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RESEARCH ARTICLE

Divergent effects of conditioned pain modulation on subjective pain and nociceptive-related brain activity

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Abstract

Background and objectives Pain is a complex experience involving both nociceptive and affective–cognitive mechanisms. The present study evaluated whether modulation of pain perception, employing a conditioned pain modulation (CPM) paradigm, is paralleled by changes in contact heat-evoked potentials (CHEPs), a brain response to nociceptive stimuli.

Methods Participants were 25 healthy, pain-free, college students (12 males, 13 females, mean age 19.24 ± 0.97 years). Twenty computer-controlled heat stimuli were delivered to the non-dominant forearm and CHEPs were recorded at Cz using a 32-channel EEG system. After each stimulus, participants rated the intensity of the heat pain using the 0–100 numerical rating scale. The latency and amplitude of N2, P2 components as well as single-sweep spectral analysis of individual CHEPs were measured offline. For CPM, participants had to submerge their dominant foot into a neutral (32 °C) or noxious (0 °C) water bath. CHEPs and heat pain ratings were recorded in 3 different conditions: without CPM, after neutral CPM (32 °C) and after noxious CPM (0 °C).

Results The noxious CPM induced a facilitatory pain response ($p = 0.001$) with an increase in heat pain following noxious CPM compared to neutral CPM ($p = 0.001$) and no CPM ($p = 0.001$). Changes in CHEPs did not differ between conditions when measured as N2–P2 peak-to-peak amplitude ($p = 0.33$) but the CPM significantly suppressed the CHEPs-related delta power ($p = 0.03$). Changes in heat pain in the noxious CPM were predicted by trait catastrophizing variables ($p = 0.04$).

Conclusion The current study revealed that pain facilitatory CPM is related to suppression of CHEPs delta power which could be related to dissociation between brain responses to noxious heat and pain perception.

Keywords Conditioned pain modulation · Pain facilitation · Pain inhibition · Contact heat-evoked potentials · Single-sweep spectral analysis · Delta EEG activity

Introduction

Conditioned pain modulation (CPM) is an experimental paradigm used to assess the function of endogenous pain modulatory systems in humans. In this paradigm, a painful conditioning stimulus is presented that affects the perception of a painful test stimulus (Yarnitsky 2010). CPM is believed to reflect the perceptual manifestation of diffuse noxious inhibitory controls (DNIC). Animal studies have shown that a descending inhibitory control system is triggered when a noxious conditioning stimulus is presented at a site distant to the noxious test stimulus. The conditioning stimulus activates ascending nociceptive transmission neurons that project to supraspinal structures, which in turn trigger descending inhibitory projections in the dorsal horn of the spinal cord that attenuate the response to the test stimulus (Basbaum and Fields 1984). Although most studies of DNIC and CPM focus on pain inhibition, it is now becoming clear that descending pain facilitation is also observed (Bannister and Dickenson 2017).

A growing body of research has studied the clinical relevance of CPM reporting impaired endogenous pain modulation in populations with chronic pain (Lewis et al. 2012). In addition, reduced pain inhibition has been shown to predict acute and chronic postoperative pain (Goubert et al. 2015; Yarnitsky 2010), whereas increased CPM-inhibitory responses have been shown to prospectively

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predict treatment-related changes in clinical pain (Edwards et al. 2016). However, important limitations of the use of CPM such as lack of consensus in the appropriate design and reliability of reported pain-related measures remain to be addressed.

Electrophysiological studies indicate that CPM is sustained by complex mechanisms that in addition to spinal–bulbar–spinal loop involve modulation by supraspinal structures (Villanueva and Le Bars 1995). Subjective pain reports to CPM interventions express a global change in the perception of the test stimulus, although several mechanisms such as descending inhibition, habituation to the test stimulus, and cognitive–affective modulation of pain may contribute to the reduction in pain perception during CPM (Eitner et al. 2018; Treister et al. 2010). Recording cortical-evoked potentials to nociceptive stimulation in addition to subjective pain during CPM could increase our understanding of the contribution of supraspinal mechanisms to endogenous pain modulation.

Recent electrophysiological studies suggest that CPM can activate supraspinal mechanisms that modulate perception of non-noxious sensations in parallel with descending and spinal modulation of pain. Piche et al. (2014) reported reduced amplitude of a late component of somatosensory-evoked potentials from the sural nerve following CPM, without changes in the intensity of pain or the related nociceptive flexion reflex (RIII reflex), suggesting that somatosensory-evoked potentials suppression depends on supraspinal mechanisms related to, but independent of, descending inhibition. Other studies reported CPM-induced suppression of event-related potentials to stimuli selectively activating nociceptive and non-nociceptive fibers (Rustamov et al. 2016; Torta et al. 2015), including the inhibition of A-beta fibers (Rustamov et al. 2016) and auditory-evoked potentials (Torta et al. 2018) that are not relayed at the spinal level. Taken together, these findings suggest that during CPM both spinal and supraspinal inhibitory mechanisms must be recruited (Rustamov et al. 2016; Torta et al. 2018).

