

# Impaired pain-related threat and safety learning in patients with chronic back pain

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## Abstract

Pain-related learning mechanisms likely play a key role in the development and maintenance of chronic pain. Previous smaller-scale studies have suggested impaired pain-related learning in patients with chronic pain, but results are mixed, and chronic back pain (CBP) particularly has been poorly studied. In a differential conditioning paradigm with painful heat as unconditioned stimuli, we examined pain-related acquisition and extinction learning in 62 patients with CBP and 61 pain-free healthy male and female volunteers using valence and contingency ratings and skin conductance responses. Valence ratings indicate significantly reduced threat and safety learning in patients with CBP, whereas no significant differences were observed in contingency awareness and physiological responding. Moreover, threat learning in this group was more impaired the longer patients had been in pain. State anxiety was linked to increased safety learning in healthy volunteers but enhanced threat learning in the patient group. Our findings corroborate previous evidence of altered pain-related threat and safety learning in patients with chronic pain. Longitudinal studies exploring pain-related learning in (sub)acute and chronic pain are needed to further unravel the role of aberrant pain-related learning in the development and maintenance of chronic pain.

**Keywords:** Chronic back pain, Chronic pain, Pain-related conditioning, Acquisition learning, Extinction learning

## 1. Introduction

Acute pain signals tissue damage and potential threat to an organism's integrity. It is therefore essential to differentiate between situations or cues predicting harm and those predicting safety.<sup>64</sup> In chronic pain, however, imminent physical threat is often missing, and an imbalance between threat and safety learning might promote maladaptive behavioral and emotional responses (eg, excessive avoidance behavior and pain-related fear). Over time, these can lead to physical deconditioning and

affective distress, which in turn can drive the development or maintenance of chronic pain, as, for instance, described in the fear-avoidance model of pain.<sup>65</sup>

While pain-related and fear learning have been thoroughly investigated in healthy participants,<sup>26,44,46,59</sup> mechanisms underlying their role in chronic pain is still insufficiently understood. Pain-related or fear learning is usually investigated using neutral stimuli as conditioned stimuli (CS), which predict the delivery (CS<sup>+</sup>) or absence (CS<sup>-</sup>) of aversive stimuli (= unconditioned stimuli [US]). Behavioral and physiological responses to CS were collected to quantify acquisition and extinction of conditioned responses.<sup>43</sup> First studies in patients with chronic pain have suggested alterations in pain-related learning.<sup>22,46</sup> For instance, impaired differential fear and contingency learning has been found in several pain conditions, such as fibromyalgia, chronic hand pain, or chronic neck pain.<sup>23,30,47,48</sup> Of interest, these patient groups showed not only impaired threat learning but also reduced safety learning. Patients with irritable bowel syndrome, on the other hand, displayed enhanced safety learning compared with healthy volunteers.<sup>28</sup>

Although chronic back pain (CBP) is amongst the most common types of chronic pain, surprisingly few studies have investigated pain-related learning in this patient group so far. Two studies reported enhanced conditioned muscular responses in patients with CBP compared with those in healthy volunteers, which either persisted<sup>57</sup> or disappeared<sup>34</sup> after extinction training. A recent study found reduced differential learning in patients with persistent neck pain, with lower CS<sup>+</sup> and higher CS<sup>-</sup> pain expectancies compared with those in healthy individuals, but comparable extinction rates.<sup>23</sup> One reason for these inconsistent findings might be the sample sizes of these studies, which were rather small (ie, N = 30 or lower) for an investigation in a highly heterogeneous clinical population.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site ([www.painjournalonline.com](http://www.painjournalonline.com)).

PAIN 163 (2022) 1560–1570

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<http://dx.doi.org/10.1097/j.pain.0000000000002544>

In this study, we examined potential alterations in pain-related learning in a sample of 62 patients with nonspecific CBP in comparison with 61 age- and sex-matched healthy volunteers (= healthy controls [HCs]). We used a differential conditioning paradigm to investigate group differences in acquisition and extinction of associations between visual cues as CS and phasic heat pain stimuli serving as US. To elucidate both, emotional and cognitive aspects of pain-related threat and safety learning, we obtained behavioral data (CS valence ratings, US-CS contingency ratings), as well as physiological data (electrodermal responses). We hypothesized that patients with CBP show impaired pain-related differential learning in comparison with HCs. More specifically, we assumed that this entails alterations in both pain-related threat (CS<sup>+</sup>) and safety (CS<sup>-</sup>) learning. Furthermore, we conducted exploratory analyses on the effects of psychological trait and state variables and pain-related parameters on learning.

## 2. Methods

### 2.1. Participants

Based on effect sizes reported in previous patient studies investigating pain-related learning,<sup>47,49</sup> we calculated a required sample size of  $n = 63$  per group to detect group differences in differential acquisition learning. Calculations were performed using the *pwr* package in R<sup>12</sup> with the following parameters:  $d = 0.5$ ,  $\alpha = 0.05$ , and  $1 - \beta = 0.80$ .

Sixty-seven patients with nonspecific CBP and 74 healthy volunteers (HCs) participated in a 2-day differential conditioning paradigm. Participants were recruited using local advertisements or through the local back pain center at the University Hospital Essen (U.B.) and a structured telephone screening. General inclusion criteria for both groups were as follows: age older than 18 and younger than 80 years, normal or corrected-to-normal vision, no acute infection, no participation in trials using investigational medicinal products within the last 3 months, and no alcohol consumption within the past 24 hours (assessed through self-report). Patients interested in study participation were screened for eligibility through telephone screening by trained study personnel. Further on-site screening of eligible patients was performed by physicians specialized in pain medicine (U.B. and J.K.-B.) through medical history and clinical examination. Patients experiencing nonspecific CBP (ie, exclusion of specific spinal pathologies, nerve root, postsurgical, or post-traumatic pain) were included in the study. In accordance with the European guidelines on CBP, the definition of CBP was given as remitting or persistent pain >12 weeks.<sup>1</sup> Further exclusion criteria for the patients with CBP comprised a history of malignant diseases within the past 5 years, severe mental disorders (eg, major depression, psychosis, and schizophrenia), as well as opioid treatment with >100 mg of morphine equivalent per day. Any treatment had to be kept stable in the period of 3 weeks before study participation. Exclusion criteria for HCs comprised actual or history of internal, neurological, mental, pain-related, or dermatological diseases or cancer, regular consumption of recreational drugs, or intake of pain medication within the past 24 hours, all based on self-report. Five patients and 13 HCs had to be excluded from the analysis. In 3 patients with CBP and 2 HCs, pain intensity ratings did not reach the envisaged baseline level during calibration. In 2 patients with CBP and 1 HC, the mean pain intensity ratings remained below 30 on a 0 to 100 Visual Analogue Scale (VAS) during acquisition training. Two HCs showed clinically relevant levels of anxiety or depression, as assessed with the Depression Anxiety Stress Scale questionnaire (cutoff values: anxiety = 6, stress = 10, and depression = 10). Furthermore, 8 HCs were excluded because

of protocol violation (eligibility after inclusion). The final data analysis was therefore based on 62 patients with CBP (18 male patients, age:  $34.56 \pm 13.37$  (M  $\pm$  SD) years) and 61 HCs (21 male individuals, age:  $33.80 \pm 11.83$  years). Demographic information of the analyzed sample and pain-related patient characteristics are listed in **Table 1**.

The study was approved by the local Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (University of Duisburg-Essen, Germany; 16-7248-BO). All participants gave their informed oral and written consent to participate, including their consent to publish, and were free to withdraw from the study at any time. Participants received a small monetary reimbursement for their study participation.

