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Is conditioned pain modulation (CPM) affected by negative emotional state?

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Abstract

Background: Conditioned pain modulation (CPM) is an experimental paradigm, which describes the inhibition of responses to a noxious or strong-innocuous stimulus, the test stimulus (TS), by the additional application of a second noxious or strong-innocuous stimulus, the conditioning stimulus (CS). As inadequate CPM efficiency has been assumed to be predisposing for clinical pain, the search for moderating factors explaining inter-individual variations in CPM is ongoing. Psychological factors have received credits in this context. However, research concerning associations between CPM and trait factors relating to negative emotions has yielded disappointing results. Yet, the influence of anxious or fearful states on CPM has not attracted much interest despite ample evidence that negative affective states enhance pain. Our study aimed at investigating the effect of fear induction by symbolic threat on CPM.

Methods: Thirty-seven healthy participants completed two experimental blocks: one presenting aversive pictures showing burn wounds (high-threat block) and one presenting neutral pictures (low-threat block). Both blocks contained a CPM paradigm with contact heat as TS and hot water as CS; subjective numerical ratings as well as contact-heat evoked potentials (CHEPs) were assessed.

Results: We detected an overall inhibitory CPM effect for CHEPs amplitudes but not for pain ratings. However, we found no evidence for a modulation of CPM by threat despite threat ratings indicating that our manipulation was successful.

Discussion: These results suggest that heat/thermal CPM is resistant to this specific type of symbolic threat induction and further research is necessary to examine whether it is resistant to fearful states in general.

Significance: The attempt of modulating heat conditioned pain modulation (CPM) by emotional threat (fear/anxiety state) failed. Thus, heat CPM inhibition again appeared resistant to emotional influences. Pain-related brain potentials proved to be more sensitive for CPM effects than subjective ratings.

1 | INTRODUCTION

Pain sensation can be inhibited by a second noxious or strong-innocuous stimulus applied at a remote site. This phenomenon was termed 'conditioned pain modulation' (CPM) (Yarnitsky et al., 2015) and is seen as psychophysical equivalent to the physiological mechanism 'diffuse noxious inhibitory controls' (DNIC) (Le Bars, 2002). In recent years, CPM has been assumed as risk factor for clinical pain, with inadequate CPM inhibition being observed in several chronic pain conditions (Lewis et al., 2012; Staud, 2012; Yarnitsky, 2015; Yarnitsky et al., 2014).

Although CPM is likely mediated by a circuit in the spinal cord reaching the brainstem (Bingel & Tracey, 2008; Youssef et al., 2016a), it is also open to higher brain regions as shown in imaging studies (Bogdanov et al., 2015; Moont et al., 2011; Piché et al., 2009; Youssef et al., 2016b). Further evidence for such influences is given by the association with higher order perceptual and cognitive processes (Bjørkedal & Flaten, 2012; Cormier et al., 2013; France et al., 2016; Goffaux et al., 2007; Larivière et al., 2007; Nir et al., 2011, 2012). CPM may also be related to general (e.g., depression) or pain-specific affectivity (e.g., pain catastrophizing). Although such associations have been made plausible by previous findings (Bair et al., 2003; Burke et al., 2015; Quartana et al., 2009), strict evidence obtained just in CPM paradigms is largely missing as underscored by the results of a meta-analysis presenting only few and weak correlations (Nahman-Averbuch et al., 2016). We also found no relationship between CPM and trait fear (threat-potentiated startle) as well as pain-specific trait anxiety (questionnaires) (Horn-Hofmann et al., 2016).

Despite this negative evidence concerning a relationship between trait fear and anxiety on the one hand and CPM on the other hand, it may well be that CPM is altered by negative emotional states. The finding that pain perception is temporarily enhanced by negative emotional states has often been replicated (Bushnell et al., 2013; Wiech & Tracey, 2009). However, the effect of fear/anxiety states on CPM has yet been scarcely investigated. The effects of a threat manipulation on CPM have been investigated only once by Bernaba et al. (2014), who instructed participants that cold water used as conditioning stimulus (CS) might have harmful effects like frostbite and gangrene, without success because CPM could not be affected. A limitation of this threat induction might be additional information guaranteeing the subjects' safety for ethical reasons.

Our study aimed at testing the effects of affective picture viewing, which has proven efficacy for pain modulation (e.g., Meagher et al., 2001; Rhudy et al., 2005, 2013), on CPM. Burn injuries were shown as aversive pictures, realizing content-related associations with the painful sensations elicited by heat for both test stimulus (TS) and CS. In addition to pain ratings, we also recorded contact-heat evoked potentials (CHEPs) as physiological measure without cognitive biases to ensure capturing a CPM effect. We hypothesized that the CPM effect would be diminished or even abolished in the high-threat block; that is, emotional threat was assumed to minimize the CPM effect.

2 | MATERIALS AND METHODS

2.1 | Participants

Thirty-seven healthy volunteers of both genders and within an age range between 20 and 60 years were recruited by advertisement at the University of Bamberg and on social media. The age range was intentionally raised above the level of student population to also include people with an age that is already associated with the first onset of certain forms of chronic pain. We think that this age span is informative because certain risk factors for the development of chronic pain start to play their role at this time, the consideration of which has therefore become a general routine in our lab.

No participant had taken any analgesic medication or alcohol at least 24 h prior to the test session. Exclusion criteria (assessed by a telephone interview) included all acute or chronic diseases, especially those associated with acute and chronic pain. In addition, participants were screened for psychiatric disorders by the Mini-DIPS diagnostic interview based on DSM-IV and ICD-10 (Margraf et al., 2017) at the beginning of the experimental session and excluded from participation in the case of any current diagnosis (except for minor anxiety disorders, e.g., specific phobia). All subjects provided written informed consent and received either course credits or monetary compensation for their participation. The experimental procedure was approved by the ethics committee of the University of Bamberg (06/11/2013).

2.2 | Materials and procedures

All experimental sessions took place in the morning (always starting at 9 a.m.). Participants sat upright in a comfortable chair in front of a computer screen. The whole experiment lasted about 3 h and consisted of two experimental blocks ('low threat', 'high threat'). The sequence of these two blocks was balanced across participants in a randomization protocol with the boundary condition of both sequences