Cognitive–affective modulation of pain perception could contribute to the magnitude of the CPM and to the modulation of related brain-evoked potentials. Top–down attention or distraction manipulations concomitantly with CPM produce additive analgesic effects (Ladouceur et al. 2012; Moont et al. 2010). Moreover, suggestion of hyperalgesia led to increased RIII amplitude and perception of shock pain (Cormier et al. 2013) or blocked the effects of endogenous analgesia on RIII and shock perception (Goffaux et al. 2007), while expectation of analgesia led to the inhibition of both parameters (Cormier et al. 2013; Goffaux et al. 2007). Psychological factors such as anxiety, depression, and pain catastrophizing seem to be associated with modality-specific CPM responses (Nahman-Averbuch et al. 2016).

Pain-related evoked potentials, such as laser-evoked potentials (LEP) and contact heat-evoked potentials (CHEP), have been used extensively to investigate nociceptive processing at supraspinal levels due to their selective activation of nociceptive fibers and significant correlations between CHEP amplitude and pain ratings (Granovsky et al. 2008, 2016). CHEPs consist of an early N1 component, which is considered to reflect the arrival of the afferent nociceptive input to the S1 cortex and late N2 and P2 components that have been attributed to supraspinal processing that generates the perceptual experience (Mobascher et al. 2009; Roberts et al. 2008; Valentini et al. 2012; Wager et al. 2006).

Pain studies using CHEPs are based on visual inspection and measures of evoked potentials amplitude averaged over multiple stimuli. CHEPs have smaller amplitudes compared to LEP, longer latencies and higher within-subject and between-subject latency variability that are confounded by jitter between sweeps; therefore, single-sweep spectral analyses could provide advantages over conventional CHEPs analyses (Gram et al. 2013; Hansen et al. 2015). No studies have used CHEPs to evaluate changes in supraspinal pain modulation induced by CPM.

The current study investigated whether modulation of subjective pain experience in CPM paradigms using a sequential heterotopic design will be paralleled by changes in nociceptive brain-evoked potentials. We hypothesize that noxious CPM will inhibit the heat pain which will be associated with the suppression of related CHEPs amplitude and power. We will also correlate the CPM response and changes in CHEPs with psychological variables.

Materials and methods

Participants

A total of 32 healthy, pain-free, college students (13 males, 19 females, mean age 19.09 ± 0.96 years) were enrolled in the study. Individuals reporting acute or chronic pain, physical or mental illness, skin conditions and those taking medication or recreational drugs on a regular basis were not included in the study. During experiments, seven participants discontinued: three individuals had very low tolerance to noxious CPM (could not tolerate the cold water bath for more than 10 s) and one participant had low tolerance to heat pain, two participant presented excessive blinking during EEG acquisition and 1 subject discontinued because of equipment malfunction. Consequently, valid data were obtained and analyzed from 25 individuals (12 males, 13 females, mean age 19.24 ± 0.97 years).

Psychometric instruments

Before pain and CPM testing, participants completed questionnaires to evaluate psychological factors that may interfere with pain perception.

The Center for Epidemiologic Studies Depression Scale was administered as a screening instrument to measure the current level of depression symptoms. This questionnaire consists of 20 self-report items scored on a 4-point Likert scale ranging from 0: rarely or none of the time to 3: most or all of the time. A score of 16 points or more is considered indicative of "significant" or "mild" depressive symptoms (Radloff 1977).

The State and Trait Anxiety Inventory was used to evaluate anxiety symptoms. The STAI consists of two questionnaires of 20 items, each describing emotional conditions rated on a 4-point Likert scale. The range of scores for each subscale is 20–80, the higher score indicating greater anxiety. A score greater than 40 has been suggested to be indicative of a clinically significant anxiety state (Knight et al. 1983).

The Pain Catastrophizing Scale was administered to evaluate catastrophic thinking associated with pain. The PCS is a 13-item questionnaire and includes three subscales that evaluate rumination, magnification and helplessness (Sullivan et al. 1995). Participants are asked to recall thoughts and feelings related to past pain experiences and to indicate the degree to which they experienced each catastrophizing thought using a 0 (not at all)–4 (all the time) Likert scale.

Experimental design and protocol

The study protocol was approved by the Texas A&M University Institutional Review Board and was carried out in accordance with the Declaration of Helsinki (World Medical Association 2013). Written informed consent was obtained from all participants before inclusion in the study. In exchange for participation, students received course credit. All experiments were conducted in a single visit of 2 h with participants seated in a comfortable reclining armchair in a soundproof room with an ambient temperature 22–23 C. CHEPs and evoked heat pain were recorded in three different conditions: no CPM, after neutral CPM (32 °C) and after noxious CPM (0 °C). To control for confounding factors such as learning and CHEPs or pain habituation due to repeated noxious stimulation, the order of experiments was counterbalanced between subjects. Breaks of 15 min were maintained between two consecutive experimental conditions.