### 2.2. Experimental paradigm and procedures

The study was performed on 2 consecutive days. On the first day, participants filled in questionnaires assessing demographic information, anxiety, depression, stress, and pain-related psychological processing (see self-report questionnaires). We then determined the individual heat pain threshold at the location of stimulus application (left volar forearm, approximately 12 cm proximally from the wrist) and performed a calibration procedure to determine the temperature level that induced a pain intensity of 70 on a 0 to 100 VAS ("How painful was this stimulus?", anchors: 0 = "not painful at all" and 100 = "unbearably painful") using established procedures.<sup>19</sup>

To acquire skin conductance responses (SCRs), 2 electrodes were attached to the thenar and hypothenar surfaces of the participant's nondominant hand (for details, see SCRs). Participants were then asked to rate their level of arousal and pain-related fear on a 0 to 100 VAS (arousal: "How tense are you right now?" anchors: 0 = "not tense at all" and 100 = "very tense"; pain-related fear: "How fearful are you regarding the upcoming pain stimulus?" anchors: 0 = "not fearful at all" and 100 = "extremely fearful").

Please note that data were acquired as part of a larger pharmacological trial with a double-blind hydrocortisone/placebo intervention on the second examination day to investigate the effects of pharmacologically induced stress on the recall and reinstatement of former acquired threat and safety associations. Results pertaining to the effect of the pharmacological intervention (day 2) will be reported elsewhere. Within this article, we report only the results of the first examination day.

### 2.3. Differential conditioning paradigm

We used an established differential conditioning paradigm<sup>56</sup> comprising 3 experimental phases, ie, habituation phase, acquisition training, and extinction training (**Fig. 1**). During acquisition training, 2 geometrical figures served as cues predicting the delivery (CS<sup>+</sup>) or absence (CS<sup>-</sup>) of a painful heat stimulus (US). In the consecutive extinction training, only CS were presented to examine extinction learning. Physiological responses to the CS and US were monitored using continuous skin conductance recordings.

#### 2.3.1. Habituation phase/familiarization

In the initial habituation phase, 6 CS (3 CS<sup>+</sup>, 3 CS<sup>-</sup>; duration: 9 seconds), but no US were presented. After each CS presentation, participants provided a valence rating (see below for details).

#### 2.3.2. Acquisition training

After that, participants were informed about a potential association of CS and US but not about the exact contingencies between

**Table 1**  
**Demographic information and patient characteristics.**

	CBP group (N = 62)	HC group (N = 61)
Demographic data		
Age in years, M ± SD [range]	34.6 ± 13.4 [16–69]	33.8 ± 11.8 [19–70]
Sex		
Female/male, n (%)	44/18 (71.0/29.0)	40/21 (65.6/34.4)
Education, n (%)		
Basic (≤10 years)	12 (19.4)	7 (11.5)
High school (13 years)	29 (46.7)	40 (65.5)
University (>13 years)	21 (33.9)	14 (23.0)
Pain-related data, M ± SD [range]		
Pain duration in years	9.79 ± 8.73 [1–38]	—
Mean back pain intensity (last 4 weeks), 1–10 NRS	4.99 ± 1.56 [2–8]	—
Maximum back pain intensity (last 4 weeks), 1–10 NRS	7.48 ± 1.22 [5–10]	—
Current back pain intensity on study day, 1–10 NRS	3.38 ± 1.98 [0–8]	—
Pain severity*, n (%)		
Grade I (low pain intensity and disability)	23 (37.1)	—
Grade II (high pain intensity, low disability)	27 (43.5)	—
Grade III (high pain intensity and disability, moderately limiting)	8 (12.9)	—
Grade IV (high pain intensity and disability, severely limiting)	4 (6.4)	—
Type of medication, n (%)		
Antidepressants	2 (3.2)	—
Nonopioid analgesics	1 (1.6)	1 (1.6)†
Pregabalin	1 (1.6)	—
Others‡	10 (16.1)	10 (16.4)

\* Pain grading according to Von Korff et al., 1992.

† Daily dose: ASS 100 mg.

‡ Other medication includes nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, antihistamines, antidiabetic medication, levothyroxine, HIV medication, asthma medication, bronchodilators, statins, COX-2 inhibitors, proton pump inhibitors, angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, angiotensin II type 1 (AT1) receptor antagonists, and calcium channel blockers. None of the patients with CBP took benzodiazepines, NSAID, or opioids (>100 mg of morphine equivalent/day according to our inclusion criteria).  
 CBP, chronic back pain; HC, healthy control; NRS, numeric rating scale.

specific cues and painful stimulation, or experimental phases (exact instructions can be found in Supplementary Methods, available at <http://links.lww.com/PAIN/B544>). During acquisition training, a total of 32 CS were presented (16 CS<sup>+</sup>, 16 CS<sup>-</sup>). CS<sup>+</sup> were paired with the US at a reinforcement rate of 75% (ie, 12 CS<sup>+</sup> + US), whereas the CS<sup>-</sup> were never followed by US (differential conditioning). By choosing a partial reinforcement rate of 75%, we aimed to ensure the initial acquisition of CS-US associations in both groups and to prolong the process of extinction learning (for review, see Lonsdorf et al.<sup>43</sup>). CS<sup>+</sup> were presented exclusively for 8 seconds before US onset (delay conditioning, 1 second overlap), which lasted 2.5 seconds in total. Furthermore, the first and last CS<sup>+</sup> were always reinforced. To track individual learning and extinction rates of CS-induced emotional responses over the course of the experiment, participants were repeatedly asked to provide valence ratings for the CS<sup>+</sup> and CS<sup>-</sup> using VAS during every fourth CS<sup>+</sup>/CS<sup>-</sup> presentation, resulting in 4 valence ratings per CS type. After every fourth US presentation, participants rated the pain intensity of the US, resulting in 3 pain intensity ratings. At the end of acquisition training, participants rated the contingency of CS-US coupling (see below for details).

### 2.3.3. Extinction training

Subsequently, extinction training followed without further instructions. A total of 24 CS (12 CS<sup>+</sup>, 12 CS<sup>-</sup>) were presented without US following. Participants provided a valence rating during every fourth CS<sup>+</sup>/CS<sup>-</sup> presentation (ie, 3 valence ratings per CS type). At the end of extinction training, participants again provided contingency ratings regarding CS-US coupling.

During acquisition and extinction training, CS types were presented in a pseudorandomized order with no more than 2 trials of the same CS presented consecutively. The intertrial interval was jittered between 6 and 11 seconds.

