1) Title: Stress-induced analgesia in patients with chronic musculoskeletal pain and healthy controls

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Abstract

Introduction: Individuals with chronic musculoskeletal pain show impairments in their pain-modulatory capacity. Stress-induced analgesia (SIA) is a paradigm of endogenous pain inhibition mainly tested in animals. It has not been tested in patients with chronic pain despite the important role of stress in pain modulation and the chronicity process.

Methods: SIA was tested in 22 patients with chronic musculoskeletal pain and 18 healthy participants matched for age and gender. Pain thresholds, pain tolerance and suprathreshold pain sensitivity were examined before and after a cognitive stressor. Additionally, chronic stress levels, pain catastrophizing and pain characteristics were assessed as potential modulating factors.

Results: Patients with chronic musculoskeletal pain compared to healthy controls showed significantly impaired SIA ($F(1,37)=5.63, p=.02$) for pain thresholds, but not pain tolerance ($F(1,37)=0.05, p=.83$) and stress-induced hyperalgesia (SIH) to suprathreshold pain ratings ($F(1,37)=7.76, p=.008$). Patients ($r(22)=-0.50, p=.05$) but not controls ($r(18)=-0.39, p=.13$) with high catastrophizing had low SIA as assessed by pain thresholds. In controls suprathreshold pain ratings were significantly positively correlated with catastrophizing ($r(18)=0.57, p=.03$) and life-time stress exposure ($r(18)=0.54, p=.03$). In patients neither catastrophizing ($r(22)=0.21, p=.34$) nor stress exposure ($r(22)=0.34, p=.34$) were associated with suprathreshold SIH.

Discussion: Our data suggest impairments of SIA and SIH in patients with chronic musculoskeletal pain. Catastrophizing was associated with deficient SIA in the patients and higher pain ratings in controls. High life time stress also increased pain ratings in the controls.
Keywords: stress-induced analgesia, descending inhibition, stress-induced hyperalgesia, musculoskeletal pain, chronic pain
Summary

Patients with chronic musculoskeletal pain compared to controls show deficient stress-induced analgesia and stress-induced hyperalgesia to a cognitive stressor.
Introduction

Mechanisms of endogenous pain modulation represent the body’s ability to regulate pain responses by activating regulatory pathways such as the descending inhibitory pain pathways. Previous research, using painful stimulation within a conditioned pain modulation (CPM) paradigm as an activating stimulus for the descending pain-inhibitory system, has shown that patients with chronic pain often show deficiencies in pain inhibition [31]. However, it would also be interesting to employ pain-inhibitory stimuli that do not involve painful stimulation to establish the generality of deficient pain inhibition beyond nociceptive stimulation. Stress-induced analgesia (SIA) is such a paradigm, where an acute non-pain-related stressor inhibits pain perception. SIA involves stressors such as social isolation [40] or restraint stress [7] in animals and video game playing [25] or exposure to mental arithmetic plus noise [19; 61] in humans. Stress has been proposed as an important factor in the onset of pain chronicity [3; 56], and patients with fibromyalgia perceive stress as an aggravating factor for their pain [37], show elevated stress reactivity [53] and an impaired circadian rhythm of blood cortisol levels [10]. Further, acute stress impairs pain inhibition in CPM in healthy persons [23; 36] and patients with fibromyalgia [6]. However, deficiencies in SIA have not been systematically studied in chronic pain populations. Stress cannot only induce analgesia, but also hyperalgesia. This bidirectional modulation was associated with the duration of immobilization stress in rats, with analgesia after a single exposure and hyperalgesia after a repetition over 7 days[7]. Further, stress-induced hyperalgesia (SIH) could be induced in patients with fibromyalgia, but not in controls when pressure pain thresholds were used as a test stimulus [8], while SIH was present in controls when thermal pain thresholds were used as a test stimulus [8; 43].
Psychological factors can modulate the response to stress and pain [33]. The exposure to chronic stress may augment the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis to subsequent stressors [11]. High pain catastrophizing has been associated with flattened morning salivary cortisol profile [41] and reduced pain inhibition in a CPM paradigm [55; 58] and a paradigm on exercise-induced analgesia [4], and therefore may be interfering with SIA. Further, the spatial extent of pain was reported to be higher in back pain patients who were exposed to stressful life-events, such as a psychological trauma [52], compared to patients without trauma exposure. A high spatial extent of clinical pain has been associated with lower heat and cold pain thresholds in pain-free body sites [21], and a higher number of pain areas has been associated with lower levels of pain inhibition in a CPM paradigm in patients with chronic back pain [22]. Therefore, clinical pain extent may be associated with pain-inhibitory capacity.