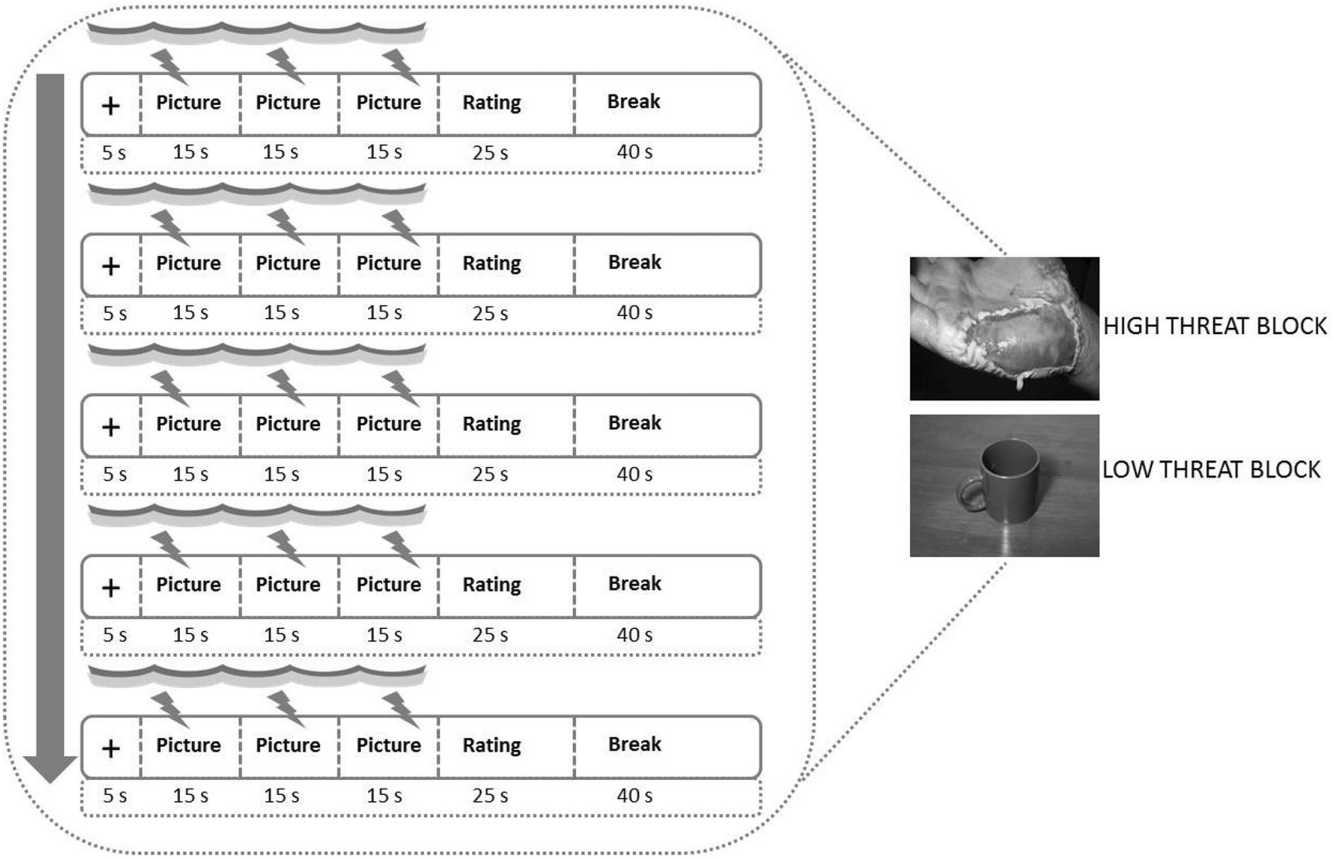

FIGURE 1 Illustration of the experimental protocol. Each condition consisted of five 75 s trials, containing stimulation intervals with three heat pulses (TS, indicated by the flash) and three pictures (neutral pictures in the low-threat block and aversive pictures in the high-threat block). Hot water immersion (CS, indicated by the wave line) was applied only in the CPM conditions.

being equally frequent. Within each block, participants completed a standard CPM paradigm consisting of a baseline condition (test stimuli alone) and a CPM condition (test stimuli + CS). The baseline condition was always applied prior to the CPM condition (see Figure 1). There was a 10-min break between the two blocks where participants filled in a set of questionnaires. The present study was part of a larger study, in which the inhibition of startle EMG responses to loud tones during hand immersion in hot water were assessed in addition (Metzger et al., 2023).

2.2.1 | Conditioned pain modulation

Test stimuli (TS): TS were applied at the participant's left volar forearm by a computer-controlled contact-heat evoked potential stimulator (CHEPS, Medoc, Israel) with a round 27 mm-diameter surface thermode. A pair of thermocouples is embedded in the thermode lamination, which provides an assessment of the skin temperature at the stimulated area.

All TS had a peak temperature of 52°C and a baseline temperature of 40°C, which was held constant between stimuli. Temperature increased with a rate of 70°C/s and decreased with a rate of 40°C/s. Plateau duration of all stimuli was 10 ms. We applied three TS within each stimulation interval, that is, 15 TS per condition (see Figure 1).

The thermode was handheld by the experimenter, who slightly changed thermode position after each TS to prevent receptor fatigue (Granovsky et al., 2008). The timing of TS application was determined in a pseudo-random fashion with the following three limitations: (a) TS should not be presented within the first 2 seconds after picture appearance or in the rating period; (b) the inter-stimulus interval should be at least 10 s; (c) one TS should be applied during each of the three pictures. The exact timing of the TS within the 45 s stimulation interval was as follows: 8 s, 20 s, 37 s (stimulation interval 1); 5 s, 22 s, 33 s (stimulation interval 2); 7 s, 19 s, 34 s (stimulation interval 3); 8 s, 20 s, 37 s (stimulation interval 4); 2 s, 19 s, 36 s (stimulation interval 5).

Conditioning stimuli (CS): A heat stimulus was administered as CS in the CPM conditions by using a circulating water bath (Witeg GmbH, WiseCircu WCB-22, Wertheim, Germany), containing 46°C hot water. The temperature of 46°C was selected as the painful intensity

of the CS based on the results of previous studies (Horn-Hofmann et al., 2016; Karmann et al., 2018; Lautenbacher et al., 2008), which leads to moderate levels of pain with small inter-individual variance and a low risk of reaching intolerable pain levels; the latter would make a premature ending of stimulation necessary. The participants immersed their right hands up to 2 cm above the wrist in this water bath (during baseline the hand laid on an armrest in a distance to the water bath far enough to avoid any heating by convection). The water temperature was controlled by a thermostat, and the water was stirred with a force and suction pump to avoid layers of lower temperature around the hand. The CS was always applied to the right hand.

Conditioning stimulation was applied during the five stimulation intervals when programmed for a CPM condition (see Figure 1). Participants were instructed to immerse their hand as soon as the fixation cross-appeared on the screen and to remove the hand upon appearance of the rating scales until the next trial started by appearance of the fixation cross. The message 'Please immerse hand now' was additionally displayed on the screen below the fixation cross.

2.2.2 | Threat manipulation: Affective pictures

As stated in the introduction, experimental threat was manipulated by presenting either aversive pictures showing burn wounds (high-threat condition) or neutral pictures (low-threat condition). Our experimental protocol required 30 pictures per category. These pictures were selected in a two-step procedure which will be described in detail below: (a) pre-selection from the International Affective Picture System (IAPS; Lang, 2005) or the internet based on picture content and reference to normative data (in the case of IAPS pictures); (b) final selection based on affective ratings collected in a pilot study.

Pre-selection of pictures: Neutral pictures were selected from the IAPS based on normative data regarding valence and arousal ratings and on picture content. As described in the IAPS technical manual, pictures are classified as neutral in the case of valence ratings at or around the midline of the Self-Assessment Manikin scale which ranges from 1 to 9 (SAM; Lang, 1980); it is also stated that neutral pictures are commonly rated as less arousing than pleasant or unpleasant pictures (Lang, 2005). Accordingly, our selection criteria for neutral pictures were (a) valence ratings ≥4 and ≤6, (b) arousal ratings ≤4, and (c) neutral contents (e.g., household objects, vehicles; no people).

Aversive pictures were selected from the internet based on picture content; we decided to use pictures depicting burn injuries at the hand due to their associative relation to the pain stimulation used in our experiment (hot water immersion of the right hand as CS). Pictures were retrieved using Google image search with key words such as 'burn' or 'burn wound' in various languages (e.g., German 'Brandwunde', Dutch 'Brandwond', French 'Brûlure', etc.). All pictures were proportionally altered to be approximately of the same size (about 13 × 9 cm).

Final selection of pictures – pilot study: The pre-selection procedure resulted in 40 neutral and 60 aversive pictures, which were used in randomized order as stimulus material in a pilot study. Thirty participants (female: $N = 19$) were recruited among psychology students of the University of Bamberg. Participants were asked to download the complete picture set and detailed instructions at home. Ratings should be given on SAM scales, ranging from 1 to 9, with 9 corresponding to positive valence and high arousal, respectively. Participants were asked to return the completed SAM ratings to us per e-mail.

