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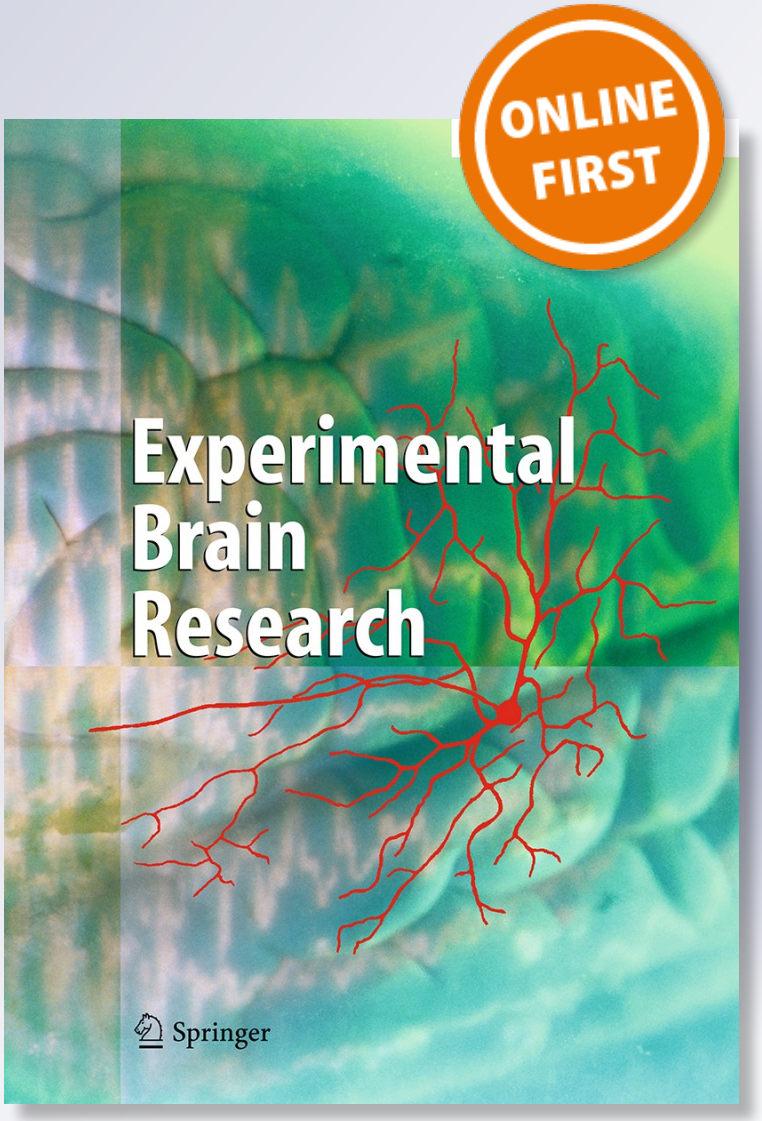


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RESEARCH ARTICLE

# Lack of predictive power of trait fear and anxiety for conditioned pain modulation (CPM)

**Claudia Horn-Hofmann[1] · Janosch A. Priebe[1] · Jörg Schaller[1] · Rüdiger Görlitz[1] · Stefan Lautenbacher[1]**

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**Abstract** In recent years the association of conditioned pain modulation (CPM) with trait fear and anxiety has become a hot topic in pain research due to the assumption that such variables may explain the low CPM efficiency in some individuals. However, empirical evidence concerning this association is still equivocal. Our study is the first to investigate the predictive power of fear and anxiety for CPM by using a well-established psycho-physiological measure of trait fear, i.e. startle potentiation, in addition to two self-report measures of pain-related trait anxiety. Forty healthy, pain-free participants (female: $N = 20$; age: $M = 23.62$ years) underwent two experimental blocks in counter-balanced order: (1) a startle paradigm with affective picture presentation and (2) a CPM procedure with hot water as conditioning stimulus (CS) and contact heat as test stimulus (TS). At the end of the experimental session, pain catastrophizing (PCS) and pain anxiety (PASS) were assessed. PCS score, PASS score and startle potentiation to threatening pictures were entered as predictors in a linear regression model with CPM magnitude as criterion. We were able to show an inhibitory CPM effect in our sample: pain ratings of the heat stimuli were significantly reduced during hot water immersion. However, CPM was neither predicted by self-report of pain-related anxiety nor by startle potentiation as psycho-physiological measure of trait fear. These results corroborate previous negative findings concerning the association between trait fear/anxiety and CPM efficiency and suggest that shifting the focus from trait to state measures might be promising.

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**Keywords** Conditioned pain modulation · Anxiety · Fear · Pain catastrophizing · Startle reflex · Heat pain

## Introduction

Conditioned pain modulation (CPM) is an experimental protocol commonly used to assess endogenous pain modulation in humans. This protocol is based on the diffuse noxious inhibitory controls (DNIC) effect observed in animal models (Le Bars 1979a, b; Dickenson et al. 1980; Villanueva and Le Bars 1994), which is mediated by a spino-bulbo-spinal loop with involvement of the nucleus reticularis dorsalis (Bingel and Tracey 2008). A regular CPM effect is defined as attenuated response to a noxious stimulus ("test stimulus", TS) during application of a second remote noxious stimulus ("conditioning stimulus", CS) compared to a baseline when the TS is presented alone (Yarnitsky et al. 2010).