In this study we set out to investigate (1) if SIA is impaired in patients with chronic musculoskeletal pain (2) the influence of psychological factors on SIA, hypothesizing that SIA would be impaired in subjects with higher catastrophizing, increased life-time exposure to chronic stress and patients with a higher spatial extent of their pain.
Methods

Participants

Twenty-two patients (15 women, age: mean (M)=55.90 standard deviation (SD)=12.36, see Table 1 for demographic and clinical data) with chronic localized and widespread musculoskeletal back pain (of whom 9 fulfilled the diagnostic criteria for fibromyalgia by Wolfe et al [60]) and 18 healthy controls (15 women, age: M=52.94, SD=11.93) participated in this study. Participants with comorbid mental disorders, infections, neurological disorders, possible pregnancy, cardiovascular problems or brain injuries were excluded. Patients refrained from their acute medication (e.g. nonsteroidal anti-inflammatory drugs, NSAIDs; muscle relaxants) in agreement with their physician one to three days before prior to testing (one day for NSAIDs, three days for muscle relaxants and other acute medication other than NSAIDs). The Ethics Committee of the Medical Faculty Mannheim, University of Heidelberg, Germany, approved the study and written informed consent was obtained from each participant.

|                          | Patients with chronic pain | Healthy controls | Group test Chi²/t(df), p |
|--------------------------|----------------------------|------------------|-------------------------|
| N (male/female)          | 22 (7/15)                  | 18 (3/15)        | Chi²(1)=0.54, p=.54     |
| Age: M±SD                | 56.55±12.43                | 52.94±11.93      | t(36.45)=-0.76, p=.54   |
| HADS Anxiety: M±SD       | 7.09±3.12                  | 5.28±2.22        | t(34.67)=-2.05, p=.08   |
| HADS Depression: M±SD    | 13.32±2.44                 | 13.48±1.64       | t(35.28)=0.35, p=.73    |
| PRSS Catastrophizing: M±SD| 1.54±0.95                  | 0.41±0.42        | t(30.81)=-3.96, p=.003  |
| PRSS Active Coping: M±SD | 3.08±0.79                  | 4.14±0.73        | t(36.33)=3.30, p=.008   |
| TICS Stress: M±SD        | 1.54±0.58                  | 0.84±0.38        | t(35.58)=-2.60, p=0.03  |
| MPI pain severity: M±SD  | 3.05±1.30                  | n.a.             | n.a.                    |
| MPI interference: M±SD   | 2.34±1.69                  | n.a.             | n.a.                    |
| MPI affective distress: M±SD| 2.38±0.73                | n.a.             | n.a.                    |
Table 1: Demographic and clinical characteristics of the patients and controls. Significant differences (p<.05) are depicted in bold. HADS: Hospital Anxiety and Depression Scale, PRSS: Pain-Related Self Statements Scale, TICS: Trier Inventory of Chronic Stress; MPI: Multidimensional Pain Inventory; WPI: Widespread Pain Index, SS: Symptom Severity Scale, CPG: Chronic Pain Grade, M: mean, SD: standard deviation, df: degrees of freedom, IQR: Interquartile range; n.a.: not applicable.

| Metric                         | Mean (SD) | df | Median (IQR) |
|-------------------------------|-----------|----|--------------|
| MPI support: M±SD             | 2.63±1.28 | n.a. | n.a.         |
| MPI self-control: M±SD        | 2.26±1.64 | n.a. | n.a.         |
| WPI Widespread Pain: M±SD     | 6.50±4.10 | n.a. | n.a.         |
| SS Symptom Severity: M±SD     | 4.07±3.36 | n.a. | n.a.         |
| CPG Chronic Pain Grade: Median (IQR) | 2(1-3) | n.a. | n.a.         |

