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Pain modulates early sensory brain responses to task-irrelevant emotional faces

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Abstract

Background: Pain can have a significant impact on an individual's life, as it has both cognitive and affective consequences. However, our understanding of how pain affects social cognition is limited. Previous studies have shown that pain, as an alarm stimulus, can disrupt cognitive processing when focal attention is required, but whether pain also affects task-irrelevant perceptual processing is unclear.

Methods: We examined the effect of laboratory-induced pain on event-related potentials (ERPs) to neutral, sad, and happy faces before, during, and after a cold pressor pain. ERPs reflecting different stages of visual processing (P1, N170, and P2) were analyzed.

Results: Pain decreased the P1 amplitude for happy faces and increased the N170 amplitude for happy and sad faces compared to the pre-pain phase. The effect of pain on N170 was also observed in the post-pain phase. The P2 component was not affected by pain.

Conclusions: Our results suggest that pain alters both featural (P1) and structural face-sensitive (N170) visual encoding of emotional faces, even when the faces are irrelevant to the task. While the effect of pain on initial feature encoding seemed to be disruptive and specific to happy faces, later processing stages showed long-lasting and increased activity for both sad and happy emotional faces.

Significance: The observed alterations in face perception due to pain may have consequences for real-life interactions, as fast and automatic encoding of facial emotions

is important for social interactions.

Keywords: Event-related potential; Facial emotion; Pain; Sensory response; Social cognition

Pain modulates early sensory brain responses to task-irrelevant emotional faces

1. Introduction

Pain, as a salient stimulus warning of potential tissue damage, is often difficult to ignore. Research now shows that chronic pain (Dick & Rashiq, 2007; Moore et al., 2019; for reviews, see Crombez et al., 2013; Moriarty et al., 2011) and experimentally induced pain (Attridge et al., 2016; Moore et al., 2012, 2019; for a review, see Gong et al., 2019) can disrupt attentional processes. However, research is limited regarding the effects of pain on pre-attentive levels, where focal attention is not required. Previous studies have reported the disruptive nature of pain on task-irrelevant auditory brain functions (Dick et al., 2006; Yao et al., 2011), but little is known about its effects on task-irrelevant visual processing. This study aims to investigate the effects of experimentally induced pain on early sensory event-related potentials (ERPs) to faces, as face is an important source of social cognition (Hugenberg & Wilson, 2013), and pain has been linked to socio-emotional problems (for reviews, see Gatchel, 2004; Hooten, 2016). ERPs are utilized because they provide a means to investigate different processing phases of face perception in a time-resolved manner.

Here, we focused on sensory ERPs (P1, N170, and P2) that reflect different processing stages of face perception (for task-irrelevant face processing, see Batty & Taylor, 2003; Chang et al., 2010; Ruohonen et al., 2020; Stefanics et al., 2012; L. Zhao & Li, 2006). P1, elicited at approximately 100 ms latency at the occipital electrode sites, is associated with initial low-level visual feature and emotion processing in faces (Batty & Taylor, 2003; Linkenkaer-Hansen et al., 1998; Schindler et al., 2021) although it is not face-sensitive

(Rossion & Caharel, 2011). The subsequent N170, evoked in the occipital temporal lobe region, is face-sensitive (Bentin et al., 1996) and modulated by facial expressions (Astikainen & Hietanen, 2009; Chang et al., 2010; Zhao & Li, 2006, for reviews, see Hinojosa et al., 2015; Schindler & Bublatzky, 2020). The posteriorly distributed P2 is a visual component that has been less investigated, but in the context of face processing, it seems to be an automatic emotional significance index (Carretié et al., 2004; Chang et al., 2010; Zhao & Li, 2006) and reflects spatial relations of facial features (Schweinberger & Neumann, 2016; Wang et al., 2016).

We presented participants with visual stimuli consisting of low-probability happy and sad "deviant" faces interspersed with neutral "standard" faces—a stimulus condition that reflects the brain's predictive coding processing (Friston, 2005; Stefanics et al., 2014), and is similar to some previous studies in individuals with depression. This comparison is meaningful as pain and depression share some of the same neural pathways and neurotransmitter changes (Bair et al., 2003; Sheng et al., 2017). ERPs recorded before, during, and immediately after the induction of acute cold pressure pain were anticipated to show pain-induced decreases in the P1 amplitude, as reported previously for effects of pain on attended emotional face processing (Wieser et al., 2012). In addition, if pain has similar effects to acute depression, we would expect to see a negative bias, reflected by enhanced N170 and P2 specifically to sad faces (Dai & Feng, 2012; Xu et al., 2018; Q. Zhao et al., 2015), or a general diminishment of these later responses (Chang et al., 2010; Xu et al., 2018). Pain, as a stressor, may also elicit long-lasting effects on cortisol secretion and blood oxygenation in the brain (Makovac et al., 2020; Vaisvaser et al., 2013), even after the pain

has subsided.

2. Methods

2.1. Participants

The statistical power of the study was ensured by a priori estimation of the sample size for the repeated measures analysis of variance (ANOVA) using G*Power 3.1.9.2 (Faul et al., 2007), with an effect size of $\eta^2_p = 0.16$, as reported by Wiser et al. (2012). Other input parameters included: α error probability = 0.05; power ($1 - \beta$ error probability) = 0.95; number of groups = 1; number of measurements = 9; correlation among repeated measures = 0.50; nonsphericity correction e = 1; and effect size specification as in SPSS. These parameter settings indicated a minimum sample size requirement of 17 participants.

In total, 20 participants (6 males, 14 females) were recruited using email lists, online advertisements, flyers, and notice board announcements posted in public places around the University of Jyväskylä. Inclusion criteria were age 18 to 44 years, right-handedness, normal or corrected-to-normal vision, and a normal body weight (body mass index 18.5–24.9 kg/m^2; Park et al., 2012) to avoid any possible effects of abnormal sympathetic responses to the cold pressor test in overweight individuals. Exclusion criteria included pregnancy and breastfeeding, current or past history of any circulatory and cardiovascular diseases, hypertension, diabetes mellitus, drug or alcohol abuse (more than 16 or 24 portions of alcohol per week in women and in men, respectively), and any psychiatric or neurological disorders. Individuals with recurrent pain symptoms in the last three months (e.g., headache, abdominal pain, lower back pain, neck/shoulder pain, muscle aches, joint

pain) or with frostbite, open cuts, or sores on hands or limbs were also excluded from this study. A phone interview was used to ensure that these inclusion and exclusion criteria were met. Those who were found suitable in the first screening phase were asked to fill in questionnaires, including the Finnish version of the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), Beck Anxiety Inventory (BAI; Beck et al., 1993), Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1996), and Symptom Checklist-90-revised (SCL-90-R; Derogatis & Unger, 2010), prior to the experiment. Participants who met the cut-off scores in one or more of the questionnaires (Table 1) were excluded from the study.