However, there are considerable inter-individual variations in size and direction of the CPM effect, with some individuals showing substantial pain inhibition and others even presenting with enhanced pain perception (facilitation) during application of the CS (Yarnitsky et al. 2014; Rabey et al. 2015). The clinical significance of the identification of these sub-groups is stressed by findings of an association between inefficient CPM and various chronic pain syndromes (e.g. Lautenbacher and Rollman 1997; Pielsticker et al. 2005; Daenen et al. 2013; see Lewis et al. 2012 for a review) and observations that poor CPM efficiency predicts high postsurgical pain levels (Yarnitsky et al. 2008; Wilder-Smith et al. 2010).

In the search for factors explaining the inter-individual variations in CPM efficiency, negative emotions, i.e. anxiety and fear, have become focus of interest because they

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are known to modulate other descending pain modulatory systems, leading to enhanced pain perception (Wiech and Tracey 2009; Villemure and Schweinhardt 2010). In accord, pain-related fear and anxiety are believed to play a pivotal role for the development and maintenance of chronic pain (e.g., Leeuw et al. 2007). The most discussed psychological variable in this context is pain catastrophizing (Sullivan et al. 1995), which is characterized by anxious cognitions about pain. Catastrophizing is associated with enhanced experimental pain sensitivity as well as more severity of clinical pain (Quartana et al. 2009) and is to date the most frequently investigated affective influence on CPM.

Some studies found a negative correlation (Weissman-Fogel et al. 2008; Goodin et al. 2009; Honigman et al. 2013) between catastrophizing and CPM whereas others reported no association (e.g. Nir et al. 2012; Bouhassira et al. 2013; Lee et al. 2013; Martel et al. 2013; Tsao et al. 2013; Marouf et al. 2014; Grosen et al. 2014). As regards other anxiety and fear parameters, high fear of pain has been found to be associated with less efficient CPM in one study (Geva and Defrin 2013); trait anxiety (STAI; Spielberger et al. 1968) has been found to be related to CPM in one study (Honigman et al. 2013) but unrelated in three others (Granot et al. 2008; Nir et al. 2012; Marouf et al. 2014).

A promising new perspective, which may shed light on these inconsistencies, might be provided by using psychophysiological measures relating to fear and anxiety as such measures indicate more automatic affective reactions and are less susceptible to response bias (Mauss and Robinson 2009). One of the most established paradigms in anxiety research is the startle paradigm. The startle reflex is a defensive whole body reflex, which occurs in response to sudden intense stimuli (Lang et al. 1990). Its most reliable component is a spontaneous eye blink, which can be quantified by surface EMG of the *M. orbicularis oculi* (Blumenthal et al. 2005). This measure has gained importance in anxiety research as its amplitude is reliably potentiated by threatening stimuli and can thus be interpreted as a measure of defensive activation (Lang et al. 1998). Inter-individual differences in the degree of threat-related startle potentiation—when assessed under standard conditions (e.g., presentation of emotional pictures)—have been assumed to be indicative of trait fear (Vaidyanathan et al. 2009a,b).

Based on these considerations we investigated the predictive value of trait fear and anxiety for CPM using (1) startle potentiation by threatening pictures as psychophysiological indicator of trait fear and (2) two established self-report measures relating to pain-specific trait anxiety, namely the Pain Catastrophizing Scale (PCS; Sullivan et al. 1995) and the Pain Anxiety Symptoms Scale (PASS; McCracken et al. 1992). We chose these two latter measures because they capture different aspects of pain-related anxiety: anxious cognitions are targeted by the PCS, whereas the PASS predominantly assesses affective reactions.

Strength of the startle potentiation, PCS score, and PASS score were entered as predictors in a linear regression model with CPM magnitude as criterion. We hypothesized that higher values of trait fear (startle) and pain-specific trait anxiety (questionnaires) would predict lower CPM efficiency or even the reversal from inhibition to facilitation under CPM conditions.

## Methods

### Subjects

Forty healthy, pain-free volunteers (female: $N = 20$; age: $M = 23.62$ years; SD $= 3.4$) were recruited by advertisement at the University of Bamberg; 10 subjects were students of psychology. None suffered from severe acute or chronic illness, mental disorders, or facial paralysis. Because contacts are known to enhance blink frequency, persons wearing contacts were asked to wear their glasses instead during the experimental session. None had taken any CNS affecting medication in the last 7 days. Prior to the test session subjects gave written informed consent. After testing, some of the subjects were reimbursed for participation; the others received course credits (psychology students). The experimental procedure was approved by the local ethics committee.

