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Novel neurophysiological evidence for preserved pain habituation across chronic pain conditions

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HIGHLIGHTS

- Pain habituation is not a sensitive marker for central sensitization across a variety of patients with chronic pain.
- Patients show prolonged latencies of contact-heat evoked potential and sympathetic skin response compared to healthy controls.
- Prolonged latencies potentially reflect a compensatory inhibitory tone within the nociceptive system in chronic pain patients.

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ABSTRACT

Objective: The present study aimed to investigate whether subjective and objective measures of pain habituation can be used as potential markers for central sensitization across various chronic pain patients.
Methods: Two blocks of contact-heat stimuli were applied to a non-painful area in 93 chronic pain patients (low back pain, neuropathic pain, and complex regional pain syndrome) and 60 healthy controls (HC). Habituation of pain ratings, contact-heat evoked potentials (CHEP), and sympathetic skin responses (SSR) was measured.
Results: There was no significant difference in any measure of pain habituation between patients and HC. Even patients with apparent clinical signs of central sensitization showed no reduced pain habituation. However, prolonged baseline CHEP and SSR latencies (stimulation block 1) were found in patients compared to HC (CHEP: Δ-latency = 23 ms, p = 0.012; SSR: Δ-latency = 100 ms, p = 0.022).
Conclusion: Given the performed multimodal neurophysiological testing protocol, we provide evidence indicating that pain habituation may be preserved in patients with chronic pain and thereby be of limited use as a sensitive marker for central sensitization. These results are discussed within the framework of the complex interactions between pro- and antinociceptive mechanism as well as methodological issues. The prolonged latencies of CHEP and SSR after stimulation in non-painful areas may indicate subclinical changes in the integrity of thermo-nociceptive afferents, or a shift towards antinociceptive activity. This shift could potentially affect the relay of ascending signals.
Significance: Our findings challenge the prevailing views in the literature and may encourage further investigations into the peripheral and central components of pain habituation, using advanced multimodal neurophysiological techniques.

1. Introduction

Chronic pain is a significant public health issue affecting up to 40% of the European population (Todd et al., 2019). While the

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understanding of pathomechanisms underlying chronic pain has grown in the past decades (Berger and Baria, 2022), the precise mechanisms leading to the development and maintenance of chronic pain remain unknown. Yet, identifying the underlying pathomechanism is a prerequisite for more successful chronic pain treatment approaches.

Frequently, there is a discrepancy between the assumed peripheral pain generator and the severity of chronic pain. This discrepancy or non-linearity in the input–output relationship could be partially explained by an imbalance in endogenous pro- and antinociceptive pain modulation (Yarnitsky, 2015). Patients with chronic pain often present with a shift towards pronociceptive modulation within neural networks possibly due to central sensitization (Nijs et al., 2021). Although the existence of central sensitization has been demonstrated in animal models (Simone et al., 1991), it cannot be directly assessed in humans. From a clinical point of view, ‘‘human-assumed” central sensitization is commonly reflected by extended pain patterns and widespread hypersensitivities (Arendt-Nielsen et al., 2018). Additionally, several experimental approaches have been proposed to indirectly investigate an increased responsiveness of central pain networks in humans, including experimental pain habituation (Arendt-Nielsen et al., 2018; Scheuren et al., 2020). Specifically, pain habituation is reflected as a response decrement following repetitive noxious stimulation and can be assessed by various subjective and objective readouts, such as pain ratings and pain-related evoked brain potentials (De Schoenmacker et al., 2022b). In addition, habituation of pain-related sympathetic skin responses (SSR) can be used as another objective readout (De Schoenmacker et al., 2022b), leveraging the intricate multilevel interaction between nociceptive and autonomic systems (Benarroch, 2006). The value of studying multiple readouts of pain habituation is that it allows a more comprehensive investigation of nociceptive processing.

Reduced pain habituation has been demonstrated in human surrogate models of central sensitization (Iannetti et al., 2013; Scheuren et al., 2020). Furthermore, reduced habituation of subjective and objective readouts following repetitive noxious stimulation has been shown in some (Hüllemann et al., 2017; Lütolf et al., 2022; Olesen et al., 2013; Scheuren et al., 2022; De Tommaso et al., 2011; Valeriani et al., 2003), but not all patients with chronic pain (Uglem et al., 2017; Zohsel et al., 2008). It thus remains unclear to what extent central sensitization (indexed by reduced pain habituation) is a common underlying pathomechanism across different chronic pain cohorts. In addition, the relationship between pain habituation and clinical pain characteristics or psychological factors has not been investigated often. However, pain characteristics and psychological factors were previously shown to be associated with pain modulation including experimental pain habituation (Lütolf et al., 2022; Nakamura et al., 2014).

The main objective of this study was to investigate experimental pain habituation using psychophysical (subjective) and neurophysiological measures (objective) across distinct cohorts of patients with chronic pain including complex regional pain syndrome (CRPS), low back pain (LBP), neuropathic pain after spinal cord injury (SCI), and healthy controls (HC). For this purpose, pain habituation was evaluated during repetitive contact-heat stimulation in a remote, pain-free area to investigate generalized ‘central’ sensitization. In addition, the relationships between pain habituation and pain characteristics or psychological factors were assessed.

