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Hydrocortisone Differentially Affects Reinstatement of Pain-related Responses in Patients With Chronic Back Pain and Healthy Volunteers

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Abstract: **Despite the crucial role of effective and sustained extinction of conditioned pain-related fear in cognitive-behavioral treatment approaches for chronic pain, experimental research on extinction memory retrieval in chronic pain remains scarce. In healthy populations, extinction efficacy of fear memory is affected by stress. Therefore, we investigated the effects of oral hydrocortisone administration on the reinstatement of pain-related associations in 57 patients with non-specific chronic back pain (CBP) and 59 healthy control (HC) participants in a differential pain-related conditioning paradigm within a placebo-controlled, randomized, and double-blind design. Participants' skin conductance responses indicate hydrocortisone-induced reinstatement effects in HCs but no observable reinstatement in HCs receiving placebo treatment. Interestingly, these effects were reversed in patients with CBP, that is, reinstatement responses were only observed in the placebo and not in the hydrocortisone group. Our findings corroborate previous evidence of stress-induced effects on extinction efficacy and reinstatement of fear memory in HCs, extending them into the pain context, and call for more research to clarify the role of stress in fear extinction and return of fear phenomena possibly contributing to treatment failure in chronic pain treatment.**

Perspective: ***Opposing effects in HCs and patients with non-specific CBP may be associated with changes in the patients' stress systems. These findings could be of relevance to optimizing psychological, extinction-based treatment approaches.***

Key words: *Chronic pain, Reinstatement, Hydrocortisone, Stress, Skin conductance response*

Conceptual models of chronic pain propose that pain-related learning and memory processes play a key role in the development and maintenance of persistent pain.[1] These assumptions are supported by evidence that threat and safety learning is altered in various chronic pain conditions.[2–10] While the adaptive acquisition of pain-related fear based on CS-US associations (CS: conditioned stimulus, US: unconditioned

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stimulus) is the basis for successful avoidance of painful experiences, achieving efficient and long-lasting extinction of pain-related fear constitutes a crucial element of therapeutic approaches[11,12] for preventing pain chronification. However, only few studies have examined mechanisms relevant to impaired extinction efficacy, such as reinstatement of previously extinguished pain-related conditioned responses as a risk for relapse phenomena in patients with chronic pain, and the few existing reports in healthy volunteers yielded mixed results.[13,4,14-16]

Stress is known to affect learning and memory processes,[17–22] but the underlying mechanisms in chronic pain, especially on extinction memories (eg, retrieval and reinstatement), are still unclear. Chronic pain and stress are intricately linked to both the behavioral and neural levels.[23,24] Here, a dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis[25,26] and altered corticolimbic brain functions and connectivity were reported in patients with chronic pain.[27] Furthermore, stress, especially in the context of exposure therapy (or multimodal treatment programs involving re-exposure to physical activity and specific movements) could lead to a stronger relapse of fear memories. Although evidence for the fundamental role of (altered) stress systems in the development of chronic pain is accumulating, our understanding of the complex relationship between stress, chronic pain, and fear learning is still rudimentary.[26,28]

We have performed a comprehensive study to investigate aspects of fear learning and extinction in a large sample of patients with non-specific chronic back pain (CBP) as compared to healthy control (HC) participants. Results of day 1 on the acquisition and extinction of conditioned fear responses are published in Schlitt et al,[9] supporting impaired differential learning in patients with CBP versus HCs at the behavioral level. The present study now aims to elucidate the effects of hydrocortisone (20 mg, administration ~30 minutes prior to a retrieval test) on previously formed fear and extinction memory traces and the reinstatement of fear memory 24 hours later. We hypothesized that hydrocortisone administration impairs extinction efficacy and therefore leads to a stronger reinstatement effect (ie, mimicking relapse). While expecting enhanced reinstatement in patients with CBP compared to HCs in general (ie, in the placebo conditions), we additionally aimed to explore the role of cortisol effects on reinstatement in patients with CBP compared to HCs.[25,29] The study focuses on skin conductance responses (SCRs), which is a sensitive and established indicator of reinstatement effects,[30] further capitalizing on the advantage of no evidence of prior group differences for this psychophysiological outcome measure during acquisition and extinction training.[9]

Methods

A two-day differential conditioning paradigm was implemented in this study. The first day included preparatory steps (ie, a calibration procedure and the completion of self-report questionnaires) as well as acquisition and extinction training phases (see *Differential Conditioning Paradigm*). A detailed description of the results from day 1 was reported in Schlitt et al.[9] These comprise information on demographics and questionnaires, experimental procedures including heat pain calibration, ratings on arousal and pain-related fear, and details on the experimental paradigm. Herein, we focus on day 2, on which the effects of hydrocortisone administration on previously formed fear and extinction memory traces, as well as the reinstatement of fear memory were tested. Participants were pseudo-randomly allocated with respect to sex and experimental group to either receive oral hydrocortisone or placebo in a double-blind fashion (between-group design, for detailed information, see *Treatment)*. Thirty minutes after tablet administration, experimental procedures were accomplished in a paradigm including a retrieval test, reinstatement procedure, and a reinstatement test (see Fig 1A).

The study was approved by the local Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (protocol number 16-7248-BO). All participants gave informed written consent to participate and were free to withdraw from the study at any time. All participants received a small remuneration for study participation. The study was not pre-registered.

Participants

Sample sizes for the study were calculated for study day 1 based on previous studies examining acquisition and extinction learning[6,8] using the *pwr* package in *R*,[31] which functions are based on the book 'Statistical Power Analysis for the Behavioral Sciences' of Jacob Cohen (1988).[32] Here, estimations using parameters $d = .5$, $\alpha = .05$ and $1\text{-}\beta = .80$ resulted in a minimum sample size of $n = 63$ volunteers per group to detect significant group differences. Power analyses were not performed for the present analysis (ie, study day 2).

67 patients with non-specific chronic back pain (CBP) and 74 healthy volunteers (HCs) were included in the study. Participants were recruited via the local Back Pain Center of the University Medicine Essen (Head of Unit: UB), local media advertisements, and the local database of our research group. The following general inclusion criteria applied to both groups: age > 18 and < 80 years, normal or corrected-to-normal vision, no acute infection, no participation in trials using medicinal products within the last 3 months, and no consumption of alcohol within the past 24 hours (assessed through self-report). The eligibility of patients interested in study participation was confirmed by trained study personnel via telephone screening. Further, physicians specialized in pain medicine (UB and JKB) performed on-site screenings of eligible patients via medical history and clinical examination.