### Procedure

Figure 1 illustrates the procedure of our study. After giving their informed consent, participants completed the two blocks, i.e. startle paradigm and CPM procedure, in counter-balanced order. There was a 5 min break between the two blocks. In the end of the experimental session, participants completed the German version of the Pain Anxiety Symptoms Scale (PASS) (McCracken et al. 1992; German version: Walter et al. 2002) and the Pain Catastrophizing Scale (PCS) (Sullivan et al. 1995). This order was chosen to avoid any bias induction and priming effects in the startle and CPM protocol due to reading the pain- and emotion-related items of the PASS and PCS. The whole experiment lasted about 90 min.

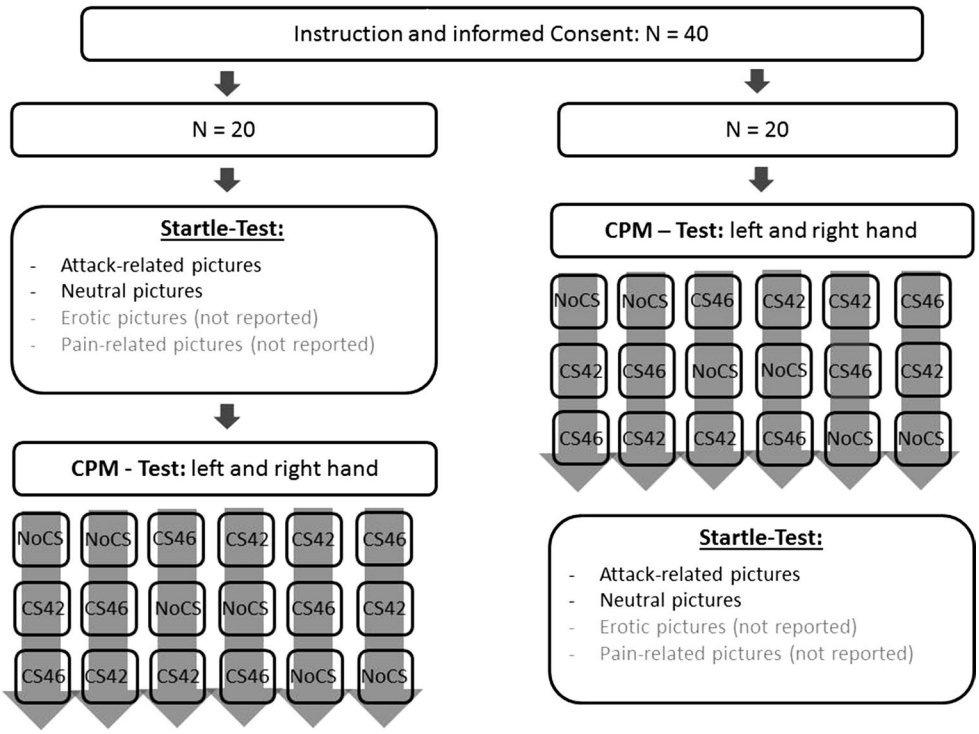


**Fig. 1** Overview of the experimental procedure

## Assessment of predictor variables

### *Startle potentiation*

*General principle of the startle paradigm* We applied the classical paradigm for measuring affective startle modulation, i.e. presentation of affective pictures (Vrana et al. 1988). In this paradigm the startle reflex is elicited by short noise bursts and recorded by surface EMG of the *M. orbicularis oculi* (Blumenthal et al. 2005) while the participant views pictures of negative, positive and neutral valence. It has been shown that in reference to neutral pictures the startle amplitude is potentiated by negative and inhibited by positive pictures which is interpreted as activation of the defensive and appetitive system, respectively (Vrana et al. 1988; Lang et al. 1998). Startle potentiation by negative pictures—a psycho-physiological index of trait fear (Vaidyanathan et al. 2009a, b)—was used as predictor for CPM efficiency in our study.

*Affective picture presentation* Affective pictures were selected from the International Affective Picture System (IAPS; Lang et al. 2005). We used four picture categories displaying diverse affective content: Erotic scenes to represent positive valence, attack scenes and pain-related scenes to represent negative valence, and neutral scenes as reference category. Startle potentiation was defined as the difference in participants' startle response to attack pictures in comparison to neutral pictures (termed as "Δstartle"). The two other picture categories (pain-related and erotic pictures) were applied to investigate affective priming effects as part of another study not reported here and served in the present study as filler trials. For each valence category, we chose six representative pictures, resulting in a total of 24 pictures.[1] Pictures were presented in blocks of the same valence category (four blocks altogether). Each picture was shown for 55 s and was followed by a 10 s rating period (valence and arousal were rated, data not reported here), resulting in a total duration of 6.5 min for each valence block. The sequence of pictures within each category was randomized once and then set for all subjects, while the sequence of categories was randomized across subjects.