The final set of pictures (30 aversive, 30 neutral[i]) were then selected according to the following criteria: Neutral pictures were required to have mean valence ratings of 5 ± 1 and mean arousal ratings ≤2.5; aversive pictures were required to have mean valence ratings ≤2.5 and mean arousal ratings ≥5.5. Outliers from the respective picture category (neutral or aversive) were excluded.

Picture presentation: Each condition ($Baseline_{low\ threat}$, $CPM_{low\ threat}$; $baseline_{high\ threat}$, $CPM_{high\ threat}$) consisted of five 75 s trials, which were separated each time by a 40 s break, resulting in a total duration of about 9 min per condition (see Figure 1). Each trial started with a fixation cross, which was shown for 5 s, followed by a 45 s stimulation interval where pictures were presented and noxious stimulation was applied and ended with a 25 s rating period. Within each stimulation interval, three pictures were presented for 15 s each. Thus, 15 pictures were shown in each condition. For this purpose, the 30 pictures of each category (neutral, aversive) were randomly split in two subsets containing 15 pictures; the sequence of the 15 pictures within the subset was randomized once by a randomization program also simulating lottery draws and then set. The sequence of the two picture sets within each block ($neutral_1$, $neutral_2$; $aversive_1$, $aversive_2$) was balanced across participants.

2.2.3 | Ratings

Participants verbally provided pain and threat intensity ratings during the last 25 s of each trial. For this purpose, we used three numerical pain rating scales (NRS) each ranging from 0 to 10; participants were asked to rate the intensity of the TS (0 = not painful, 10 = extremely painful), the threat of the situation (0 = not threatening,

10 = extremely threatening) and (in the CPM conditions) the intensity of the CS (0 = not painful, 10 = extremely painful). The use of these rating scales was explained to the participants at the beginning of the experiment and practiced in a familiarization interval. In addition, rating scales were displayed on the screen during the rating period combined with a visual instruction.

For each of the four conditions ($Baseline_{low\ threat}$, $CPM_{low\ threat}$; $baseline_{high\ threat}$, $CPM_{high\ threat}$), TS ratings and threat ratings were averaged across the five rating assessments and then subjected to further analysis. Similarly, CS ratings were averaged across the five rating assessments for each of the two CPM conditions ($CPM_{low\ threat}$, $CPM_{high\ threat}$) before subjecting them to further analysis.

2.2.4 | EEG recording and parametrization (CEPS)

EEG recording was accomplished by a DC Brain Amp amplifier (Brain Products GmbH, Germany) with a sampling rate of 1024 Hz and a recording bandwidth from 0.1 Hz to 300 Hz. For electrode placement, a commercial CI Electro-Cap Electrode system realizing the international 10–20 system was used (Electro-Cap International, USA). Cz served as reference. The impedances of all electrodes were kept below 5 kΩ. Furthermore, tin electrodes were placed on the mastoids for offline re-referencing the data to regain Cz. In addition, an electro-oculogram (EOG) was recorded. The EOG-biosignal was sampled at a rate of 512 Hz.

EEG data from Cz were analysed offline (Brain Vision analyser, Brain Products, Germany) to determine N2 and P2 latencies as well as N2P2 peak-to-peak amplitudes following mostly the protocol described by Granovsky et al. (2008), which have appeared to be valid indicators of the intensity dimension of central nociception. The 15 potentials evoked by the TS were averaged within each of the four conditions ($Baseline_{low\ threat}$, $CPM_{low\ threat}$; $baseline_{high\ threat}$, $CPM_{high\ threat}$). The averaged signals were used to determine two components: N2 was defined as the most negative peak in a time window from 200 to 500 ms, P2 was defined as the most positive peak in a time window from 400 to 650 ms (Priebe et al., 2016). For further analysis, the peak-to-peak N2P2 amplitude, that is, the absolute difference between the voltage of the N2 and the P2 was calculated. Consequently, four N2P2-complex amplitude scores resulted for each participant, one for the baseline condition and one for the CPM condition both in the low threat and high-threat block. Additionally, the same number of N2 and P2 latencies for the baseline and CPM conditions both in the low-threat and high-threat block was kept for further analysis.

2.2.5 | Questionnaires

Participants filled in a set of questionnaires assessing affective processing in general and relating to pain. This set consisted of German versions of the Anxiety Sensitivity Index (ASI-3; Taylor et al., 2007; German version: Kemper et al., 2009), the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983; German version HADS-D: Herrmann et al., 1995), the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995; German version: Meyer et al., 2008) and the Fear of Pain Questionnaire (FPQ-III; McNeil & Rainwater, 1998).

The ASI-3 is a 16-item self-report questionnaire designed to measure anxiety sensitivity, that is, the fear of anxiety-related sensations due to the belief that they might have harmful consequences. It is composed of 3 subscales: Fear of somatic sensations, fear of cognitive dyscontrol, and fear of socially observable anxiety reactions. The items (e. g., 'It scares me when my heart beats rapidly') are rated on a 5-point scale. In the present study, only the sum score was used, which can range from 0 to 64 (min = 0, max = 64; high scores indicating high anxiety sensitivity). Similar to the original English version, the German version (Kemper et al., 2009) demonstrated good internal consistency, with Cronbach's α for the three subscales ranging from 0.83 to 0.92 in two samples (Kemper et al., 2012).

The HADS (Zigmond et al., 1983) was developed as a screening instrument for depression and anxiety, which is applicable in patients treated in non-psychiatric hospital clinics. This is also true for persons with chronic pain, who are often affected by depression and increased anxiety levels. Thus, this questionnaire was selected to ensure the applicability of the complete study design in a chronic pain sample, which we are planning to investigate next. It consists of two subscales (depression and anxiety), each containing seven items. The items are rated on a 4-point scale. The score can range from 0 to 42 (depression: min = 0, max = 21; anxiety: min = 0, max = 21; high scores indicating high levels). Commonly, a cut-off score of 8+ on each scale is used to identify 'possible cases' (Zigmond et al., 1983). In accordance with the original English version, the German version (Herrmann et al., 1995) demonstrated good internal consistency: Cronbach's $\alpha = 0.80$ for the anxiety scale and Cronbach's $\alpha = 0.81$ for the depression scale.

The PCS (Sullivan et al., 1995) is designed to measure catastrophizing related to pain. It contains 13 items that can be divided into 3 subscales, namely rumination, magnification, and helplessness. The items (e.g., 'I worry all the time about whether the pain will end') are rated on a 5-point scale ('not at all' = 0, 'all the time' = 4). In the present study, only the sum score was used, which can range from 0 to 52 (min = 0, max = 52; higher scores indicating higher pain

catastrophizing). The PCS showed good internal consistency (English version: Cronbach's $\alpha = 0.95$ [Sullivan et al., 1995]; German version: Cronbach's $\alpha = 0.92$ [Meyer et al., 2008]).

The FPQ-III (McNeil & Rainwater, 1998) was developed as a comprehensive measure of fear of pain. Participants are instructed to rate the degree of fear they would likely experience if confronted with a variety of potentially painful situations. The FPQ-III contains 30 items that can be divided into three subscales regarding the fear of three types of pain: severe pain ('breaking an arm'), minor pain ('paper cut on the finger') and medical pain ('receiving an injection in the mouth'). The items are rated on a 5-point scale. In the present study, only the sum score was used, which can range from 30 to 150 (min = 30, max = 150; higher scores indicating higher fear of pain). The FPQ-III demonstrated good internal consistency: Cronbach's $\alpha = 0.92$ (McNeil & Rainwater, 1998).