The patient group consisted of individuals with non-specific CBP (ie, absence of specific spinal pathologies, nerve root, post-surgical or post-traumatic pain). In accordance with the European guidelines, CBP was defined as recurring or persistent pain present for more than 12 weeks.[33] Further exclusion criteria were a history of malignant diseases within the past 5 years (eg, tumor diseases, cancer), severe mental disorders (eg,

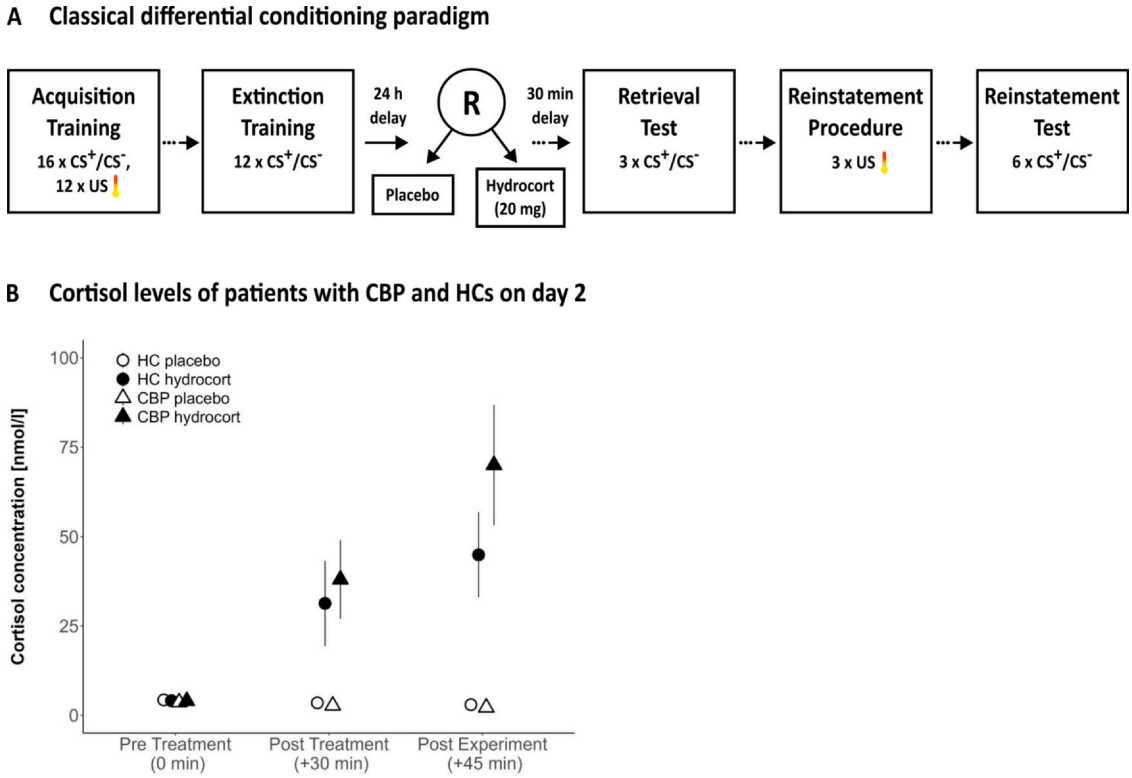

Figure 1. **(A)**The conditioning paradigm comprised 6 experimental phases. Day 1 comprised *acquisition training* (16 CS^+/CS^-, 12 US, 75% reinforcement rate) and *extinction training* (12 CS^+/CS^-). Day 2 comprised a *randomization phase* (double-blind administration of either 20 mg hydrocortisone (hydrocort) or an inactive placebo ~24 h after day 1) administered 30 min prior to *retrieval test* (3 CS^+/CS^-; valence ratings after the 1st and 3rd CS presentation of each CS type), *reinstatement procedure* (3 US only; pain intensity ratings after each US), and *reinstatement test* (6 CS^+/CS^-; valence ratings after the 1st, 3rd, and 5th CS presentation of each CS type) to test extinction retrieval on day 2. **(B)** Mean salivary cortisol concentrations ± SEM (standard error of the mean) of healthy participants (HC, circles) and patients with chronic back pain (CBP, triangles) that either received hydrocortisone (black) or placebo treatment (white) on day 2. Saliva samples were collected pre-treatment, ~30 min post-treatment and ~45 min post-treatment (post-experiment). CS, conditioned stimulus (ie, geometrical figures); US, unconditioned stimulus (ie, heat stimulus); R, randomization; Placebo, placebo treatment; Hydrocort, hydrocortisone treatment; mg, milligrams; h, hours; min, minutes; nmol, nanomol (10^{-9} mol); l, liter.

schizophrenia, psychoses, personality or addictive disorders), and opioid treatment > 100 mg morphine equivalent per day. Any other treatment had to be kept stable in the period of 3 weeks before study participation. Exclusion criteria for HCs comprised current or past internal, neurological, mental, pain-related, or dermatological diseases or other visible signs of acute dermatological abnormalities, cancer, regular consumption of recreational drugs, or intake of pain medication within the past 24 hours, all based on self-report. HCs with clinically relevant levels of anxiety or depression according to the Depression Anxiety Stress Scales[34] were excluded from final data analyses (cut-off values: anxiety = 6, stress = 10, depression = 10). In total, data of 10 patients and 18 HCs had to be discarded for final data analysis (for details see Supplementary Material—Supplementary Methods: *Excluded participants*).

Experimental Paradigm and Procedures

Differential Conditioning Paradigm

We used an established *differential conditioning paradigm*[16] comprising 6 experimental phases, that is, habituation phase, acquisition training, and extinction training on day 1 as well as a retrieval test, reinstatement procedure, and reinstatement test on day 2 (Fig 1A). On day 1, during acquisition training, 2 geometrical figures served as cues for the delivery (conditioned stimulus, CS^+, 75% reinforcement rate) or omission (CS^-) of a painful heat stimulus at the volar forearm (unconditioned stimulus, US) delivered using a thermode. During subsequent extinction training, the CS was presented without a US application.

On day 2, 30 minutes after tablet administration, participants were instructed before the retrieval test that the subsequent task would be comparable to the task they had performed on day 1. To assess reinstatement effects, participants were then confronted with unannounced US as reinstatement procedure[30,35] followed by CS-only presentations during the reinstatement test (see Fig 1A).

Physiological responses to CS and US were acquired using continuous skin conductance recordings. Behavioral responses were assessed by CS valence and US pain intensity ratings (see *Outcome measures*).

Retrieval Test. During the retrieval test, 6 CS (3 CS^+, 3 CS^-; duration: 9 seconds each), but no US were presented.

Following the first and the third CS presentation, participants provided a valence rating (see Supplementary Material—Supplementary Methods: *Valence as an additional outcome measure* for details).

Reinstatement procedure. During subsequent reinstatement procedure, participants received 3 unannounced US for 2.5 seconds each without subsequent CS presentation, followed by pain intensity ratings after each US in order to ensure comparable pain perception between groups. Temperature levels were set based on the calibration temperatures from day 1.

Reinstatement Test. Immediately following the reinstatement procedure, 12 CS (6 CS^+, 6 CS^-; duration: 9 seconds each), but no US were presented. Valence ratings were obtained after the first, third, and fifth CS presentation of each CS type.