CHEPs and evoked heat pain

For CHEPs recordings, we used a 32-channel (according to the international 10–20 system) EEG system (BioSemi, Amsterdam, Netherlands; band-pass filters: 0.4 and 100 Hz; sampling rate: 512 Hz with 24-bit resolution, average reference montage) and stored on disk for subsequent offline analysis. The electrodes were applied over an elastic cap available in three sizes, with plastic electrode holders (BioSemi headcap) filled with electrode gel (Signa gel by Parker). The active electrode has an output impedance of less than 1 Ω (compared to tens of kOhms with other systems), ensuring that the signal in the cable is fully insensitive to interference (Metting van Rijn et al. 1990). To ensure a good signal quality, the electrode offset was kept below 40 mV.

Twenty short-lasting heat stimuli (35 °C constant baseline, 52 °C target temperature, 70 °C/s heating rate, 40 °C/s return rate, 20–30-s interstimulus interval) were applied to the volar mid-forearm, using a computer-controlled thermofoil heating system (Pathway System, Medoc Ltd, Ramat Yishai, Israel) (Kramer et al. 2013). The duration of each stimulus was 667.86 ms (242.86 ms to achieve the target temperature and 425.0 ms to return to the baseline temperature). The heat stimulus was sent from the Pathway system, marked by a 100-ms square TTL wave (transistor–transistor logic) which was recorded on a separate EEG channel at the beginning of each stimulus that permitted future offline EEG processing and extracting of the epochs containing the CHEPs. The site on the forearm was divided into five adjacent non-overlapping skin areas each on the radial and ulnar side. The thermode was moved counter-clockwise across these ten sites after each stimulus to prevent heat pain and amplitude suppression of CHEPs due to rapid habituation and fatigue of peripheral nociceptive neurons over time (Greffrath et al. 2007). After each stimulus, subjects were asked to evaluate the intensity of the perceived pain using the 0–100 numerical rating scale (NRS), where "0" represents "no pain" and "100" represents the "most intense pain imaginable". The mean HEAT PAIN was calculated based on 20 subjective pain ratings. To familiarize participants with the testing procedure and the sensations induced by heat stimulation, two heat stimuli were applied without recording. To reduce contamination of the CHEPs with blink activity, subjects were instructed to keep their eyes closed in a fixed neutral position for at least 2 s after perception of each stimulus. Horizontal and vertical electrooculographic signals were simultaneously monitored using FLAT ActiveTwo electrodes.

Conditioned pain modulation

In our study, the CPM stimuli were applied using a heterotopic, sequential design in agreement with the CPM

consensus meeting recommendations (Yarnitsky et al. 2015). Specifically, the conditioning stimulus was either a water bath at a neutral (+32 °C) or painful (0 °C) temperature applied to the dominant foot through submersion. The test stimulus was the short-lasting heat stimulus applied over the non-dominant forearm for CHEPs recording. The water was continuously recirculated to prevent local warming. Subjects submerged their dominant foot in the water bath up to the ankle and rated the intensity of the conditioning stimulus at 30, 60, 90 and 120 s following immersion using the previously described NRS. The mean pain intensity of the conditioning stimulus was calculated for each participant from these ratings. Participants were instructed that they could remove the foot from the water bath, if an intolerable pain sensation was perceived. A new series of 20 CHEPs were recorded immediately after the last pain rating.

EEG data analysis

The continuous EEG recordings were imported to EEGLab, an interactive Matlab toolbox.

For CHEPs analysis, we extracted 1000-ms EEG epochs after delivery of the heat stimuli, which were then plotted and visually inspected for artifacts. When at least one channel was contaminated with eye movements, blinking or muscle twitches, the entire EEG epoch was rejected. Maximum five trials per person and experimental condition were removed during data analysis. The average rejection of CHEPs was: 1 ± 1.6 trials in the no CPM; 1 ± 1.7 trials in the neutral CPM and 0.7 ± 1 trials in the noxious CPM. CHEPs were detected visually on the grand average waveforms (15–20 trials). Because CHEPs had maximum amplitude over Cz, further EEG analysis was performed in one channel. The N2 peak of CHEPs was identified as the most negative component within the time window 200–400 ms and the P2 peak was identified as the most positive component within the time window 300–500 ms after the onset of heat stimulation. The latency of the N2 and P2 peaks and the N2–P2 peak-to-peak amplitude were measured on the grand average of 15–20 artifact-free trials.