The FPQ-III was translated into German by our workgroup using a standard 'forward-backward-procedure'; translation to German was improved until the original English version and the final German version were sufficiently similar. This German version of the FPQ-III was successfully used in previous studies (Baum, Kappesser, et al., 2013; Baum, Schneider, et al., 2013; Priebe et al., 2015) and demonstrated good internal consistency (Cronbach's $\alpha = 0$ 0.90; Baum, Schneider, et al., 2013).

2.3 | Data reduction and analysis

We computed CPM scores (difference CPM - baseline) as a measure of CPM directionality, that is, inhibition versus facilitation, for each of the two blocks (low threat, high threat) both for TS ratings and N2P2-complex amplitudes. Thus, negative CPM scores were indicative of inhibition (pain ratings and N2P2-complex amplitudes reduced in the CPM conditions compared with baseline), whereas positive CPM scores were indicative of facilitation (pain ratings and N2P2-complex amplitudes increased in the CPM conditions compared with baseline). The descriptive values are presented in Table S1 of the supplementary material. In addition to the absolute CPM difference scores, CPM percent change scores were computed and are included in Table S1.

To investigate the effects of the CPM test and the threat manipulation on TS ratings and EEG parameters (N2P2-complex amplitudes as well as N2 and P2 latencies), we computed separate repeated measurement ANOVAs with 'condition' (baseline, CPM) and 'block' (low threat, high threat) as within-subject factors. Effects of threat on CS ratings were tested using a paired samples t-test (low threat vs. high-threat block).

As manipulation check, threat ratings were analysed by a repeated measurement ANOVA with 'block' (low threat, high threat) and 'condition' (CPM, baseline) as within-subject factors.

Post-hoc *t*-tests were computed for detailed analyses in case of significant ANOVA results. Adjusting degrees of freedom with Greenhouse–Geisser correction was necessary in case of violation of sphericity. For *F*-tests, partial eta squared (η^2) is reported as an estimate of effect size; Cohen's s d is reported to describe effect size for paired comparisons.

To test for the stability of responses across conditions and for associations between the two methods of pain assessment (EEG and subjective ratings), we computed Pearson correlations among and between N2P2 peak-to-peak amplitudes and TS ratings in the four experimental conditions. Additionally, correlations between the four CPM scores (CPM rating$_{\text{low threat}}$, CPMrating $_{\text{high threat}}$, CPM EEG$_{\text{low threat}}$, CPM EEG$_{\text{high threat}}$) were computed to evaluate the reliability of CPM across measures and conditions.

Bonferroni correction was applied to correct for multiple testing. The alpha-level was set to 5% for significance testing. SPSS 25 (IBM) was used for all calculations.

3 | RESULTS

3.1 | Sample characteristics

The gender ratio of the 37 participants was female = 21 to male = 16. The age range was between 22 and 54 years (mean age 34.9 years; SD = 11.0). Four women took oral contraceptives; of the remaining 17, three were in the first, five in the second, and six in the third phase of their menstrual cycle; two were postmenopausal and information was missing from one participant. Descriptive statistics of questionnaire scores are reported in Table 1.

3.2 | Manipulation check: Threat ratings

Descriptive statistics of threat ratings in both blocks and conditions are displayed in Table 1. The ANOVA yielded a significant main effect of 'block' on threat ratings ($F(1,36) = 31.302$, $p < 0.001$, $\eta^2 = 0.465$); as intended, ratings were higher in the high-threat block compared with the low-threat block (see Table 1). There was no significant main effect of 'condition', but a significant interaction 'condition' × 'block' ($F(1,36) = 4.422$, $p = 0.043$, $\eta^2 = 0.109$): Within the low-threat block, threat ratings were descriptively higher in the CPM condition compared with baseline whereas the opposite was the case for the high-threat block. However, paired comparisons failed to reach significance (baseline$_{\text{low threat}}$ vs. CPM$_{\text{low threat}}$: $p = 0.248$; baseline$_{\text{high threat}}$ vs. CPM$_{\text{high threat}}$: $p = 0.211$). Thus, according to these findings, our experimental threat

TABLE 1 Descriptive statistics of questionnaire sum scores (mean, standard deviation [SD]).

	Questionnaire	*N*	Mean	SD
Questionnaire	ASI-3	37	17.2	10.0
	PCS	36	19.1	8.1
	FPQ-III	36	66.3	17.6
	HADS Depression	36	2.5	2.6
	HADS Anxiety	36	4.7	3.1
Manipulation check	Threat rating – Baseline low threat	37	1.8	2.0
	Threat rating – CPM low threat	37	2.1	2.1
	Threat rating – Baseline high threat	37	4.0	2.4
	Threat rating – CPM high threat	37	3.7	2.3
	Threat rating – Low threat (averaged)	37	1.9	−1.9
	Threat rating – High threat (averaged)	37	3.9	2.2

Abbreviations: ASI-3, Anxiety Sensitivity Index – 3; CPM, Conditioned Pain Modulation; FPQ = III, Fear of Pain Questionnaire – 3; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; all scores are given in arbitrary scale units.

Note: Questionnaire data was incomplete (i.e., 50% or more of the items missing) for three participants (HADS: $N = 1$; PCS: $N = 1$; FPQ: $N = 1$). These participants were removed from the descriptive analysis for the respective questionnaire.

manipulation was successful with only higher ratings in the threat blocks and no other unwanted differences.

3.3 | CS pain ratings

We detected no effect of 'block' (low threat vs. high threat) on CS ratings: $t(36) = 0.180$, $p = 0.858$, $d = 0.014$). Overall, the CS (hot water immersion) was rated as moderately painful ($M = 3.7$, SD = 2.3) and provided by the latter ideal conditions for CPM modulation.

3.4 | TS pain ratings

Mean values of TS ratings in all four conditions are displayed in Figure 2. The ANOVA yielded no significant main effects of 'block' (low threat vs. high threat) or 'condition' (CPM vs. baseline) on TS ratings and there was also no significant interaction ('block': $F(1,36) = 0.935$, $p = 0.340$, $\eta^2 = 0.025$; 'condition': $F(1,36) = 0.587$, $p = 0.449$, $\eta^2 = 0.016$; 'block' × 'condition': $F(1,36) = 0.256$, $p = 0.616$, $\eta^2 = 0.007$). Thus, we detected no CPM effect and no effect of threat (see Figure 2).

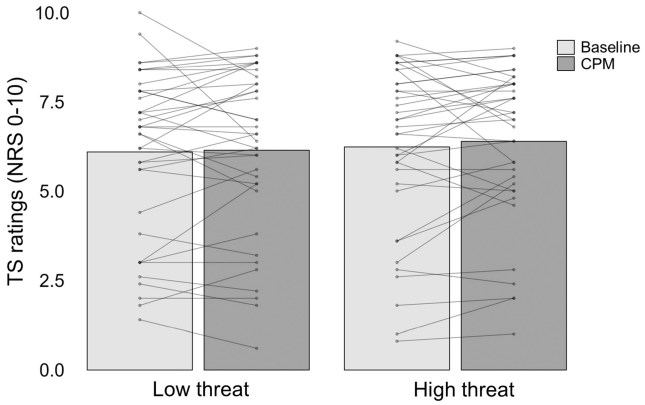

FIGURE 2 TS ratings (mean, and individual scores) in the baseline and CPM conditions for the two experimental blocks.

TABLE 2 Descriptive statistics of N2 and P2 latencies (mean, standard deviation [SD]) in the four experimental conditions.