Clinical pain assessments

Prior to the experiments, the participants completed the Chronic Pain Grade (CPG [57]), the Fibromyalgia Symptom Scale (FS [60]), the Pain-Related Self Statements Scale (PRSS [17]) and the Multidimensional Pain Inventory (MPI). The CPG [57] is a seven-item instrument that measures chronic pain severity in the two dimensions intensity and disability. It classifies patients into five hierarchical grades: Grade 0 (pain free), Grade I (low disability–low intensity), Grade II (low disability–high intensity), Grade III (high disability–moderately limiting) and Grade IV (high disability–severely limiting). It was found to be valid and reliable for use in a general population as a self-completion questionnaire [47]. The FS [60] assesses the severity of fibromyalgia symptoms on two different scales. The Widespread Pain Index (WPI) assesses pain or tenderness in 19 body regions. When summed, these items result in a score between 0 and 19. The Symptom Severity Scale assesses additional somatic, cognitive and affective symptoms related to fibromyalgia. When summed, these items result in a score between 0 and 12. The FS was shown to have a sensitivity of 96.6% and a specificity of 91.8% for the diagnosis of fibromyalgia. The PRSS [17] assesses catastrophizing and active coping and is a German language equivalent of the Coping Strategies Questionnaire [44]. It has excellent reliability.
(α=.92 for catastrophizing and α=.88 for active coping) and validity, as shown by significantly higher values for pain catastrophizing and significantly lower values for active coping in pain patients compared to healthy controls, and low to moderate correlations with other pain-related variables such as amount of daily activities, affective distress or pain severity. The MPI assesses patients’ pain severity, interference of the pain, self-control, negative mood and social support. The MPI has been used in a large number of studies with a diverse sample of chronic pain patients and has excellent reliability and validity [20; 30].

Psychological assessments

Prior to the experiments, the participants completed the Hospital Anxiety and Depression Scale (HADS [48]), and a short version of the Trier Inventory of Chronic Stress (TICS [45]). The TICS [45] measures chronic stress with a mean score of six scales (work overload, worries, social stress, lack of social recognition, work discontent, and intrusive memories). The answers are recorded on a 0–4 rating scale, with a total number of 30 items. The scale is validated in German participants and has a reliability between α=.84 and α=.91. The HADS [48] assesses anxiety and depressive symptoms on 7 items each. The scale has excellent reliability (α ranges from 0.78–0.93 for the HADS-A and from 0.82–0.90 for the HADS-D). It was found to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in both somatic, mental disorders and primary care patients and in the general population [2].

All participants were interviewed by a psychologist using the German version of the Structured Clinical Interviews (SCID I and II) for DSM IV Axes I and II disorders [59] to assess comorbid mental disorder. One patient fulfilled the criteria of an acute
depressive episode and three patients reported a single depressive episode in the past. No healthy participant reported any axis I or II disorders.

**Experimental procedure**

All participants were examined on two separate days. On the first day, the difficulty of the cognitive stressor was determined to ensure successful stress induction during the SIA experiment. The SIA experiment was carried out on the second day. Electrical pain thresholds, pain tolerance and suprathreshold pain sensitivity were assessed before and after stress induction, see Figure 1 and below for details.

![Figure 1: Experimental procedure](image)

*Figure 1: Experimental procedure: first pain threshold and pain tolerance were measured in three ascending series followed by a series of 10 stimuli with an intensity corresponding to 50% of the pain tolerance intensity. These 10 stimuli were rated on a numerical rating scale with respect to pain intensity (0 = not painful; 100 = worst pain imaginable) and unpleasantness (0 = not unpleasant; 100 = extremely unpleasant). In the pre-stress scanning phase, 10 electrical stimulation blocks were delivered. Before and during stress induction, blood pressure and heart rate data were gathered. Before and after the stress induction, subjects were asked to rate the perceived stress before or during stress induction respectively on a numerical rating scale (0 = no stress; 100 = extreme stress). Finally, as post-stress measurement, application and rating (intensity and unpleasantness) of 10 painful stimulus blocks and pain threshold and pain tolerance determination were repeated.*