All participants were instructed not to use any analgesics or sedatives for at least 48 h before the measurements and not to take any other drugs (except contraceptives) or alcohol within 24 h before the experiment. Hormonal fluctuations in pain perception were minimized by requesting that all female participants attend the experiment during the follicular phase of their menstrual cycle (Lapotka et al., 2017; Vincent & Tracey, 2010). All participants signed a written informed consent form before participating in the experiment, and the experimenter stressed that any participant could withdraw from the experiment at any moment, with no consequences. The procedures of the study complied with the Declaration of Helsinki and were approved by the ethical committee of the University of Jyväskylä.

2.2. Materials

2.2.1. Materials for pain induction

In a laboratory setting, several different stimuli, such as noxious cold and heat, pressure, and electrical shock, can be employed to induce pain (for reviews, see Gong et al., 2019; Julius & Basbaum, 2020). Of these, the cold pressor test is recognized as a valid and effective way to mimic the effects of chronic pain conditions in healthy individuals (De Wied & Verbaten, 2001; Meagher et al., 2001; Mitchell et al., 2004). However, the traditional cold pressor test requires individuals to submerge their hands in ice water; therefore, combining this stimulus with other state-of-the-art techniques is difficult when investigating the neural mechanism underlying face responses. For this reason, an alternative to the traditional method, namely the cold pressor arm wrap, has been developed (Porcelli, 2014). Similar to the responses obtained with the traditional cold pressor test, the responses to this arm wrap are associated with levels of hypothalamic-pituitary-adrenal and sympatho-adrenomedullary axis activation (Porcelli, 2014). Therefore, following the protocol described by Porcelli (2014), six custom cold pressor arm wraps were created with hot and cold compatible gel packs (SISSEL ® Pack). Two arm wraps were stored at room temperature and used alternately in the no-pain conditions, and the other four arm wraps were used alternately in the four blocks of the pain conditions to avoid temperature differences in the arm wraps between blocks due to warming by the participant's body temperature. The arm wrap used for the pain condition was stored in a -18°C freezer, taken out 30 min before the experiment, and left at room temperature to let it warm back to a desired temperature of approximately -5°C (this temperature was selected based on the results of our pilot study, in which participants reported pain and unpleasantness but could

withstand the cold for at least 3 min). During the experiment, the mean temperature of the arm wrap during the pain phase was -4.26°C (SD = 1.40), while the mean temperatures of the pre- and post-pain arm wraps were 23.69°C (SD = 0.51) and 23.78°C (SD = 0.62), respectively. The arm wrap temperature during the pain phase was significantly lower than that of the pre-pain ($p < 0.001$) and post-pain ($p < 0.001$) phases, but no significant difference was detected between the pre- and post-pain phases ($p = 0.234$).

2.2.2. Materials for the oddball task

The visual stimuli were black-and-white photographs selected from the Karolinska Directed Emotional Faces (KDEF) stimulus set (Lundqvist et al., 1998). A total of 6 female and 6 male facial images were selected based on the evaluations of unbiased hit rates (sad > 0.58; happy > 0.8; neutral > 0.73; averaged across different expressions > 0.79) of each facial expression from a prior study (Goeleven et al., 2008). The IDs and the corresponding mean intensity and arousal for each stimulus are reported in the supplementary material. All selected facial pictures were transformed to grayscale and adjusted to an equalized mean luminance level using the SHINE toolbox (Willenbockel et al., 2010) in MATLAB. Subsequently, all facial images were covered with a gray frame that obscured features other than the inner face. The stimuli were presented at a visual angle of 3.03° × 4.11° and a resolution of 209 × 283 pixels (width × height).

2.3. Procedure

Upon arrival at the laboratory, the participants were informed about the procedures of the experiment and their right to stop the experiment whenever they wanted, and they provided written informed consent. During the experiments, the participants were seated on a comfortable chair in a soundproofed, electrically shielded, and dimly lit room. The entire experiment consisted of three phases: the pre-pain phase, the pain phase, and the post-pain phase. The three phases were otherwise identical, except for the temperature of the arm wraps used: the room-temperature arm wraps were used for the pre-pain phase and post-pain phase, while cold arm wraps were used for the pain phase. To reduce the possibility of too long a cold pain exposure and possible fatigue, each phase was further divided into four blocks, during which the arm wraps were moved to a different arm (Fig. 1). The order of the arm wearing the arm wrap was counterbalanced among the participants, with half the participants wearing it on the left arm and the other half on the right arm. Each block lasted approximately 3 min, and the total duration, including short breaks, was approximately 15 min for each phase.

For each block, the participants were asked to report their sensations of pain and unpleasantness using two 11-point Numerical Rating Scale (NRS-11) questionnaires at the beginning and at the end of each block. These two scales scored two dimensions of pain: intensity and unpleasantness. The intensity scale was anchored with “no pain at all” (in Finnish: “ei ollenkaan kipua”) at the 0-point end and “the most intense pain imaginable” (in Finnish: “voimakkain kipu, jonka pystyn kuvittelemaan”) at the 10-point end. The unpleasantness scale was anchored with "not at all unpleasant" (in Finnish: "ei ollenkaan epämiellyttävä") at the 0-point end and "the most unpleasant imaginable" (in Finnish

"epämiellyttävin tuntemus, jonka pystyn kuvittelemaan") at the 10-point end.