	Condition	Mean	SD
N2 latency (ms)	Baseline low threat	330.5	74.7
	CPM low threat	322.9	77.7
	Baseline high threat	306.4	58.7
	CPM high threat	317.3	64.5
P2 latency (ms)	Baseline low threat	476.5	73.8
	CPM low threat	492.2	80.5
	Baseline high threat	490.1	81.3
	CPM high threat	497.8	80.5

Abbreviation: CPM, Conditioned Pain Modulation.

3.5 | CHEPs parameters

3.5.1 | N2 and P2 Latencies

Descriptive statistics of N2 and P2 latencies are displayed in Table 2. There were no significant effects of 'condition' or 'block' on N2 latencies (all p's > 0.10). However, for P2 latencies, we detected a significant main effect of 'condition' ($F(1,36) = 4.310$, $p = 0.045$, $\eta^2 = 0.107$), with shorter latencies in the baseline compared with

the CPM conditions ($t(36) = 2.076$, $p = 0.045$, $d = 0.161$; see Table 2). There was no effect of 'block' (low threat vs. high threat) ($F(1,36) = 2.479$, $p = 0.124$, $\eta^2 = 0.064$) and no interaction 'condition' × 'block' ($F(1,36) = 0.244$, $p = 0.624$, $\eta^2 = 0.007$).

3.5.2 | N2P2 peak-to-peak Amplitudes

Mean values of N2P2 amplitudes in all four conditions are displayed in Figure 3. We detected a significant main effect of 'condition' ($F(1,36) = 11.980$, $p = 0.001$, $\eta^2 = 0.250$), with lower N2P2-complex amplitudes in the CPM compared with the baseline condition ($t(36) = 3.461$; $p = 0.001$, $d = 0.297$; see Figure 3), indicating a classical inhibitory CPM effect. However, there was no significant effect of 'block' (low threat vs. high threat) (all p's > 0.40) and no interaction 'condition' × 'block' (all p's > 0.80).

3.6 | Association between CHEPs amplitudes and subjective ratings

Pearson correlations among and between psycho-physiological and subjective indicators of pain responses (N2P2 peak-to-peak amplitudes and TS ratings) are displayed in Table 3. Within each of the two methods, we obtained significant high correlations between the four conditions (see Table 3). However, there were no significant correlations across the two methods (EEG and TS pain ratings; Bonferroni-corrected $\alpha = 0.001$), suggesting that these two indicators of pain processing were only weakly related in the present study.

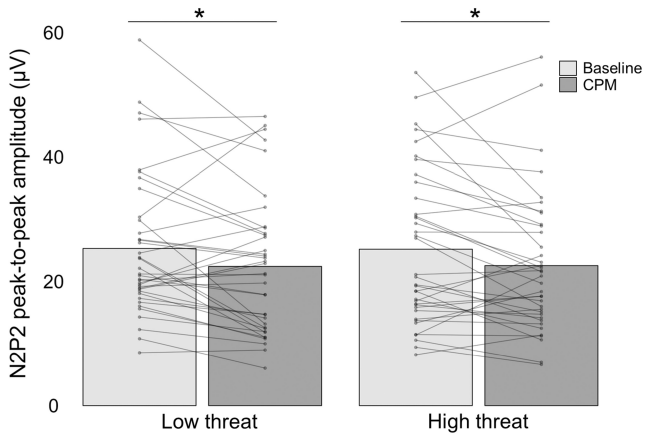

FIGURE 3 N2P2 peak-to-peak amplitudes (mean, and individual scores) in the baseline and CPM conditions for the two experimental blocks. Asterisks indicate significant differences ($p < 0.05$).

TABLE 3 Pearson correlations among and between N2P2 peak-to-peak amplitudes and TS ratings in the four experimental conditions.

	N2P2 baseline low threat	N2P2 CPM low threat	N2P2 baseline high threat	N2P2 CPM high threat	TS rating baseline low threat	TS rating CPM low threat	TS rating baseline high threat	TS rating CPM high threat
$N2P2_{baseline\ low\ threat}$					0.026	−0.099	−0.012	−0.122
$N2P2_{CPM\ low\ threat}$	**0.814**				−0.093	−0.182	−0.224	−0.246
$N2P2_{baseline\ high\ threat}$	**0.786**	**0.715**			−0.056	−0.178	−0.069	−0.135
$N2P2_{CPM\ high\ threat}$	**0.772**	**0.701**	**0.844**		0.016	−0.022	0.031	0.024
$TS\ rating_{baseline\ low\ threat}$								
$TS\ rating_{CPM\ low\ threat}$					**0.903**			
$TS\ rating_{baseline\ high\ threat}$					**0.796**	**0.782**		
$TS\ rating_{CPM\ high\ threat}$					**0.811**	**0.844**	**0.894**	

Abbreviation: TS, Test Stimulus.

Note: Significant correlations are marked in bold script. Bonferroni-corrected $\alpha = 0.001$.

3.7 | Reliability of CPM

Pearson correlations among the four CPM scores (CPM rating$_{low\ threat}$, CPM rating$_{high\ threat}$, CPM EEG$_{low\ threat}$, CPM EEG$_{high\ threat}$), indicating the absolute CPM effects, are displayed in Table 4. None of the correlation coefficients passed the level of significance. These findings do not allow for assuming high reliability of the CPM effects, neither across nor within the method of pain assessment (EEG and TS pain ratings; Bonferroni-corrected $\alpha = 0.008$). Similar non-significant outcomes were obtained when using percent change CPM scores (see Table S2 in the supplementary material).

4 | DISCUSSION

To our knowledge, our study is one of the few, which have investigated the effect of experimentally induced threat on CPM and the first to use symbolic threat. Symbolic, that is, content-related threat was induced by presenting photographs of burn injuries while participants underwent a CPM paradigm with contact heat as TS and hot water immersion of the contralateral hand as CS. The success of our threat manipulation was confirmed by increased subjective threat ratings. Furthermore, we could demonstrate CPM inhibition by nociceptive evoked brain potentials (CHEPs). However, despite of positive threat and CPM effects, their interaction did not become significant. Thus, contrary to our hypotheses, there was no effect of threat on CPM. The key findings and their implications will be discussed in more detail in the following paragraphs.

4.1 | Threat effects on CPM

Our analyses showed a clear inhibitory CPM effect (main effect of 'condition') as regards the CHEPs amplitudes (N2P2) and a smaller CPM effect as regards P2 latency. However, there was no interaction with 'block', indicating no differences in CPM between the low-threat block (neutral pictures) and the high-threat block (burn injury pictures) although subjective ratings confirmed a significant difference in perceived threat between the two blocks. Thus, we could not demonstrate an effect of subjective threat on CPM. This is in line with the one preceding study investigating threat effects on CPM (Bernaba et al., 2014). The authors used cold water immersion as CS and manipulated threat by asking participants to either imagine that the CS might have harmful consequences like frostbite or to focus on the safety of this procedure. This threat manipulation was adapted from a study by Jackson et al. (2005) where it led to lower pain tolerance and increased pain catastrophizing. However, Bernaba and colleagues found that the CPM effect was unaffected by threat, with both experimental conditions (instructed threat and instructed safety) not differing from a neutral control condition. Taken together, these findings of CPM being immune to two established threat manipulation procedures with proven effects on pain measures (instructed threat and affective pictures) suggest that negative affective states might have a negligible influence on the CPM effect. Combined with the also predominantly negative evidence concerning an association between affect-related personality traits like trait anxiety or pain catastrophizing and CPM (Bouhassira et al., 2013; Granot et al., 2008; Grosen et al., 2014; Horn-Hofmann et al., 2016; Ibancos-Losada et al., 2020; Lee et al., 2013; Marouf et al., 2014; Martel et al., 2013; Nir et al., 2012), the assumption that CPM might be a pain inhibitory circuit, which operates widely independent from emotional influences seems plausible.