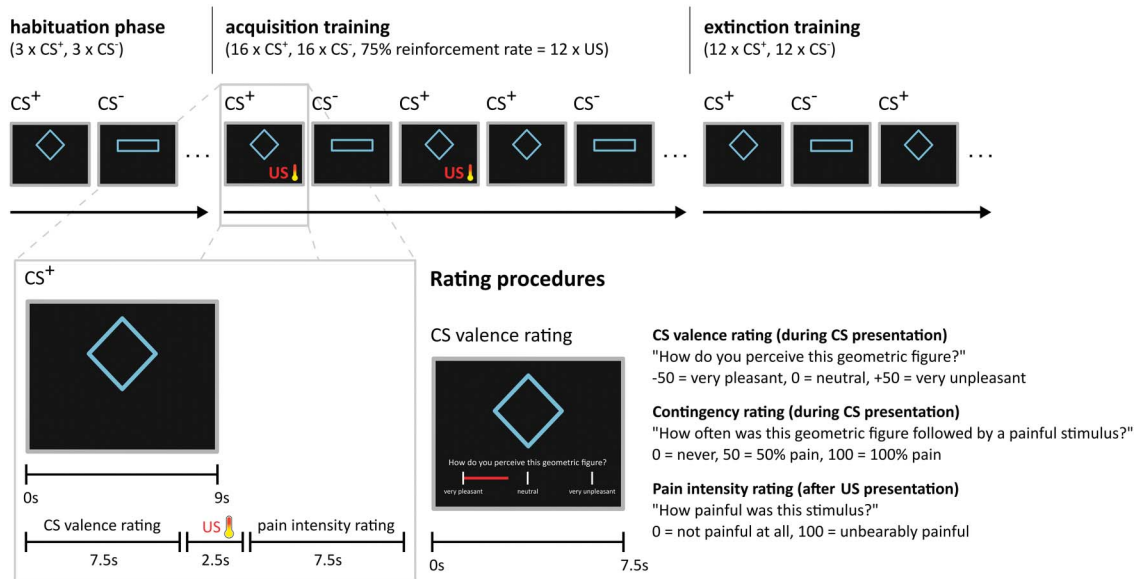
### 2.4. Stimuli

The Presentation software, version 18.0 (Neurobehavioral Systems, Inc, Berkeley, CA, <https://www.neurobs.com>), was used to present visual (including the VAS) and thermal stimuli and to record behavioral data. Geometrical figures with softened edges (color: RGB code 142, 180, 227) on a black background (rectangle: visual angle 8.3 × 3.14°, square: visual angle 4.99 × 4.99°, and rhombus: visual angle 7.38 × 5.36°) were presented on a computer screen positioned in front of the participant and served as CS. Heat pain stimuli, which served as US, were applied using a thermal device (PATHWAY system, model CHEPS, 27 mm diameter; Medoc, Israel), which was attached to the left volar forearm by an elastic tape. Baseline temperature was set to 35°C. Rates for heating and cooling were set to maximum (70 and 40°C/s, respectively). Total stimulation time was 2.5 seconds.

### 2.5. Skin conductance responses

Skin conductance responses were continuously recorded throughout all experimental phases by a constant voltage system (0.5 V) using a BIOPAC MP150 device (BIOPAC Systems, Inc, Goleta, CA) in combination with AcqKnowledge 5.0.2 software. Single-use, radiotranslucent dry electrodes (EL509, BIOPAC Systems, Inc) and a conductive electrode cream (SYNAPSE; Kustomer Kinetics) were applied to the thenar and hypothenar

### Differential conditioning paradigm



**Figure 1.** Differential conditioning paradigm. The experimental paradigm consisted of 3 experimental phases, ie, habituation phase, acquisition training, and extinction training. Assignment of the geometrical figures to experimental conditions was randomized (example shown here). Habituation phase: 6 CS, no US, valence ratings for each CS. Acquisition training: 32 CS, 12 US. Valence (CS<sup>+</sup>/CS<sup>-</sup>) and pain intensity ratings (US) after each fourth CS<sup>+</sup>/CS<sup>-</sup>/US. Extinction training: 24 CS, no US. Valence ratings (CS<sup>+</sup>/CS<sup>-</sup>) after each fourth CS<sup>+</sup>/CS<sup>-</sup>. Each CS was displayed for 9 seconds; US presentation was set to 2.5 seconds; CS<sup>+</sup>-US overlap was set to 1 second. VAS was displayed for 7.5 seconds (valence rating, pain intensity rating) or 15 seconds (contingency rating). Intertrial interval was jittered between 6 and 11 seconds. CS, conditioned stimuli; US, unconditioned stimuli.

eminences of the participants' nondominant (left) hand. The sampling rate was set to 2 kHz. External triggers were recorded to mark the exact onset of an event.

### 2.6. Self-report questionnaires

Psychological trait and state variables are known to modulate pain perception, pain chronification, and pain-related learning.<sup>51</sup> To thoroughly characterize the patient sample and to explore the potential role of maladaptive pain-related cognitions in modulating pain-related learning, all participants completed the German version of the following questionnaires: (1) State-Trait-Anxiety-Depression-Inventory<sup>41</sup>; (2) Depression Anxiety Stress Scales<sup>52</sup>; (3) Center for Epidemiological Studies-Depression Scale: ADS-K<sup>25</sup>; (4) Pain Catastrophizing Scale: PCS<sup>40</sup>; (5) Pain Anxiety Symptom Scale: PASS-D<sup>68</sup>; (6) Trier Inventory of Chronic Stress: TICS<sup>58</sup>; (7) Questionnaire for Experiences of Attention Deficits<sup>70</sup>; and (8) Perceived Stress Questionnaire: PSQ20.<sup>17</sup> All questionnaires were analyzed according to their respective manuals.

### 2.7. Outcome measures

Emotional and affective aspects of pain might shape pain perception particularly in patients with chronic pain.<sup>45,60,67</sup> We thus focused on the emotional aspects of pain-related learning and assessed cue valence ratings repeatedly throughout the different experimental phases. This allowed us to capture the temporal dynamics of pain-related threat and safety learning.<sup>56</sup> Changes in CS valence were assessed during every fourth CS<sup>+</sup>/CS<sup>-</sup> presentation through a -50 to +50 VAS with the question "How do you perceive this geometric figure?" (anchors: -50 = "very pleasant," 0 = "neutral," and +50 = "very unpleasant"). Thus, positive CS valence is indexed by negative VAS ratings, whereas negative CS valence is indexed by positive VAS ratings. To also

capture cognitive aspects of pain-related learning, we assessed contingency awareness at the end of the acquisition and extinction training. Therefore, participants answered the following question using a 0 to 100 VAS separately for both CS: "How often was this geometric figure followed by a painful stimulus?" (anchors: 0 = "never," 50 = "50% pain," and 100 = "100% pain"). In addition, pain intensity ratings were collected to control for comparable pain perception between groups. Subjective pain intensity was assessed after every fourth US presentation using a 0 to 100 VAS: "How painful was this stimulus?" (anchors: 0 = "not painful at all" and 100 = "unbearably painful").

For all ratings, the scale was positioned below the CS with the cursor placed at a random starting position between VAS 25 and VAS 75. Except for contingency ratings (15 seconds), VAS were presented for 7.5 seconds for CS valence and US intensity ratings.

### 2.8. Statistical analysis

All statistical analyses were performed using the R software.<sup>55</sup> Group differences in pain-related variables (pain threshold, temperature level corresponding to VAS70, and mean pain intensity ratings) and person-related variables (age, arousal, pain-related cognitive variables, such as fear of pain, pain catastrophizing, pain-related anxiety, state and trait anxiety, depression, perceived stress, chronic stress, and perceived deficits in attention) were tested using 2-sample *t* tests or the nonparametric 2-sample Wilcoxon rank sum test, where appropriate.