*Startle noise presentation* To elicit the blink reflex, we applied brief acoustic stimuli (white noise bursts), 50 ms in duration, with an intensity of 105 dB binaurally over headphones superimposed over constant white noise of 68 dB as masking background. In keeping certain restrictions (two to four tones per minute, first tone presentation after 3–15 s in each minute, inter-stimulus interval of 12 s or more, no

[1] The IAPS identification numbers were as follows: *Erotic pictures*: 4652, 4659, 4660, 4670, 4687, 4695; *Attack pictures*: 1120, 1300, 1525, 6250.1, 6300, 6510; *Pain-related pictures*: 3010, 3180, 3261, 3350, 9253, 9410; *Neutral pictures*: 2200, 5120, 5534, 7002, 7031, 7150.

tones during the rating period), startle tone presentations were timed in random intervals to be unpredictable. There were 18 tone presentations in each valence block.

*EMG recording and analysis* Startle blinks were measured by recording surface EMG activity on the *M. orbicularis oculi* beneath the right eye (recording device: SIGMA Plpro/Type Databox DB 36). The signal was sampled at a rate of 512 Hz. EMG signals were analyzed offline using the program "Vision Analyzer" (Brain Products, Munich). Analysis incorporated filtering of the signals (50 Hz notch filter, 20 Hz high-pass filter and 256 Hz low-pass filter), as well as rectifying and integrating the signal. The rectifying and integration procedures were executed over a time interval from 0 to 250 ms after startle noise onset. Responses with their peak not occurring between 30 and 100 ms after stimulus onset were excluded (automatic selection). Furthermore, trials with responses that did not fit the typical shape of a startle response or trials without startle response at all (visual inspection) were not considered for further analysis. Startle amplitude was defined as voltage difference between the averaged baseline and voltage peak within a time frame of 30–100 ms after noise onset. Our algorithm for the recording and analysis of startle responses was based on the recommendations by Blumenthal et al. (2005) and has been repeatedly applied in previous studies (Horn et al. 2012a, b; Horn-Hofmann and Lautenbacher 2015).

Mean values of startle amplitude were calculated for the two picture categories "attack" and "neutral" by averaging the valid trials. Finally, the difference in startle amplitude between attack and neutral pictures was determined for each participant in order to create a measure for the strength of the startle potentiation (termed as "Δstartle").

*Self-report measures*

In addition to startle potentiation as psycho-physiological measure of trait fear, we included two established self-report measures relating to pain-specific trait anxiety, i.e. German versions of the Pain Catastrophizing Scale (PCS; Sullivan et al. 1995)[2] and the Pain Anxiety Symptoms Scale (PASS; McCracken et al. 1992; German version: Walter et al. 2002), as predictors of CPM efficiency. Both questionnaires have been repeatedly used in our lab (Lautenbacher et al. 2009, 2010; Baum et al. 2011; Dimova et al. 2013) and have demonstrated sufficient similarity to the original English versions as regards internal consistency and intercorrelations (Baum et al. 2011).

*Pain Catastrophizing Scale (PCS)* The PCS (Sullivan et al. 1995) was developed as a measure of 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. For further analyses, we used the combined sum score of the PCS. The PCS showed good internal consistency: Cronbach's $\alpha = .95$ (Sullivan et al. 1995).

*Pain Anxiety Symptoms Scale (PASS)* The PASS is designed to measure fear of pain across cognitive, behavioral, and physiological domains. It is composed of 4 subscales: cognitive anxiety, escape/avoidance, fearful appraisal, and physiological anxiety. The items are rated on a 6-point scale. For further analyses, we used the sum score (40 items) of the PASS. PASS total score demonstrated good internal consistency: Cronbach´s $\alpha = .94$ (McCracken et al. 1992).

**Assessment of CPM (criterion)**

CPM was induced using hot water (conditioning stimulus); test stimuli were heat pulses delivered by a contact thermode. The CPM assessment comprised three conditions amongst which the intensity of the CS was varied (no stimulation vs. non-painful stimulation vs. painful stimulation) and pain ratings both of the conditioning stimulus (CS) and test stimulus (TS) were taken (see Fig. 1).

*Stimulation apparatus*

Heat stimuli which served as TS were generated and applied by a computer-controlled contact-heat evoked potential stimulator (CHEPS, Medoc, Israel) with a round 27 mm-diameter surface thermode. Additionally, a pair of thermocouples is embedded in the lamination which provides an assessment of the skin temperature at the stimulated area.

A water bath apparatus was used for tonic heat stimulation which served as conditioning stimulus (CS). The water temperature was controlled with a thermostat (Variostat, Huber), and the water was stirred with a force and suction pump to avoid regional temperature difference within the water bath and heat layers of different intensities around the immersed hand.

*Test stimuli (TS)*

Contact-heat stimuli with a fixed temperature of 41 °C alternatively 48 °C served as TS. The 48 °C stimuli were

[2] We translated the PCS into German, using a standard "forward–backward" procedure. Only if the resulting backward English version was very similar to the original version according to the evaluation of an English native speaker, translation accuracy was considered sufficient.

intended to be painful while the 41 °C stimuli were intended to be hot and non-painful alternatively at the most slightly painful. We introduced a non-painful TS in order to control for CPM-like effects on non-noxious TS, which has repeatedly been reported (Lautenbacher and Rollman 1997; Lautenbacher et al. 2002). All TS had a baseline temperature of 35 °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.