**Pain threshold, pain tolerance and suprathreshold pain testing**

Pain perception thresholds and pain tolerance were assessed before and after the stressor. For pain site–specific electrical stimulation, a pair of needle electrodes (20 mm long, 0.35-mm uninsulated tip, 2-mm² stimulation area, model: 9013R0272, 28G, Alpine Biomed ApS, Skovunde, Denmark) was placed subcutaneously at the left
lower back, 2 cm lateral to the spine, between L1 and L3 (1 mm needle separation). Electric stimuli were applied using a constant current stimulator (model DS7A; Digitimer, Hertfordshire, England). The experiment was performed using Presentation® software (Version 14.0, http://www.neurobs.com/). The participants received ascending electrical stimulation trains (Stimulation train: 8 stimuli of 2ms, inter stimulus interval = 112msec, inter train interval = 2sec) via the subcutaneous needle electrodes and were instructed to press a button when they felt that the stimulus had become just noticeably painful (pain threshold) and when they could no longer tolerate a higher stimulus intensity (pain tolerance). Each measure was determined three times and the last two trials of each stimulation train were used. After the first threshold determination, the stimulation intensity was calibrated at a perceived pain intensity rating of 50 on a numerical rating scale (endpoints 0=“no pain” and 100=“worst pain imaginable”). The first threshold assessment was discarded and 50 percent of the difference between pain threshold and pain tolerance were added to the pain threshold, to calculate a preliminary stimulation intensity. In test trials (duration 12.5 seconds each, stimulus duration 2ms, 112 stimuli, inter stimulus interval 112msec) the perceived pain intensity was assessed using a numerical rating scale. The stimulation intensity was adapted between the test trials to reach a pain intensity rating of 50 out of 100 points, or to reach a rating closest possible to 50. The resulting stimulation intensity of each subject was used for testing of suprathreshold pain sensitivity. Participants received trains of electrical stimulation before and after the stressor. They received 10 stimulation blocks (duration 11.8 sec each, stimulus duration 2ms, 105 stimuli, inter stimulus interval = 112 ms), which were always followed by off blocks of 11.8 seconds duration. The mean levels of perceived pain intensity and pain unpleasantness were assessed using numerical rating scales with the endpoints 0 (“no pain” / “not unpleasant”) and
100 ("worst pain imaginable" / “extremely unpleasant”). In total, four SIA indices were derived by subtracting the (1) mean pain threshold, (2) mean pain tolerance, (3) pain intensity ratings and (4) pain unpleasantness ratings before the stressor from the respective values after the stressor.

Stress induction

The stressor used in this study was mental arithmetic combined with white noise. The mental arithmetic tasks were similar to those from the Konzentrations- und Leistungstest (Concentration and Performance Test: [13; 34]) and were presented by a female voice via earphones. Such mental arithmetic tasks have previously shown to be effective in the induction of stress [19; 54; 61]. Each task consisted of a series of two sets of three numbers (e.g. 5,9,4 and 3,8,11) that had to be added or subtracted. If the sum of the second set was smaller than the sum of the first set, the second result had to be subtracted, if the sum of the first set was smaller than that of the second set, the first result had to be added (i.e. 18+22 in this example). In our experiment an additional third arithmetic operation had to be executed after subtraction or summation (e.g. 40*2) and the subject had to verbally report the final result (i.e. 80 in this example). Each task had to be solved within 30s. In total subjects had to solve 30 tasks, resulting in a duration of the stressor of 15 minutes.

To account for individual cognitive performance, five parallel versions of the mental arithmetic task with varying difficulty (based on the arithmetic operations) were prepared. The individual difficulty level was determined for each participant on a separate day. For that purpose, 5 tasks of the lowest level of difficulty were presented. If the participant solved at least three of those, the next level was presented. If the participant solved at least three tasks at the second level again, the next level was presented. This was continued until the participant made more than
one error within a level or the highest level was reached. In the main experiment one level above the resulting difficulty level was used for stress induction. In order to increase the stressfulness of the task white noise was presented continuously and increased from 65 to 80 dB from the first to the last arithmetic calculation. The perceived stressfulness of the task was assessed before and after the stressor using a numerical rating scale with the endpoints 0 (“no stress”) and 100 (“extreme stress”).

*Physiological stress response: heart rate and blood pressure*

To assess physiological effects of the stressor, blood pressure and heart rate were measured with the Criticare 506N vital signs monitor (Criticare Systems Inc., Waukesha, USA), using a sampling rate of one per minute. Heart rate and blood pressure were measured during a 5 minute resting interval immediately before the stress phase and throughout the 15 minutes of the stress phase as well as for 5 minutes after the stressor.
Statistical analysis

Statistical analyses were performed using RStudio 1.0.143 (RStudio, Inc.) with R 3.4.0 (The R Foundation for Statistical Computing, https://www.r-project.org/). Missing values were imputed using the MICE package in R, applying predictive mean matching for numeric variables and a proportional odds model for ordered variables (maximum number of imputed values per variable: controls=2, patients=3). Outliers, which were defined as values more than two standard deviations above or below the respective mean, were removed from the analysis (maximum number of outliers per variable: controls=2, patients=2).