The N2–P2 complexes can vary in latency, canceling amplitude when averaged across multiple trials due to asynchronous activation of A-delta fibers with different heat thresholds and attention interference (see an example in Fig. 1). Spectral analysis of single-sweep CHEPs was previously employed to study pain-related cerebral-evoked potentials (Arendt-Nielsen 1990), the effects of drugs on supraspinal pain modulation mechanisms (Gram et al. 2013; Hansen et al. 2015) as well as more sensitive measure to quantify changes in cerebral-evoked potentials to CPM (Plaghki et al. 1994). In this regard time–frequency analysis of single-sweep evoked potentials could present some advantages over conventional CHEPs measures because it allows evaluating

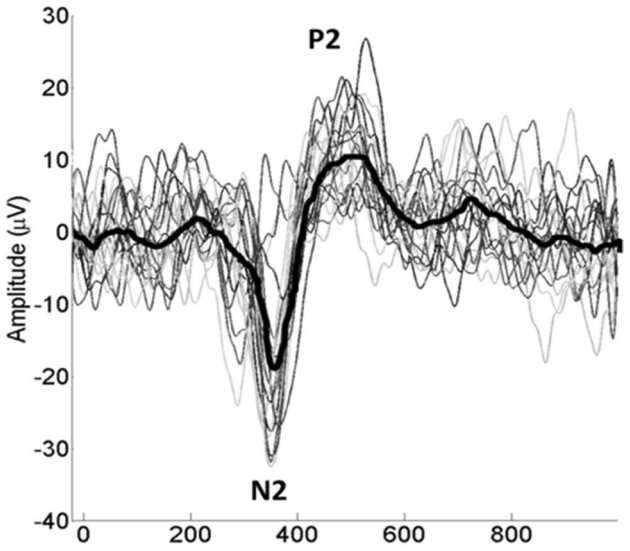

Fig. 1 Grand-average waveforms of the CHEPs recorded at the vertex (Cz) with average reference following A-delta-fibers stimulation. Individual trials are represented with thin gray lines and the grand average of evoked potentials is represented with a bold black line. This example shows CHEPs latency variability due to asynchronous activation of A-delta fibers and canceling of amplitude when averaging multiple trials

transient changes in the magnitude of brain oscillations that are time-locked to the noxious heat stimulus. The spectrum analysis was conducted on artifact-free single-sweep EEG data from 200 ms until 700 ms after stimulus onset using the fast-Fourier transformation in EEGLab (Nuwer et al. 1994). The fast-Fourier transformation was applied to calculate the spectral power distribution in each single sweep, and the spectral power was averaged over all sweeps for each condition. The absolute powers were computed for the standard frequency bands [delta (1–4 Hz), theta (> 4–8 Hz), alpha-1 (> 8–10 Hz), alpha-2 (> 10–12 Hz), and beta-1 (> 12–16 Hz) and beta-2 (> 16–32 Hz)] (Cook et al. 1998).

Reliability of heat pain as test stimulus

The test–retest reliability of heat pain (absolute values on the 0–100 NRS) evoked by CHEPs was assessed using data from our laboratory collected from 17 healthy participants who underwent standard CHEPs recording (without conditioning) in two different days. The intraclass correlation coefficient (ICC) (the 95% confidence intervals) and the standard error of measurement (SEM) were calculated. SEM was calculated using the formula: $\mathrm{SEM} = \mathrm{SD}_{\mathrm{heat\ pain}} \times \sqrt{1 - \mathrm{ICC}}$ (Locke et al. 2014). Heat pain showed high test–retest reliability (ICC 0.79, 95% CI 0.43–0.93), ($F(16.16) = 4.85$, $p = 0.001$). SEM = 4.9; therefore, any change in heat pain ± 4.9 (0–100 NRS) would be considered as non-significant.

CPM effect

For correlation and regression analyses, we calculated the magnitude of the CPM effect on heat pain, CHEPs amplitude and power (Horn-Hofmann et al. 2016; Treister et al. 2010).

CPM-pain effect = (heat pain intensity during noxious CPM) − (heat pain intensity in no CPM).
CPM-amplitude effect = (N2–P2 amplitude during noxious CPM) − (N2–P2 amplitude in no CPM).
CPM-power effect = (CHEPs power during noxious CPM) − (CHEPs power in no CPM).

Therefore, negative CPM-effect values reflect inhibitory CPM, whereas positive values reflect facilitatory CPM of pain and evoked potentials. To compare between CPM effects, these variables are expressed as percent change from the no CPM (Yarnitsky et al. 2015).

Statistical analysis

Statistical analysis was performed with a commercial software package (IBM SPSS, version 23, SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk's test was used to examine normality of the data. If the normality assumption was violated, non-parametric tests were used. A repeated-measures ANOVA was conducted for the dependent variables heat pain, CHEPs parameters (N2–P2 amplitude, N2 amplitude and P2 amplitude) and CPM paradigm as independent variable (no CPM, neutral CPM and noxious CPM). A Bonferroni correction was used for multiple comparisons. RM-ANOVA was also conducted for individual heat pain ratings as dependent variables and stimulation trial as independent variable to evaluate within-trial effect of repeated heat stimulation. Simple pairwise correlation analyses (Pearson's correlation) were conducted to study association between heat pain, CPT, CPM pain, CPM amplitude, CPM power. Multiple regression analyses were conducted to study whether psychological measures (state and trait anxiety, depression, helplessness, magnification and rumination scores) predicted heat pain, CPT, CPM pain, CPM amplitude, CPM power.