#### 2.8.1. Valence ratings

To investigate whether healthy volunteers and patients with CBP differed in pain-related learning behavior, we followed a 2-step analysis

strategy. First, we focused on differential learning, ie, the development of valence differences between CS<sup>+</sup> and CS<sup>-</sup> ( $\Delta$ CS valence = valence CS<sup>+</sup> - valence CS<sup>-</sup>). To further explore the nature of any valence differences, we also examined nondifferential changes in valence ratings separately for both CS types to specify whether differences are due to altered learning about the aversive CS<sup>+</sup>, the safety signal (CS<sup>-</sup>), or both. Differential and nondifferential learning (ie, threat and safety learning) were investigated using separate linear mixed models (LMMs) on valence ratings, as implemented in the R package *lme4*.<sup>5</sup>

### 2.8.1.1. Model estimation for acquisition and extinction training

First, LMM analyses were performed separately for acquisition and extinction training to test for changes in differential CS valence. The mean  $\Delta$ CS valence ratings of the habituation phase were included as a baseline in the analysis of acquisition training. Likewise, the extinction training model included the last  $\Delta$ CS valence rating of acquisition training as a baseline rating.<sup>56</sup>

To compare  $\Delta$ CS valence ratings and their changes over time between patients with CBP and HCs, the factors time and group (HCs and patients with CBP), as well as interactions of these factors, were included as fixed effects into the models. The factor time was included as a continuous factor to account for increases or decreases of  $\Delta$ CS valences during the experiment.<sup>56</sup> We tested whether including a random intercept for each participant (ie, allowing for interindividual differences in baseline valence ratings) and allowing variation for the factors time, group, and participants by adding random effects for these factors improved model fit, which would indicate a better prediction of data when accounting for random variance in changes over time and differences between groups and participants.

Model selection was based on the Akaike information criterion (AIC) provided by the *anova* (analysis of variance) function in R, which computes  $\chi^2$  between each model to detect improvements in model fit, ie, explained variance (maximum likelihood method). The model comparison showed that including random slopes for each subject and the factor time into the models best predicted the data (LMM acquisition training:  $\Delta$  AIC = -70.6,  $P < 0.001$ ; LMM extinction training:  $\Delta$  AIC = -75.5,  $P < 0.001$ ). Final (ie, best-fitting) models were estimated according to the restricted maximum likelihood method. Effects with  $P$  values  $< 0.05$  were considered statistically significant. Cohen's  $d$  values, as calculated using the R package *EMAtools*,<sup>33</sup> were given as effect sizes. Nondifferential analyses on valence ratings were performed analogously to the differential analyses including the additional factor CS type (CS<sup>+</sup>, CS<sup>-</sup>). As determined by model comparison, the model including random effects for each participant and the factors time and CS type best predicted the data (LMM acquisition training:  $\Delta$  AIC = -685.5,  $P < 0.001$ ; LMM extinction training:  $\Delta$  AIC = -629.6,  $P < 0.001$ ).

### 2.8.2. Contingency ratings

To investigate differences in contingency ratings of CS-US coupling between CS types and groups and to test for changes between phases, LMM analyses were performed.

#### 2.8.2.1. Model estimation

The calculated model comprised the factors phase, CS type, and group and their interactions as fixed effects. We again tested whether including a random intercept for each participant and accounting for variation of the factors CS type, phase, group and participants by adding random slopes for these factors improved

model fit. The factor phase was included as a categorical factor. The model including random slopes for the participants and the factors CS type and phase best predicted the data ( $\Delta$  AIC = -34.7,  $P < 0.001$ ).

### 2.8.3. Modulatory influence of pain duration, maladaptive cognitions, and disease-related variables on pain-related threat and safety learning

For patients with CBP particularly, we were interested in exploring whether potential impairments in pain-related threat and safety learning and extinction scaled with pain duration. Thus, we included pain duration (in years) as a covariate of interest while controlling for age. Furthermore, we performed exploratory analyses on person-related and pain-related variables aiming to explore whether those covariates differentially modulated threat and safety learning (CS valence) or contingency awareness.

### 2.8.4. Analysis of skin conductance response data

Note that 3 participants ( $n = 2$  patients with CBP,  $n = 1$  HC) had to be excluded from the SCR analysis because of technical issues during acquisition training. Skin conductance response analyses were thus based on 60 patients with CBP and 60 HCs. Skin conductance response data were processed and analyzed using the R software. In a first step, data were down-sampled to 20 Hz and smoothed using a low-pass filter with a cutoff frequency of 2 Hz. Local minima and maxima of electrodermal activity were automatically detected. To calculate the amplitude of stimulus-related SCRs, the local minimum at the onset of the first SCR after stimulus onset was subtracted from the maximum peak.<sup>54</sup> The maximum amplitude was analyzed within a time window of 1 to 4 seconds after CS onset (first-interval response, FIR<sup>8,31</sup>). For the US-related SCR, a time window of 0.5 to 7 seconds after US onset was chosen. The minimum amplitude criterion was set to 0.01  $\mu$ S, and responses below were scored as 0  $\mu$ S.

Data were transformed with the natural logarithm to reduce the skew of the amplitude distribution and attain a normal distribution.<sup>29</sup> Trials in which VAS ratings had to be provided were excluded to avoid a contamination of CS/US-related SCRs with movement-induced signal changes. Skin conductance responses that deviated more than 3 SDs from the individual mean were treated as outliers and removed from the analyses ( $n = 2$  SCRs in total). Skin conductance responses between valence ratings were pooled for 3 consecutive trials each, resulting in 4 pooled responses for acquisition training and 3 pooled responses for extinction training.

#### 2.8.4.1. Model calculation

Linear mixed model analyses were performed on CS-induced SCR amplitudes for each experimental phase separately to test for changes in SCR amplitudes over time (ie, SCR increase or decrease) and differences between CS types and groups according to the analyses of valence ratings. To analyze CS-related SCRs, we included the factors CS type, time, and group and the interactions of these factors as fixed effects into the models. Furthermore, we tested whether a random intercept for each participant and allowing variation for the factors CS type, time, group, and participants by adding random slopes for these factors improved model fit. The LMM on CS-related SCR including random slopes for each participant and the factors time, CS type, and group best predicted the data for acquisition training ( $\Delta$  AIC = -89.4,  $P < 0.001$ ). For extinction training, the model including random

slopes for each participant and the factor CS type best predicted the data ( $\Delta AIC = -49.6, P < 0.001$ ). For LMM analyses on US-related SCR, including random slopes for each participant and the factor time into the model best predicted the data ( $\Delta AIC = -70.9, P < 0.001$ ).

### 3. Results

#### 3.1. Pain-related variables and self-report measures

Patients with CBP and HCs did not show differences in heat pain thresholds, individually calibrated temperature levels corresponding to VAS 70, arousal ratings, and ratings of pain-related fear (Table 2). Of importance, as intended, pain intensity ratings were moderate to high and comparable between patients with CBP and HCs during acquisition training. Patients with CBP and HCs showed significant difference in all psychological state and trait variables, as well as pain-related cognitive variables. However, for all the assessed psychological state and trait variables, most of the patients with CBP showed values in a normal range.

#### 3.2. Valence ratings

Figure 2 shows valence ratings of patients with CBP and HCs during the habituation phase, acquisition training, and extinction training for both CS. During the habituation phase, valence ratings for CS<sup>+</sup> and CS<sup>-</sup> were comparable within and between groups indicating that the affective connotation of the visual stimuli did not differ before conditioning (see Supplementary

Table 2 and Supplementary Results, available at <http://links.lww.com/PAIN/B544>, for statistics).

#### 3.2.1. Acquisition training

##### 3.2.1.1. Differential learning

As expected, both groups showed differential learning ( $\Delta CS$  valence) throughout acquisition training (patients with CBP:  $\beta = 3.45 \pm 0.84; t(121.98) = 4.11, P < 0.001, d = 0.74$ ; HCs:  $\beta = 6.02 \pm 0.84; t(119.75) = 7.15, P < 0.001, d = 1.31$ ). However, differential learning was significantly weaker in patients with CBP than in HCs (interaction (IA) time  $\times$  group for  $\Delta CS$  valence:  $\Delta\beta = -2.57 \pm 1.19; t(120.86) = -2.17, P = 0.03, d = -0.39$ ).