Between the two ratings, the facial stimuli were presented in a passive oddball stimulus condition, during which a frequently occurring neutral "standard" face (p = 0.8) was randomly interspersed with rarely occurring emotional "deviant" faces (sad and happy, p = 0.1 for each). All stimuli were pseudo-randomly presented in compliance with the following two conditions: 1) at least two standard faces were presented between two consecutive deviant faces; and 2) the identities of the two adjacent faces differed from each other. The duration was 200 ms for each stimulus, and the interstimulus interval (ISI, offset-to-onset) was randomly set as 450 ms, 500 ms, or 550 ms. For each phase (pre-pain, pain, or post-pain), a total of 1000 stimuli, including 800 neutral standard faces, 100 sad deviant faces, and 100 happy deviant faces, were presented. During the visual stimulus presentation, an audiobook was played through a speaker on the ceiling above the participants. The participants were instructed to ignore the face stimuli and to focus on the audiobook. After each block, the participants were asked one question about the audiobook content to encourage them to attend carefully to the story. The mean accuracy of the responses across the study was 76.67% (SD = 0.11), and no significant difference was noted in accuracy ($F(2,38) = 1.568$, $p = 0.222$, $\eta_p^2 = 0.076$) between different pain phases after conducting a one-way repeated-measures analysis of variance (ANOVA) with pain phases (pre-pain, pain, and post-pain) as the within-subjects factor.

The face stimuli and the ratings of sensation of pain and unpleasantness were presented in the center of a 23-inch monitor (1920 × 1080 pixels, refresh rate 100 Hz) approximately

1 m away from the participants. The stimuli and the rating responses were controlled by a Windows PC using the E-prime software. The participants were informed that they should sit still, keep their gaze in the middle of the screen, and try to refrain from extensive blinking and movement during the recording. At the end of the experiment, the overall pain experience during the measurement was assessed using the Finnish version of Short-Form McGill Pain Questionnaire (Melzack, 1987), modified to ask participants for a report of their subjective description of pain during the experiment (rather than the pain experienced during the past week, as stated in the original form).

2.4. EEG recording and analysis

During the visual stimulus presentation, continuous electroencephalography (EEG) recordings were obtained using a 128-channel EEG system (NeurOne, Mega Electronics). The EEG signals were collected with reference to the vertex electrode (Cz), with an online bandpass filter of 0.1–250 Hz, and were sampled at 1000 Hz.

The EEG data were analyzed off-line using the Brain Vision Analyzer software (Brain Products, Munich, Germany). Noisy channels were initially replaced by signals from neighboring channels by topographic interpolation transformation. The ocular correction algorithm provided by the Brain Vision Analyzer was then applied to eliminate artifacts caused by eye movements. The data were subsequently re-referenced against an average reference. A bandpass filter from 0.1–30 Hz and a notch filter of 50 Hz were applied to eliminate noise from muscle artifacts, external environmental noise, and other interferences

not of interest. The data were then segmented according to different stimulus events, with a 200 ms pre-stimulus and 600 ms post-stimulus onset. A similar signal-to-noise ratio was obtained for each stimulus by averaging only the standard responses immediately preceding the deviant stimulus. The epochs were baseline corrected for each epoch by subtracting the mean voltage value of the 200 ms pre-stimulus interval from the epoch data. Segments with signal amplitudes larger than ±100 μV in any recording channel, including the electro-oculography (EOG) channel, were rejected from further analysis. The resulting segments were averaged separately for happy deviant, sad deviant, and neutral standard faces, and for each phase (pre-pain phase, pain phase, and post-pain phase). For the neutral faces, only responses before the deviants were included. The mean number (and standard deviation) of the EEG segments for the neutral standard before sad deviant, sad deviant, neutral standard before happy deviant, and happy deviant stimuli across all three phases were 87 (11.40), 88 (10.61), 88 (10.42), and 88 (10.57), respectively. All participants had at least 50 segments averaged for each type of stimulus (Astikainen et al., 2013; Kreegipuu et al., 2013).

The amplitudes of P1, N170, and P2 were investigated. The electrodes and time windows for the analysis were selected based on visual inspection of the waveforms, the topographies of the activity, and previous literature (Astikainen et al., 2013; Ruohonen et al., 2020). The regions of interest (ROIs) were set on the left and right occipital sites for P1 and P2 responses (the left hemisphere: the electrodes 65, 69, and 70; the right hemisphere: the electrodes 83, 89, and 90) and on the left and right parietal-occipital sites for N170 response (the left hemisphere: the electrodes 45, 50, 56, 57, 58, 63, and 64; the

right hemisphere: the electrodes 95, 96, 99, 100, 101, 107, and 108). Time windows were 60–130 ms after the stimulus onset for P1, 120–170 ms for N170, and 160–230 ms for P2. The mean amplitude values within the corresponding time windows for each component were calculated.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 24 for Windows. For behavioral ratings, one-way repeated-measures analysis of variance (ANOVA) with Pain phases (pre-pain, pain, and post-pain) as the within-subjects factor was conducted separately for pain intensity and unpleasantness ratings. For one participant, the pain intensity and unpleasantness ratings in the pre-pain phase were accidentally overwritten; thus, the ratings for that participant were replaced by the average value of the corresponding attribute.

For the ERP mean amplitude, the responses for the neutral standard before sad and happy faces were averaged to a "neutral standard" to reduce the levels for the ANOVA analysis, as they both reflected responses to physically identical stimuli (i.e., neutral faces). This setting allows us to keep all possible trials for the best possible signal-to-noise ratio for each stimulus category without considerably increasing the trial number difference between standards and deviants. A three-way repeated-measures ANOVA was conducted separately for each ERP component (P1, N170, P2) including Hemisphere (left, right), Pain phase (pre-pain, pain, and post-pain), and Emotion (sad, happy, and neutral). A repeated-measures analysis of covariance (ANCOVA) was also conducted separately for P1, N170

and P2, with pain as a covariate, and this yielded similar results to the original analysis (for more details, see the Supplementary material). Significant interaction effects were decomposed by simple effect analysis with planned pairwise comparison (Bonferroni correction was applied, p-value after correction [p_{corr}]) to contrast the effects of pain on different types of facial stimuli. All statistics with p or p_{corr} values smaller than 0.050 were considered significant, and p or p_{corr} values between 0.050 and 0.080 were considered marginally significant. In addition, JASP (Version 0.16, JASP Team, 2022) was used to provide Bayes factors to indicate whether the t-test results supported the alternative hypothesis or null hypothesis (Rouder et al., 2009; Schmalz et al., 2021), thereby providing an odds ratio for the alternative/null hypotheses (values < 1 favor the null hypothesis and values > 1 favor the alternative hypothesis). The default priors in JASP were used.