As on day 1, CS types were presented in a pseudo-randomized order with no more than 2 trials of the same CS presented consecutively within all experimental phases. The inter-trial-interval (ITI) between all trials was jittered between 6 and 11 seconds.

Stimuli

The software *Presentation* (Version 18.0, Neurobehavioral Systems, Inc, Berkeley, CA, https://www.neurobs.com) was used to present visual and thermal stimuli as well as a visual analog scale (VAS) to record behavioral data. Geometrical figures with softened edges (color: RBG code 142, 180, 227) served as CS. The figures were superimposed on a black background (rectangle: visual angle 8.3° × 3.14°, square: visual angle 4.99° × 4.99°, rhombus: visual angle 7.38° × 5.36°) and were presented on a computer screen positioned in front of the participant. Heat pain stimuli (ie, US) were administered using a thermal device (PATHWAY system, model CHEPS, 27 mm diameter; Medoc, Israel) attached to the left volar forearm with elastic tape. The baseline temperature was set to 35 °C. Rates for heating and cooling were set to maximum (70 °C/second and 40 °C/second, respectively). The total stimulation time was 2.5 seconds on each trial. Pain intensity was calibrated as 70 on a 0 to 100 VAS ("How painful was this stimulus?", verbal anchors: 0 = "not painful at all" and 100 = "unbearably painful"). Please note that all rating scales were presented as visual (ie, non-numeric) scales to the participants with visible verbal anchors only. For analysis purposes only, we internally converted the ratings to values between 0 and 100 or –50 to 50, respectively.

Treatment

Participants received either 2 10 mg tablets of hydrocortisone (JENAPHARM, MIBE Arzneimittel GmbH, Brehna, Germany) or placebo (P-Tablets, 7 mm Lichtenstein, Winthrop Arzneimittel GmbH, Frankfurt/Main, Germany) 30 minutes prior to the experiment on day 2. Tablets were administered in capsules of identical shapes. Participants were pseudo-randomly assigned to hydrocortisone or placebo groups by a predetermined 1:1 balanced randomization list (https://www.random.org/).

Saliva Sampling and Cortisol Analysis

To assess free salivary cortisol levels, saliva samples were collected using commercial sampling devices (Salivette Cortisol, Sarstedt, Nümbrecht, Germany). Three samples were collected on day 2: 1) prior to tablet administration, 2) 30 minutes post-treatment, and 3) immediately after the conditioning task (ie, 45 minutes post-treatment). Samples were first stored at 5 °C for up to 7 days before they were centrifuged and kept at –20 °C until biochemical analysis. Please note that cortisol analyses are based on data of n = 57 patients with CBP and n = 55 HCs since data of n = 1 additional HC was missing due to sample loss. Salivary cortisol concentrations were analyzed by enzyme-linked immunosorbent assay (Cortisol Saliva ELISA, IBL International, Hamburg, Germany) according to the manufacturer's instructions. Cross-reactivity of the anti-cortisol antibody with other relevant steroids was 8.5% (11-deoxycortisol), 2.6% (cortisone), 1.0% (corticosterone), and < .1% (estrone, estradiol, estriol, progesterone, testosterone). Inter- and intra-assay coefficients of variation were < 10%. All samples of an individual participant were analyzed in the same run.

Outcome Measures

We assessed emotional arousal through sympathetic nervous system activation in the presence of affective or salient stimuli[36,37] by continously recording skin conductance responses (SCRs). SCRs were recorded across all experimental phases using a BIOPAC MP150 device (BIOPAC Systems, Inc., Goleta, CA) with *AcqKnowledge 5.0.2* software. A conductive electrode cream (SYNAPSE; Kustomer Kinetics) and 2 single-use, radio translucent, dry electrodes (EL509; BIOPAC Systems, Inc, Goleta, CA) were applied to the thenar and hypothenar eminences of the participants' non-dominant (left) hand. Data was sampled at 2 kHz and saved as text files for offline analyses. External triggers were recorded to capture the exact timing of events (CS and US).

SCRs can be partitioned in different time windows, reflecting different learning processes.[38,39] While the first interval response (FIR), ie, early conditioned SCR, reflects orienting behavior to novel stimuli and usually habituates over time, the second interval response (SIR), ie, late conditioned SCR (see below for timing), has been linked to emotional reactions to the CS when the US is expected to follow.[40,41] Since orienting behavior to novel stimuli is more relevant to the first part of the experimental paradigm, the SIR is more suitable to quantify changes during both fear acquisition and extinction learning.[39] Therefore, we herein focus on late conditioned SCRs, and all findings on SCRs reported in the results and discussion sections refer to the SIR. Results of the analyses of the FIR are provided in the Supplementary Material.

Psychological and Self-Report Questionnaires

To explore potential moderation by psychological trait or state variables as well as maladaptive pain-related

cognitive processes of pain-related learning,[42] all participants completed German versions of the following questionnaires: 1) State-Trait-Anxiety-Depression-Inventory[43]; 2) Depression Anxiety Stress Scales[34]; 3) Center for Epidemiological Studies-Depression Scale: ADS-K[44]; 4) Pain Catastrophizing Scale: PCS[45]; 5) Pain Anxiety Symptom Scale: PASS-D[46]; 6) Trier Inventory of Chronic Stress: TICS[47]; 7) Questionnaire for Experiences of Attention Deficits[48]; 8) Perceived Stress Questionnaire: PSQ20.[49] Analyses of all questionnaires were accomplished according to their respective manuals.

Statistical Analyses

For all statistical analyses and processing steps, we used the software *R* (version 1.4.1103).[50] Linear mixed model (LMM) analyses were conducted on behavioral and physiological data acquired during the retrieval and reinstatement test. More specifically, we investigated changes in SCRs and CS valence ratings (for the latter, please see Supplementary Material—Supplementary Methods: *Statistical analyses of valence ratings*) comparing the end of the extinction training to the beginning of the retrieval test and the end of the retrieval test to the beginning of the reinstatement test, respectively. Overall, we focused on *differential learning*, that is, changes in differential SCR amplitudes (ΔSCRs = SCR amplitudes CS^+ - SCR amplitudes CS^-) and differential valence ratings (= valence CS^+ - valence CS^-). We examined the main effects and interactions for the factors *time*, *group (*ie*, CBP vs HCs)*, and *treatment (*ie*, hydrocort vs placebo)*. All variables were assessed using LMMs and analyses of variance as implemented in the R package *lme4*.[51] Partial eta-square (η_p^2) are reported as effect sizes. Following significant LMM results, we performed Bonferroni-Holm adjusted post-hoc tests and calculated *Cohen's d* as effect size.

Skin Conductance Responses

In the first processing step, data were down-sampled to 20 Hz and smoothed using a low-pass filter with a cut-off frequency of 2 Hz. After automatic detection of local minima and maxima in the skin conductance trace, the local minimum at the onset of the first SCR following stimulus onset was subtracted from the subsequent peak[52] to calculate the amplitude of stimulus-related SCRs.