##### 3.2.1.2. Threat and safety learning

We further tested whether group differences in differential learning were due to altered responses to the CS<sup>+</sup>, the CS<sup>-</sup>, or both. While both groups showed significant increases in negative valence for the CS<sup>+</sup> (patients with CBP:  $\beta = 2.54 \pm 0.45; t(315.43) = 5.62, P < 0.001, d = 0.63$ ; HCs:  $\beta = 3.81 \pm 0.45; t(312.62) = 8.37, P < 0.001, d = 0.95$ ) and significant increases in positive valence for the CS<sup>-</sup> over time (patients with CBP:  $\beta = -0.88 \pm 0.45; t(313.07) = -1.94, P = 0.05, d = -0.22$ ; HCs:  $\beta = -2.27 \pm 0.45; t(307.97) = -5.02, P < 0.001, d = -0.57$ ), both these effects were less pronounced in patients with CBP than in HCs (IA time  $\times$  group, CS<sup>+</sup>:  $\Delta\beta = -1.26 \pm 0.64; t(314.02) = -1.96, P = 0.05, d = -0.22$ ; CS<sup>-</sup>:  $\Delta\beta = 1.40 \pm 0.64; t(310.50) = 2.18, P = 0.03, d = 0.25$ ).

**Table 2**

**Group differences in heat pain-related data, fear and arousal ratings, and self-report questionnaires.**

	CBP group (M $\pm$ SD)	HC group (M $\pm$ SD)	Statistics	P
<b>Heat pain-related data</b>				
Heat pain thresholds (°C)	43.8 $\pm$ 2.46	43.8 $\pm$ 1.63	W = 1809.50	0.68
Temperature US (°C)	47.5 $\pm$ 1.84	47.7 $\pm$ 1.48	W = 2020.00	0.52
Pain intensity rating during acquisition training (0-100 VAS)	62.5 $\pm$ 12.8	64.4 $\pm$ 10.4	t(121) = 0.91	0.37
<b>Fear and arousal ratings</b>				
Pain-related fear (0-100 VAS)	25.2 $\pm$ 23.1	19.1 $\pm$ 15.4	W = 1225.50	0.41
Arousal (0-100 VAS)	31.0 $\pm$ 21.4	23.8 $\pm$ 19.6	W = 632.50	0.08
<b>Questionnaire data</b>				
STADI				
State anxiety	18.00 $\pm$ 5.48	15.20 $\pm$ 3.02	W = 1318.50	<b>0.005</b>
State depression	18.10 $\pm$ 4.51	15.80 $\pm$ 2.88	W = 1203.00	<b>&lt;0.001</b>
Trait anxiety	21.20 $\pm$ 6.19	17.00 $\pm$ 4.37	W = 1097.50	<b>&lt;0.001</b>
Trait depression	17.80 $\pm$ 4.29	15.50 $\pm$ 3.23	W = 1255.50	<b>0.002</b>
CES-D*	9.68 $\pm$ 6.85	6.22 $\pm$ 5.28	W = 1265.00	<b>0.002</b>
PCS	20.40 $\pm$ 9.16	11.80 $\pm$ 10.10	W = 971.50	<b>&lt;0.001</b>
PASS 20-D	31.90 $\pm$ 12.40	26.30 $\pm$ 14.40	t(120) = -2.30	<b>0.023</b>
DASS				
Depression†	3.97 $\pm$ 3.85	1.30 $\pm$ 1.60	W = 947.00	<b>&lt;0.001</b>
Anxiety‡	3.39 $\pm$ 3.07	1.11 $\pm$ 1.39	W = 970.00	<b>&lt;0.001</b>
Stress§	7.15 $\pm$ 4.65	2.26 $\pm$ 2.59	W = 619.50	<b>&lt;0.001</b>
TICS	20.90 $\pm$ 8.89	16.00 $\pm$ 7.71	t(120) = -3.23	<b>0.002</b>
PSQ20	55.5 $\pm$ 18.9	43.9 $\pm$ 17.2	t(120) = -3.57	<b>&lt;0.001</b>
FEDA	100.00 $\pm$ 13.10	107.00 $\pm$ 10.00	W = 2384.00	<b>0.007</b>

Note that questionnaire data (except for DASS) of 1 HC is missing due to technical problems. Bold entries indicate significant p-values (p<0.05).

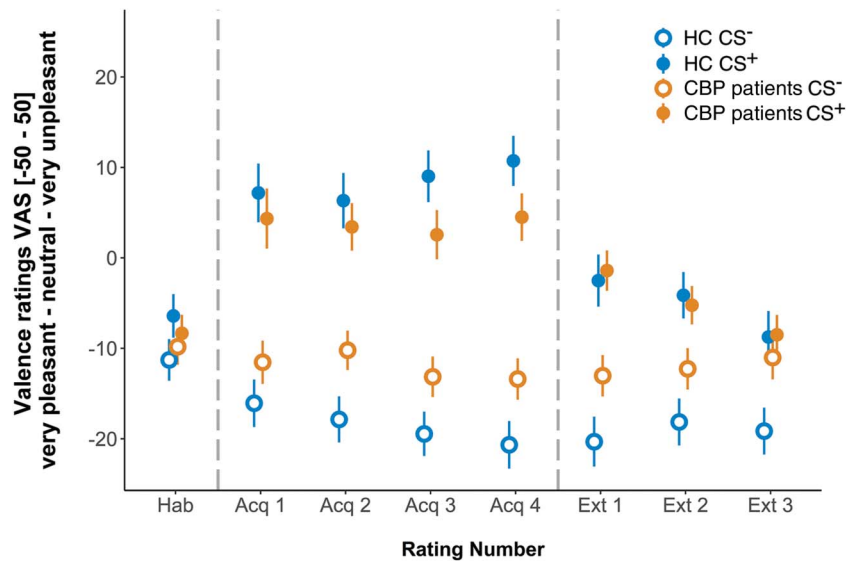
\* Nine patients with CBP (14.5%) scored above the cutoff of 16.

† Four patients with CBP (6.5%) scored above the cutoff of 10.

‡ Eleven patients with CBP (17.7%) scored above the cutoff of 6.

§ Fourteen patients with CBP (22.6%) scored above the cutoff of 10.

CBP, chronic back pain; HC, healthy control; CES-D, Center for Epidemiologic Studies Depression Scale; DASS, Depression Anxiety Stress Scales; FEDA, Questionnaire for Experiences of Attention Deficits; PASS 20-D, Pain Anxiety Symptom Scale; PCS, Pain Catastrophizing Scale; PSQ20, Perceived Stress Questionnaire; STADI, State-Trait-Anxiety-Depression-Inventory; TICS, Trier Inventory of Chronic Stress; US, unconditioned stimuli.



**Figure 2.** Reduced pain-related threat and safety learning (acquisition) in patients with chronic back pain compared with pain-free healthy volunteers: The mean valence ratings ( $\pm$ SEM) of patients with nonspecific chronic back pain (CBP, orange) and healthy volunteers (HCs, blue) for CS<sup>-</sup> (empty circles) and CS<sup>+</sup> (filled circles) during the habituation phase (Hab), acquisition training (Acq 1–Acq 4), and extinction training (Ext 1–Ext 3). Experimental phases are separated by dashed lines. Note that positive CS valence is indexed by negative VAS ratings, and negative CS valence is indexed by positive VAS ratings. CBP, chronic back pain; CS, conditioned stimuli; HC, healthy control.

