differential response of the complex to the task conditions in the parietal (memory: 2.69 ± 0.42 μV, control: 1.91 ± 0.41 μV, $P < 0.001$) and frontal (memory: -0.37 ± 0.41 μV, control: 0.49 ± 0.47 μV, $P < 0.001$) regions. Furthermore, post hoc analysis of the LR × Intensity interaction revealed that the N2-P2 amplitude was significantly larger (left: 2.35 ± 0.28 μV, right: 0.83 ± 0.21 μV, $P < 0.001$) on the contralateral side (left) than on the ipsilateral (right) side.

As N2 and P2 may reflect different brain origins and significances, the two components were also analyzed separately. The analysis of P2 component revealed a main effect of Intensity [$F_{1,13} = 12.65 P = 0.004$, $\eta^2 = 0.493$] and a FP × Condition interaction effect [$F_{2,26} = 12.39 P = 0.001$, $\eta^2 = 0.488$], whereas N2 component did not show such a difference (Table 1). Further multivariate ANOVA tests on FP × Condition interaction effect at each of the frontal, central, and parietal locations showed that the significant Condition effect of N2-P2 [$F_{1,13} = 5.60 P = 0.034$] at the frontal recording electrodes was mainly contributed by the P2 [$F_{1,13} = 4.89 P = 0.046$] but not N2 [$F_{1,13} = 0.67 P = 0.426$] component.

**ULC.** Main effects were found for the location factors FP [$F_{2,26} = 39.3 P < 0.001$, $\eta^2 = 0.752$] and LR [$F_{2,26} = 8.94 P < 0.001$, $\eta^2 = 0.407$] (Table 1). A two-way interaction, FP × Condition [$F_{2,26} = 15.0 P < 0.001$, $\eta^2 = 0.536$], and a three-way interaction, FP × LR × Condition [$F_{4,52} = 3.27 P = 0.018$, $\eta^2 = 0.201$], were also observed. Post hoc analysis of both two-way and three-way interactions demonstrated significant differences in ULC amplitude between conditions in the frontal (memory: -1.22 ± 0.29 μV, control: -0.43 ± 0.20 μV, $P < 0.001$) and parietal (memory: 2.04 ± 0.26 μV, control: 1.16 ± 0.19 μV, $P < 0.001$) regions (Fig. 3 and Fig. 4, bottom right). However, the ULC amplitude showed neither difference between high- and low-intensity trials for all elec-
trodes nor difference between left and right electrodes (Fig. 4, bottom left).

**LNC and alpha oscillations.** As indicated in Table 1, a three-way interaction, FP × LR × Condition \([F_{(4,52)} = 2.59, P < 0.05, \eta^2 = 0.166]\), and a two-way interaction, FP × Intensity \([F_{(2,26)} = 3.35, P < 0.05, \eta^2 = 0.205]\), were observed for the LNC. Post hoc analysis of FP × LR × Condition revealed a significant \((P < 0.006)\) difference in the LNC between the memory and control conditions in the central-medial region. The FP × Intensity interaction was next examined to evaluate the effect of intensity across the different brain regions. Pairwise comparisons indicated significant differences between the high- and low-intensity stimuli at the frontal-left \((P < 0.001)\) and frontal-medial \((P < 0.02)\) recording sites. Moreover, a two-way (Intensity × Condition) ANOVA analysis within the electrode of interests (Fz) showed an interaction between Intensity and Condition \([F_{(2,26)} = 4.03, P < 0.05]\); further analysis revealed that the difference between the high- and low-intensity stimuli in LNC was significant in the memory condition \((P < 0.01)\) but not in the control condition \((P = 1.000)\; \text{Fig. 5A}\).

Since the frontal recording regions demonstrated a differential response to the stimulus intensities in both the N2-P2 complex and the LNC in the memory condition, differences in the amplitude of the two components between the high- and low-intensities were analyzed with Pearson’s correlation coefficient. A significant \((r = 0.55, P < 0.05)\) positive correlation was observed (Fig. 5B).
A power spectral analysis during the last 500 ms in the delay period (1,500–2,000 ms) revealed that the alpha band (8–13 Hz) at the parietal-right electrode cluster demonstrated significantly higher oscillatory power ($P < 0.05$) in the memory condition ($4.45 \pm 1.12 \mu V^2$) compared with the control condition ($3.29 \pm 0.64 \mu V^2$; Fig. 6). No oscillatory power difference was observed in any other frequency band.