For the perceived stress ratings, systolic and diastolic blood pressure, heart rate as well as the SIA variables, analyses of variance were computed with group (healthy versus patient) as between and time (baseline versus post) as within effect. We used pairwise post-hoc t-tests (false discovery rate, FDR [1] corrected) to compare the SIA measures within and between groups. Possible modulatory effects of depressive symptom severity, anxiety or pain chronicity on SIA effects were examined using correlations of the respective effects with the HADS subscales and the CPG. In addition, we correlated the PRSS catastrophizing scale, the TICS and the WPI with the difference in pain thresholds, pain tolerance and ratings during the experiment. We used the false discovery rate (FDR [1]) to correct for multiple comparisons.
Results

*Perceived stress during SIA*

Perceived stress increased significantly after the stressor compared to before (time: $F(1,33)=78.10$, $p<.001$) but did not significantly differ between healthy participants and patients (group: $F(1,33)=1.59$, $p=.22$; time*group: $F(1,33)=1.01$, $p=.32$). Heart rate, systolic and diastolic blood pressure significantly increased during the stressor compared to before the stressor (time: heart rate: $F(1,37)=11.26$, $p=.002$; systolic blood pressure: $F(1,37)=30.68$, $p<.001$; diastolic blood pressure: $F(1,37)=15.99$, $p<.001$). HR, systolic and diastolic blood pressure did not significantly differ between patients and controls (group: heart rate: $F(1,37)=0.37$, $p=.54$; systolic blood pressure: $F(1,37)=0.61$, $p=.44$; diastolic blood pressure: $F(1,37)=0.84$, $p=.36$), neither did the increase in HR during the stressor (time*group: $F(1,37)=0.41$, $p=.53$). However, the increase in systolic (time*group: $F(1,37)=6.79$, $p=.01$) and diastolic (time*group: $F(1,37)=5.32$, $p=.03$) blood pressure was significantly higher in patients than controls (see Table 2).

| Patients with chronic pain | Healthy Controls |
|----------------------------|------------------|
| **Perceived stress (NRS)** | Before (M±SD)    | During (M±SD)  | Before (M±SD)    | During (M±SD)  |
| 17.11±21.56                | 64.21±22.50      | 14.19±21.23    | 51.56±27.19      |
| **Heart Rate**             | 66.35±11.11      | 73.24±9.47     | 65.77±10.59      | 70.41±9.59     |
| **Blood pressure: systolic**| 128.22±14.65     | 144.02±16.52   | 129.81±16.51     | 135.12±16.23   |
| **Blood pressure: diastolic**| 74.19±9.24       | 82.53±9.23     | 74.86±10.99      | 76.84±8.73     |

Table 2: Change in perceived stress levels and associated changes in heart rate and blood pressure. The table depicts the stress ratings, systolic and diastolic blood pressure and heart rate before and during the stressor. All values are depicted as mean (M) and standard deviation (SD). NRS: Numerical Rating Scale.
Differences between pain patients and healthy individuals in stress-induced pain modulation

For pain thresholds, there was a significant SIA effect (time: F(1,37)=6.56, p=.01) and healthy participants showed significantly higher pain thresholds than patients with chronic pain (group: F(1,37)=7.85, p=.008). The time x group effect was significant (F(1,37)=5.63, p=.02). Post-hoc comparisons of pain thresholds before and after the stressor revealed a significant SIA effect for the healthy participants (t(17)=-2.56, p=.04), but not for the patients with chronic pain (t(21)=-0.51, p=.62), see Figure 2a.