### 3.2.2. Extinction training

#### 3.2.2.1. Differential learning

Both groups showed extinction learning as indicated by a significant decrease of  $\Delta$ CS valences over the course of extinction training (patients with CBP:  $\beta = -4.96 \pm 0.98$ ;  $t(121.48) = -5.06$ ,  $P < 0.001$ ,  $d = -0.92$ ; HCs:  $\beta = -7.06 \pm 0.98$ ;  $t(119.59) = -7.17$ ,  $P < 0.001$ ,  $d = -1.31$ ). In patients with CBP,  $\Delta$ CS valence ratings returned to baseline level (ie, ratings provided in the habituation phase) in the last extinction trial ( $\beta = 1.41 \pm 2.23$ ;  $t(116.32) = 0.63$ ,  $P = 0.53$ ,  $d = 0.12$ ). By contrast,  $\Delta$ CS valence ratings were still elevated in HCs ( $\beta = 5.20 \pm 2.24$ ;  $t(115.77) = 2.33$ ,  $P = 0.02$ ,  $d = 0.43$ ). Because slopes did not differ between groups (patients with CBP vs HCs:  $\Delta\beta = 2.10 \pm 1.39$ ;  $t(120.53) = 1.51$ ,  $P = 0.13$ ,  $d = 0.27$ ), this difference is likely due to the stronger conditioning effect in HCs during acquisition training, which may have resulted in a floor effect in the patient group.

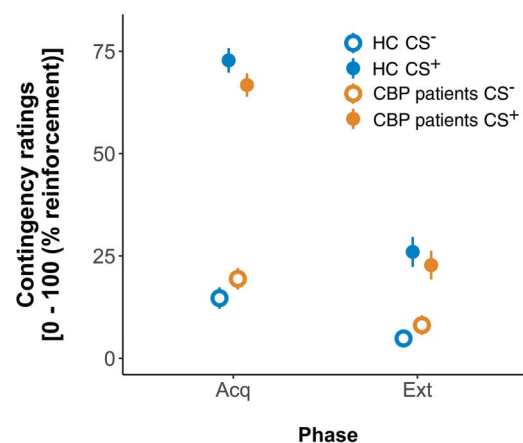
#### 3.2.2.2. Threat and safety learning

Both groups showed a significant decrease of negative valence for the CS<sup>+</sup> (patients with CBP:  $\beta = -4.20 \pm 0.60$ ;  $t(246.98) = -7.06$ ,  $P < 0.001$ ,  $d = -0.90$ ; HCs:  $\beta = -6.02 \pm 0.60$ ;  $t(247.00) = -10.04$ ,  $P < 0.001$ ,  $d = -1.28$ ), reaching baseline (ie, habituation) level at the end of extinction training (patients with CBP:  $\beta = 0.15 \pm 2.04$ ;  $t(204.46) = 0.07$ ,  $P = 0.94$ ,  $d = 0.01$ ; HCs:  $\beta = -2.24 \pm 2.10$ ;  $t(204.49) = -1.09$ ,  $P = 0.28$ ,  $d = -0.15$ ). The decrease of negative CS<sup>+</sup> valence was significantly less pronounced in patients with CBP when compared with HCs (IA time  $\times$  group:  $\Delta\beta = 1.82 \pm 0.84$ ;  $t(246.99) = 2.15$ ,  $P = 0.03$ ,  $d = 0.27$ ), which might again be reflective of the stronger conditioning effect in HCs. Of interest, CS<sup>-</sup> valence remained at a stable (positive) level across extinction training in both groups (patients with CBP:  $\beta = 0.87 \pm 0.60$ ;  $t(251.47) = 1.44$ ,  $P = 0.15$ ,  $d = 0.18$ ; HCs:  $\beta = 0.90 \pm 0.60$ ;  $t(244.58) = 1.50$ ,  $P = 0.13$ ,  $d = 0.19$ ). Of note, CS<sup>-</sup> valence assessed at the end of the extinction training phase was significantly more positive than during the habituation

phase in HCs, whereas patients with CBP showed no significant difference (patients with CBP:  $\beta = -0.97 \pm 2.05$ ;  $t(206.38) = -0.47$ ,  $P = 0.64$ ,  $d = -0.07$ ; HCs:  $\beta = -7.44 \pm 2.05$ ;  $t(204.53) = -3.62$ ,  $P < 0.001$ ,  $d = -0.51$ ).

### 3.3. Contingency ratings

In general, participants correctly identified the CS to predict the delivery or absence of the US (**Fig. 3**). Contingency ratings for the CS<sup>+</sup> were significantly higher than those for the CS<sup>-</sup> in both experimental phases and both groups (patients with CBP, acquisition training:  $\beta = 47.41 \pm 3.97$ ;  $t(227.71) = 11.94$ ,  $P < 0.001$ ,  $d = 1.58$ ; HCs, acquisition training:  $\beta = 58.00 \pm 4.02$ ;  $t(229.34) = 14.44$ ,  $P < 0.001$ ,  $d = 1.91$ ; patients with CBP, extinction training:  $\beta = 14.38 \pm 4.00$ ;  $t(232.53) = 3.60$ ,  $P <$



**Figure 3.** Comparable contingency awareness in patients with chronic back pain and healthy volunteers. The mean contingency ratings (with SEM) of patients with nonspecific chronic back pain (CBP, orange) and healthy participants (HCs, blue) provided for CS<sup>+</sup> (filled circles) and CS<sup>-</sup> (empty circles) after acquisition (Acq) and extinction training (Ext). CBP, chronic back pain; CS, conditioned stimuli; HC, healthy control.

0.001,  $d = 0.47$ ; HCs, extinction training:  $\beta = 21.24 \pm 4.02$ ;  $t(230.69) = 5.28$ ,  $P < 0.001$ ,  $d = 0.69$ ). Furthermore, contingency ratings for both CS were significantly lower after extinction training than after acquisition training (patients with CBP, CS<sup>+</sup>:  $\beta = -43.98 \pm 3.28$ ;  $t(242.67) = -13.42$ ,  $P < 0.001$ ,  $d = -1.72$ ; HCs, CS<sup>+</sup>:  $\beta = -46.68 \pm 3.33$ ;  $t(243.95) = -14.04$ ,  $P < 0.001$ ,  $d = -1.80$ ; patients with CBP, CS<sup>-</sup>:  $\beta = -10.96 \pm 3.34$ ;  $t(247.14) = -3.29$ ,  $P = 0.001$ ,  $d = -0.42$ ; HCs, CS<sup>-</sup>:  $\beta = -9.92 \pm 3.34$ ;  $t(244.81) = -2.97$ ,  $P < 0.001$ ,  $d = -0.38$ ). CS-specific contingency ratings did not differ significantly between patients with CBP and HCs, neither after acquisition nor after extinction training (no significant IA group  $\times$  CS type) and did not change differentially over time (no significant IA group  $\times$  time  $\times$  CS type).