Conditioned responses (CRs) to the CS were analyzed within time windows of 1 to 5 seconds (FIR) and 5 to 9.5 seconds after CS onset (SIR).[38,39] To investigate ***unconditioned responses (URs)*** to the US, the time window was set to .5 to 7 seconds after US onset. The minimum amplitude criterion was set to .01 μS and responses below were scored as 0 μS.

To reduce the skewness of the SCR amplitude distribution and attain a normal distribution,[53] data transformation was performed using the natural logarithm. Trials in which participants provided valence ratings were excluded to avoid contamination of CS-related SCRs with movement-induced signal changes. Testing for ***reinstatement*** effects, models on SCR analysis included the second trials of the retrieval and reinstatement test, respectively. A search for SCR outlier responses (defined as SCRs deviating more than 3 standard deviations (SDs) from the individual mean) revealed that none of the responses met this criterion.

Model calculation. We included the factors *time*, *group*, and *treatment* and the interactions of these factors as fixed effects into the models. Further, we tested whether a random intercept for each participant and allowing variation for the factors *time*, *group*, *treatment,* and *participants* by adding random slopes for these factors, improved model fit. The LMMs including random slopes for each participant best predicted the data for analyzing differential reinstatement effects in CS-related SCRs. Further, US-related SCRs were analyzed including random slopes for each participant. Here, model calculation including random slopes for the factors *time*, *group*, and/or *treatment* was not possible due to an insufficient number of observations.

Modulatory Influence of Maladaptive Cognitions and Disease-related Variables on Extinction Efficacy of Conditioned Responses

For patients with CBP, we were interested in exploring whether disease-related variables and maladaptive cognitions influence extinction efficacy. Thus, we performed exploratory analyses including person- and pain-related variables as covariates to test whether these variables differentially modulated extinction efficacy in either group.

Please note that detailed statistics are only presented for statistically significant results of the SCRs in the main text. Results of the analysis of the valence ratings as well as other non-significant and additional supplementary results are listed in the Supplementary Tables and Supplementary Fig sections (see Supplementary Tables 1–12 and Supplementary Fig. 1–6).

Results

Participant Characteristics

Demographic information and pain-related patient characteristics of the final sample are presented in Table 1.

Pain-related Variables and Self-Report Measures

All psychological state and trait variables as well as pain-related cognitive variables differed significantly between HCs and patients with CBP. However, most patients with CBP showed values in a normal range in all assessed variables, although results were more pronounced with respect to the psychological constructs (eg, anxiety). Mean pain intensity ratings that were acquired during reinstatement were comparable (ie, moderate to high) in both groups and treatment conditions (M ± SD: $HCs_{placebo}$: 69.15 ± 11.16; HCs_{hydro}: 65.86 ± 13.55; $CBP_{placebo}$: 67.59 ± 12.08; CBP_{hydro}: 69.40 ± 14.64, 0–100 VAS). Data of pain-related variables and self-report

Table 1. Demographic Information of Patients With CBP and HCs and Pain-Related Characteristics of the Patient Sample

	CBP (N = 57)		*HCs (N = 56)*	
Treatment	*Placebo*	*Hydrocort*	*Placebo*	*Hydrocort*
n (%)	28 (49.1)	29 (50.9)	23 (41.1)	33 (58.9)
Demographic data				
Age in years, *M ± SD [Range]*	31.0 ± 10.7 [19–66]	36.9 ± 15.2 [20–69]	36.3 ± 13.8 [19–70]	32.8 ± 10.3 [19–68]
Gender				
Women/men, *n (%)*	20/8 (71.4/28.6)	21/8 (72.4/27.6)	14/9 (60.9/39.1)	21/12 (63.6/36.4)
Pain-related data, *M ± SD [Range]*				
Pain duration in *years*	8.82 ± 8.30 [1–38]	9.6 ± 7.8 [1–34]	–	–
Mean back pain intensity (last 4 weeks), *1–10 NRS*	5.0 ± 1.7 [2–8]	4.9 ± 1.5 [2–8]	–	–
Max. back pain intensity (last 4 weeks), *1–10 NRS*	7.7 ± 1.1 [6–10]	7.2 ± 1.2 [5–9]	–	–
Current back pain intensity on day, *1–10 NRS*	3.6 ± 2.1 [0–7]	3.0 ± 1.9 [0–8]	–	–
Pain severity*, *n (%)*				
Grade I (low pain intensity and disability)	9 (32.1)	12 (41.4)	–	–
Grade II (high pain intensity, low disability)	13 (46.4)	12 (41.4)	–	–
Grade III (high pain intensity and disability, moderately limiting)	4 (14.3)	4 (13.8)	–	–
Grade IV (high pain intensity and disability, severely limiting)	2 (7.1)	1 (3.5)	–	–
Type of medication, *n (%)*				
Antidepressants	1 (3.6)	1 (3.56)	–	–
Non-opioid analgesics	1 (3.6)	–	1 (3.9)†	–
Pregabalin	1 (3.6)	–	-	–
Others‡	4 (14.3)	4 (13.8)	3 (11.5)	7 (21.2)

Abbreviations: CBP, patients with chronic back pain; HCs, healthy control participants; Hydrocort, hydrocortisone; NRS, numeric rating scale.
*Pain grading according to Von Korff et al, 1992.
†Daily dose: ASS 100 mg.
‡Other medication includes non-steroidal anti-inflammatory drugs (NSAID), antipsychotics, antihistamines, anti-diabetic 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 took benzodiazepines, NSAID, or opioids (< 100 mg morphine equivalent/day according to our inclusion criteria).

questionnaire measures as well as statistical results can be found in Supplementary Table 1.

Salivary Cortisol Concentrations

As a manipulation check, salivary cortisol concentrations assessed prior to and post-treatment as well as after the experiment were analyzed for each treatment condition and group (see Fig 1B). As expected, within both HCs and patients with CBP the change in cortisol concentrations of the placebo and hydrocortisone treatment groups differed significantly from each other comparing pre- and post-treatment (~30 minutes in between; interaction (IA) time × treatment: $F(1,112) = 13.24$, $P < .001$, $\eta 2 = .11$). In detail, significant effects for the factor time indicated that cortisol concentrations of the hydrocortisone group increased ($t(60) = 2.39$, $P < .001$, $d = .62$), while cortisol concentrations in the placebo group decreased over time ($t(52) = -2.73$, $P < .001$, $d = -.76$; see Supplementary Fig 1). Additionally, these findings were also true, and further, even more pronounced, when comparing the participants' cortisol levels pre-treatment and post-experiment (~45 minutes in between; interaction (IA) time × treatment: $F(1,112) = 24.79$, $P < .001$, $\eta 2 = .18$; hydrocort: $t(60) = 2.81$, $P < .001$, $d = .73$; placebo: $t(52) = -5.07$, $P < .001$, $d = -1.41$). There was no significant main effect and no interaction with the factor group, indicating no significant differences in cortisol concentration changes between HCs and patients with CBP (see Supplementary Table 12).