There was no significant SIA effect for pain tolerance: F(1,37)=0.16, p=.69). Overall, healthy participants showed significantly higher pain tolerance (group: F(1,37)=8.08, p=.007) than patients with chronic pain. The time x group effect was not significant for pain tolerance (F(1,37)=0.05, p=.83). Post-hoc comparisons of pain tolerance before and after the stressor revealed no significant SIA effect for the healthy participants (t(17)=0.31, p=.76), or the patients with chronic pain (t(21)=0.31, p=.76), see Figure 2b.
Figure 2: Group differences in SIA. Thresholds and ratings before and after the stressor are depicted as mean and standard error of the mean. Patients with chronic pain are depicted with triangles and orange lines, healthy participants are depicted with circles and blue lines. Significant post hoc (FDR corrected) differences are labeled with asterisks (*p<.05). Figure 2a (top left) shows electrical pain threshold before (pre) and after (post) the stressor, figure 2b (top right) shows electrical pain tolerance before (pre) and after (post) the stressor, figure 2c (bottom left) shows pain intensity ratings before (pre) and after (post) the stressor, figure 2d (bottom right) shows pain unpleasantness ratings before (pre) and after (post) the stressor.

The analysis of the effect of stress on pain intensity and pain unpleasantness ratings revealed a significant increase in pain intensity ratings, indicating SIH (time: F(1,37)=5.13, p=.03), but not for pain unpleasantness ratings (F(1,37)=0.30, p=.58).
Overall, patients with chronic pain did not show significantly higher pain intensity (group: F(1,37)=2.55, p=.12) or pain unpleasantness ratings (group: F(1,37)=0.00, p=.99) than healthy participants. However, the SIH effect was significantly greater in patients with chronic pain compared to healthy participants for pain intensity ratings (time*group: F(1,37)=7.76, p=.008) but not pain unpleasantness ratings (F(1,37)=2.36, p=.13). Post-hoc comparisons of pain intensity revealed a significant SIH effect for patients with chronic pain (t(21)=-3.07, p=.01), but not for healthy participants (t(17)=0.75, p=.47), see Figure 2c and 2d. Neither the SIA effect nor the supratreshold SIH effect were significantly modulated by depressive symptom severity, anxiety or pain chronicity (all r<.30, p>.46).

Association of affective symptoms and coping with descending inhibition of pain

Compared to healthy controls, we found significantly higher levels of pain catastrophizing, lower levels of active coping and higher levels of chronic stress in our sample of patients with chronic musculoskeletal pain, see Table 1. Further, we found a significant correlation of pain catastrophizing with the stress effect on pain thresholds for patients with chronic musculoskeletal pain (r(22)=-0.50, p=.05), indicating lower SIA in patients with high catastrophizing. In healthy participants high catastrophizing (r(18)=0.57, p=.03) and increased life-time exposure to stress were significantly correlated with SIH effects on pain intensity ratings (r(18)=0.54, p=.03). We could not find further significant correlations of the pain-modulatory stress effect with pain catastrophizing, chronic stress, or clinical pain extent (all r<.42, p>.21), see Table 3.
|            | r(18)= | r(22)= | r(18)= | r(22)= | r(18)= | r(22)= | r(18)= | r(22)= | r(18)= | r(22)= |
|------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| TICS       | 0.37,  | 0.07,  | 0.42,  | 0.08,  |        | 0.34,  | 0.08,  |        | 0.34,  | 0.08,  |
|            | p=13,  | p=90,  | p=22,  | p=81,  | p=.03, | p=.34, | p=.76, | p=.52  | p=.76, | p=.52  |
| PRSS       | 0.39,  | 0.50,  | 0.33,  | 0.35,  |        | 0.21,  |        |        | 0.21,  |        |
| Catastrophizing | p=.13 | p=.05 | p=.22  | p=.32  | p=.03, | p=.34, |        |        | p=.34, |        |
| WPI        |        |        | r(22)=0.03 |        |        | r(22)= | r(22)= | r(22)= | r(22)= |
|            |        |        | , p=.90 |        |        | , p=.76 | , p=.76 | , p=.95 | , p=.70 |

Table 3: Association of stress induced pain-modulation with psychological factors and spatial pain extent. The table depicts the correlation of the stress effect on electrical pain thresholds, electrical pain tolerance, pain intensity and pain unpleasantness ratings with chronic stress, pain catastrophizing and clinical pain extent. Significant correlations (p<.05, fdr corrected) are depicted in bold. TICS: Trier Inventory of Chronic Stress, PRSS: Pain-Related Self Statements Scale, WPI: Widespread Pain Index, df: degrees of freedom.
Discussion and conclusions

This study investigated if stress-induced pain inhibition is deficient in patients with chronic musculoskeletal pain. Further, we examined the association of stress-induced pain modulation with pain catastrophizing, chronic stress exposure and the spatial extent of ongoing clinical pain. We found maladaptive stress-induced pain modulation in patients with chronic musculoskeletal pain, which manifested itself as deficient SIA for pain threshold and as SIH in suprathreshold measures of pain sensitivity. Pain catastrophizing was associated with SIA deficiencies as well as increased levels of SIH and chronic stress was related to increased levels of SIH. The spatial extent of the clinical pain was neither associated with SIA nor SIH.