3. Results

3.1. Pain intensity and unpleasantness ratings

The results patterns for the behavioral ratings are depicted in Fig. 2. For the pain intensity ratings, one-way repeated-measures ANOVA showed a significant main effect of Pain phases, $F(2,38) = 49.049$, $p < 0.001$, $\eta_p^2 = 0.721$, indicating that participants felt more pain during the pain phase (range: 0.125–6.125, 2.763 ± 1.854) than during the pre-pain (range: 0–2.500, 0.467 ± 0.693, $p_{corr} < 0.001$, $BF_{10} = 17725.137$) and post-pain (range: 0–1.500, 0.200 ± 0.428, $p_{corr} < 0.001$, $BF_{10} = 20185.100$) phases. The pain sensation also differed between the pre-pain and the post-pain phase ($p_{corr} = 0.024$, $BF_{10} = 6.135$).

Similarly, for the unpleasantness rating, a significant main effect was found for the Pain phase, $F(2,38) = 93.967$, $p < 0.001$, $\eta_p^2 = 0.832$. Participants reported more unpleasant feelings in the pain phase (range: 0.500–6.625, 3.894 ±1.778) than in the pre-pain (range: 0–3.000, 0.974 ± 0.980, $p_{corr} < 0.001$, $BF_{10} = 8233000.000$) or the post-pain phase (range: 0–1.500, 0.381 ± 0.526, $p_{corr} < 0.001$, $BF_{10} = 3334000.000$), and more unpleasantness was experienced in the pre-pain phase than in the post-pain phase ($p_{corr} = 0.018$, $BF_{10} = 7.969$). In the Short-Form McGill Pain Questionnaire, the participants reported overall total pain scores of 8.650 (SD = 4.283, range: 1–14; sensory pain: M = 8.350, SD = 4.107, range: 1–14; affective pain: M = 0.450, SD = 0.686, range: 0–2), and the overall visual analog scale pain intensity score was 35.000 (SD = 22.485, range: 3–79).

3.2. P1

The repeated-measures ANOVA with the within-subject variables Hemisphere (Left, Right), Pain phase (Pre-pain, Pain, Post-pain), and Emotion (Sad, Happy, Neutral) yielded a significant main effect of Hemisphere, $F(1,19) = 4.776$, $p = 0.042$, $\eta_p^2 = 0.201$, due to the larger responses at the right hemisphere (5.273 ± 2.361 μV) compared to the left hemisphere (4.418 ± 2.066 μV, $p_{corr} = 0.042$). A main effect of Emotion ($F(2,38) = 16.523$, $p < 0.001$, $\eta_p^2 = 0.465$) was also observed and was modified by an interaction effect between Pain phase × Emotion, $F(4,76) = 2.528$, $p = 0.047$, $\eta_p^2 = 0.117$. Planned comparisons conducted for testing the simple main effect of Pain at each level of Emotion showed that, for happy faces, the responses were larger in the pre-pain phase (4.839 ± 2.037 μV) than

in the pain phase (4.226 ± 2.250 μV, p_{corr} = .023, BF_{10} = 6.422), while no differences were found between the pre-pain and post-pain phase (4.678 ± 2.104, p_{corr} = 1.000, BF_{10} = 0.308), or the pain and post-pain phase (p_{corr} = 0.176, BF_{10} = 1.225). However, when the stimulus was a sad or neutral face, no differences were detected between the pain phases in P1 amplitude (all p_{corr} > 0.372, all BF_{10s} < 0.699). The other main effects and interaction effects were not statistically significant (all p-values > 0.152). The main results of P1 are depicted in Fig. 3.

3.3. N170

The repeated measure ANOVA with within-subject variables Hemisphere (Left, Right), Pain phase (Pre-pain, Pain, Post-pain), and Emotion (Sad, Happy, Neutral) yielded significant main effects of pain phase (F(2,38) = 6.423, p = 0.004, η_p^2 = 0.253), and emotion, (F(2,38) = 11.778, p < 0.001, η_p^2 = 0.383), which were modified by a marginally significant interaction effect of Pain phase × Emotion (F(4,76) = 2.272, p = 0.069, η_p^2 = 0.107). The planned comparison was conducted to contrast the effects of pain on different types of facial stimuli, and the results indicated that the responses to emotional faces were larger during the pain and post-pain phases than in the pre-pain phase. For the sad faces, the responses were more negative for both the pain (-0.493 ± 1.289 μV, p_{corr} = 0.046, BF_{10} = 3.586) and post-pain (-0.622 ± 1.323 μV, p_{corr} = 0.015, BF_{10} = 8.957) phases than for the pre-pain phase (0.079 ± 1.006 μV), while no difference was observed between pain and post-pain phases (p_{corr} = 1.000, BF_{10}=0.265). Similarly for the happy faces, the responses

were more negative and marginally significantly more negative in amplitude for the pain (-0.467 ± 1.394 μV, p_{corr} = 0.020, BF_{10} = 7.142) and post-pain (-0.425 ± 1.162 μV, p_{corr} = 0.053, BF_{10} = 3.218) phases than for the pre-pain phase (0.043 ± 1.052 μV), while no difference was evident between pain and post-pain phases (p_{corr} = 1.000, BF_{10} = 0.236). By contrast, no differences were found for the responses to the neutral faces between all three different pain phases (all p_{corr} > 0.107, all BF_{10} < 1.817). The other main effects and interaction effects were not statistically significant (all p-values > 0.142). The main results of N170 are depicted in Fig. 4.

3.4. P2

For the P2 mean amplitudes of 160–230 ms, the repeated measure ANOVA with the within-subject variables Hemisphere (Left, Right), Pain phase (Pre-pain, Pain, Post-pain), and Emotion (Sad, Happy, Neutral) yielded a significant main effect of Hemisphere (F(1,19) = 17.030, p = 0.001, η_p^2 = 0.473), due to the larger responses on the right hemisphere (7.399 ± 3.308 μV) than on the left hemisphere (5.212 ± 2.059 μV). Furthermore, a significant main effect was found for Emotion (F(2,38) = 7.767, p = 0.001, η_p^2 = 0.290). A pairwise comparison for the emotion effect showed that responses were smaller for happy faces (6.077 ± 2.363 μV, p_{corr} = 0.001, BF_{10} = 87.010) than for neutral faces (6.532 ± 2.450 μV), but not for sad faces (6.309 ± 2.690 μV, p_{corr} = 0.176, BF_{10} = 1.224), and no difference was found between neutral and sad face responses (p_{corr} = 0.272, BF_{10} = 0.875). The main effect of the Pain phase was not statistically significant (F(2,38) = 2.512, p = 0.094, η_p^2 = 0.117)

and no interaction effects were observed (all p-values > 0.150). The main results of P2 are depicted in Fig. 3.