*Conditioning stimuli (CS)*

Immersion of one hand into a water bath served as conditioning stimulation. The total duration of the CS was three minutes. All participants ran through three CS conditions: no CS, 42 °C water temperature (intended to be non-painful) and 46 °C water temperature (intended to be painful). We included a non-painful condition (42 °C) in order to control for attentional effects and for potential pain inhibition due to mere somatosensory stimulation.

*Exact procedure*

Each of the three CS conditions was realized two times in each participant to increase the reliability of the findings. In one run the left hand was immersed into the water bath while the TS were applied to the right arm. In the second run the right hand was immersed into the water bath while the TS were applied to the left arm. This results in a total of 6 CPM blocks (2 with no CS applied, 2 with a 42 °C CS and two with a 46 °C CS). A series of 18 TS (9× non-painful 41 °C and 9× painful 48 °C) was applied in each of the six blocks. The sequence of 41 °C and 48 °C stimuli was randomized once and then set for all participants. Inter-stimulus intervals (ISI) for the TS were between 8 and 11 s. All TS were applied to participants' volar site of the forearm while the thermode was held by the experimenter, who slightly changed thermode position after each TS to prevent receptor fatigue (Granovsky et al. 2008).

In the 42 °C and 46 °C CS conditions, TS stimulation started immediately after having immersed the hand into the water bath. As long as TS were applied, the hand remained in the water bath (3 min). The order of the three CS conditions as well as the order of body side used for CS stimulation (right/left hand) was balanced between participants. Furthermore, breaks of 5 min were taken between the single CPM blocks in order to avoid carry-over effects.

Participants were asked to verbally rate the perceived temperature intensity elicited by each TS on a numerical rating scale from 0 ("no sensation") to 100 ("highest pain imaginable") with 50 representing "beginning pain sensation". A high tone 4 s after onset of the TS signaled participants to express their rating. As a manipulation check participants were also asked to rate the CS intensity on the same scale once per minute; this rating was signaled by a low tone.

*Calculation of CPM scores*

Rating data both of the CS and the TS were averaged across stimulation sites (left/right arm). The averaged ratings were kept for further analyses. For the purpose of correlation and regression analyses (see below) CPM magnitude scores were calculated: CPM magnitude was defined as the difference between TS ratings in the No CS condition and the 42 °C alternatively CS 46 °C CS condition. Thus, four CPM magnitude scores resulted in our study (CS 42 °C/TS 41 °C, CS 42 °C/TS 48 °C, CS 46 °C/TS 41 °C, CS 46 °C/TS 48 °C) which were used for all main analyses.

In addition, we also averaged these four separate CPM scores in order to get one robust measure of CPM directionality ($CPM_{av}$) indicating predominantly inhibition or facilitation for each participant. This composite score was however only used for descriptively analyzing the distribution of CPM-inhibitors or CPM-facilitators ("CPM-type") in our sample. Participants with $CPM_{av}$ values >0 (TS rating with CS < TS rating without CS) were defined as inhibitors while participants with $CPM_{av}$ values <0 were defined as facilitators (TS rating with CS > TS rating without CS).

**Statistical analysis**

As a manipulation check, CS ratings were subjected to a repeated-measurements ANOVA with the factors CS condition (42 °C vs. 46 v) and time (1st vs. 2nd vs. 3rd min). Furthermore, in order to explore the CPM effect, TS rating data were subjected to a repeated- measurements ANOVA with the factors TS intensity (41 °C vs. 48 °C) and CS condition (no CS vs. 42 °C vs. 46 °C). For post hoc testing of the ANOVAs paired-sample t-tests were used. As estimates of effect size, partial eta squared ($\eta^2$)(ANOVA) alternatively $R^2$ (regression) are reported.

In order to test the prediction of CPM magnitude by trait fear/anxiety, four standard regression models were computed in which respectively one of the CPM scores (CS 42 °C/TS 41 °C, CS 42 °C/TS 48 °C, CS 46 °C/TS 41 °C and CS 46 °C/TS 48 °C) served as criterion while the PCS score, PASS score and Δstartle were entered as predictors.

Furthermore, for the purpose of testing the direction of the relationship among the predictors and among the criterion variables, correlations between PCS, PASS and Δstartle alternatively between the CPM scores (CS 42 °C/

**Table 1** Means (*M*) and standard deviations (SD) of the pain ratings of the CS (0–100) for each minute of stimulation and averaged (av) across the 3 min of stimulation (main effect CS condition)

| | | CS condition | | | | | |
|---|---|---|---|---|---|---|---|
| | | No CS | | 42 °C | | 46 °C | |
| | | *M* | SD | *M* | SD | *M* | SD |
| Minute of stimulation | 1 | – | – | 28.8 | 9.9 | 59.6 | 14.0 |
| | 2 | – | – | 27.8 | 9.8 | 61.5 | 15.7 |
| | 3 | – | – | 26.6 | 11.4 | 64.5 | 16.3 |
| | av | – | – | 27.7 | 9.8 | 61.9 | 15.0 |

TS 41 °C, CS 42 °C/TS 48 °C, CS 46 °C/TS 41 °C, CS 46 °C/TS 48 °C (Pearson) and CPM-type (biserial)) were calculated.