In agreement with most previous studies, we hypothesized that an overall reduced pain habituation in chronic pain patients would exist when compared to HC, which would be most pronounced in the subgroup of patients with ‘‘human-assumed” central sensitization (Schuttert et al., 2021) independent of the pain etiology. Moreover, we hypothesized that patients with reduced pain habituation would report more widespread/intense pain and higher depression, anxiety, and pain catastrophizing scores.

2. Methods

2.1. Participants

From November 2019 to April 2022, chronic pain patients with CRPS, LBP, and neuropathic pain after SCI were recruited from the Balgrist University Hospital in Zurich Switzerland. Patients were enrolled through referrals from different departments (i.e., Rheumatology, Department of Chiropractic Medicine, and Spinal Cord Injury Center). HC were recruited through advertisements and matched to pain patients based on age and sex. However, due to time limitations in conducting the study, not every pain patient was matched to a HC; therefore, only a subgroup of pain patients was matched. Exclusion criteria for all study participants comprised of the inability to adhere to research instructions, pregnancy, neurological diseases (other than SCI, such as polyneuropathy or disk herniation), systemic diseases (such as autoimmune sickness or diabetes), or clinically manifested mental illnesses. Moreover, SCI patients were not included if the injury occurred less than 1 year ago or if the neurological level of the lesion was above C8, since the hand was used as a test area. Patients with LBP who had other primary symptoms of pain or LBP with “red flags” (e.g., infection, fractures, inflammation) were excluded from the study. Additional exclusion criteria for HC were acute pain, a history of chronic pain (>3 months), or LBP lasting more than three consecutive days during the previous year.

The Declaration of Helsinki (2013) was followed in all aspects of the study and each participant gave written informed consent before being enrolled in the study. The study was approved by the local ethics committee (Kantonale Ethikkommission (KEK) Zürich, (EK-04/2006, PB 2016-02051 and PB 2019-00136) and is registered on clinicaltrials.gov identifiers: NCT02138344 and NCT04433299.

2.2. Study design

This study was part of a larger initiative known as the Clinical Research Priority Program (CRPP) Pain at the University of Zurich. The overall testing battery comprised of two visits of three hours each and included psychological and pain questionnaires, clinical bedside testing, quantitative sensory testing (QST), experimental pain paradigms (i.e., conditioned pain modulation and temporal summation of pain), and neurophysiological measures (i.e., contact-heat evoked potential (CHEP) and SSR). For this study, data from pain and psychological questionnaires, clinical examination including pain drawings, QST, and neurophysiological investigations (i.e., CHEP and SSR) were used.

To evaluate a potential association between pain habituation and psychological factors (i.e., pain catastrophizing, depression, and anxiety), participants completed the German versions of the Pain Catastrophizing Scale (PCS) (Sullivan and Bishop, 1995) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The questionnaires were completed online and outside the two study visits (within one week of the first visit). The study protocol was conducted in a quiet room with an ambient temperature of ~ 22 °C. The investigation started with the assessment of the pain extent (% of total body surface) using pain drawings on body charts. Next, the test area was defined. Here, the focus was predominantly on a remote, pain-free area in order to investigate systemic alterations in sensory function and pain habituation.

The test area was typically the dorsal aspect of the hand contralateral to the most painful area. In patients with LBP, the non-dominant hand was chosen as the test area. In one participant (LBP), the upper arm was used as the test area due to scar tissue in the non-dominant hand. Moreover, in patients with CRPS who experienced pain in the hand, the contralateral shoulder was used as the test area. The test area of the HC was always matched to the corresponding pain patient. Further, a short sensory clinical bedside testing (i.e., vibration, thermosensation, pinprick, and light touch) was performed to exclude participants showing gross sensory dysfunction in the test area. Afterwards, contact-heat stimulation with concomitant recordings of pain ratings, CHEP, and SSR was performed followed by a QST test battery.

2.3. Pain characteristics and pain medication

Patients were asked to mark their current painful body areas by drawing on two printed standard body charts (dorsal and frontal body views). The investigator then highlighted the boundaries of each region before running the data through a custom-made program to calculate their pain extent (i.e., the proportion of the defined body area (pixels) to the whole-body surface) (Rosner et al., 2021).

The average pain intensity over the last four weeks was retrieved using the painDETECT questionnaire (Freynhagen et al., 2006). Moreover, the regular intake of pain medication was assessed. Pain medication was classified using the World Health Organization Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) classification (Hollingworth and Kairuz, 2021) into categories including anti-inflammatory and antirheumatic products, analgesics (i.e., opioidergic and non-opioidergic), anticonvulsants, psycholeptics, and psychoanaleptics.

2.4. Quantitative sensory testing (QST)

QST was performed using the established guidelines published by the German Research Network on Neuropathic Pain (DFNS) (Rolke et al., 2006) and testing was performed by trained investigators. To assess signs of central sensitization (widespread hypersensitivity), QST was performed in a pain-free test area (defined in Section 2.2). As we were interested in the presence of hypersensitivities, only QST tests assessing a sensory gain of function were performed. Before conducting QST in the test area, a familiarization session was held at the contralateral body side. As for mechanosensation, the QST battery included the pressure pain threshold (PPT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), and wind-up ratio (WUR). To assess thermosensation, the heat and cold pain threshold (HPT and CPT, respectively) were measured. The DFNS's eQuiSTA software was used to z-transform each participant's QST measures.