Variables are presented as mean and standard deviation (SD). A two-tailed test with an alpha level of 0.05 was used for all analyses.

Results

Demographic and psychological characteristics of the participants are presented in the Table 1.

Table 1 Demographic and psychological characteristics of participants

	Mean	SD
Gender (M/F)	25 (12/13)	
Age (years)	19.24	0.97
CES depression	5.76	2.71
State anxiety	26.88	4.42
Trait anxiety	29.72	3.78
Pain catastrophizing (total score)	8.48	5.67
Pain catastrophizing helplessness	2.64	2.51
Pain catastrophizing magnification	2.04	1.54
Pain catastrophizing rumination	3.80	2.75

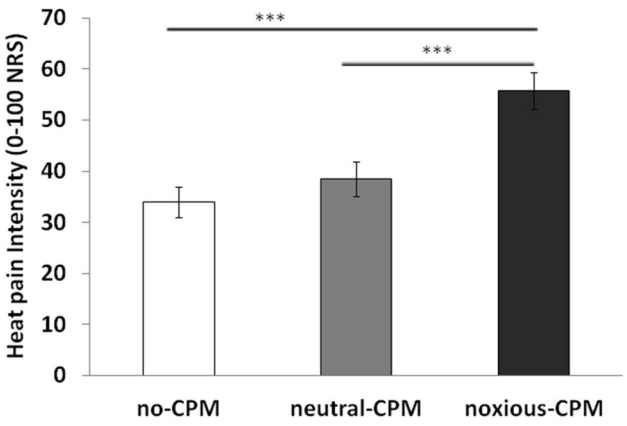

Fig. 2 Modulation of evoked heat pain following CPM. ***$p = 0.001$, Repeated measures ANOVA with Bonferroni test

Perception and tolerance of the CPT

The average intensity of the CPT computed over four pain ratings (every 30 s) was 59.2 ± 16.4 (NRS 0–100). The intensity of the conditioning stimulus increased to 47.3 ± 19.7 (30 s) and 60.6 ± 17.1 (60 s) and then remained stable until the end of conditioning stimulus application [61.5 ± 15.5 (90 s) and 63.2 ± 15.9 (120 s)]. Only two individuals could not tolerate the CPT for the time set in the study (120 s), and removed their foot from the water bath (one participant removed the foot after 40 s and the other participant after 60 s). The average tolerance to the CPT was 114.17 ± 20.0 s.

Modulation of heat pain by CPM

Overall, the study revealed statistically significant facilitatory CPM, $F(2,48) = 30.80$, $p = 0.001$, $\eta^2 = 0.56$. Specifically, the intensity of heat pain was highest in the noxious-CPM paradigm (55.67 ± 18.10, NRS) compared to neutral-CPM (38.44 ± 16.90, NRS; $p = 0.001$) and no-CPM paradigm (33.95 ± 14.70, NRS; $p = 0.001$) (Fig. 2). When the SEM

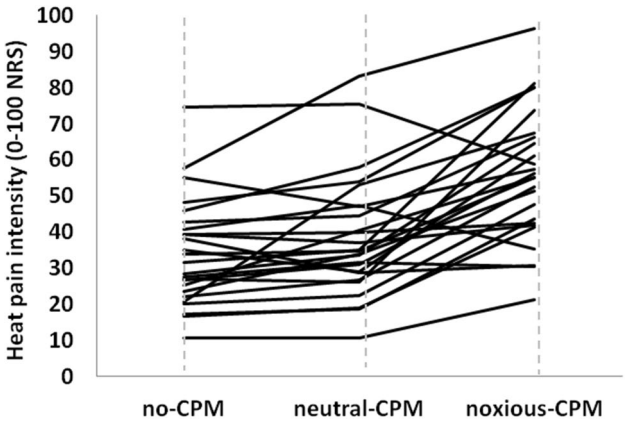

Fig. 3 Single-subject heat pain perception across experiments

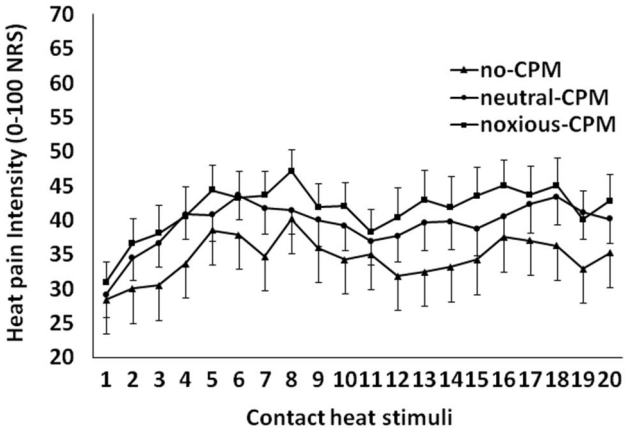

Fig. 4 Within-trial heat pain sensitization. Sensitization effect of heat pain due to repeated application of 20 heat stimuli in the no CPM [$F(19,228)=3.80$, $p=0.004$, $\eta^2=0.24$], neutral CPM [$F(19,266)=2.58$, $p=0.03$, $\eta^2=0.16$] and the noxious CPM [$F(19,247)=2.69$, $p=0.04$, $\eta^2=0.17$]