Differences between pain patients and healthy individuals in stress-induced pain modulation

The endogenous regulation of pain is an important homeostatic function [49]. We report that the endogenous inhibition of pain by stress is impaired in patients with chronic musculoskeletal pain. Previous studies found that stress systems such as the hypothalamic-pituitary-adrenal (HPA) axis show a dysregulation in chronic pain, as seen by low basal cortisol secretion in patients with fibromyalgia [9]. This dysregulation was identified as an important factor driving the development of chronic pain, as shown by studies which found that a dysregulation of the circadian cortisol profile predicted the development of chronic musculoskeletal pain [35] and a low hypothalamic-pituitary-adrenal (HPA) axis response to acute stress at the age of 18 predicted musculoskeletal pain at the age of 22 [38]. Our data add evidence that the capacity to downregulate pain after a stressor is impaired in patients with chronic musculoskeletal pain. We further found an increase in perceived pain intensity, i.e. a SIH in patients with chronic musculoskeletal pain. Although prior studies using the
same stressor found SIA but no SIH responses in healthy subjects [18; 61], sensitization rather than habituation has previously been reported in musculoskeletal pain patients [12]. Further, hyperalgesia instead of analgesia has been reported previously in patients with fibromyalgia in a paradigm of exercise-induced analgesia [50] where pain ratings were used. Further, our data are in line with a study using the “Trier Social Stress Test“, a standardized procedure to induce psychosocial stress, which showed that patients with fibromyalgia displayed a SIH effect, which could not be observed in healthy controls [8]. Our results that there is no significant relationship between pain extent and SIH indicates that SIH as a maladaptive mechanism of pain modulation does not seem to be limited to widespread pain syndromes, but is also relevant in localized pain disorders. Both SIA [5] and SIH [27] have been shown to be mediated via central mechanisms which induce pain inhibition or facilitation via modulation of the descending pathways in the periaqueductal grey and the rostral ventromedial medulla. It is therefore plausible that both localized and widespread clinical pain are affected by deficiencies in these mechanisms. Future studies should examine whether impairments in SIA and SIH can also be found when painful test stimuli are applied in non-affected body sites, as pain testing was carried out at the site of the clinical pain in the current study.

**Association of psychological factors with stress-induced pain modulation**

Pain catastrophizing is a maladaptive coping style with feelings of helplessness, active rumination and excessive magnification of negative cognitions and feelings toward the painful situation and is more common in patients with chronic pain [29]. Pain catastrophizing was linked to pain severity, pain-related interference, disability and depressive symptoms of patients with chronic pain [15; 28; 51]. Longitudinal data further show that pain catastrophizing predicted the aggravation of pain in patients
with back pain and the development of back pain in formerly healthy individuals [39].

The mechanism by which pain catastrophizing modulates the pain experience is not completely understood, but it was proposed that catastrophizing amplifies sensitization and interferes with endogenous inhibition of pain in the central nervous system, including spinal pain processing [15; 16]. We found that SIA and SIH were associated with catastrophizing. The modulation of pain by catastrophizing has been related to activity in the anterior cingulate cortex (ACC) [24; 46], a brain region which is also involved in the inhibitory top-down control of the SIA effect. Further, a study on dental pain showed that catastrophizing did not modulate the perceived pain intensity per se, but that high catastrophizing was related to an enhanced SIH response [32]. This modulatory effect of catastrophizing, however, was not related to ACC activity, but to activity in the posterior hippocampus. In summary, pain catastrophizing seems to be related to the modulatory effect of stress on pain. Our results add that catastrophizing may modulate the SIA response and confirm the association of catastrophizing with augmented SIH responses. Future studies should clarify whether the enhancement of SIH and the reduction of SIA by catastrophizing share a common mechanism, or represent separate pathways. Neuronal targets for possible pathways could be the ACC and the hippocampus [5].