4.2 | Threat effects on pain perception in general

Our observation that aversive pictures did not even modulate TS and CS ratings considered separately and independently from their CPM interaction is definitely surprising because a wealth of studies suggests effects of emotional pictures viewing on pain perception (Bartley & Rhudy, 2008; De Wied & Verbaten, 2001; Kamping et al., 2013; Kenntner-Mabiala et al., 2007; Meagher et al., 2001; Rhudy et al., 2005, 2013; Roy et al., 2009, 2011; Zunhammer et al., 2016). One possible reason for this finding is that our study did not include positive pictures and some studies suggest that emotional pain modulation is driven more strongly by pain reduction

TABLE 4 Pearson correlations among the four CPM scores.

	CPM rating$_{low\ threat}$	CPM rating$_{high\ threat}$	CPM EEG$_{low\ threat}$
CPM rating$_{high\ threat}$	0.224		
CPM EEG$_{low\ threat}$	0.148	0.374	
CPM EEG$_{high\ threat}$	0.401	0.194	0.035

Abbreviation: CPM, Conditioned Pain Modulation; EEG, Electroencephalogram.

Note: Bonferroni-corrected $\alpha = 0.008$; none of the correlations were significant.

induced by positive pictures than by pain enhancement induced by negative pictures (De Wied & Verbaten, 2001; Kenntner-Mabiala & Pauli, 2005, Kenntner-Mabiala et al., 2007; Rhudy et al., 2005). In addition, our pictures might have induced disgust instead of or additionally to fear/anxiety in some of the participants, and disgust-evoking pictures have been shown to be less efficient in modulating pain than fear-evoking pictures (Meagher et al., 2001). Furthermore, picture presentation over 15 s was long compared with other studies (De Wied & Verbaten, 2001; Kenntner-Mabiala & Pauli, 2005, Kenntner-Mabiala et al., 2007; Rhudy et al., 2005), which may have reduced its emotional efficiency in the course of presentation. Since pain is very imperative and definitely efficient also in our experiment in the forms of TS and CS, it may also be that the participants may have been distracted from the pictures. Also, it has been previously stressed that effects of affective pain modulation are possibly overestimated due to publication bias (Zunhammer et al., 2016).

4.3 | Dissociation between electrophysiological and subjective measures

An additional interesting finding of our study is the discrepancy between a clear inhibitory CPM effect in CHEPs amplitudes, but no CPM effect in TS pain ratings. This dissociation between subjective and electrophysiological measures is in line with a previous study (Albu & Meagher, 2019), detecting a facilitatory CPM effect for pain ratings which was accompanied by (non-significant) the suppression of CHEPs amplitudes. Similar results have been obtained by two studies using electrical stimulation (Goffaux et al., 2007; Piché et al., 2014), which observed inhibitory CPM effects on evoked potentials that were not mirrored by changes in ratings and nociceptive flexion reflex responses. In addition, two other recent studies found an inhibitory CPM effect for both pain ratings and evoked potentials, but no correlation between the respective change scores (Do et al., 2020; Squintani et al., 2021). Hence, there is quite some evidence for a dissociation between brain activity and subjective or spinal measures of pain perception in CPM paradigms that calls for further investigation. Factors like the subjective painfulness of the CS should be considered as a few studies have shown effects on CPM as regards the TS pain ratings (Nir et al., 2011, 2012) if CS ratings, which were low in the present study, are more substantial as in previous studies from our lab using the same physical stimulus and intensity (Horn-Hofmann et al., 2016; Lautenbacher et al., 2008). The neutral influence of rather weak CS stimuli might have preferentially affected the CPM effects indicated by TS pain ratings because evoked brain potentials (EBP) have shown to be very sensitive to detect subtle CPM effects (Höffken et al., 2017; Jutzeler et al., 2017; Kunz et al., 2014). Worth mentioning is that our CS also suppressed the intensity ratings and startle reflexes evoked by aversive loud tones (Metzger et al., 2023).

4.4 | Strengths and weaknesses

There was no evidence given by our questionnaires for heightened general or pain-related anxiety or depressiveness in our non-clinical sample (Baum, Kappesser, et al., 2013; Bocéréan & Dupret, 2014; Horn-Hofmann et al., 2016; Peterson & Reiss, 1992). This is not very surprising given that we excluded participants with mental disorders and pain problems. Thus, we obtained a sample allowing experimental threat manipulation without ethical risk.

To our knowledge, our study is the first to investigate the effects of experimentally induced threat on CPM using both CHEPs and pain ratings as two separate indicators of CPM. The observed dissociation between these two measures which has already been reported before (Albu & Meagher, 2019; Goffaux et al., 2007; Piché et al., 2014) stresses the importance of not solely relying on pain ratings in CPM studies as CPM effects might not be sufficiently captured by the subjective measures. CHEPs have been shown in several studies to be valid indicators of central nociception (e.g., Granovsky et al., 2008; Priebe et al., 2016); however, not completely excluding artefacts from other physiological sources. The correlations between CHEPs and subjective pain rating were low in the present study, which is – as just stated – not the regular but also no exceptional finding. We applied our CPM paradigm in the standard order with a baseline condition first including only TS and thereafter the treatment condition including concurrently both TS and CS. This frequently used design, however, does not control for order effects.

We intentionally selected burn injury pictures as stimulus material as we aimed to maximize the threat value by the symbolic, that is, content-related association between the noxious heat stimulation and the pictures. However, these pictures might have partly induced other emotions as intended (e.g., disgust) and our findings cannot be generalized to aversive pictures with a different content. Threat ratings clearly differentiated between the two blocks but were generally low even in the high-threat block. However, this might be a problem inherent to most experimental threat inductions as assuring the participants of the safety of all procedures

is a necessity due to ethical concerns. It should also be stressed that the correlations between CPM scores across conditions were low, indicating insufficient reliability of CPM effects. The problem of CPM reliability has been discussed repeatedly (Kennedy et al., 2016; Lewis et al., 2012; Martel et al., 2013; Valencia et al., 2013) and still needs to be addressed in future research.

5 | CONCLUSIONS

Our study showed no modulation of the CPM effect by pictures of burn injuries that were used as an experimental threat induction. Taken together with a previous study, which found no modulation of CPM by threatening instructions (Bernaba et al., 2014), there is now evidence against CPM being counteracted by situational threat. Future studies should investigate the effects of other threat induction methods on CPM (the introduction of unpredictable variations in CS intensity might be particularly promising) before finally assuming that CPM is a pain inhibitory circuit without major emotional influences due to threat induction.

AUTHOR CONTRIBUTIONS

Conception and design (SL and CHH), acquisition of data (LJ, MM), analysis and interpretation of data (SL, CHH, MM), drafting the article (CHH, LJ, MM), revising it critically for important intellectual content (SL); final approval of the version to be published (all).

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ENDNOTE

[i] The IAPS picture identification numbers were as follows: 2446, 5534, 7002, 7009, 7010, 7020, 7025, 7030, 7031, 7034, 7035, 7036, 7037, 7038, 7040, 7041, 7055, 7059, 7060, 7110, 7130, 7150, 7161, 7175, 7180, 7217, 7235, 7491, 7750, 7950.

REFERENCES

Albu, S., & Meagher, M. W. (2019). Divergent effects of conditioned pain modulation on subjective pain and nociceptive-related brain activity. *Experimental Brain Research*, *237*(7), 1735–1744.