2.5. Contact-heat stimulation and pain ratings

Two blocks of 16 to 20 noxious contact-heat stimuli were delivered using a thermode measuring 27 mm in diameter (PATHWAY Pain and Sensory Evaluation System; Medoc, Ramat Yishai, Israel). The exact number of stimuli per block depended on the online evaluation of the investigator, evaluating the occurrence of blink-artifacts and alpha waves. Here, the investigator aimed for at least 16 artifact-free trials. The thermofoil allows a heating rate of 70 °C/s and a Peltier element allows for cooling rate of 40 °C/s.

The destination temperature of the noxious heat stimulation was set to 52 °C starting from a baseline temperature of 42 °C, which is a commonly used stimulation protocol (Jutzeler et al., 2016; Kramer et al., 2013; Rosner et al., 2018a). If participants did not tolerate the stimulation during familiarization, the stimulation intensity was adapted to a less painful paradigm by lowering the baseline temperature to 35 °C with the same destination temperature (Jutzeler et al., 2016; Rosner et al., 2018b). The reduction in baseline temperature is thought to result in less synchronous peripheral fiber activation which in turn results in less temporal summation and thereby less perceived pain (Jutzeler et al., 2016; Kramer et al., 2013; Rosner et al., 2018a). After every stimulus, the participant reported their experienced pain on a numeric rating scale (NRS) from 0 (no pain) to 10 (maximum pain tolerable).

The inter-stimulus-interval was randomized between 13–17 s and a 2–3 min break was conducted between the two stimulation blocks (Fig. 1) (Lütolf et al., 2021; De Schoenmacker et al., 2022b). In order to minimize peripheral adaptation/receptor fatigue, the thermode was moved slightly within the tested area after each contact-heat stimulus (Greffrath et al., 2007). It was ensured that for hand and shoulder stimulation the thermode remained within the key sensory zone of the dermatome C6 and C4, respectively.

2.6. CHEP acquisition

The detailed set-up for CHEP acquisition has been published previously (Jutzeler et al., 2016). Briefly, the participants were lying prone (LBP and their matched HC), or supine (CRPS, SCI, and their matched HC) with their gaze fixed on a spot on the floor/-ceiling. Because negative and positive potentials, i.e., N2 and P2, have been consistently detectable at Cz (Kramer et al., 2012) a single cup electrode was placed at Cz referenced to earlobes. Skin prep gel (Nuprep®, weaver and company, United States) and ethanol 96% (Softasept® N, B. Braun Medical AG, Switzerland) were used to scrub and degrease the recording locations. As per the 10–20 system (Klem et al., 1999), single cup electrodes (9 mm Ag/AgCl cup electrodes) were filled with adhesive conductance paste (Elefix, Nihon Kohden Europe GmbH, Germany) and attached to the vertex (Cz) and to the ear lobes (A1-A2, as references). A wet wristband was used as a ground and placed at the forearm of the stimulated side. The electroencephalography (EEG) signal was preamplified (20′000x) and sampled at 2000 Hz (ALEA Solutions, Zurich, Switzerland). Data were recorded in a time frame of 0.5 s pre- to 1 s post-stimulus trigger by a customized LabVIEW software (V2.6.1. CHEP, ALEA Solutions, Zurich, Switzerland) and band-pass filtered within 0.5–30 Hz. Moreover, electrooculography (EOG) was obtained using two surface electrodes placed above and below the eye (Ambu BlueSensor NF, Ambu A/S, Ballerup, Denmark). EEG trials contaminated with eye movement or motion artifacts, as well as overlaid with alpha waves were removed offline by two independent investigators. A minimum of 10 artifact-free trials out of the 16 to 20 recorded trials for each block were averaged and baseline corrected based on the 500 ms pre-trigger time window. For the habituation analysis it was ensured that both blocks included the same number of trials.

Peak detection (i.e., N2 and P2) of the averaged CHEP was performed using a custom-made semiautomated algorithm in R. CHEP with a signal-to-noise ratio (SNR) below 3 dB, as calculated previously (De Schoenmacker et al., 2022a), were considered abolished (i.e., amplitude: 0 μV, latency: N/A) (De Schoenmacker et al., 2021). If the SNR was above 3 dB, the P2 peak was defined as the maximal positive deflection exceeding 2SD of the noise signal (500 ms pre-trigger time window) within the expected time window based on normative data (200–700 ms post-trigger) (Granovsky et al., 2016; Jutzeler et al., 2016). The N2 peak was defined as the maximal negative deflection exceeding 2SD of the noise signal prior to the P2 peak. If the peaks did not exceed 2SD of the noise signal, an amplitude of 0 μV and missing latency (N/A) were assigned for the N2 and P2 peak separately. Accurate peak labeling was verified by two independent investigators in a cohort-blinded manner.