**DISCUSSION**

In the present study, we have identified neural processes that may underlie encoding of pain and maintenance of the encoded pain information in the brain. Our results suggest for the first time in the temporal domain that neural activation represented by ERP components is involved in working memory of intensity of pain.
CHEPs have been commonly used in the neurophysiological evaluation of nociceptive activity in the brain (Chen et al. 2001; Granovsky et al. 2008; Greffrath et al. 2007; Hankins et al. 2000; Le Pera et al. 2002; Valeriani et al. 2002). To elucidate the temporal processes of neuronal activity in the network of pain working memory, CHEPs were recorded and analyzed in our study. In agreement with previous observations (Granovsky et al. 2008; Greffrath et al. 2007; Kanda et al. 2002), our recordings showed that the amplitude of the N2-P2 complex at the vertex was strongly associated with both the intensity of pain stimuli and the subjective pain ratings. In addition, we found that this association was present persistently, regardless of task conditions (memory or control). These results are consistent with the role of N2-P2 complex proposed previously in encoding stimulus and providing precise sensory information for an appropriate, rapid, and safe motor response (Iannetti et al. 2005; Ploner et al. 2002). Interestingly, such an intensity dependence of the N2-P2 amplitude was also observed at the frontal site.

In our experimental conditions, the N2-P2 complex recorded at both frontal and parietal sites displayed significant difference between memory and control conditions. In particular, the P2 component displayed the significant main effect of Condition in the frontal recording sites. This condition-dependent difference is probably due to higher cognitive processes involved in DMS tasks, such as attention and working memory. We assume that the frontal-parietal circuitry is likely to play a role in imparting information of sensory intensity to short-term memory during our DMS tasks, as the frontal-parietal network is crucial in working memory (Miller and Cohen 2001). Previous studies have suggested that N2 and P2 components reflect different brain activities and functions (Moont et al. 2011; Tarkka and Treede 1993). Thus N2 could be generated by bilateral activity mainly in secondary somatosensory cortices, whereas the source of the P2 component was likely located in the medial frontal cortex. The P2 Intensity effect found in the present results further confirms that the encoding of the pain information may involve both sensory and affective aspects of pain information, but further dissecting specific components of pain is beyond the scope of the study.

In our study, we observed a LNC in the frontal recording region during the 1,500–2,000 ms period after the onset of S-1 (a 500-ms period immediately prior to the onset of S-2). This frontal LNC displayed a significant difference between high and low intensities of pain stimuli that was detected merely in the frontal LNC. More notably, the LNC was positively correlated with the amplitude of the intensity-related N2-P2 complex evoked by S-1 in the memory trials but not in the control trials. Collectively, these findings suggest that the pain intensity is encoded by the N2-P2 complex and retained by the frontal LNC, which represents the ERP index of maintenance of pain intensity.

Several studies indicate that the LNC encompasses components contributed from the cortical activities associated with short-term memory of sensory stimuli (Mittenberg et al. 1985; Ohara et al. 2006). A recent FMRI study of the spatial discrimination of pain has revealed that the prefrontal cortex is involved in working memory of the spatial location of painful information (Oshiro et al. 2007). Analysis of source localization has shown that the LNC reflects the involvement of frontoparietal networks (Nagai et al. 2004; Rektor 2002). The information from these studies implies that the frontal LNC in the present study may reflect the activity of neural networks (including frontal cortical regions) associated with the process of working memory. Thus the maintenance of encoded pain intensity in working memory likely involves the activation of the prefrontal cortex during the delay period, which may share the same neural network involved in maintenance of nonpainful sensory information in working memory (Fuster 2008; Wood and Grafman 2003). For example, the ERP index of maintenance of visual information has been found over prefrontal cortical areas in both humans and nonhuman primates (Reinhart et al. 2012), and an ERP component of a sustained frontal negativity has also been observed in a auditory working memory task (Chao and Knight 1996). Of course, our assumption of the involvement of frontoparietal networks remains to be experimentally confirmed.

The LNC has been found to be also related to a number of other neural processes, such as motor preparation, stimulus anticipation, and time estimation (Frohlich et al. 1980; Minnissi et al. 1999; Mittenberg et al. 1985; Praamstra et al. 2006). However, there is no significant difference in stimulus anticipation, motor preparation, and time estimation between the high- and low-intensity conditions in our study. These processes are therefore unlikely major factors underlying the difference in the LNC observed in the present study.