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: A literature review. *Archives of Internal Medicine*, *163*(20), 2433–2445.

Bartley, E. J., & Rhudy, J. L. (2008). The influence of pain catastrophizing on experimentally induced emotion and emotional modulation of nociception. *The Journal of Pain*, *9*(5), 388–396.

Baum, C., Kappesser, J., Schneider, R., & Lautenbacher, S. (2013). Does vigilance to pain make individuals experts in facial recognition of pain? *Pain Research and Management*, *18*(4), 191–196.

Baum, C., Schneider, R., Keogh, E., & Lautenbacher, S. (2013). Different stages in attentional processing of facial expressions of pain: A dot-probe task modification. *The Journal of Pain*, *14*(3), 223–232.

Bernaba, M., Johnson, K. A., Kong, J. T., & Mackey, S. (2014). Conditioned pain modulation is minimally influenced by cognitive evaluation or imagery of the conditioning stimulus. *Journal of Pain Research*, *7*, 689.

Bingel, U., & Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology*, *23*(6), 371–380.

Bjørkedal, E., & Flaten, M. A. (2012). Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females. *Journal of Pain Research*, *5*, 289.

Bocéréan, C., & Dupret, E. (2014). A validation study of the hospital anxiety and depression scale (HADS) in a large sample of French employees. *BMC Psychiatry*, *14*(1), 1–11.

Bogdanov, V. B., Viganò, A., Noirhomme, Q., Bogdanova, O. V., Guy, N., Laureys, S., Renshaw, P. F., Dallel, R., Phillips, C., & Schoenen, J. (2015). Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: An fMRI study in healthy subjects. *Behavioural Brain Research*, *281*, 187–198.

Bouhassira, D., Moisset, X., Jouet, P., Duboc, H., Coffin, B., & Sabate, J. M. (2013). Changes in the modulation of spinal pain processing are related to severity in irritable bowel syndrome. *Neurogastroenterology & Motility*, *25*(7), 623 e468.

Burke, A. L., Mathias, J. L., & Denson, L. A. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology*, *54*(3), 345–360.

Bushnell, M. C., Čeko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*, *14*(7), 502–511.

Cormier, S., Piché, M., & Rainville, P. (2013). Expectations modulate heterotopic noxious counter-stimulation analgesia. *The Journal of Pain*, *14*(2), 114–125.

de Wied, M., & Verbaten, M. N. (2001). Affective pictures processing, attention, and pain tolerance. *Pain*, *90*(1–2), 163–172.

Do, A. L., Enax-Krumova, E. K., Özgül, Ö., Eitner, L. B., Heba, S., Tegenthoff, M., Maier, C., & Höffken, O. (2020). Distraction by a cognitive task has a higher impact on electrophysiological measures compared with conditioned pain modulation. *BMC Neuroscience*, *21*(1), 1–10.

France, C. R., Burns, J. W., Gupta, R. K., Buvanendran, A., Chont, M., Schuster, E., Orlowska, D., & Bruehl, S. (2016). Expectancy effects on conditioned pain modulation are not influenced by naloxone or morphine. *Annals of Behavioral Medicine*, *50*(4), 497–505.

Goffaux, P., Redmond, W. J., Rainville, P., & Marchand, S. (2007). Descending analgesia–when the spine echoes what the brain expects. *Pain*, *130*(1–2), 137–143.

Granot, M., Weissman-Fogel, I., Crispel, Y., Pud, D., Granovsky, Y., Sprecher, E., & Yarnitsky, D. (2008). Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? *Pain*, *136*(1–2), 142–149.

Granovsky, Y., Granot, M., Nir, R. R., & Yarnitsky, D. (2008). Objective correlate of subjective pain perception by contact heat-evoked potentials. *The Journal of Pain*, *9*(1), 53–63.

Grosen, K., Vase, L., Pilegaard, H. K., Pfeiffer-Jensen, M., & Drewes, A. M. (2014). Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: A prospective observational cohort study. *PLoS One*, *9*(2), e90185.

Herrmann, C., Buss, U., & Snaith, R. P. (1995). *HADS-D hospital anxiety and depression scale–deutsche version*. Huber.

Höffken, O., Özgül, Ö. S., Enax-Krumova, E. K., Tegenthoff, M., & Maier, C. (2017). Evoked potentials after painful cutaneous electrical stimulation depict pain relief during a conditioned pain modulation. *BMC Neurology*, *17*(1), 1–11.

Horn-Hofmann, C., Priebe, J. A., Schaller, J., Görlitz, R., & Lautenbacher, S. (2016). Lack of predictive power of trait fear and anxiety for conditioned pain modulation (CPM). *Experimental Brain Research*, *234*(12), 3649–3658.

Ibancos-Losada, M. D. R., Osuna-Pérez, M. C., Castellote-Caballero, M. Y., & Díaz-Fernández, Á. (2020). Conditioned pain modulation effectiveness: An experimental study comparing test paradigms and analyzing potential predictors in a healthy population. *Brain Sciences*, *10*(9), 599.

Jackson, T., Pope, L., Nagasaka, T., Fritch, A., Iezzi, T., & Chen, H. (2005). The impact of threatening information about pain on coping and pain tolerance. *British Journal of Health Psychology*, *10*(3), 441–451.

Jutzeler, C. R., Warner, F. M., Wanek, J., Curt, A., & Kramer, J. L. (2017). Thermal grill conditioning: Effect on contact heat evoked potentials. *Scientific Reports*, *7*(1), 1–8.

Kamping, S., Bomba, I. C., Kanske, P., Diesch, E., & Flor, H. (2013). Deficient modulation of pain by a positive emotional context in fibromyalgia patients. *Pain*, *154*(9), 1846–1855.

Karmann, A. J., Lauer, C., Ziegler, E., Killian, L., Horn-Hofmann, C., & Lautenbacher, S. (2018). Associations of nocturnal sleep with experimental pain and pain catastrophizing in healthy volunteers. *Biological Psychology*, *135*, 1–7.

Kemper, C. J., Lutz, J., Bähr, T., Rüddel, H., & Hock, M. (2012). Construct validity of the anxiety sensitivity index–3 in clinical samples. *Assessment*, *19*(1), 89–100.

Kemper, C. J., Ziegler, M., & Taylor, S. (2009). Psychometric properties of the German version of the anxiety sensitivity index 3. *Diagnostica*, *55*(4), 223–233.

Kennedy, D. L., Kemp, H. I., Ridout, D., Yarnitsky, D., & Rice, A. S. (2016). Reliability of conditioned pain modulation: A systematic review. *Pain*, *157*(11), 2410–2419.

Kenntner-Mabiala, R., & Pauli, P. (2005). Affective modulation of brain potentials to painful and nonpainful stimuli. *Psychophysiology*, *42*(5), 559–567.

Kenntner-Mabiala, R., Weyers, P., & Pauli, P. (2007). Independent effects of emotion and attention on sensory and affective pain perception. *Cognition and Emotion*, *21*(8), 1615–1629.

Kunz, M., Mohammadian, P., Renner, B., Roscher, S., Kobal, G., & Lautenbacher, S. (2014). Chemo-somatosensory evoked potentials: A sensitive tool to assess conditioned pain modulation? *Somatosensory & Motor Research*, *31*(2), 100–110.

Lang, P. J. (1980). *Self-assessment manikin*. The Center for Research in Psychophysiology, University of Florida.

Lang, P. J. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual*. Technical Report.

Larivière, M., Goffaux, P., Marchand, S., & Julien, N. (2007). Changes in pain perception and descending inhibitory controls start at middle age in healthy adults. *The Clinical Journal of Pain*, *23*(6), 506–510.