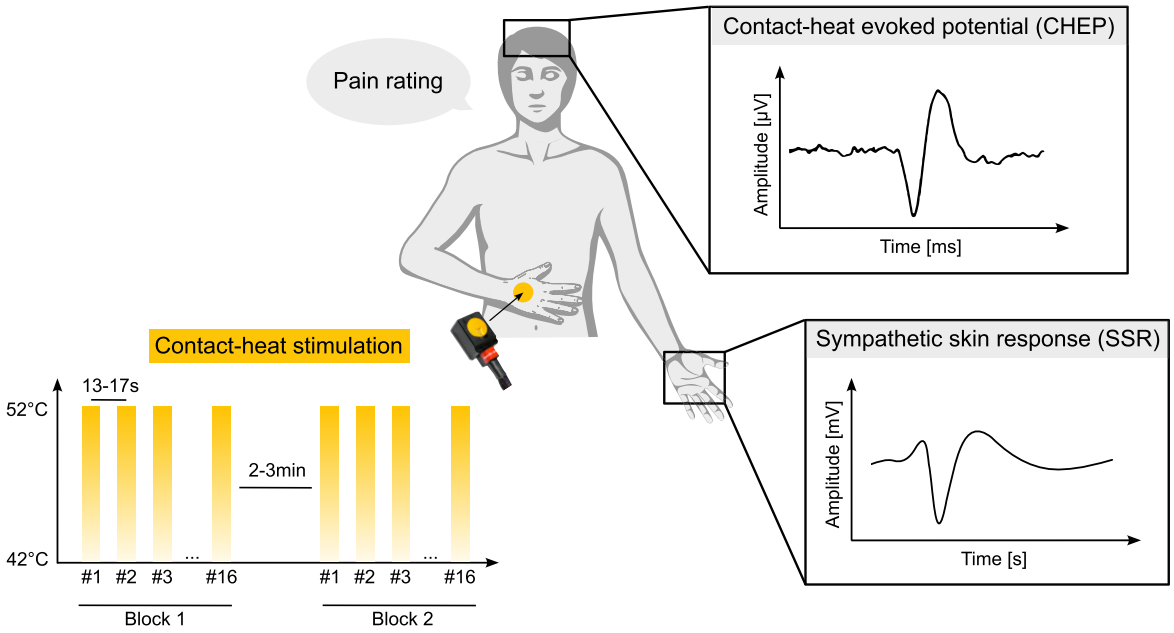

Fig. 1. Study design. Pain ratings, contact-heat evoked potentials (CHEP) and palmar sympathetic skin responses (SSR) were recorded in response to two blocks of 16 to 20 repetitive noxious contact-heat stimuli. The test area was a non-painful area (typically dorsal aspect of the hand). The human icon is adapted from BioRender.com.

In a consensus meeting, the two investigators re-evaluated unclear instances.

2.7. SSR acquisition

In addition to CHEP, simultaneous palmar SSR in response to noxious contact-heat stimuli were recorded. Surface electrodes (Ambu® BlueSensor NF, Ballerup, Denmark) were used to record SSR from the hand contralateral to the stimulation site. In case the hand of CRPS patients was affected, the hand ipsilateral to the stimulation site was chosen as recording site. Skin prep sandpaper tape (Red DotTM Trace Prep, 3 M, United States) and ethanol 96% (Softasept® N, B. Braun Medical AG, Switzerland) were used to clean the recording locations. The active electrode was positioned on the palm and the reference electrode on the hand dorsum. The skin temperature was kept above 32 °C throughout the measurement using heaters if needed because the skin temperature was shown to affect SSR latencies and amplitudes (Deltombe et al., 1998). SSR were sampled at a rate of 2000 Hz using a preamplifier and bandpass filtered within 0.1–12 kHz. The recording window was set to 1 s pre- to 9 s post-stimulus trigger (V2.6.1. CHEP, ALEA Solutions, Zurich, Switzerland). SSR amplitudes and latencies were assessed by a custom-made semiautomated algorithm in R. To guarantee accurate labeling, two independent investigators marked the first point of signal deflection defining the SSR latency. The maximal peak-to-peak deflection determining the amplitude was further set by the algorithm. Absent SSR amplitudes (flat lines) were given a missing latency (N/A) and an amplitude of 0 mV. SSR with an artifact (e.g., not time-locked SSR or with superposing signals) were assigned a missing latency and amplitude (N/A). A minimum of 10 artifact-free trials were averaged for each stimulation block. Again, when investigating habituation, it was ensured that each block contained the same number of trials.

2.8. Pain habituation indices

In order to perform correlation analyses between habituation and pain characteristics (i.e., pain intensity, extent, and duration) or psychological factors (i.e., HADS and PCS score), a habituation index was calculated as follows (Eq. (1)):

$$Habituationindex = 100 * \frac{(X_2 - X_1)}{X_1} \quad (1)$$

"X" was the readout of interest (i.e., pain ratings, CHEP N2P2 or SSR amplitudes) and "1″ and "2″ refers to the first and second stimulation block, respectively. While a negative habituation index meant a reduction (habituation), a positive value signified an increase from the first to the second block (facilitation). In case of technical issues during CHEP or SSR recordings for any of the blocks, no habituation index was calculated (N/A). Also, participants that did not perceive the stimulation as painful or who displayed abolished CHEP or SSR in the first block were excluded from further habituation analysis (N/A). Complete habituation (i.e., -100%) was assumed if participants did not perceive the stimulation as painful or displayed abolished CHEP or SSR in the second block. The maximal value of facilitation (positive habituation index) was set to + 100%.