In our study, an ULC was detected at 850–950 ms after the onset of S-1. Although our present stimulus protocol and EEG signal processing technique were not designed to dissociate neural components of Aδ and C fibers, the latency of this ULC is compatible with cortical activation of unmyelinated C afferents (Hu et al. 2014; Opsommer et al. 2001; Tran et al. 2001), suggesting its relation to second pain (Chen et al. 2001; Le Pera et al. 2002).

The ULC only exhibited a significant difference in amplitude between memory and control conditions in both frontal and parietal recording regions, without any difference between stimulus intensities. This memory task-related difference suggests that rather than encoding the intensity of first pain stimulus, ULC was more likely involved in other cognitive functions, such as the neural process of anticipation of next pain stimulus, as well as attention that is critical in working memory (Awh et al. 2006). Indeed, cognitive factors associated with anticipation and attention have been found to significantly influence neural responses to pain perception (Porro et al. 2002; Seminowicz et al. 2004).

Alpha oscillations are often interpreted to reflect cortical idiing (Pfurtscheller et al. 1996). In humans, the power of the activity in the alpha frequency band is suppressed by eye opening, visual stimuli, and visual scanning but increases during the performance of internal tasks, such as mental calculations and working memory (Johnson et al. 2011; Palva and Palva 2007). Alpha-band oscillations at posterior sites in nonvisual task demands are thought to reflect top-down-controlled inhibition or disengagement of task-irrelevant areas (Haegeles et al. 2010; Spitzer et al. 2010). A number of studies lately have shown that posterior alpha power increases with successful maintenance of visual item information (Hsieh et al. 2011; Jensen et al. 2002). Our data reveal significantly higher alpha power in posterior parietal recording regions under the memory condition during the time period that overlaps with that of the LNC (1,500–2,000 ms). These findings may indi-
cate that alpha oscillations, together with the LNC, represent neural processes that preserve information regarding pain intensity in the working memory task.

In addition to memory, attention and anticipation are also involved in task performance. The requirement of attention and the degree of anticipation in the memory task were conceivably greater than those in the control task, which could be attributed to the observed differences in N2-P2 complex and ULC between conditions in the present study. These differences should be minimal though, as control and memory trials were randomly mixed within a recording session to hold the subjects’ attention at a relatively similar level in both conditions. However, with regard to the frontal LNC, this ERP component showed a difference between high and low intensities of pain stimuli during the delay period in the memory task but not in the control task. The intensity differences were compared within the same condition (either memory or control), in which the attention and anticipation levels were essentially identical. It is unlikely that the differential changes of LNC in the memory task are due to factors other than the active memory of the intensity of pain stimuli. Thus both attention and anticipation can be excluded as significant factors in determining the differential changes in LNC.

Conclusions

The neural and behavioral findings in the present study show that 1) regardless of the task condition (memory or control), pain intensity is represented by the vertex and frontal N2-P2 complex; 2) the neural process of active maintenance of pain-related information during the delay period of the DMS task may be represented by the frontal LNC and posterior alpha oscillations; and 3) the ULC was more likely involved in other cognitive functions, such as anticipation and attention associated with working memory. Our findings provide the first ERP evidence of the involvement of frontal recording areas in pain working memory.

ACKNOWLEDGMENTS

We thank Drs. F. A. Lenz, M. Ringkamp, and S. Ohara at Johns Hopkins University for their constructive suggestions for this study.

GRANTS

This work was supported by National Science Foundation of China 31070980 to X.-W. Dong and by the Young Scientist Foundation of East China Normal University to L. Wang. This work was also supported by the Blaustein Pain Research Fund and a research fund from the MIND Research Institute to Y.-D. Zhou.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: L.W., P.G., L.L., Y.K., M.B., Y.-D.Z., and X.-W.D. conception and design of research; L.W., P.G., L.L., and Y.K. performed experiments; L.W., P.G., L.L., Y.K., and G.F. analyzed data; L.W., P.G., Y.K., M.B., Y.-D.Z., and X.-W.D. interpreted results of experiments; L.W., P.G., L.L., and Y.-D.Z. prepared figures; L.W., Y.-D.Z., and X.-W.D. drafted manuscript; L.W., Y.K., Y.-D.Z., and X.-W.D. edited and revised manuscript; L.W., Y.-D.Z., and X.-W.D. approved final version of manuscript.

REFERENCES