of heat pain was considered as classifier, 4 subjects were categorized as no responders to CPM, 3 subjects presented inhibitory CPM and 18 subjects presented facilitatory CPM (Fig. 3). There was a sensitization effect of heat pain due to repeated application of 20 heat stimuli in the no CPM [$F(19,228)=3.80$, $p=0.004$, $\eta^2=0.24$], neutral CPM [$F(19,266)=2.58$, $p=0.03$, $\eta^2=0.16$] and the noxious CPM [$F(19,247)=2.69$, $p=0.04$, $\eta^2=0.17$] (Fig. 4).

Modulation of CHEPs amplitude and power by CPM

We calculated a non-significant suppression of the N2–P2 peak-to-peak amplitude in the noxious CPM (26.21 ± 8.00 µV) compared to neutral CPM (27.61 ± 9.31 µV) and no CPM (27.10 ± 9.99 µV) [$F(2,48)=1.25$, $p=0.33$, $\eta^2=0.045$] (Table 2; Fig. 5). The decrease in CHEPs amplitude was determined by suppression of the P2 wave amplitude which only approached significance [$F(2,48)=2.56$, $p=0.08$, $\eta^2=0.09$]. The RM-ANOVA yielded significant effect of CPM on CHEPs delta power [$F(2,48)=3.90$, $p=0.03$, $\eta^2=0.14$]. CHEPs delta power decreased from 47.83 ± 8.06 µV^2 during no CPM and 47.69 ± 7.05 µV^2 during neutral CPM to 40.69 ± 6.20 µV^2 following noxious CPM (Fig. 6).

Correlations and regression analyses between CPT, CPM effects and psychological measures

There was a positive correlation between the intensity of heat pain in the no CPM and the intensity of the perceived CPT ($R^2=0.73$, $p=0.001$) indicating that participants usually rated high both types of thermal pain (heat pain and CPT). CPM-pain effect correlated with the intensity of the CPT ($R^2=-0.40$, $p=0.045$) indicating that perception of more intense perception of the CPT was associated with less heat pain facilitation. The intensity of heat pain in the no CPM correlated with CPM-pain effect ($R^2=-0.68$, $p=0.001$) suggesting that individuals who perceived low heat pain in the no CPM expressed facilitatory CPM. Simple pairwise correlation analyses between either CPM-amplitude or CPM-power effect and the intensity of the conditioning stimulus (CPT) or the CPM-pain effect were not significant ($p<0.05$ for all correlations).

A further regression analysis showed that psychological measures (state and trait anxiety, depression, helplessness, magnification and rumination scores) significantly predicted the CPM-pain effect [$F(6, 24)=2.81$, $p=0.04$, $R^2=0.48$)] but only catastrophizing subscores (helplessness,

Table 2 Changes in CHEPs parameters

CHEPs parameters	No CPM		Neutral CPM		Noxious CPM		*p* value RM-ANOVA
	Mean	SD	Mean	SD	Mean	SD	
N2 peak latency (ms)	365.86	31.91	364.77	28.83	368.99	28.57	0.43
N2 amplitude (µV)	13.77	7.79	13.55	6.55	13.28	6.78	0.82
P2 peak latency (ms)	487.98	36.95	480.47	23.93	481.25	27.24	0.20
P2 amplitude (µV)	13.33	6.38	14.06	5.69	12.92	5.56	0.08
N2–P2 peak-to peak amplitude (µV)	27.10	9.99	27.61	9.31	26.21	8.00	0.33