Our data indicate no significant relationship between chronic stress and SIA. On the other hand, higher lifetime stress exposure was associated with SIH in healthy participants. SIH has been demonstrated to be associated with experimental paradigms which implement longer stressors [27] and is thus more likely to be modulated by chronic stress than SIA, which is usually induced in paradigms with short stressors [7]. The absence of SIH modulation by chronic stress in patients, for whom we found higher lifetime stress exposure than for controls, indicates that the
effect of chronic stress may result in maladaptive pain modulation, i.e. SIH, at low levels of exposure. Neither SIA nor SIH were mediated by depressive symptoms or anxiety, indicating that deficient SIA and SIH are associated with chronic pain as a clinical entity and not with comorbid affective symptoms in these patients.

Limitations

This study has several limitations. First, there is a high variety in the employed experimental paradigms in studies on stress-induced pain modulation (for an overview on experimental paradigms on SIA see [5] and [26; 27] for SIH). Especially in animal models of SIA, other kinds of stressors, such as exposure to painful stimulation, have been employed. Therefore, our results cannot be generalized to all SIA paradigms, as differences in experimental parameters may account for differences in the effects. Second, our sample included patients with localized and widely spread musculoskeletal pain and was too small for a subsample analyses. We did not find a relationship between spatial extent of the clinical pain and SIA or SIH. However, there may be subgroups of patients who show only changes in either SIA or SIH and our sample size did not allow for further examination of such groups. Third, blood pressure increases during the stressor were higher in patients than in controls and these differences in blood pressure might therefore explain differences in stress-induced pain modulation. Increased levels of blood pressure are associated with analgesic effects induced by activation of descending inhibition via stimulation of arterial baroreceptors [14; 42]. It is therefore unlikely that the increased blood pressure responses in our patients explain the lack of SIA in these patients. However, changes in stress-reactivity may represent a core symptom in chronic pain disorders. Future studies should therefore address the question whether changes in stress-induced pain modulation are a mere representation of altered intensity of
induced stress levels or represent a change in the nature of the interaction effects of stress systems with pain modulatory pathways, such as the descending inhibition of pain.

**Conclusion**

The present study uncovers impaired SIA and SIH as possible mechanisms involved in chronic musculoskeletal pain. SIA was impaired in patients with chronic musculoskeletal pain and patients with high catastrophizing showed the greatest deficiencies. Further, healthy participants did not show SIH which may be a result of low life-time exposure to stress, since we found a significant correlation of SIH with chronic stress levels in the controls. Future research should target the neuronal and neurochemical mechanisms underlying these maladaptive effects of stress.
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Author contribution

ML, SK, PS, SSH, FN & HF designed the study; ML analyzed the data and wrote the paper; PS acquired the data, SSH, SK, KU, FN, RDT & HF revised the paper, FN, RDT & HF acquired the funding. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final version of the manuscript.

Conflict of interest

There is no conflict of interest.
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Figure legends

**Figure 1**: Experimental procedure: first pain threshold and pain tolerance were measured in three ascending series followed by a series of 10 stimuli with an intensity corresponding to 50% of the pain tolerance intensity. These 10 stimuli were rated on a numerical rating scale with respect to pain intensity (0 = not painful; 100 = worst pain imaginable) and unpleasantness (0 = not unpleasant; 100 = extremely unpleasant). In the pre-stress scanning phase, 10 electrical stimulation blocks were delivered. Before and during stress induction, blood pressure and heart rate data were gathered. Before and after the stress induction, subjects were asked to rate the perceived stress before or during stress induction respectively on a numerical rating scale (0 = no stress; 100 = extreme stress). Finally, as post-stress measurement, application and rating (intensity and unpleasantness) of 10 painful stimulus blocks and pain threshold and pain tolerance determination were repeated.

**Figure 2**: Group differences in SIA. Thresholds and ratings before and after the stressor are depicted as mean and standard error of the mean. Patients with chronic pain are depicted with triangles and orange lines, healthy participants are depicted with circles and blue lines. Significant post hoc (FDR corrected) differences are labeled with asterisks (*p<.05). Figure 2a (top left) shows electrical pain threshold before (pre) and after (post) the stressor, figure 2b (top right) shows electrical pain tolerance before (pre) and after (post) the stressor, figure 2c (bottom left) shows pain intensity ratings before (pre) and after (post) the stressor, figure 2d (bottom right) shows pain unpleasantness ratings before (pre) and after (post) the stressor.