### 3.4. The modulatory influence of pain duration, maladaptive cognitions, and pain-related variables on pain-related threat and safety learning

To test whether pain duration significantly modulates the acquisition or extinction of CS<sup>+</sup> or CS<sup>-</sup> valence ratings in patients with CBP, we added pain duration as a covariate of interest, while controlling for age. We found that during acquisition training, valence ratings for the CS<sup>+</sup> showed a slower increase (ie, reduced slope) with increasing pain duration (IA time  $\times$  pain duration:  $\beta = -0.09 \pm 0.05$ ;  $t(179.08) = -1.84$ ,  $P = 0.067$ ,  $d = -0.27$ ). Moreover, during extinction training, the decrease of CS<sup>+</sup> valence ratings was significantly slower (ie, less extinction) with increasing pain duration (IA time  $\times$  pain duration:  $\beta = 0.17 \pm 0.06$ ;  $t(114.76) = 2.84$ ,  $P = 0.005$ ,  $d = 0.53$ ). Valence ratings for the CS<sup>-</sup> were not significantly modulated by pain duration. Similar results were found when testing an association between contingency awareness and pain duration, while controlling for the modulatory effects of age. Longer pain duration was associated with significantly lower contingency awareness after acquisition training for the CS<sup>+</sup> ( $\beta = -1.53 \pm 0.32$ ;  $t(97.25) = -4.79$ ,  $P < 0.001$ ,  $d = -0.97$ ), whereas no significant effect was found for the CS<sup>-</sup>. Contingency awareness assessed after extinction training was not modulated by pain duration. The decline in CS<sup>+</sup>-related contingency ratings from post acquisition to post extinction training was significantly less pronounced for patients with CBP with longer pain duration (IA time  $\times$  pain duration:  $\beta = 1.15 \pm 0.38$ ;  $t(117.15) = 3.00$ ,  $P = 0.003$ ,  $d = 0.56$ ).

Note that exploratory analyses of the modulatory influence of maladaptive cognitions and other pain-related variables will only be briefly described in this article. Detailed results on covariates and statistics are given in the Supplementary Results, available at <http://links.lww.com/PAIN/B544>. The level of pain chronicity (according to the von Korff scale<sup>37</sup>) and back pain intensity at the day of study participation did not modulate threat and safety learning during acquisition and extinction training in patients with CBP. However, covariate analyses revealed a significant influence of maladaptive cognitions in both groups. Higher levels of state anxiety, for instance, were linked to increased threat learning in patients with CBP and enhanced safety learning in healthy participants (valence ratings). In patients with CBP only, enhanced levels of state anxiety and depression were associated with an overestimation of the association between the safety cue and the US (contingency ratings). Trait anxiety and depression did not significantly modulate learning behavior. Neither threat nor safety learning (valence and contingency ratings) was modulated by the individual level of US-related fear. However, differential learning was significantly enhanced in more aroused HCs—an effect that was driven by more pronounced threat learning with higher levels of arousal. In patients with CBP with high pain

anxiety and pain catastrophizing scores, threat learning and extinction were enhanced. This effect was not reflected in contingency ratings.

## 3.5. Skin conductance responses

### 3.5.1. Unconditioned responses

US-related SCR amplitudes significantly decreased during acquisition training in both groups (patients with CBP:  $\beta = -0.003 \pm 0.001$ ;  $t(118.60) = -4.97$ ,  $P > 0.001$ ,  $d = -0.91$ ; HCs:  $\beta = -0.003 \pm 0.001$ ;  $t(117.40) = -3.57$ ,  $P < 0.001$ ,  $d = -0.66$ ). However, the groups did not differ in US-related SCR amplitudes or amplitude changes over time.

### 3.5.2. Conditioned responses

During acquisition training, we observed a general decrease in CS-related SCR amplitudes over time in both groups (patients with CBP, CS<sup>+</sup>:  $\beta = -0.008 \pm 0.002$ ;  $t(209.40) = -4.93$ ,  $P < 0.001$ ,  $d = -0.68$ ; HCs, CS<sup>+</sup>:  $\beta = -0.003 \pm 0.002$ ;  $t(219.50) = -2.06$ ,  $P = 0.04$ ,  $d = -0.28$ ; patients with CBP, CS<sup>-</sup>:  $\beta = -0.005 \pm 0.002$ ;  $t(252.00) = -3.08$ ,  $P = 0.002$ ,  $d = -0.39$ ; HCs, CS<sup>-</sup>:  $\beta = -0.005 \pm 0.002$ ;  $t(245.50) = -2.81$ ,  $P = 0.005$ ,  $d = -0.36$ ; see Supplement, Figure S1, available at <http://links.lww.com/PAIN/B544>). Of interest, the decrease of CS<sup>+</sup>-induced SCR amplitudes was more pronounced in patients with CBP when compared with HCs ( $\Delta\beta = -0.004 \pm 0.002$ ;  $t(214.90) = -1.97$ ,  $P = 0.05$ ,  $d = -0.27$ ). There were no significant differences between CS types (all  $P > 0.05$ ). No significant effects were found in extinction training.

## 4. Discussion

In this study, we examined potential differences in pain-related acquisition and extinction learning in a large sample of patients with nonspecific CBP and age- and sex-matched healthy volunteers (HCs). In a differential conditioning paradigm with painful heat stimuli (US), valence ratings indicated less differential learning during acquisition training in patients with CBP. Of importance, this effect was driven by both reduced threat (CS<sup>+</sup>) and safety (CS<sup>-</sup>) learning. Furthermore, both groups showed a decrease of negative valence ratings for the CS<sup>+</sup> but no significant change in CS<sup>-</sup> valuation in the subsequent extinction training phase.

### 4.1. Successful differential acquisition and extinction in patients with chronic back pain and healthy volunteers

In both groups, CS<sup>+</sup> ratings increased in negative valence whereas CS<sup>-</sup> ratings increased in positive valence during acquisition training, indicating that, in general, stimulus valence was modulated because of the conditioning procedure. Contingency ratings after acquisition training confirmed that both groups were equally able to differentiate between CS types. Furthermore, during extinction training, CS<sup>+</sup> ratings decreased in negative valence in both groups. These findings are in line with previous reports of successful pain-related differential learning, as well as extinction learning in other pain conditions.<sup>18,23,28,48,49</sup>

### 4.2. Impaired threat and safety learning in patients with nonspecific chronic back pain

Although valence ratings indicated differential learning in both groups, differences between CS<sup>+</sup> and CS<sup>-</sup> were smaller in the patient group, indicating weaker learning, which corroborates



earlier findings in patients with chronic pain.<sup>22,46</sup> In principle, impaired differential learning can be caused by a deficit in threat learning, safety learning, or both. Our data suggest that in patients with CBP, both threat and safety learning are affected, which is in line with reports of diminished threat learning<sup>23</sup> and safety learning<sup>7,23,47</sup> in various chronic pain conditions. Diminished differential learning has previously been found in healthy individuals under conditions of high uncertainty about probabilistic cue–outcome contingency.<sup>9,69</sup> Given that, in our study, contingencies were identical in both groups, such uncertainty is unlikely to be the direct effect of outcome probabilities but might reflect the degree of participants' certainty about the reinforcement schedule. In this study, CS<sup>+</sup> was followed by an unexpected outcome (ie, omission of US after CS<sup>+</sup> presentation) in a quarter of CS<sup>+</sup> trials. The degree to which this deviant information is taken into account during acquisition training may have differed between groups. Less extreme valence ratings in the patient group could be reflective of more emphasis on the unexpected outcome than in HCs. Another reason for the impaired discrimination between CS<sup>+</sup> and CS<sup>-</sup> might be diminished perceptual discrimination in patients with CBP, as suggested by Catley et al.<sup>10</sup> However, in our sample, proxies of pain-related sensory discrimination (eg, pain thresholds and pain intensity ratings during acquisition training) did not differ between groups, which does not support this view. Rather, patients may have adopted a “better safe than sorry” strategy on an affective-motivational level. Moreover, impaired discrimination learning could contribute to increased avoidance behavior when patients are not able to properly distinguish the safety from the threat stimulus. Whether other processes such as generalization and avoidance behavior also played a role here<sup>23,47,49</sup> was not addressed in this study. Another explanation for our findings might be a difference in US salience or emotional relevance. Although the US was rated as equally painful in both groups, its threat value or emotional relevance might have differed between the groups. Predictable, short-lasting heat stimuli may not be as salient and emotionally relevant for patients with CBP as for healthy individuals because their chronic pain with its oftentimes unpredictable symptom fluctuations is far more bothersome. In line with this, the threat value or salience of US has been shown to shape the acquisition and extinction of conditioned responses, especially in the context of several aversive stimuli.<sup>35,56</sup>