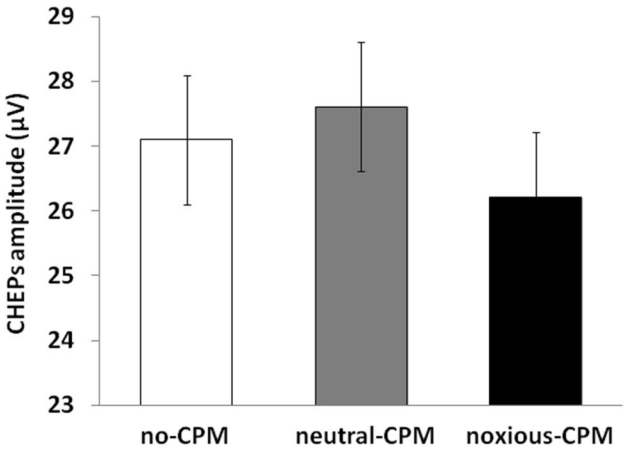

Fig. 5 Modulation of CHEPs amplitude following CPM

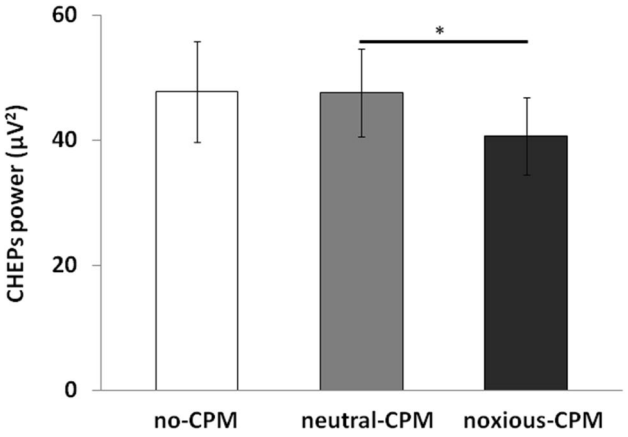

Fig. 6 Modulation of CHEPs delta power following CPM. *$p = 0.02$, RM-ANCOVA with Bonferroni test

magnification and rumination) added statistically significantly to the prediction ($p = 0.03$, $\beta = -0.63$ for helplessness; $p = 0.02$, $\beta = 0.63$ for magnification; and $p = 0.01$, $\beta = 0.68$ for rumination subscore). The same regression model did not predict the CPT intensity, CPM-amplitude or CPM-power effect ($p > 0.05$ for each analysis).

Discussion

The current study investigated changes in pain-related evoked potentials induced by CPM. Noxious CPM induced a facilitatory pain modulation response compared to neutral CPM and no CPM. However, pain facilitation was associated with a non-significant reduction of CHEPs amplitude but with significant suppression of CHEPs delta power when spectral analyses of single-sweep evoked potentials were conducted.

Facilitatory CPM, determinant factors

The results showed mixed responses (i.e., pain inhibition, facilitation, or no change) to noxious heterotopic stimulation, with most participants presenting facilitatory CPM. Variable CPM responses were previously reported in both pain-free individuals (Bogdanov et al. 2015; Egsgaard et al. 2012; Locke et al. 2014; Piche et al. 2014; Rabey et al. 2015; Youssef et al. 2016) and individuals with chronic pain (Rabey et al. 2015; Vaegter and Graven-Nielsen 2016). Most studies only report the main CPM effects without disclosing the proportion of responders/no-responders as no consensus exists on how best to determine a meaningful CPM effect. Generally, any decrease in pain intensity during noxious CPM compared to baseline is considered as pain inhibition; whereas, any increase in pain intensity during noxious CPM compared to baseline is considered as pain facilitation (Yarnitsky et al. 2015). Evaluation of responders/non-responders between two different days for ten different CPM protocols revealed that many subjects (from 11.5 to 73.1%, depending on the modality of conditioning and test stimulus) were classified as non-responders when the test stimulus standard error of measurement was used as a classifier (Vaegter et al. 2018). The high prevalence of persons showing pain facilitation to CPM in our study could be explained, in part, by methodological specifics. Previous studies employed a concomitant design (the test stimuli generating scalp-evoked potentials were applied concomitantly with the conditioning stimulus) (Hoffken et al. 2017; Piche et al. 2014; Rustamov et al. 2016; Torta et al. 2015). We employed the CPM paradigm in a sequential heterotopic design, which is in agreement with recommendations of CPM testing (Yarnitsky et al. 2015). This paradigm yields lower inhibition than simultaneous application of conditioning and test stimuli because of the gradual decrease of the CPM effect (Pud et al. 2009). In our study, we recorded CHEPs during the period immediately after the application of the CPT, which lasted about 10 min. However, we observed consistent pain facilitation with no transitory hypoalgesia. Another difference is related to counterbalancing the order of the experimental and control conditions to account for habituation to the test stimulus. Previous studies have recorded scalp-evoked potentials before, during and after CPM, and the modulatory effects were reported as changes from baseline (Hoffken et al. 2017; Piche et al. 2014; Rustamov et al. 2016; Torta et al. 2015). In this condition, perceptual habituation of the test stimulus could have occured simultaneously with the descending inhibition of pain (Treister et al. 2010). Furthermore, the habituation effect can be more prominent when the repeated test stimuli are applied over the same area (Hoffken et al. 2017; Piche et al. 2014; Rustamov et al. 2016). In addition, compared to heat stimulation in variable locations, heat stimulation in a fixed location produces habituation of CHEPs and