Pain Intensity Ratings and US-related Responses During Reinstatement Procedure

To ensure adequate and comparable pain perception during unannounced US exposure in the reinstatement procedure, mean pain intensity ratings and mean US-related SCRs of both patients with CBP and HCs as well as the different treatment conditions were compared between groups. There was no significant interaction for the factors *group* and *treatment* neither in mean pain intensity ratings nor in mean US-induced SCRs, indicating that both mean pain intensity ratings and US-induced SCR amplitudes were comparable between groups and treatments, that is, no effect of cortisol level on pain perception (see Supplementary Tables 1 and

11). However, a significant main effect of *time* ($F(1108.27) = 51.62$, $P < .001$, $\eta_p^2 = .34$) indicated that across groups and treatments, US-induced SCR amplitudes significantly habituated during the reinstatement procedure (see Supplementary Table 11) as depicted in Supplementary Fig 2.

Reinstatement Test

To examine the return of fear following unannounced US presentations, SCRs obtained during the retrieval test were compared to those obtained during the reinstatement test. Changes in ΔSCRs significantly differed between placebo and hydrocortisone treatment groups (Fig 2*)*. Critically, this effect showed opposite patterns in HCs and patients with CBP as indicated by an interaction of the factors (IA time × group × treatment [$F(1,118) = 10.94$, $P = .001$, $\eta 2 = .08$]. In HCs this time × treatment IA [$F(1,37.56) = 4.37$, $P = .04$, $\eta 2 = .10$] revealed an increased differential reinstatement for the hydrocortisone treatment compared to the placebo group ($t(37.56) = 2.09$, $P = .04$, $d = .68$). In the patients, however, the time × treatment IA [$F(1,57) = 6.75$, $P = .01$, $\eta 2 = .11$] showed a decreased differential reinstatement for the hydrocortisone treatment compared to the placebo group ($t(57) = -2.59$, $P = .01$, $d = -.69$). In other words, in the placebo groups, ΔSCRs significantly increased from the recall to the reinstatement test in the patient group ($t(30) = 2.49$, $P = .01$, $d = .91$), whereas HCs showed no significant changes in ΔSCRs ($t(28) = -.81$, $P = .42$, $d = -.31$). In the hydrocortisone treatment groups, ΔSCRs significantly increased in HCs ($t(19.61) = 3.10$, $P = .002$, $d = 1.40$), but not in patients ($t(27) = -1.08$, $P = .28$, $d = -.41$). Thus, cortisol induced a return of fear in HCs only. No further significant main effects or interactions were observed for SCRs of both groups (see Supplementary Table 7).

Questionnaire measures related to distress and pain did not improve model fit and revealed no significant effects when tested as potential covariates.

Discussion

To date experimental research on extinction memory retrieval in chronic pain is scarce although effective and sustained extinction of conditioned pain-related fear is of high relevance for cognitive-behavioral treatment approaches in chronic pain. Stress mediators of the HPA axis, including the stress hormone cortisol, likely play a role in the pathophysiology and persistence of chronic pain and may hamper extinction memory retrieval.[26] However, the effects of increased cortisol concentrations on the return of pain-related fear after extinction have never been tested in patients with chronic pain. We herein report on a randomized, double-blind, placebo-controlled study designed to test the effects of oral hydrocortisone (20 mg) versus placebo administration on the return of fear in patients with non-specific chronic back pain (CBP) and healthy volunteers (healthy controls, HCs). Changes in differential skin conductance responses (SCRs) to conditioned stimuli (CS) were analyzed comparing extinction retrieval to reinstatement.

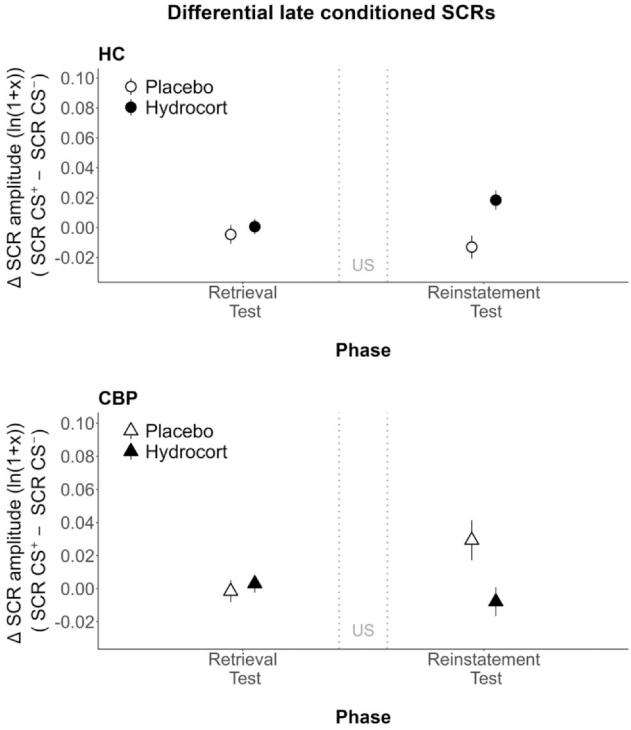

Figure 2. Differential late conditioned skin conductance responses (second interval responses, SIRs) as mean amplitudes ± standard error of the mean (SEM) for the Retrieval and Reinstatement test in healthy control participants (HCs, circles) and patients with chronic back pain (CBP, triangles) that either received hydrocortisone (black) or placebo (white). Dashed lines indicate reinstatement, that is, unannounced unconditioned stimulus (US) presentations.

Given first evidence suggesting greater reinstatement of differential neural responses in patients with irritable bowel syndrome (IBS) compared to HCs,[4] we hypothesized that the unexpected experience of pain (ie, reinstatement) should result in larger differential SCRs in placebo-treated patients with CBP compared to HCs during the reinstatement test when compared to the retrieval test. Indeed, the analysis of the placebo groups revealed a return of previously extinguished differential SCRs only in the patients, but not in HCs. These findings support greater reinstatement effects of conditioned pain-related fear responses in patients with non-specific CBP, in line with our hypothesis. This evidence of impaired extinction memory retrieval in CBP corroborates the results of the only other pain-related conditioning study that tested for reinstatement effects in chronic pain (IBS),[4] and expands evidence of altered fear extinction learning in various chronic pain conditions, including CBP[10] and IBS,[4,54] despite some contradictory evidence.[3,5] These findings are complemented by data supporting altered fear generalization, thus far shown in patients with fibromyalgia[7,8] and chronic hand pain.[6] Together, these converging findings support the role of extinction deficits across chronic pain conditions, supporting efforts to elucidate mediators and moderators, including the role of stress that could increase or decrease relapse phenomena after (initially) successful extinction training. Indeed, looking beyond mere extinction training is important, and well-established in the broader field of fear conditioning accomplished in the context of stress- and

anxiety-related conditions like phobias and post-traumatic stress disorders.[55,56] The body of research supports the notion that a return of fear after successful extinction training can be induced by unexpected re-exposure to the US (ie, reinstatement).[57]