4. Discussion

We investigated effects of pain on ERPs to task-irrelevant neutral, happy, and sad faces prior to, during, and after laboratory-induced cold pressure pain in healthy participants. Pain attenuated the P1 amplitude for happy faces, but did not modify the P1 responses to sad and neutral faces. By contrast, the N170 responses increased in amplitude for both sad and happy faces in the presence of pain. Pain also had long-term effects, as evidenced by the similar alterations in N170 responses in the post-pain and pain phases. Notably, the P2 component had no response to pain.

In accordance with our hypothesis, pain affected early face processing. The specific effect on P1 amplitude to happy faces agrees with previous studies (Gerdes et al., 2012; Godinho et al., 2008; for a review see, Wieser et al., 2014), suggesting that pain selectively affects processing of positive stimuli. Our results also agree in part with the findings of the only ERP study (Wieser et al., 2012), which also reported a pain-related decrease in P1 amplitude. However, the previous effect was not specific to happy faces, but also occurred for neutral and fearful faces. This discrepancy may reflect the different tasks and stimuli employed. Wieser et al. (2012) used an attentive paradigm, which required participants to rate the valence and arousal of fearful, happy, and neutral faces, whereas we had no task related to faces and we presented sad, happy, and neutral faces as stimuli. Despite these

differences, our results and those of Wieser et al. (2012) suggest that pain can exert its influence at the very early stages of face processing.

Previous studies have associated the P1 component with low-level facial feature processing (Carretié, 2014; Schindler & Bublatzky, 2020), and our results may reflect interrupted low-level feature encoding during acute pain. It is possible that even in the absence of an attentive task, pain could affect visual encoding by decreased automatic attention to happy faces because pain is highly attention-grabbing and requires processing capacity that could detract from other cognitive processes (Eccleston & Crombez, 1999; Khera & Rangasamy, 2021; Wieser et al., 2012). A happy face is perceived as non-threatening and as a sole member in a category of positive basic emotions (Ekman, 1999). Therefore, it may not require thorough and fast encoding during pain, whereas sad and neutral faces may be more difficult to categorize and may urge immediate processing (Kauschke et al., 2019; Xu et al., 2021). The discrepancies between previous results (Wieser et al., 2012) and ours require further studies that replicate our findings while systematically manipulating the task and stimuli.

Unlike the specific pain effect for happy face in P1 observed as decreased amplitude to happy faces during pain, the subsequent N170 component showed an increased amplitude for both happy and sad faces in the pain phase but no response for neutral expressions. Notably, the pain effect on N170 persisted even after removal of the external pain stimulus and was observed in the post-pain phase. By contrast, Wieser et al. (2012), who investigated the effect of pain on task-relevant emotional faces, found no effect of pain on

the N170 response. However, our results align with a previous EEG study (Godinho et al., 2008) that found a nonspecific increase (for both positive- and negative-valence pictures) in activity under pain compared with the non-pain condition at 150–250 ms latency. Although our study design differs from that of Godinho et al. (2008), we speculate that pain, as a stressor, could trigger a widespread nonspecific vigilance state, thereby enhancing the responses to emotional stimuli. This possibility warrants further investigation.

The finding of a persistent effect of pain on the N170 component aligns with the finding of increased functional connectivity (FC) between the rostral anterior insula and ventromedial prefrontal cortex regions during cold pain stimulation in a previous resting-state functional magnetic resonance imaging (rsfMRI) study and persistence of this alteration in the post-pain measurement (Makovac et al., 2020). To our knowledge, our study is the first to report the effects of persistent pain on sensory brain responses and suggests that brain activity may not return to baseline immediately upon pain removal. Nevertheless, the ERP modulation observed in the post-pain phase did not appear to reflect subjectively perceived pain, as the reported pain ratings did not indicate any residual pain after removal of the physical pain-evoking stimulus.

P2 did not show any effect of pain or any interaction effect. Instead, our observation of an overall lower activity for happy faces than for neutral faces, irrespective of pain conditions, suggested that pain did not affect the perceptual encoding of the spatial relations of facial features (Latinus & Taylor, 2006; Schweinberger & Neumann, 2016). However, our P1 and

P2 results did reveal a significant hemisphere main effect, with greater activity observed in the right than in the left hemisphere. This right laterality agrees with the traditional "right hemisphere hypothesis," which posits that the right side of the brain is primarily responsible for processing emotional information (Batty & Taylor, 2003; Borod et al., 1998). However, the effect of P2 has been much less investigated, and the emotional effects on P1 and P2 are quite mixed in the field of emotion and attention (for a recent review, see Schindler & Bublatzky, 2020). Future studies should test a larger sample or incorporate other brain imaging techniques to further explore the underlying processing mechanisms corresponding to different cortical responses.

The aim of this study was to use a similar experimental setting to that previously used in depression studies (Chang et al., 2010; Ruohonen et al., 2020) to compare the effects of pain versus acute depression on face processing. Contrary to previous findings on acute depression (Chang et al., 2010; Xu et al., 2018), we found no decrease in the amplitudes of the N170 and P2 responses. Instead, we observed an overall increase in the N170 amplitude and no effect on P2 responses. We also observed a reduction in the P1 amplitude for happy faces but did not detect the negative bias (i.e., an enhanced response specifically to sad faces) commonly reported in early sensory ERP responses in previous depression studies(Dai & Feng, 2012; Ruohonen et al., 2020; Xu et al., 2018; Zhang et al., 2016; Q. Zhao et al., 2015). Thus, even though pain and depression are commonly co-morbid, and even though chronic pain patients (Dick et al., 2006; Yao et al., 2011) and neuropsychiatric patients (for reviews, see Kangas et al., 2022; Toshihiko Maekawa et al., 2013) display some similar anomalies in task-irrelevant auditory processing, visual face processing may

not be similarly affected in acute pain and depression.