Significance level was set $\alpha = 5\ \%$.

## Results

### Sample characteristics

One male participant had to be excluded from further analyses due to technical problems. Mean PCS score of the remaining 39 subjects (20 female) was $M = 20.31$ (SD = 6.75), mean PASS score was $M = 90.62$ (SD = 24.81). Mean difference between the startle response to threatening pictures in comparison to neutral pictures (Δstartle) was $M = .36$ µV ($SD = 8.26$ µV). Twenty-two participants were CPM-inhibitors (mean $CPM_{av}$ $M = 7.73$, SD = 5.60), while 17 were CPM-facilitators (mean $CPM_{av}$ $M = -3.36$, SD = 2.48).

### Manipulation check: CS ratings

Table 1 provides descriptive data of the CS ratings. The ANOVA for the CS pain ratings revealed a significant main effect of CS condition, $F(1,37) = 245.73$, $p < .001$, $\eta^2 = .886$, which was based on overall lower ratings for the 42 °C CS compared to the 46 °C CS. As expected, the 42 °C CS was rated as non-painful (<50), whereas the 46 °C CS was rated as mainly painful (>50). There was also a significant two-way interaction of CS condition and time, $F(2,74) = 13.27$, $p < .001$, $\eta^2 = .259$. Ratings of the CS in the 46 °C condition were higher in the 2nd compared to the 1st min of CS stimulation, $t(38) = 2.022$, $p = .025$ (one-tailed), and in the 3rd compared to the 2nd and 1st min of CS stimulation, $t(38) = 4.36$, $t(38) = 4.14$, $p$'s < .001 (one-tailed), while all other comparisons were not significant (all $p$'s > .10). Thus we observed—as to be expected—the typical pattern of sensitization only for painful heat stimulation.

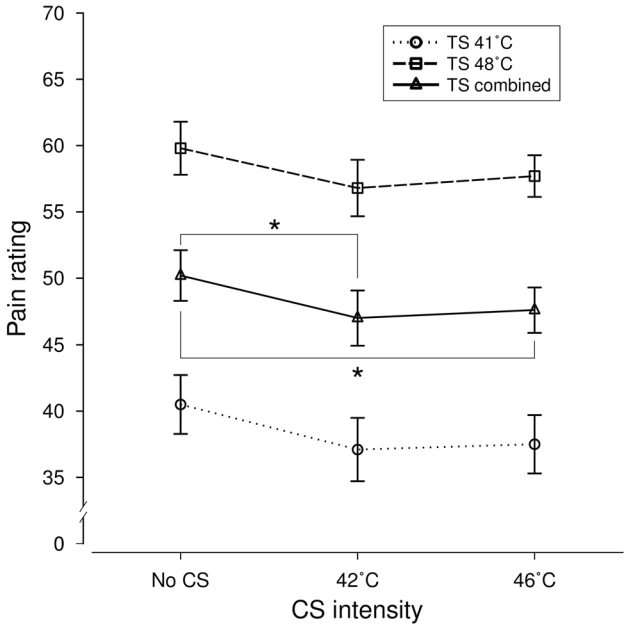


**Fig. 2** Means and SE of the TS ratings [41 °C, 48 °C and averaged over both intensities (main effect CS condition)] in the three CS conditions (*lines*) are illustrated

### CPM effect

The ANOVA for the TS pain ratings revealed a significant main effect of CS condition ($F(1,38) = 4.26$, $p = .024$, $\eta^2 = .101$). In order to test the latter, the pain ratings were combined across TS intensities. *T* tests revealed significantly higher TS pain ratings in the No-CS condition compared to the 42 °C CS condition ($t(38) = 2.96$, $p = .003$; one-tailed) and compared to the 46 °C CS condition ($t(38) = 2.96$, $p = .035$; one-tailed) while there was no difference between the 42 °C and 46 °C CS condition ($t < 1$). Additionally, the main effect of TS intensity ($F(1,38) = 159.70$, $p < .001$, $\eta^2 = .808$) was significant with overall higher pain ratings for the 48 °C TS compared to the 41 °C TS. The interaction of CS condition and TS intensity was not significant ($F < 1$). Thus, across