Aberrant pain-related learning and extinction in chronic pain states may be further related to structural and functional changes in emotion regulation networks<sup>3,24,32</sup> and networks underlying higher cognitions.<sup>11,32,61</sup> Especially, safety learning deficits might be the result of functional and neurochemical changes in the mesolimbic dopamine circuitry in chronic pain.<sup>36,42,60</sup>

#### **4.3. Differences in extinction learning between patients with chronic back pain and healthy volunteers**

Studies investigating extinction processes in patients with chronic pain are scarce, and results differ between pain syndromes.<sup>18,23,28,49</sup> In this study, patients with CBP showed less decrease in negative CS<sup>+</sup> valence during extinction training than HCs. However, these findings may indicate a floor effect because patients with CBP had shown weaker threat and safety learning during acquisition training.<sup>23</sup> More robust conclusions regarding extinction learning deficits would ideally require similarly strong US-CS associations after acquisition training. Of importance, the difference between CS<sup>+</sup> and CS<sup>-</sup> valence ratings assessed at the end of extinction training was comparable with the difference at baseline, indicating successful extinction in

patients. Hence, our data do not support the assumption of a general deficit in extinction learning in patients. In HCs, after extinction training, ratings for the CS<sup>+</sup> were still significantly higher than for the CS<sup>-</sup>, which suggests a lingering differential conditioning effect. Of interest, CS<sup>-</sup> valence ratings did not change significantly during extinction training in either group, as has previously been discussed for evaluative conditioning.<sup>15,21,27</sup>

#### **4.4. Modulatory influence of pain duration and trait and state variables on pain-related learning**

Of importance, our study is the first to show that longer pain duration is associated with reduced threat learning in patients with CBP both on the emotional (CS valence) and cognitive (contingency awareness) level. These findings may suggest that alterations in threat learning might develop gradually (at least in patients with CBP) and could thereby contribute to the maintenance of chronic pain. However, longitudinal studies are needed to delineate whether reduced threat learning is already present at onset or before pain chronification and gradually worsens as the pain duration progresses. The increasing relative differences in salience of the clinical pain and the experimental stimulus may contribute to this effect.

Safety learning, on the other hand, was not significantly modulated by pain duration. Whether safety learning deficits precede and potentially predispose to chronic pain or, alternatively, develop at an early phase of chronic pain cannot be answered, given our experimental design and patient sample. Neural changes in emotional learning circuits and functional connectivity within these circuits<sup>4</sup> have been described to be altered in chronic pain and to contribute to the transition from subacute to chronic pain.<sup>2,39,50</sup> Given the known role of learning mechanisms in treatment responses,<sup>71</sup> especially in chronic pain,<sup>13</sup> impaired safety learning might hamper the response to therapeutic approaches in which features of the treatment can serve as (safety) cues predicting pain relief.

Chronic pain and mental disorders such as depression or anxiety disorders commonly co-occur,<sup>63</sup> and these conditions have been shown to be related to altered learning and extinction processes.<sup>6,16,53</sup> Although modulatory effects of trait anxiety were not evident in either group,<sup>62</sup> we found significant modulations of learning with state anxiety. Of interest, state anxiety showed opposing effects on patients' and healthy participants' learning behavior. Whereas state anxiety was associated with enhanced threat learning in patients, higher state anxiety increased safety learning in HCs but did not influence threat learning. This dissociation could be reflective of an adaptive mechanism in healthy individuals with an attentional focus on cues and situations signaling safety and a maladaptive mechanism in patients with chronic pain with an attentional focus on cues signaling potential threat (“better safe than sorry”). Previous results pertaining the influence of state anxiety on threat and safety learning are scarce and inconsistent.<sup>14,20,38,66</sup> Of interest, in our patient sample, other maladaptive pain-related cognitions (pain catastrophizing and pain anxiety) boosted both threat acquisition and extinction learning. The finding of enhanced threat and extinction learning in patients with CBP with higher pain anxiety and pain catastrophizing levels was not expected here. However, it has to be noted that threat acquisition in those patients was also enhanced, which could have driven the effect in extinction learning potentially in the sense of unequal starting points of US-CS associations before extinction training. To investigate the effects of pain anxiety and pain catastrophizing on the speed of extinction learning properly, one would ideally

need similar strength of US-CS associations after acquisition training.

#### 4.5. Limitations and implications for future studies

Our study results have to be interpreted in the light of several limitations. While in our controlled experimental setting, both conditions were relatively easy to distinguish (pain vs no pain), learning to predict phases of pain exacerbation or alleviation from clinical pain with its natural fluctuations (instead of complete relief) is undoubtedly more challenging. Although not explicitly tested in this study, there is reason to assume that the perceived threat value of the US in this study differed substantially between groups. Moreover, the patients with CBP investigated in this study were rather homogeneous regarding pain duration and pain-related impairments (low chronic pain grades), were younger when compared with the average patients with chronic pain, and took rather few medications.<sup>23,34,47,49</sup> In addition, patients with CBP did not show clinically relevant psychological comorbidities, which are expected to be more pronounced in more severely affected patients. However, we observed reduced acquisition and extinction of threat associations, as well as lower contingency awareness in patients with CBP with increased pain duration. Therefore, our findings might underestimate clinical effects in more severely affected patients. Future studies investigating a more heterogeneous patient sample with varying degrees of pain-related impairments or, ideally, longitudinal studies are needed to explore threat and safety learning and their modulation by psychological variables in different stages of chronic pain.

#### 5. Conclusion

Our study presents evidence that patients with CBP differentiate less between threat and safety cues than pain-free individuals. We therefore conclude that CBP is associated with altered threat and safety learning. This ambiguity to emotionally evaluate threat and safety information might lead to overly protective behavior and thus contribute to the maintenance of chronic pain. Intriguingly, state anxiety had opposing effects on threat and safety learning in patients with CBP and healthy participants. Our data also provide first evidence for reduced threat learning with pain duration. However, the functional relevance of this effect needs to be explored in longitudinal studies to discern whether learning deficits are the cause or consequence of chronic pain and when such learning deficits can be best addressed therapeutically.

#### Conflict of interest statement

The authors have no conflicts of interest to declare.

#### Acknowledgements

The authors thank Jaspreet Kaur, Vanessa Dobischat, and Ashtar Hashim for their help in recruiting participants and data acquisition, Harald Engler and Alexandra Kornowski for analyzing saliva samples, and Diana Müßgens for editing the manuscript. Author J. Kleine-Borgmann was supported as a Clinician Scientist within the University Medicine Essen Academy (UMEA) program, funded by the German Research Foundation (DFG; grant FU356/12-1) and the Faculty of Medicine, University of Duisburg-Essen. This work was supported by a grant from the German Research Foundation (DFG; project number 316803389–SFB 1280 given to U.B., K.F., S.E., C.J.M., and O.T.W.).

Data availability: Raw data are available from the corresponding author on request.

Code availability: The R code used for data analyses in this study is available from the corresponding author on request.

Preregistration statement: The conducted research was not preregistered.

#### Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B544>.

#### Article history:

Received 9 July 2021

Received in revised form 28 October 2021

Accepted 16 November 2021

Available online 25 November 2021

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