Lautenbacher, S., Kunz, M., & Burkhardt, S. (2008). The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: Does sex matter? *Pain*, *140*(3), 429–435.

Le Bars, D. (2002). The whole body receptive field of dorsal horn multireceptive neurones. *Brain Research Reviews*, *40*(1–3), 29–44.

Lee, Y. C., Lu, B., Edwards, R. R., Wasan, A. D., Nassikas, N. J., Clauw, D. J., Solomon, D. H., & Karlson, E. W. (2013). The role of sleep problems in central pain processing in rheumatoid arthritis. *Arthritis and Rheumatism*, *65*(1), 59–68.

Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *The Journal of Pain*, *13*(10), 936–944.

Margraf, J., Cwik, J. C., Suppiger, A., & Schneider, S. (2017). *DIPS Open Access: Diagnostisches Interview bei psychischen Störungen*. Ruhr-Universität Bochum (RUB).

Marouf, R., Caron, S., Lussier, M., Bherer, L., Piché, M., & Rainville, P. (2014). Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. *Pain*, *155*(3), 494–502.

Martel, M. O., Wasan, A. D., & Edwards, R. R. (2013). Sex differences in the stability of conditioned pain modulation (CPM) among patients with chronic pain. *Pain Medicine*, *14*(11), 1757–1768.

McNeil, D. W., & Rainwater, A. J. (1998). Development of the fear of pain questionnaire-III. *Journal of Behavioral Medicine*, *21*(4), 389–410.

Meagher, M. W., Arnau, R. C., & Rhudy, J. L. (2001). Pain and emotion: Effects of affective picture modulation. *Psychosomatic Medicine*, *63*(1), 79–90.

Metzger, S., Horn-Hofmann, C., & Lautenbacher, S. (2023). Counterirritation by pain inhibits responses to and perception of aversive loud tones. *Perceptual and Motors Skills*, *20*, 1801–1818.

Meyer, K., Sprott, H., & Mannion, A. F. (2008). Cross-cultural adaptation, reliability, and validity of the German version of the pain catastrophizing scale. *Journal of Psychosomatic Research*, *64*(5), 469–478.

Moont, R., Crispel, Y., Lev, R., Pud, D., & Yarnitsky, D. (2011). Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. *Pain*, *152*(7), 1469–1477.

Nahman-Averbuch, H., Nir, R. R., Sprecher, E., & Yarnitsky, D. (2016). Psychological factors and conditioned pain modulation. *The Clinical Journal of Pain*, *32*(6), 541–554.

Nir, R. R., Granovsky, Y., Yarnitsky, D., Sprecher, E., & Granot, M. (2011). A psychophysical study of endogenous analgesia: The role of the conditioning pain in the induction and magnitude of

conditioned pain modulation. *European Journal of Pain*, *15*(5), 491–497.

Nir, R. R., Yarnitsky, D., Honigman, L., & Granot, M. (2012). Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain*, *153*(1), 170–176.

Peterson, R. A., & Reiss, S. (1992). *Anxiety sensitivity index manual* (2nd edn rev. ed.). International Diagnostic Services.

Piché, M., Arsenault, M., & Rainville, P. (2009). Cerebral and cerebrospinal processes underlying counterirritation analgesia. *Journal of Neuroscience*, *29*(45), 14236–14246.

Piché, M., Watanabe, N., Sakata, M., Oda, K., Toyohara, J., Ishii, K., & Hotta, H. (2014). Basal μ-opioid receptor availability in the amygdala predicts the inhibition of pain-related brain activity during heterotopic noxious counter-stimulation. *Neuroscience Research*, *81*, 78–84.

Priebe, J. A., Kunz, M., Morcinek, C., Rieckmann, P., & Lautenbacher, S. (2016). Electrophysiological assessment of nociception in patients with Parkinson's disease: A multi-methods approach. *Journal of the Neurological Sciences*, *368*, 59–69.

Priebe, J. A., Messingschlager, M., & Lautenbacher, S. (2015). Gaze behaviour when monitoring pain faces: An eye-tracking study. *European Journal of Pain*, *19*(6), 817–825.

Quartana, P. J., Campbell, C. M., & Edwards, R. R. (2009). Pain catastrophizing: A critical review. *Expert Review of Neurotherapeutics*, *9*(5), 745–758.

Rhudy, J. L., DelVentura, J. L., Terry, E. L., Bartley, E. J., Olech, E., Palit, S., & Kerr, K. L. (2013). Emotional modulation of pain and spinal nociception in fibromyalgia. *Pain*, *154*(7), 1045–1056.

Rhudy, J. L., Williams, A. E., McCabe, K. M., Nguyêˆ n, M. A. T. V., & Rambo, P. (2005). Affective modulation of nociception at spinal and supraspinal levels. *Psychophysiology*, *42*(5), 579–587.

Roy, M., Lebuis, A., Peretz, I., & Rainville, P. (2011). The modulation of pain by attention and emotion: A dissociation of perceptual and spinal nociceptive processes. *European Journal of Pain*, *15*(6), 641 e1.

Roy, M., Piché, M., Chen, J. I., Peretz, I., & Rainville, P. (2009). Cerebral and spinal modulation of pain by emotions. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(49), 20900–20905.

Squintani, G., Rasera, A., Segatti, A., Concon, E., Bonetti, B., Valeriani, M., & Tinazzi, M. (2021). Conditioned pain modulation affects the N2/P2 complex but not the N1 wave: A pilot study with laser-evoked potentials. *European Journal of Pain*, *25*(3), 550–557.

Staud, R. (2012). Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Review of Neurotherapeutics*, *12*(5), 577–585.

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: Development and validation. *Psychological Assessment*, *7*(4), 524–532.

Taylor, S., Zvolensky, M. J., Cox, B. J., Deacon, B., Heimberg, R. G., Ledley, D. R., Abramowitz, J. S., Holaway, R. M., Sandin, B., Stewart, S. H., Coles, M., Eng, W., Daly, E. S., Arrindell, W. A., Bouvard, M., & Cardenas, S. J. (2007). Robust dimensions of anxiety sensitivity: Development and initial validation of the anxiety sensitivity Index-3. *Psychological Assessment*, *19*(2), 176–188.

Valencia, C., Kindler, L. L., Fillingim, R. B., & George, S. Z. (2013). Stability of conditioned pain modulation in two musculoskeletal pain models: Investigating the influence of shoulder pain intensity and gender. *BMC Musculoskeletal Disorders*, *14*(1), 1–10.

Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: Behavioral effects and neural mechanisms. *NeuroImage*, *47*(3), 987–994.

Yarnitsky, D. (2015). Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain*, *156*, S24–S31.

Yarnitsky, D., Bouhassira, D., Drewes, A. M., Fillingim, R. B., Granot, M., Hansson, P., & Wilder-Smith, O. H. G. (2015). Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain*, *19*(6), 805–806.

Yarnitsky, D., Granot, M., & Granovsky, Y. (2014). Pain modulation profile and pain therapy: Between pro-and antinociception. *Pain*, *155*(4), 663–665.

Youssef, A. M., Macefield, V. G., & Henderson, L. A. (2016a). Pain inhibits pain; human brainstem mechanisms. *NeuroImage*, *124*, 54–62.

Youssef, A. M., Macefield, V. G., & Henderson, L. A. (2016b). Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. *Human Brain Mapping*, *37*(7), 2630–2644.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370.

Zunhammer, M., Geis, S., Busch, V., Eichhammer, P., & Greenlee, M. W. (2016). Pain modulation by intranasal oxytocin and emotional picture viewing—A randomized double-blind fMRI study. *Scientific Reports*, *6*(1), 1–10.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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