**Table 2** Correlation coefficients between the CPM scores in each condition (CS 42 °C/TS 41 °C, CS 42 °C/TS 48 °C, CS 46 °C/TS 41 °C, CS 46 °C/TS 48 °C, and CPM-type) and PCS, PASS and Δstartle (above diagonal) and between the CPM scores among themselves and PCS, PASS and Δstartle among themselves (below diagonal)

| | 42/41 | 42/48 | 46/41 | 46/48 | CPM-type | PCS | PASS | ΔStartle |
|---|---|---|---|---|---|---|---|---|
| 42/41 | | | | | | −.172 | −.100 | −.077 |
| 42/48 | **.447** | | | | | −.171 | −.057 | .078 |
| 46/41 | **.702** | **.403** | | | | −.043 | −.077 | −.170 |
| 46/48 | **.473** | **.512** | **.565** | | | −.184 | −.157 | .112 |
| CPM-type | **.511** | **.701** | **.650** | **.675** | | −.010 | .090 | .021 |
| PCS | | | | | | | | |
| PASS | | | | | | **.564** | | |
| ΔStartle | | | | | | .167 | .137 | |

Bold numbers mark significant correlations ($p < .05$)

TS-intensities CPM-effects were found both for the CSs of 42 °C and the 46 °C while the strength of the CPM-effects was similar for both CS intensities. Figure 2 illustrates the results of this analysis.

### Prediction of CPM magnitude by trait fear/anxiety (regression analyses)

Regression analyses revealed no significant models for any of the CPM conditions: CS 42 °C/TS 41 °C ($R^2 = .032$, $F < 1$), CS 42 °C/TS 48 °C ($R^2 = .042$, $F < 1$), CS 46 °C/TS 41 °C ($R^2 = .032$, $F < 1$) and CS 46 °C/TS 48 °C ($R^2 = .060$, $F < 1$).

Thus, there was no substantial prediction of the CPM magnitude neither by the self-report measures of pain-specific trait anxiety (PCS, PASS) nor by the psycho-physiological measure of trait fear (Δstartle) ($p$'s < .10).

### Relationship among predictors and criterion variables (correlation analysis, see Table 2)

While PCS and PASS intercorrelated significantly as expected ($p < .001$), there were no significant correlations between PASS/PCS as self-report measures of trait anxiety and Δstartle as psycho-physiological measure of trait fear ($p$'s > .10). Additionally, the four CPM scores/CPM-type correlated significantly among themselves ($p$'s < .05). Table 2 provides an overview of the correlation coefficients.

## Discussion

The explanatory power of trait fear and anxiety for inter-individual differences in CPM efficiency has been much debated due to inconsistent findings. Our study aimed at contributing to clarify this issue by using for the first time a psycho-physiological measure, i.e. the startle reflex, in addition to self-report measures. We hypothesized that higher trait fear (indicated by threat-related startle potentiation) and higher pain-specific trait anxiety (indicated by PCS and PASS scores) would predict reduced CPM efficiency.

On average, we detected an inhibitory CPM effect in our sample: Pain ratings of heat pulses, which served as test stimuli (TS), were reduced during application of the hot water bath, which served as conditioning stimulus (CS). However, there were considerable inter-individual differences with around 45 % of the sample providing higher instead of lower TS ratings during the CPM task compared to baseline. The observation that CPM may lower pain ratings, suggesting the activation of pain inhibitory processing, but may also increase pain ratings, suggesting the opposite effect, namely the activation of pain excitatory processes, is in line with other studies conducted with pain-free participants (O'Neill et al. 2014; Rabey et al. 2015). Even more important for the present purpose, the variance of CPM effects was definitely large enough to allow for identifying covariates of these effects such as trait fear or anxiety.

The non-significant correlations between startle as objective measure of trait fear and the two self-report measures of pain-related trait anxiety are in line with previous findings (Horn-Hofmann and Lautenbacher 2015). This finding confirms the theoretical and empirical distinctness of our predictors and speaks against any redundancy of these variables, thus stressing the importance of such multi-method approaches. However, our regression analyses revealed that CPM efficiency could be predicted neither by the strength of startle potentiation nor by self-reported pain catastrophizing and pain anxiety.

Concerning pain catastrophizing, some other researchers found lower CPM efficiency being related to higher PCS scores (Weissman-Fogel et al. 2008; Goodin et al. 2009; Honigman et al. 2013). However, our negative findings are in line with the majority of previous studies (e.g. Nir et al. 2012; Bouhassira et al. 2013; Lee et al. 2013; Martel et al. 2013; Tsao et al. 2013; Marouf et al. 2014; Grosen et al. 2014), thus suggesting that the established association of pain catastrophizing and pain sensitivity as well as clinical pain (Sullivan et al. 2001; Kunz et al. 2008; Quartana

et al. 2009) is not primarily due to deficient CPM in high catastrophizers.

The relationship between pain anxiety as assessed by the PASS and CPM has to our knowledge only been investigated once before in a pediatric sample (Tsao et al. 2013) using the CPASS (Pagé et al. 2010), also with negative results. For not pain-specific trait anxiety assessed by the STAI (Spielberger et al. 1968), negative findings also prevail (Granot et al. 2008; Nir et al. 2012; Grosen et al. 2014) with only one study reporting associations with CPM (Honigman et al. 2013).