From a clinical perspective, impaired extinction efficacy that results in a higher vulnerability to the return of fear is critically relevant. In the context of pain, the role of pain-related fear as a key driver of maladaptive avoidance behavior is conceptually embedded within the fear-avoidance model.[1] Indeed, the vicious feedback cycle of symptom perception, fear and stress responses, hypervigilance, and sensitization, plays a key role in the transition from acute to chronic pain and ultimately increases the risk for relapse and treatment failure.[58] Based on our findings that only patients with CBP but not HCs showed a reinstatement of conditioned responses, we propose that patients have a greater vulnerability for the return of fear phenomena, possibly given the typical waxing and waning of symptoms, especially prior experiences of sudden symptom worsening without obvious triggers or predictors (which is realized in reinstatement). A lack of reinstatement effects in placebo-treated healthy controls has been reported in experimental conditioning studies.[30,4,14,59] This may be due to small effects and/or large inter-individual variability, especially in healthy individuals without vulnerability factors, the experimental paradigms, and/or a limited ecological validity for the healthy participants. These results embrace the idea that psychological and/or symptom-related vulnerability factors shape the return of fear and underscore the need for mechanistic studies in patient cohorts.

Although stress plays a broad role in the pathophysiology of chronic pain and is an important component of the fear-avoidance model, the effects of acute stress or stress mediators on extinction efficacy have never been experimentally tested in the context of pain. Oral administration of hydrocortisone constitutes an established psychopharmacological approach allowing to test the effects of elevated cortisol levels on different facets of the response to acute pain, including pain-related fear conditioning. While it has previously been applied to assess effects on differential pain-related fear acquisition in healthy individuals,[60] this study now tests cortisol effects on extinction efficacy in the field of pain. Herein, hydrocortisone administration successfully increased salivary cortisol concentrations in both patients with CBP and HCs, without evidence of group differences in the cortisol response. Compared to placebo, HCs in the hydrocortisone group showed reinstatement, indicating that acutely increased cortisol enhances the return of pain-related fear in healthy participants. This finding is consistent with previously reported stress-induced effects on extinction efficacy, i.e., the reinstatement of fear memory in healthy participants outside of the pain context.[61-63] Findings are in accordance with the 'STaR' ('Stress Timing affects Relapse') model[64] proposing timing-dependent effects of stress on extinction processes.

In patients with CBP, we observed opposite cortisol effects, which appeared to interfere with the reinstatement effect observed in the placebo-treated CBP group. When interpreting this finding and its possible clinical implications, it is important to consider that response changes induced by acutely elevated cortisol concentrations in healthy individuals constitute an evolutionary-driven, adaptive response that is fundamental to behavioral flexibility in the face of acute threats to homeostasis.[65] Indeed, adaptive defensive behaviors, including avoidance driven by pain-related fear, are normally selectively scaled and dynamically changed based on the degree or imminence of danger. Stress-induced cortisol increases conceivably impact on the assessment of the degree or imminence of danger, in line with the trans-diagnostic dimensional model of defensive behaviors[66] and consistent with earlier data that hydrocortisone administration prior to fear acquisition training impacts on fear learning.[60]

Importantly, the differential impact of hydrocortisone administration in patients with CBP was driven by altered safety learning rather than being attributable to a general reinstatement effect, which is in line with previous observations in pain-related fear conditioning studies in chronic pain.[4] Those deviations from adaptive differential responses, as observed in the patients with CBP, could reflect a stress-related impairment in mechanisms underlying pain-related safety learning. This is relevant since adequate responses to safety signals constitute an important regulatory process in the context of fear responses,[67] facilitating fear inhibition and safety-seeking, and clearly deserve further study.

While more detailed implications need to be clarified in future studies, results may further be discussed in light of alterations in HPA axis activity observed in patients with chronic pain.[25,29] A potential disturbance of the glucocorticoid receptor function and its pathophysiologic relevance has been reported for patients with fibromyalgia, chronic low back pain, depression, and post-traumatic stress disorder.[68-72] The intricate and complex interactions of stress and chronic pain are well-known,[26,29] and encompass multiple psychological and physiological response systems impacting on central and peripheral processes. The particular relevance of changes in the glucocorticoid system for the development and maintenance of chronic pain has recently been emphasized,[25] further supported by recent experimental evidence showing altered pain regulation in response to acute stress (ie, in a model of stress-induced analgesia).[73]

As a limitation, we did not obtain contingency ratings after the retrieval or reinstatement test, which would have provided more information about conscious learning procedures on study day 2. Moreover, we did not assess acute stress ratings. Perceived stress as a result of the painful stimulation or the learning task could have influenced our results and should be assessed in future studies. Importantly, our data suggest that hydrocortisone administration has no significant effect on pain perception as indicated by SCRs and US pain intensity ratings during reinstatement. This is in line with a recent report of unaltered heat pain thresholds following treatment with comparable hydrocortisone dosages in healthy participants.[60] We therefore assume

that the observed differences are indeed related to aberrant extinction retrieval rather than a direct effect of cortisol on pain sensitivity and hence the reinstatement procedure.

Contrary to the observations of day 1 showing behaviorally impaired differential learning during acquisition training indexed by CS valence ratings for patients with CBP, SCR-related reinstatement effects on day 2 were not paralleled by behavioral responses (see Supplementary Material for details). Other studies also show weak or no significant effects regarding the reinstatement of pain-related emotions assessed via CS valence.[74,4,16] Alternative behavioral measures capturing other facets of learning or testing extinction memory could elucidate whether the observed results are indeed due to a failure to reinstate at the conscious (cognitive-affective) level, or merely could not be detected with the measure of valence.

Conclusions

Together, our data confirm previous postulations of the 'STaR model' in healthy individuals and expand those to the pain context. Pharmacologically-induced increase in systemic cortisol concentration resulted in the reinstatement of previously extinguished pain-related responses in HCs, indicating impaired extinction retrieval. Patients with CBP that received a placebo were characterized by impaired extinction retrieval and enhanced return of fear induced by reinstatement, a response which was actually suppressed by hydrocortisone treatment. This observation may be discussed with respect to elevated chronic stress levels and changes in the glucocorticoid system that were previously reported for patients with chronic pain. Importantly, the influence of acute stress mediators in the context of pain treatment needs to be more fully understood. Treatment success could be optimized by considering the time-dependent impact of acute stress responses on different phases of therapeutic interventions, especially exposure therapy.

References

1. Vlaeyen JWS, Linton SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 85:317-332, 2000.

2. Harvie DS, Moseley GL, Hillier SL, Meulders A: Classical conditioning differences associated with chronic pain: a systematic review. J Pain 18(8):889-898, 2017.