2.9. Signs of "human-assumed" central sensitization

Although central sensitization cannot be assessed clinically, it is commonly assumed that extended pain patterns and widespread hypersensitivities could indicate signs of central sensitization in humans (Arendt-Nielsen et al., 2018). The pain drawings (Section 2.3) were used to calculate a widespread pain index (WPI) (Wolfe et al., 2010). The WPI score is the sum of 19 body areas affected by pain where a score ≥ 7 is part of the diagnostic criteria

of fibromyalgia, which is believed to be associated with central sensitization (Mezhov et al., 2021).

The presence of widespread hypersensitivity was assessed by a "gain of function" in the tested remote pain-free control area using the pain thresholds, the wind-up ratio, or the DMA from the QST (Section 2.4). From our experience and as shown previously (Konopka et al., 2012), even HC can exhibit one QST z-score above 1.96. Therefore, a more conservative rule was applied to classify pain patients: WPI≥7 OR at least two pathological QST measures (z-scores > 1.96 or the presence of DMA) in the remote pain-free control area.

2.10. Statistical analysis

Normal distribution was tested using one-sample Kolmogorov-Smirnov tests, histograms, and quantile–quantile plots. The statistical significance was set at α = 0.05. Holm's adjustment was applied to correct for multiple comparisons. The statistical analyses were performed using R statistical software (R version 4.1.2 for Windows).

For the demographics, pain characteristics and psychological factors, normally distributed data were tested using t-tests (2 groups, function t.test() from R package "stats") and ANOVAs (>2 groups, function aov() from R package "stats"). Non-parametric tests such as the Wilcoxon signed-rank test (2 groups, function wilcox.test() from R package "stats") or the Kruskal-Wallis test (>2 groups, function kruskal.test() from R package "stats") were used for non-normally distributed data. A Pearson's chi-squared test (function chisq.test() from R package "stats") was used to compare the sex and tested area distribution between patients and HC. To assess baseline differences (stimulation block 1) between patients and HC in terms of pain ratings, CHEP and SSR (latencies and amplitudes), t-tests or Wilcoxon signed-rank tests were performed.

Habituation between the stimulation blocks of pain ratings, CHEP, and SSR was investigated using general linear mixed models (function lmer() from R package "lme4″) with repeated measures and "individual" as random effect (Eq. (2)).

$$lmer(readout\ block + (1|individual)) \quad (2)$$

Further, potential differences in habituation between patients and HC (cohort) were investigated by including the interaction effect "block x cohort" (Eq. (3)).

$$lmer(readout\ block * cohort + (1|individual)) \quad (3)$$

Linearity, homogeneity of variance, and normal distribution of model residuals were assessed using the function check-model() from the "performance" package in R. SSR amplitudes were square root transformed to fulfill the model criteria. Correlations between the habituation index and pain characteristics (i.e., pain intensity, extent, and duration) or psychological factors (i.e., HADS, PCS) were assessed using Spearman rank correlations (function cor() from R package "stats"). Moreover, to evaluate potential differences in habituation between the "human-assumed" central sensitization subgroup (HACS_subgroup) and the remaining patients as well as HC, the same linear mixed models as previously mentioned were used with the interaction effect "block x HACS_subgroup" (Eq. (4)).

$$lmer(readout\ block * HACS\_subgroup + (1|individual)) \quad (4)$$

Lastly, a potential confounding effect of pain medication on neurophysiological measures was evaluated. For this purpose, patients were grouped depending on their regular intake of one or more pain medications (yes/no). Differences between the medication subgroups in terms of pain ratings, CHEPs, and SSRs (latencies and amplitudes) were investigated using t-tests or Wilcoxon rank sum tests. To evaluate differences in habituation, the medication subgroups were included in the previously mentioned linear mixed models as interaction effect "block x medication_subgroup" (Eq. (5)).

$$lmer(readout\ block * medication\_subgroup + (1|individual)) \quad (5)$$

3. Results

3.1. Participant demographics

In total, 164 participants were recruited for the study, which consisted of patients with CRPS (N=21), LBP (N=61), and SCI (N=19) as well as 63 HC. Eleven participants were excluded from the study due to pathological bedside testing in the pain-free area (LBP: N=1, SCI: N=2, HC: N=2), the absence of a suitable test area (CRPS: N=2, HC: N=1), refusal to take part in the neurophysiological investigation (CRPS: N=1, LBP: N=1), or due to signs of a psychiatric condition which was recognized after inclusion (LBP: N=1). Thus, the final study sample included 153 participants. Table 1 displays the demographics of the participants, the scores of the psychological questionnaires (i.e., HADS and PCS) as well as the patients' pain characteristics and information regarding pain medication intake. In addition, Table 1 provides an overview of the testing areas in all participants. Importantly, the percentage of the different testing areas, i.e., hand, shoulder, and upper arm, was comparable for HC and pain patients, even though less HC were recruited.