This study had several limitations that warrant consideration. One was the use of the oddball paradigm, with emotional faces as deviant stimuli and neutral faces as standard stimuli. This paradigm has been employed to investigate change detection in emotional faces using visual mismatch negativity (vMMN) (e.g., Astikainen & Hietanen, 2009; Chang et al., 2010; Fujimura & Okanoya, 2013; Liu et al., 2016; Susac et al., 2004; Zhao & Li, 2006) and allows comparison with previous vMMN studies and studies of depressed patients (e.g., Chang et al., 2010; Ruohonen et al., 2020). However, it does not permit disentanglement of the effects of emotion from their lower probability compared to neutral faces. Nevertheless, the N170 response to deviant emotional faces may primarily be modulated by emotional expression rather than probability (Astikainen et al., 2013; Rosburg et al., 2019), and this warrants further study. Another limitation is the unequal gender distribution in the sample (6 males versus 14 females), as previous studies have demonstrated gender differences in both pain and face perception (Kowalczyk et al., 2006; Lee et al., 2002; Oliver-Rodriguez et al., 1999; Racine et al., 2012). For instance, women tend to tolerate less pain than men, particularly cold, heat, and pressure pain (Racine et al., 2012), and they appear more sensitive to the valence of emotional faces in pre-attentive processing of facial expressions (Xu et al., 2013). We considered hormonal influences by measuring all female participants during the follicular phase of their menstrual cycle. When we designed the experiment, we also selected an equal number of male and female face stimuli; however, we were unable to obtain an equal number of male and female participants for the study. This study should be replicated with a larger sample and a

balanced gender distribution. Furthermore, in our recordings, alpha-band oscillatory activity was visually observed, and alpha activity is considered largely associated with the experience of pain (Hassaan et al., 2020; Klimesch et al., 2011; Nir et al., 2012). However, our use of short interstimulus intervals in our research design precluded investigating the contributions of the alpha oscillation to the face perception ERPs. Future studies should explore the contributions of oscillatory activity to the effects of pain on ERPs to facial expressions.

5. Conclusions

The aim of this study was to investigate the impact of pain on early sensory ERPs to task-irrelevant emotional faces. Our findings extend previous research on pain by incorporating visual modalities and examining task-irrelevant face processing. We found that pain diminishes the early visual encoding of happy faces (as measured by the P1 component) and impairs the processing of facial structure (as measured by the N170 component) for both happy and sad faces. The effect on N170 persisted into the post-pain phase. These alterations in early sensory processes may contribute to the socio-emotional difficulties observed in individuals with chronic pain. Future studies should investigate task-irrelevant face processing in chronic pain populations to determine the generalizability of these findings to clinical populations.

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Author contributions

QX and PA conceived and designed the experiments. QX, CY, and XL performed the data acquisition. QX analyzed the data. CY contributed to the data analysis. QX, PA, CY, and GZ interpreted the data. QX and PA drafted the manuscript. All the authors provided critical revisions and approved the manuscript.

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Figure legends

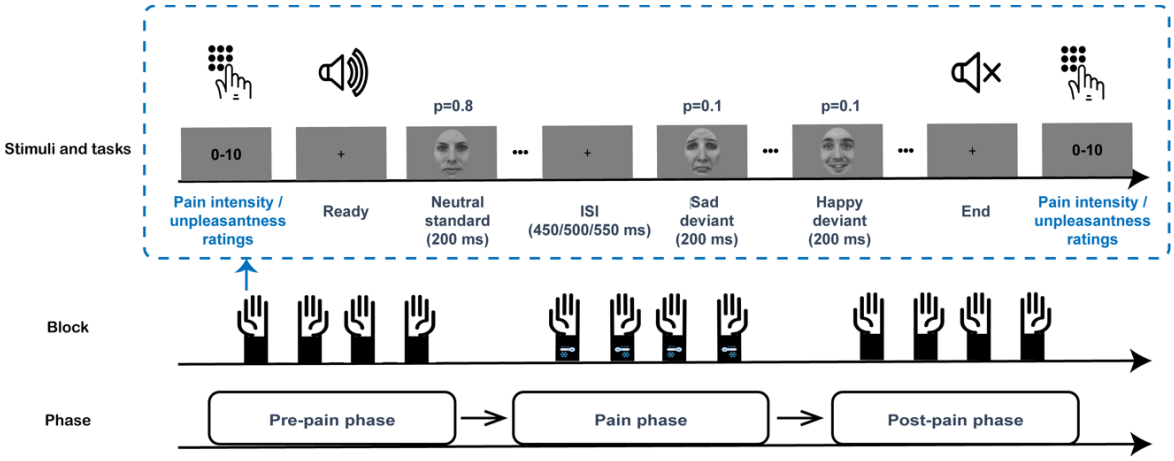

Figure 1. Illustration of the experimental protocol. The experiment consists of three phases (pre-pain, pain, and post-pain), each containing four blocks. The main difference between the different phases was that participants wore cold arm wraps (indicated by the cold temperature icon in the figure) during the pain phase and room-temperature arm wraps (arms without the cold temperature icon in the figure) during the other two phases. The arm wraps were changed after each block to the other arm, and the starting arm was counterbalanced between participants (the figure only demonstrates the case starting with the left arm, while the other half of the participants started wearing arm wraps with the right arm). The procedure was similar for each block; that is, the participants rated pain intensity and unpleasantness at the beginning and end of each block. In between, different expressions (sad or happy, p=0.1 for each) or neutral faces (p=0.8) are presented in a passive oddball condition. The faces in the figure are KDEF stimuli (the IDs from the left to right: AF07NES, AF13SAS, AM35HAS) that are taken from the actual experiment. ISI = interstimulus interval (offset-to-onset).