perceived pain intensity nearly twice as quickly (Greffrath et al. 2007). Our study controlled these effects using a counterbalanced design. Specifically, the different paradigms (no CPM, neutral CPM and noxious CPM) were applied in a counterbalanced design, and the test stimulus was moved to a different site on the forearm after each stimulus during CHEPs recording. The magnitude of pain inhibition also depends on the intensity of the conditioning stimulus, as only painful (Granot et al. 2008; Razavi et al. 2014) or very strong non-painful conditioning stimuli (Lautenbacher et al. 2002), but not neutral stimuli, can trigger effective pain inhibition. Our results showed a negative correlation between CPT and the CPM-pain effect, suggesting that stronger CPT perception was associated with pain inhibition or lower pain facilitation. However, high intensity or prolonged conditioning stimuli application did not provide additional pain inhibition in another study (Razavi et al. 2014). On the contrary, application of intense pain stimuli can be perceived as stressful and can trigger an affective reaction that enhances pain perception (hyperalgesia) or blocks descending inhibitory mechanisms.

Modulation of CHEPs by CPM

The noxious-CPM paradigm in our study induced significant pain facilitation that was associated with suppression of CHEPs. Similar to our findings, others have observed suppression of pain-related brain activity without corresponding changes in subjective pain perception and nociceptive flexion reflex responses to CPM (Goffaux et al. 2007; Piche et al. 2014). These findings indicate a dissociation of spinal and supraspinal pain modulation mechanisms.

Here, we found that the decrease in CHEPs amplitude was related to a more prominent suppression of the P2 component, which approached significance. In other studies, the P2 wave amplitude was associated with reduced pain affect (unpleasantness) due to distraction (Boyle et al. 2008), expectation of analgesia (Martini et al. 2015, Wager et al. 2006) or hyperalgesia (Goffaux et al. 2007), suggesting that the P2 component may reflect cognitive–affective pain modulation mechanisms that work in parallel with sensory mechanisms that process noxious stimuli.

Stimulus saliency constitutes a crucial determinant of heat-evoked potential amplitude. Increasing the temporal expectancy of the stimuli through stimulus repetition at a constant interstimulus interval significantly reduces the magnitudes of all components of laser-evoked brain responses and disrupts their relationship with the intensity of the perceived pain (Iannetti et al. 2008; Legrain et al. 2009; Wang et al. 2010). In our study, the heat stimuli were delivered at variable long ISI (20–30 s); therefore, we considered that salience contributed minimally to CHEPs suppression.

Psychological factors contributing to heat pain and CHEPs modulation

Expectation or application of painful stimuli can trigger stress responses and cognitive–affective mechanisms that block the endogenous analgesia and induce pain facilitation (Cormier et al. 2013; Geva et al. 2014; Goffaux et al. 2007). The tendency to "catastrophize"—a cognitive and emotional processes encompassing exaggerated negative "mental set" of pain-related stimuli—contributes to an intensified pain experience and increased emotional distress (Sullivan et al. 2001). Individuals with high levels of catastrophizing demonstrated higher pain intensities and lower CPM efficacy (Weissman-Fogel et al. 2008). In contrast, a catastrophizing manipulation led to reduced pain perception but did not modulate the spinal nociceptive flexion reflex (Terry et al. 2015). These suggest that catastrophizing is related to pain modulation at the supraspinal level. In our study, only trait pain catastrophizing, such as magnification and rumination, predicted the CPM-pain effect. However, we did not find correlations between the catastrophizing measures and CHEPs amplitude nor power. We hypothesize that intense CPT could have triggered cognitive–affective reactions and enhanced heat pain perception that was parallel to the suppression of CHEPs by noxious CPM.

Limitations

Limitations of the current study are acknowledged. CHEPs represent pain-related brain activity associated with synchronized activation of A-delta fibers to intense heat stimuli, although C-nociceptive fibers are also activated during heat stimulation (Kramer et al. 2012). A preferential A-fiber block is required to isolate EEG activity related to C-fiber responses (Bromm and Treede 1984). Cognitive mechanisms can also modulate the early components of LEP (Legrain et al. 2002). However, because CHEPs recordings in our study could not provide reliable measures of N1 waves, we did not discuss these aspects specifically. Another potential limitation is the use of moderate heat intensity to evoke CHEPs. CPM reduces LEP for the whole range of heat stimuli but the intensity of the evoked pain was only significantly affected for test stimuli near pain threshold but not for mild, warm or intense noxious heat stimuli (Plaghki et al. 1994). In addition, spinal mechanisms play a significant role in segmental and descending inhibition/facilitation of pain; therefore, further studies should employ objective measures of spinal nociceptive processing.

Conclusions

The current study revealed suppression of A-delta-fiber-related brain activity following noxious CPM paralleled by enhanced pain perception. These preliminary findings

suggest a potential dissociation between brain responses to noxious heat and pain perception in individuals with facilitatory-CPM responses.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest regarding this publication.

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