3.2. Baseline pain ratings, CHEP, and SSR

The investigation of baseline pain ratings (stimulation block 1) was performed in 136 participants, while the investigation of baseline CHEP and SSR was performed in 133 and 120 participants, respectively. A detailed flowchart of the exclusion of participants can be found in the supplementary information (Fig. S.1A). In brief, three participants were excluded as they neither tolerated the increased baseline protocol (42 °C) nor the lower baseline protocol (35 °C). Fourteen further participants were excluded from the baseline analysis as they did not tolerate the increased baseline temperature (42 °C) and underwent testing with the lower baseline temperature (35 °C). The latter needed to be excluded as a reduction in baseline temperature has been shown to influence pain perception (Jutzeler et al., 2016; Rosner et al., 2018a) and would thus not have been comparable. Other exclusion reasons were the following: (1) less than 10 artifact-free trials; and (2) technical issues during one CHEP recording.

Table 2 summarizes the neurophysiological parameters for all study participants. There was no significant difference in baseline pain ratings or CHEP and SSR amplitudes between patients and HC. However, chronic pain patients showed prolonged CHEP and SSR latencies compared to HC (Table 2). Illustrative CHEP and SSR examples of one patient (LBP) and one HC are shown in Fig. 2. A partial correlation analysis between the CHEP and SSR latency with age and height as confounding variables was conducted. Here, the CHEP N2 latency positively correlated with the SSR latency (rho = 0.366, p = 0.001). There was no significant difference in pain ratings, CHEP, or SSR between patients on or off pain medication (pain rating: Z=-0.77, p = 0.44; CHEP N2 latency: Z=-0.87, p = 0.39; CHEP N2P2 amplitude: t(51) = -0.68, p = 0.50; SSR latency: Z=-0.08, p = 0.94; SSR amplitude: Z=-1.34, p = 0.18).

3.3. Pain habituation

The habituation analysis allowed for a including a higher sample of individuals, namely 149 for the habituation of pain ratings, 142 for CHEP habituation and 124 for SSR habituation (Fig. S.1B).

Table 1
Participant demographics, psychological and pain characteristics.

Characteristic	HC N=60	Pain patients N=93	p-value	CRPS N=18	LBP N=58	SCI N=17
Gender [F/M] (% female)	33/27 (55)	54/39 (58)	0.82	15/3 (83)	37/21 (64)	2/15 (12)
Age [years]	48 (16)	51 (15)	0.45	44 (13)	51 (17)	56 (9)
Height [cm]	171.9 (8.5)	171.4 (8.2)	0.81	169.6 (6.0)	170.3 (8.0)	177.5 (8.5)
Pain intensity [NRS]		4.3 (1.9)		5.2 (2.4)	4.0 (1.7)	4.7 (1.6)
Pain extent [%]		4.5 (6.6)		5.9 (5.8)	1.7 (1.5)	13.1 (9.7)
Duration [months]		127 (143)		38 (37)	141 (163)	173 (97)
WPI [score]		2.7 (1.8)		2.6 (1.8)	2.3 (1.6)	4.47 (1.8)
Testing area (hand/shoulder/ upper arm)	N=49/10/1 % = 82/17/2	N=80/12/1 % = 86/13/1	0.76	N=6/12/0 %= 33/67/0	N=57/0/1 % = 98/0/2	N=17/0/0 %= 100/0/0
PCS [score]	5.6 (7.0)	14.7 (10.5)	**<0.001**	22.2 (11.9)	12.9 (9.7)	13.1 (8.3)
HADS [score]	5.1 (3.9)	9.9 (6.8)	**<0.001**	14.4 (8.0)	8.9 (6.2)	8.7 (6.0)
Pain medication [y/n] (% yes)		32/93 (34)		11/18 (61)	14/58 (24)	7/17 (41)

Abbreviations: HADS: hospital anxiety and depression scale, HC: healthy controls, PCS: pain catastrophizing scale, WPI: widespread pain index. Unless indicated, data are shown as mean (SD).

Table 2
Baseline (stimulation block 1) pain ratings and neurophysiological parameters.

Parameter	HC	Pain patients	Test statistics	Effect size	p-value
Pain rating [NRS]	4.1 (2.2)	3.7 (2.0)	2438.5[1]	0.08[3]	0.762
N2 latency [ms]	280 (30)	303 (36)	1192[1]	**0.28**[3]	**0.012**
N2P2 amplitude [μV]	30.4 (13.7)	25.9 (13.5)	1.73[2]	0.30[4]	0.260
SSR latency [s]	1.7 (0.2)	1.8 (0.2)	1218[1]	**0.25**[3]	**0.022**
SSR amplitude [mV]	2.4 (1.8)	2.6 (2.6)	1917[1]	0.04[3]	0.762

Abbreviations: HC: healthy controls, NRS: numeric rating scale, SSR: sympathetic skin response. Data are shown as mean (SD).
[1] Wilcoxon signed-rank test (W).
[2] t-test (t).
[3] effect size (r: small < 0.3, moderate < 0.5, large ≥ 0.5).
[4] effect size (Cohen's d: small ≈ 0.2, moderate ≈ 0.5, large ≈ 0.8).

This is due to the fact that the 14 participants that needed to be excluded in the previous (explained in section 3.2.; baseline temperature of 35 °C), could be included in the habituation analysis, as we assessed habituation from block 1 to block 2. Participants were excluded from the pain habituation analysis due to (1) no perceived pain/abolished CHEP or SSR following the first stimulation block, (2) less than 10 artifact-free trials in one of the stimulation blocks, (3) and technical issues. Fig. 3 illustrates the grand average of the recorded CHEP of the first and second stimulation block including all pain patients and healthy controls (also including abolished CHEP).