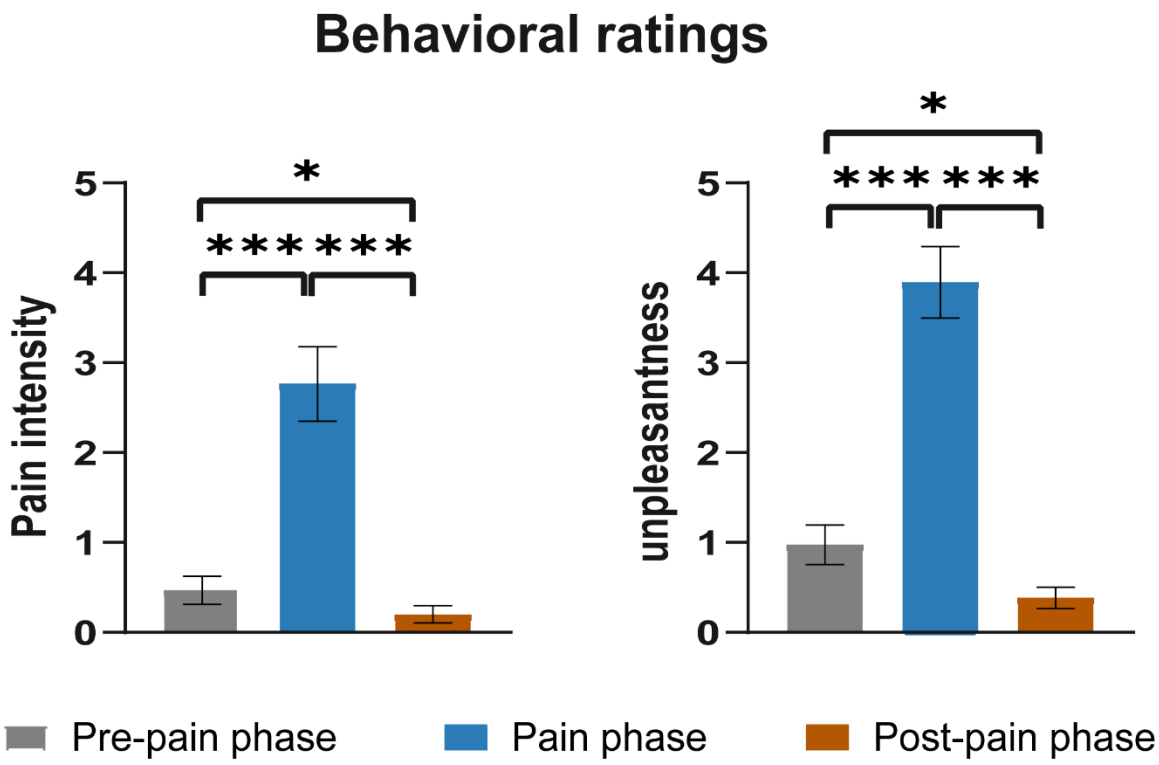

Figure 2. Results of pain intensity and unpleasantness ratings (scale 0–10 for both). Left: Bar graph of the mean pain intensity ratings for the pre-pain, pain, and post-pain phases. Right: Bar graph of the mean unpleasantness ratings for the pre-pain, pain, and post-pain phases. Gray bar: pre-pain phase; Blue bar: pain phase; Orange bar: post-pain phase. Error bars represent the standard error of the mean. *$p < 0.05$, ***$p < 0.001$.

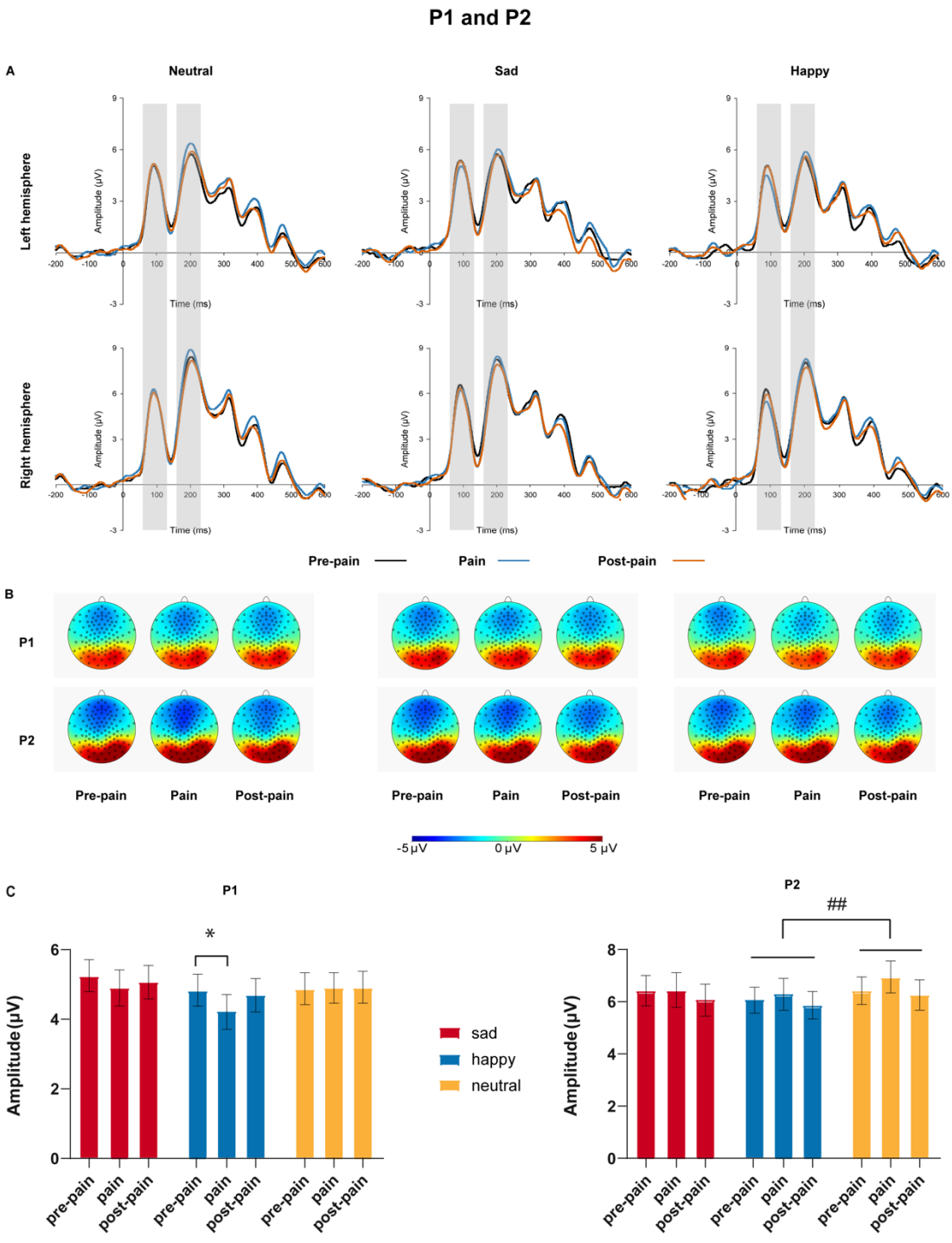

Figure 3. Main results of the P1 and P2 responses. (A) Grand-averaged P1 and P2 waveforms of different pain phases evoked by neutral (left panel), sad (middle panel), and

happy (right panel) faces on both left (upper panel) and right (lower panel) hemispheres. Shaded areas mark the intervals selected for the analysis of each component (60–130 ms for P1, 160–230 ms for P2). (B) Corresponding topographic maps of different pain phases evoked by neutral (left panel), sad (middle panel), and happy (right panel) faces. All topographies were extracted as the mean values from the time window of 60–130 ms for P1 (upper panel) and 160–230 ms for P2 (lower panel). (C) Bar graph of the P1 (left panel) and P2 (right panel) mean amplitudes for responses during the pre-pain, pain, and post-pain phases under different emotions (Red bar: sad faces; Blue bar: happy faces; Yellow bar: neutral faces; all results are averaged over the left and right hemispheres). Error bars represent the standard error of the mean. The asterisk indicates the significant effect of the post hoc test following the interaction effect between pain and emotion, $*p < 0.05$. The pound sign indicates the significant effect of the post hoc test following the main effect of emotion, $\#\# p < 0.01$.