To our knowledge, the predictive value of startle potentiation for the CPM efficiency was investigated for the first time in our study. This is somewhat surprising given the great interest in associations between CPM and fear/anxiety and the high reputation of the startle paradigm in anxiety research (Grillon 2008). Important advantages of this psycho-physiological measure over self-report are its high sensitivity to affective reactions—even to those which stay below the level of awareness—and its low susceptibility to response biases. The startle reflex is interpreted as indicator of defensive activation (Lang et al. 1998) and the individual strength of startle potentiation by threatening stimuli has been linked to the trait fear level of a person (Vaidyanathan et al. 2009a, b). As individuals with high trait fear are probably more likely to show pronounced fearful reactions to painful stimuli and these might interfere physiologically and psychologically with endogenous pain inhibition, it seems compelling to consider threat-related startle potentiation as good predictor of CPM. However, CPM efficiency could also not be predicted by the strength of startle potentiation in response to threat.

Our study aimed at clarifying the role of trait fear and anxiety for CPM using a range of methodological approaches, i.e. self-report measures of pain anxiety and pain catastrophizing and startle potentiation as psycho-physiological measure of trait fear. Neither the two questionnaire measures nor startle potentiation proved to be associated with CPM. These multi-method results add substantially more weight to the already prevailing negative findings concerning the relevance of trait anxiety or fear for explaining inter-individual variations in CPM efficiency. Thus, the well-documented associations between such trait variables and experimental pain sensitivity (e.g., Tang and Gibson 2005; Kunz et al. 2008; Quartana et al. 2009; Farmer et al. 2013) as well as their role in the development of clinical pain (e.g., Leeuw et al. 2007; Linton et al. 2011) seem to depend largely on mechanisms other than CPM efficiency.

Despite this negative evidence concerning trait fear and anxiety, it may well be that CPM is altered by anxious or fearful states. The assumption that acute top-down influences of cognitive and emotional processes are relevant also for CPM has been corroborated by the observation that a placebo/nocebo manipulation can alter the CPM effect (Nir et al. 2012). Interestingly, a psychosocial stress manipulation which also led to increases in state anxiety reduced the CPM effect in a recent study (Geva et al. 2014). Thus, the effects of experimentally induced fear and anxiety remain to be investigated. Considering previous research, divergent effects of fear versus anxiety on CPM might be expected: Rhudy and Meagher (2000) induced a state of fear or anxiety and found that pain sensitivity was decreased by fear but increased by anxiety. These findings might be explained by different evolutionary functions of these two emotional states. Fear is elicited by a specific imminent threat and requires rapid action, i.e. fight or flight behavior, which can be accomplished more efficiently when bodily signals like pain are shut down for the moment (Bolles and Fanselow 1980). In contrast, anxiety is triggered in situations of uncertain threat where heightened vigilance to bodily signals like pain might be crucial in order to enable rapid detection of danger. Building on this reasoning, we propose that activated endogenous pain inhibition might be functional during states of fear but disadvantageous during states of anxiety. Thus, we would expect the CPM effect to be reduced by state anxiety and either not altered or even slightly enhanced by state fear.

## Limitations

Several features of our study might result into limitations worth mentioning. First, CPM was intentionally not limited to painful intensities of the conditioning stimulus and the test stimuli to study the specificity of effects; both conditioning stimulus intensities, painful and non-painful, reduced pain ratings of both test stimulus intensities. This is, however, not surprising given that previous research has already reported CPM-like effects for subjectively non-painful conditioning stimuli and test stimuli (e.g. Lautenbacher et al. 2002). Second, it might have been informative to include other questionnaires assessing general trait anxiety or trait fear in addition to the two pain-specific questionnaires even if this had increased the number of statistical tests. Finally, we used hot water as CS whereas most other studies assessing the relationship between psychological variables and CPM used the cold pressor test. This decision was based on the consideration that hot water elicits moderate to strong pain sensations and reliable CPM (e.g., Lautenbacher et al. 2008) effects without triggering as much cardiovascular stress as the cold pressor pain, which helps to avoid the unwanted merge of pain inhibitory systems (DNIC, blood pressure and stress-related analgesia). Although the modality of the TS seems to be more crucial in this context (Nahman-Averbuch et al.

2015), differences in CS modality might also contribute to divergent results. As suggested by Yarnitsky et al. (2015), researchers should ideally use more than one CPM paradigm in future studies in order to accommodate effects of stimulus modality.

## Conclusions

The proven clinical relevance of insufficient CPM for chronic and postoperative pain has fostered interest in psychological factors which might explain this low efficiency of CPM in some individuals. Variables relating to pain-specific or general trait anxiety and fear have often been discussed as predictors of CPM; however, evidence corroborating this association is still scarce. Our study was the first to investigate the predictive value of startle potentiation as psycho-physiological indicator of trait fear for CPM. However, neither the strength of startle potentiation nor self-reported pain anxiety and pain catastrophizing predicted CPM efficiency, reinforcing doubts that trait measures of fear and anxiety are of relevance for this kind of pain inhibition. However, this does not exclude that state anxiety and fear alter CPM, which remains to be investigated in future research.

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**Compliance with ethical standard**

**Conflict of interest** There are no conflicts of interest.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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