Fig. 4 illustrates the pain ratings (Fig. 4A), CHEP (Fig. 4B), and SSR amplitudes (Fig. 4C) of both stimulation blocks. Overall, our study population showed a pronounced habituation for all readouts (pain rating: $F(1,147) = 67.83$, $p < 0.001$; CHEP: $F(1,140) = 86.99$, $p < 0.001$; SSR: $F(1, 122) = 185.88$, $p < 0.001$). However, there was no significant difference between patients and HC in habituation of pain ratings ($F(1,147) = 2.86$, $p = 0.28$), CHEP ($F(1,147) = 0.00$, $p = 0.99$), or SSR ($F(1, 122) = 0.57$, $p = 0.99$). The intake of pain medication did not significantly influence the habituation of pain ratings ($F(1,89) = 0.59$, $p = 0.53$), CHEP ($F(1,83) = 1.64$, $p = 0.53$), or SSR ($F(1, 122) = 0.68$, $p = 0.53$). A detailed table including the mean pain ratings and CHEP/SSR amplitudes as well as the habituation index, calculated for the correlation analyses, can be found in the supplementary information (Table S.1).

3.3.1. Psychological factors and pain characteristics

While HADS and PCS scores were significantly higher in patients compared to HC, they did not correlate with the patients' habituation indices (i.e., pain ratings, CHEP, and SSR, Table 3). Similarly, pain characteristics including pain intensity, extent, and duration did not correlate with the habituation indices (Table 3).

3.3.2. "human-assumed" central sensitization subgroup

Out of 91 patients included in the habituation analysis (see supplementary Figure S1 "neurophysiological recording"; Total N=150 minus HC N=59), 27 were grouped in the "human-assumed" central sensitization group (CRPS: N=4 (22%), LBP: N=17 (30%), SCI: N=6 (35%)). A detailed table including the QST z-scores of as well as the WPI score of all pain patients can be found in the supplementary Table S.2. WPI≥7 was found in five patients and 25 patients had at least two pathological QST measures (widespread hypersensitivity). Hence, three patients showed both a WPI≥7 and widespread hypersensitivity. Importantly, habituation of pain ratings ($F(2,146) = 2.78$, $p = 0.20$, Fig. 5A), CHEP ($F(2,139) = 0.35$, $p = 1.00$, Fig. 5B), and SSR ($F(2, 121) = 0.42$, $p = 1.00$, Fig. 5C) did not significantly differ between the two subgroups of patients and HC.

4. Discussion

This study aimed to investigate whether various measures of pain habituation could reveal pronociceptive modulation in the central nervous system across distinct cohorts of chronic pain patients. Specifically, experimental pain habituation to repetitive noxious stimulation of a non-painful area was investigated assessing both subjective (pain ratings) and objective neurophysiological readouts (CHEP and SSR). Generally, no significant difference in pain habituation was found between pain patients and HC, regardless of the outcome measure. Also, our hypothesis of reduced pain habituation especially in patients with "human-assumed" central sensitization compared to HC could not be confirmed. Moreover, the relative amount of habituation (habituation index) did not correlate with pain characteristics or psychological factors as previously hypothesized. Interestingly, however, chronic pain patients