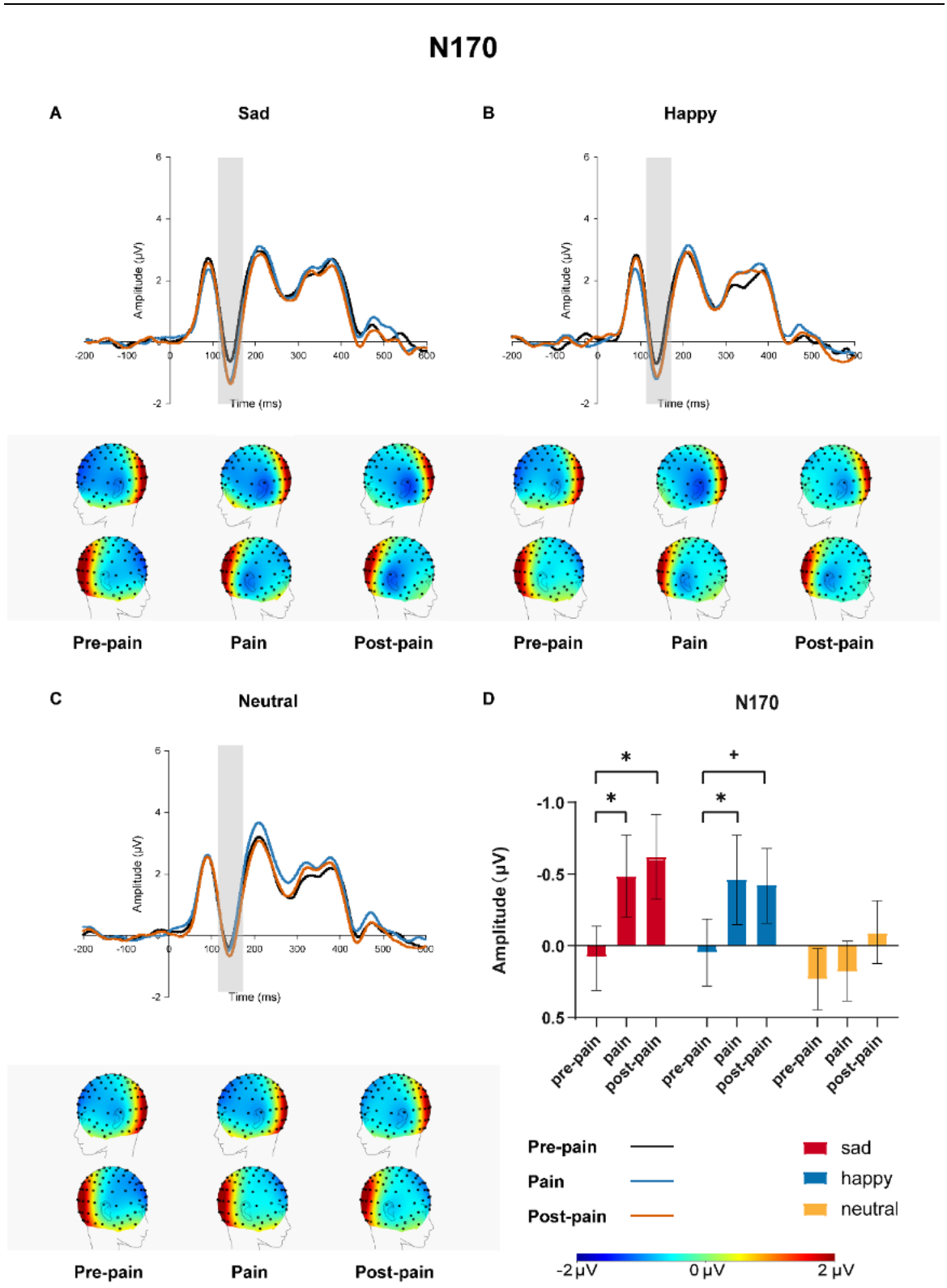

Figure 4. Main results of the grand-averaged N170 responses. (A) Grand-averaged N170 waveforms (shaded area) and corresponding topographic maps (extracted from 120–170 ms) of different pain phases (Black line: pre-pain; Blue line: pain; Orange line: post-pain) evoked by sad faces. (B) Grand-averaged N170 waveforms (shaded area) and corresponding topographic maps (extracted from 120–170 ms) of different pain phases (Black line: pre-pain; Blue line: pain; Orange line: post-pain) evoked by happy faces. (C) Grand-averaged N170 waveforms (shaded area) and corresponding topographic maps (extracted from 120–170 ms) of different pain phases (Black line: pre-pain; Blue line: pain; Orange line: post-pain) evoked by neutral faces. (D) Bar graph of the N170 mean amplitudes for responses to pre-pain, pain, and post-pain phase under different emotions (Red bar: sad faces; Blue bar: happy faces; Yellow bar: neutral faces; all results are averaged over the left and right hemispheres) at the time window of 120–170 ms. Error bars represent the standard error of the mean. *$p < 0.05$. + denotes marginal significance ($p = 0.053$).

Table

Table 1. Cut-off criteria for each questionnaire. Volunteers who showed an elevated number of symptoms in one or more of these questionnaires were excluded from the study.

Questionnaires	Cut-off Scores

Beck Depression Inventory - II (BDI-II)		**> 13**
Beck Anxiety Inventory (BAI)		**> 9**
Depression Anxiety Stress Scales (DASS)	**Depression**	**> 9**
	Anxiety	**> 7**
	Stress	**> 14**
Symptom Checklist-90 (SCL-90).	**Global Severity Index (GSI)**	**> 1.5**
	Each of the nine symptom dimensions' score	**> 2**