3. Harvie DS, Weermeijer JD, Olthof NA, Meulders A: Learning to predict pain: differences in people with persistent neck pain and pain-free controls. PeerJ 8(6):1-18, 2020.

4. Icenhour A, Langhorst J, Benson S, *et al.* Neural circuitry of abdominal pain-related fear learning and reinstatement in irritable bowel syndrome. Neurogastroenterol Motil 27(1):114-127, 2015.

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Conflict of interest statement

The authors declare that no conflicts of interest exist.

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Code Availability

The R code used for data analyses in this study is available from the corresponding author upon request.

Preregistration Statement

The conducted research was not pre-registered.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.10.028.

5. Klinger R, Matter N, Kothe R, Dahme B, Hofmann UG, Krug F: Unconditioned and conditioned muscular responses in patients with chronic back pain and chronic tension-type headaches and in healthy controls. Pain 150(1):66-74, 2010.

6. Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JWS, Moseley GL: Contingency learning deficits and generalization in chronic unilateral hand pain patients. J Pain 15(10):1046-1056, 2014.

7. Meulders A, Jans A, Vlaeyen JWS: Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. Pain 156(1):108-122, 2015.

8. Meulders A, Meulders M, Stouten I, De Bie J, Vlaeyen JWS: Extinction of fear generalization: a comparison between fibromyalgia patients and healthy control participants. J Pain 18(1):79-95, 2017.

9. Schlitt F, Schmidt K, Merz CJ, *et al.* Impaired pain-related threat and safety learning in patients with chronic back pain. Pain 163(8):1560-1570, 2021.

10. Schneider C, Palomba D, Flor H: Pavlovian conditioning of muscular responses in chronic pain patients: central and peripheral correlates. Pain 112(3):239-247, 2004.

11. den Hollander M, De Jong JR, Volders S, Goossens ME, Smeets RJ, Vlaeyen JW: JW: fear reduction in patients with chronic pain: a learning theory perspective. Expert Rev Neurother 10(11):1733-1745, 2010.

12. Meulders A: Fear in the context of pain: lessons learned from 100 years of fear conditioning research. Behav Res Ther 131:1-14, 2020.

13. Claassen J, Labrenz F, Ernst TM, *et al.* Altered cerebellar activity in visceral pain-related fear conditioning in irritable bowel syndrome. Cerebellum 16:508-517, 2017.

14. Kattoor J, Gizewski ER, Kotsis V, *et al.* Fear conditioning in an abdominal pain model: neural responses during associative learning and extinction in healthy subjects. PLoS One 8(2):1-12, 2013.

15. Meulders A, Rousseau A, Vlaeyen JWS: Motor intention as a trigger for fear of movement-related pain: an experimental cross-US reinstatement study. J Exp Psychopathol 6(3):206-228, 2015.

16. Schmidt K, Forkmann K, Elsenbruch S, Bingel U: Enhanced pain-related conditioning for face compared to hand pain. PLoS One 15(6):1-19, 2020.

17. de Quervain DJF, Aerni A, Schelling G, Roozendaal B: Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol 30(3):358-370, 2009.

18. de Quervain D, Wolf OT, Roozendaal B: Glucocorticoid-induced enhancement of extinction—from animal models to clinical trials. Psychopharmacology 236(1):183-199, 2019.

19. Merz CJ, Wolf OT: How stress hormones shape memories of fear and anxiety in humans. Neurosci Biobehav Rev 142:1-9, 2022.

20. Shields GS, Doty D, Shields RH, Gower G, Slavich GM, Yonelinas AP: Recent life stress exposure is associated with poorer long-term memory, working memory, and self-reported memory. Stress 20(6):598-607, 2017.

21. Shields GS, Sazma MA, McCullough AM, Yonelinas AP: The effects of acute stress on episodic memory: a meta-analysis and integrative review. Psychol Bull 143(6):636-675, 2017.

22. Soravia LM, Heinrichs M, Aerni A, *et al.* Glucocorticoids reduce phobic fear in humans. Proc Natl Acad Sci USA 103(14):5585-5590, 2006.

23. Daviu N, Bruchas MR, Moghaddam B, Sandi C, Beyeler A: Neurobiological links between stress and anxiety. Neurobiol Stress 11:1-9, 2019.

24. Labrenz F, Merz CJ, Icenhour A: Connecting dots in disorders of gut-brain interaction: the interplay of stress and sex hormones in shaping visceral pain. Front Psychiatry 14:1-7, 2023.

25. Nees F, Löffler M, Usai K, Flor H: Hypothalamic-pituitary-adrenal axis feedback sensitivity in different states of back pain. Psychoneuroendocrinology 101:60-66, 2019.

26. Timmers I, Quaedflieg CWEM, Hsu C, Heathcote LC, Rovnaghi CR, Simons LE: The interaction between stress and chronic pain through the lens of threat learning. Neurosci Biobehav Rev 107:641-655, 2019.

27. Vachon-Presseau E: Effects of stress on the corticolimbic system: implications for chronic pain. Prog Neuropsychopharmacol Biol Psychiatry 87:216-223, 2018.

28. Elsenbruch S, Wolf OT: Could stress contribute to pain-related fear in chronic pain? Front Behav Neurosci 9:1-8, 2015.

29. Fries E, Hesse J, Hellhammer J, Hellhammer DH: A new view on hypocortisolism. Psychoneuroendocrinology 30:1010-1016, 2005.

30. Haaker J, Lonsdorf TB, Thanellou A, Kalisch R: Multimodal assessment of long-term memory recall and reinstatement in a combined cue and context fear conditioning and extinction paradigm in humans. PLoS One 8(10):1-10, 2013.

31. Champely S, Ekstrom C, Dalgaard P, *et al.* Basic Functions for Power Analysis. R Package Version 1.3-0. University of Lyon; 2020

32. Cohen J: Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Lawrence Erlbaum Associates; 2013

33. Airaksinen O, Brox JI, Cedraschi C, *et al.* Chapter 4: European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 15(Suppl. 2):192-300, 2006.

34. Nilges P, Essau C: Die Depressions-angst-stress-skalen: Der DASS—ein Screeningverfahren nicht nur für Schmerzpatienten. Schmerz 29:649-657, 2015.

35. Lonsdorf TB, Menz MM, Andreatta M, *et al.* Don't fear 'fear conditioning': methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci Biobehav Rev 77:247-285, 2017.

36. Dawson ME, Rissling AJ, Schell AM, Wilcox R: Under what conditions can human affective conditioning occur without contingency awareness?: Test of the evaluative conditioning paradigm. Emotion 7(4):755-766, 2007.

37. Wallin BG: Sympathetic nerve activity underlying electrodermal and cardiovascular reactions in man. Psychophysiology 18(4):470-476, 1981.

38. Boucsein W: Methods of electrodermal recording. In: Boucsein W, editor. Electrodermal Activity. Springer; 2012. pp 87-258.

39. Jentsch VL, Wolf OT, Merz CJ: Temporal dynamics of conditioned skin conductance and pupillary responses

during fear acquisition and extinction. Int J Psychophysiol 147:93-99, 2020.

40. Öhman A: Factor analytically derived components of orienting, defensive, and conditioned behavior in electrodermal conditioning. Psychophysiology 9(2): 199-209, 1972.

41. Wolter J, Lachnit H: Are anticipatory first and second interval skin conductance responses indicators of predicted aversiveness? Integr Physiol Behav Sci 28(2):163-166, 1993.

42. Nees F, Becker S: Psychological processes in chronic pain: influences of reward and fear learning as key mechanisms—behavioral evidence, neural circuits, and maladaptive changes. Neurosci Elsevier 387:72-84, 2018.

43. Laux L., Hock M., Bergner-Köther R., Hodapp V.: STADI: State-Trait-Angst-Depressions-Inventar. Hogrefe, December 20, 2016. Accessed March 11, 2020. https://www.testzentrale.de/shop/das-state-trait-angst-depressions-inventar.html.

44. Radloff LS: The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1(3):385-401, 1977.

45. Lautenbacher S, Huber C, Kunz M, *et al.* Hypervigilance as predictor of postoperative acute pain: Its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. Clin J Pain 25(2):92-100, 2009.

46. Walter B, Hampe D, Wild J, Vaitl D: Die Erfassung der Angst vor Schmerzen: Eine modifizierte deutsche Version der Pain Anxiety Symptom Scale (PASS-D). Der. Schmerz 16:83, 2002.

47. Petrowski K, Kliem S, Albani C, Hinz A, Brahler E: Norm values and psychometric properties of the short version of the Trier Inventory for Chronic Stress (TICS) in a representative German sample. PLoS One 14(11):1-12, 2019.

48. Zimmermann P., Messner C., Poser U., Sedelmeier P.: Ein Fragebogen erlebter Defizite der Aufmerksamkeit (FEDA) [A questionnaire measuring self-experienced deficits of attention, in German]. University of Freiburg: Institute for Psychology. Unpublished Manuscript, 1991. Accessed March 11, 2020. https://www.gnp.de/arbeitskreise-und-regionalgruppen/ak-aufmerksamkeit-und-gedaechtnis?file=files/user_files/content/pdf/downloads/uu-AK-AufmGed-FEDA.pdf.

49. Levenstein S, Prantera C, Varvo V, *et al.* Development of the perceived stress questionnaire: a new tool for psychosomatic research. J Psychosom Res 37(1):19-32, 1993.

50. RStudio Team: RStudio: Integrated Development Environment for R. Software Version 1.4.1103. RStudio Team; 2016

51. Bates D, Mächler M, Bolker BM, Walker SC: Fitting linear mixed-effects models using lme4. J Stat Softw 67:1-48, 2015.

52. Prokasy WF, Ebel HC: Three components of the classically conditioned GSR in human subjects. J Exp Psychol 73(2):247-256, 1967.

53. Ishihara K, Miyata Y: Skin potential activity under two electrode electrolytes. Shinrigaku Kenkyu 51(1):291-294, 1980.

54. Labus JS, Hubbard CS, Bueller J, *et al.* Impaired emotional learning and involvement of the corticotropin-releasing factor signaling system in patients with irritable bowel syndrome. Gastroenterology 145(6):1253-1261, 2013.

55. Raeder F, Merz CJ, Tegenthoff M, Wolf OT, Margraf J, Zlomuzica A: Post-exposure cortisol administration does not augment the success of exposure therapy: a randomized placebo-controlled study. Psychoneuroendocrinology 99: 174-182, 2019.

56. Wicking M, Steiger F, Nees F, *et al.* Deficient fear extinction memory in posttraumatic stress disorder. Neurobiol Learn Mem 136:116-126, 2016.

57. Hartley CA, Phelps EA: Extinction learning. In: Seel NM, editor. Encyclopedia of the Sciences of Learning. 1st ed.Springer; 2012. pp 1252-1253, .

58. Dindo L, Lackner J: Effects of different coping strategies on physical and mental health of patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 15(10):1500-1503, 2017.

59. Pawlik RJ, Petrakova L, Cueillette A, *et al.* Inflammation shapes neural processing of interoceptive fear predictors during extinction learning in healthy humans. Brain Behav Immun 108:328-339, 2023.

60. Benson S, Siebert C, Koenen LR, *et al.* Cortisol affects pain sensitivity and pain-related emotional learning in experimental visceral but not somatic pain: a randomized controlled study in healthy men and women. Pain 160:1719-1728, 2019.

61. Hamacher-Dang TC, Uengoer M, Wolf OT: Stress impairs retrieval of extinguished and unextinguished associations in a predictive learning task. Neurobiol Learn Mem 104:1-8, 2013.

62. Kinner VL, Wolf OT, Merz CJ: Cortisol increases the return of fear by strengthening amygdala signaling in men. Psychoneuroendocrinology 91:79-85, 2018.

63. Raio CM, Brignoni-Perez E, Goldman R, Phelps EA: Acute stress impairs the retrieval of extinction memory in humans. Neurobiol Learn Mem 112:212-221, 2014.

64. Meir Drexler S, Merz CJ, Jentsch VL, Wolf OT: How stress and glucocorticoids timing-dependently affect extinction and relapse. Neurosci Biobehav Rev 98:145-153, 2019.

65. McEwen BS: Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87:873-904, 2007.

66. Hamm AO: Fear, anxiety, and their disorders from the perspective of psychophysiology. Psychophysiology 57(2):1-14, 2020.

67. Kong E, Monje FJ, Hirsch J, Pollak DD: Learning not to fear: neural correlates of learned safety. Neuropsychopharmacology 39(3):515-527, 2014.

68. Geiss A, Rohleder N, Anton F: Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology 37(5):671-684, 2012.

69. Griep EN, Boersma JW, Lentjes EG, Prins AP, van der Korst JK, de Kloet ER: Function of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia and low back pain. J Rheumatol 25(7):1374-1381, 1998.

70. McLean SA, Williams DA, Harris RE, *et al.* Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. Arthritis Rheum 52(11):3660-3669, 2005.

71. Rohleder N, Wolf JM, Wolf OT: Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder. Neurosci Biobehav Rev 35(1):104-114, 2010.

72. Wingenfeld K, Wolf OT: Effects of cortisol on cognition in major depressive disorder, posttraumatic stress disorder and borderline personality disorder. Psychoneuroendocrinology 51:282-295, 2015.

73. Löffler M, Schneider P, Schuh-Hofer S, *et al.* Stress-induced hyperalgesia instead of analgesia in patients with chronic musculoskeletal pain. Neurobiol Pain 13:1-11, 2023.

74. Gatzounis R, De Bruyn S, de Velde L, Van, Meulders A: No differences in return of pain-related fear after extinction and counterconditioning. Emotion 22(8):1886-1894, 2021.