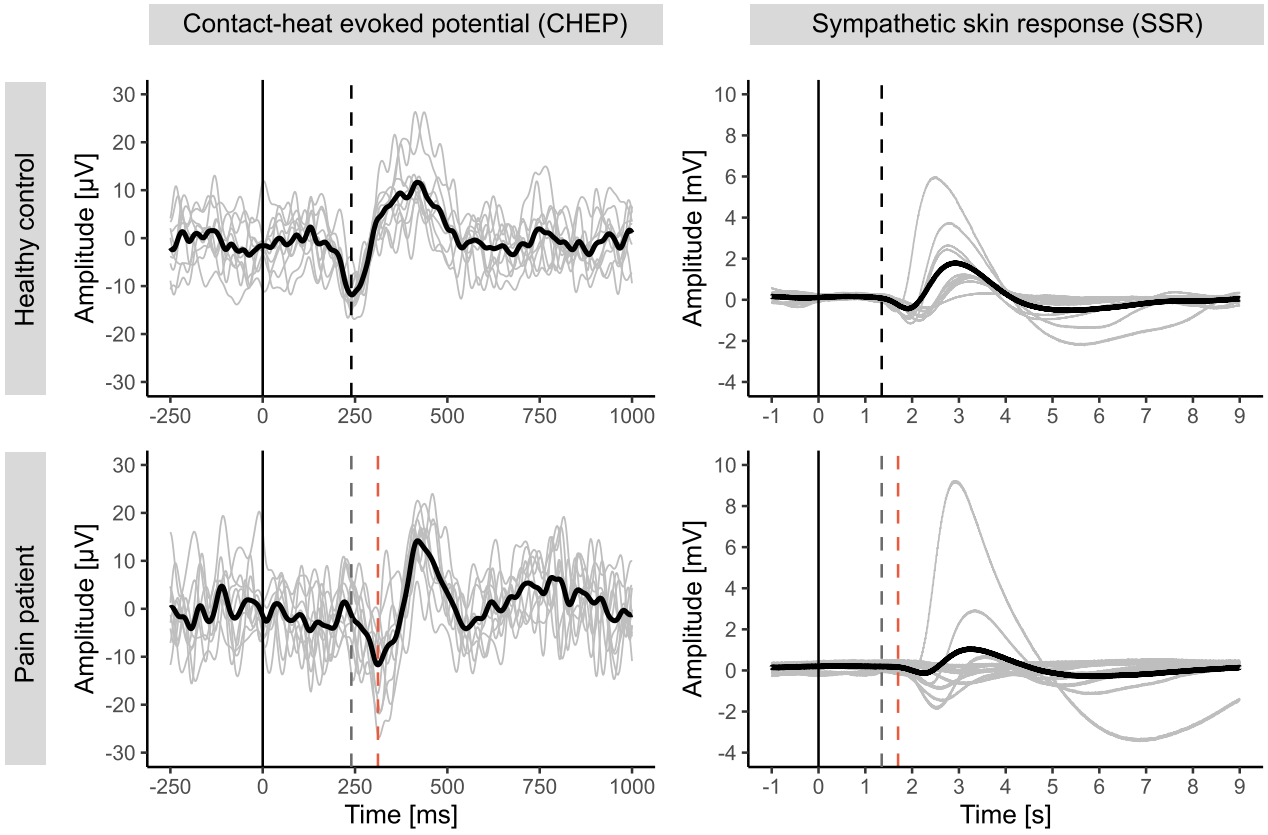

Fig. 2. Neurophysiological measures. Illustrative contact-heat evoked potential (CHEP, left) and sympathetic skin response (SSR, right) recordings of one healthy control (HC, upper row) and one patient (lower row). The grey curves illustrate the single trials and the black curve is the averaged CHEP/SSR. Both participants were stimulated on the non-dominant (left) hand and were female. The HC was 48y, 155 cm, and 54 kg. The patient (low back pain) was 56y, 159 cm, and 54 kg. The amplitude of the CHEP/SSR is comparable between the two participants but the patient has longer CHEP and SSR latencies (red dashed line) compared to the HC (grey dashed line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

showed prolonged baseline CHEP and SSR latencies (stimulation block 1) compared to HC.

The reasons for these latency prolongations remain speculative and may range from subclinical pathologies in primary afferents or changes in synaptic relay mechanisms, possibly resulting from an increased descending antinociceptive tone and seemingly physiological pain habituation. Although the precise mechanisms remain elusive, future research is warranted in order to explore the complex changes in nociceptive processing in patients with chronic pain.

To our knowledge, this is the first study investigating pain habituation across different chronic pain patients using three different concomitantly recorded readouts. Assessing different habituation readouts can be of particular interest because they do not necessarily share identical neural substrates as discussed in previous work of our group (Lütolf et al., 2021; De Schoenmacker et al., 2022b). Moreover, pain ratings, CHEPs, and SSRs might be affected differently by the influence of arousal and other emotional factors. In particular, Salameh and colleagues demonstrated that SSR is an objective measure to estimate stimulus-associated arousal (Salameh et al., 2022). We found significant habituation of all readouts (i.e., pain ratings, CHEP, and SSR) in our patient cohort, which resembled that found in HC. In contrast, previous literature mainly reported reduced habituation of pain-related evoked brain potentials in patients with, for example, fibromyalgia (de Tommaso et al., 2014; De Tommaso et al., 2011), migraine (De Tommaso et al., 2016; Valeriani et al., 2003), and radiculopathy (Hüllemann et al., 2017) compared to HC. Another study reported reduced habituation of pain-related SSR in patients with central pain in patients with Parkinson disease (Schestatsky et al., 2007). These studies show that a wide variety of chronic pain patients present with reduced pain habituation, which has been discussed as a potential state of central sensitization. However, the null finding of the present study and the substantial inter-individual variability of pain habituation in HC, ranging from slight facilitation to complete habituation (De Schoenmacker et al., 2022b), might render this a non-useful marker of central sensitization in chronic pain cohorts. There are several potential explanations for the seemingly preserved physiological habituation profile observed in our study even after subgrouping for overt clinical signs of central sensitization, indicated by an extended spatial pain extent and widespread hypersensitivity. Firstly, the heterogeneity of the study sample might have resulted in this null finding. To address this, we first performed subgroup analyses to compare individuals with and without human-assumed central sensitization. Second, we performed correlation analyses between pain habituation and pain characteristics (i.e., pain intensity, extent, duration) or psychological factors (i.e., HADS and PCS score) to investigate the heterogeneity of the study sample. Yet, neither approach revealed any indication for a lack of pain habituation in specific individuals. Thirdly, the lack of reduced pain habituation in pain patients compared to HC might be explained by the differences in methodology between the current and previous studies. Specifically, most previous studies showing a lack of pain habituation in chronic pain patients used three or more stimulation blocks (Hüllemann et al., 2017; de Tommaso et al., 2014; De Tommaso et al., 2016, 2011; Valeriani et al., 2005, 2003) or investigated pain habituation within one stimulation block (Lütolf et al., 2022; Schestatsky et al., 2007;

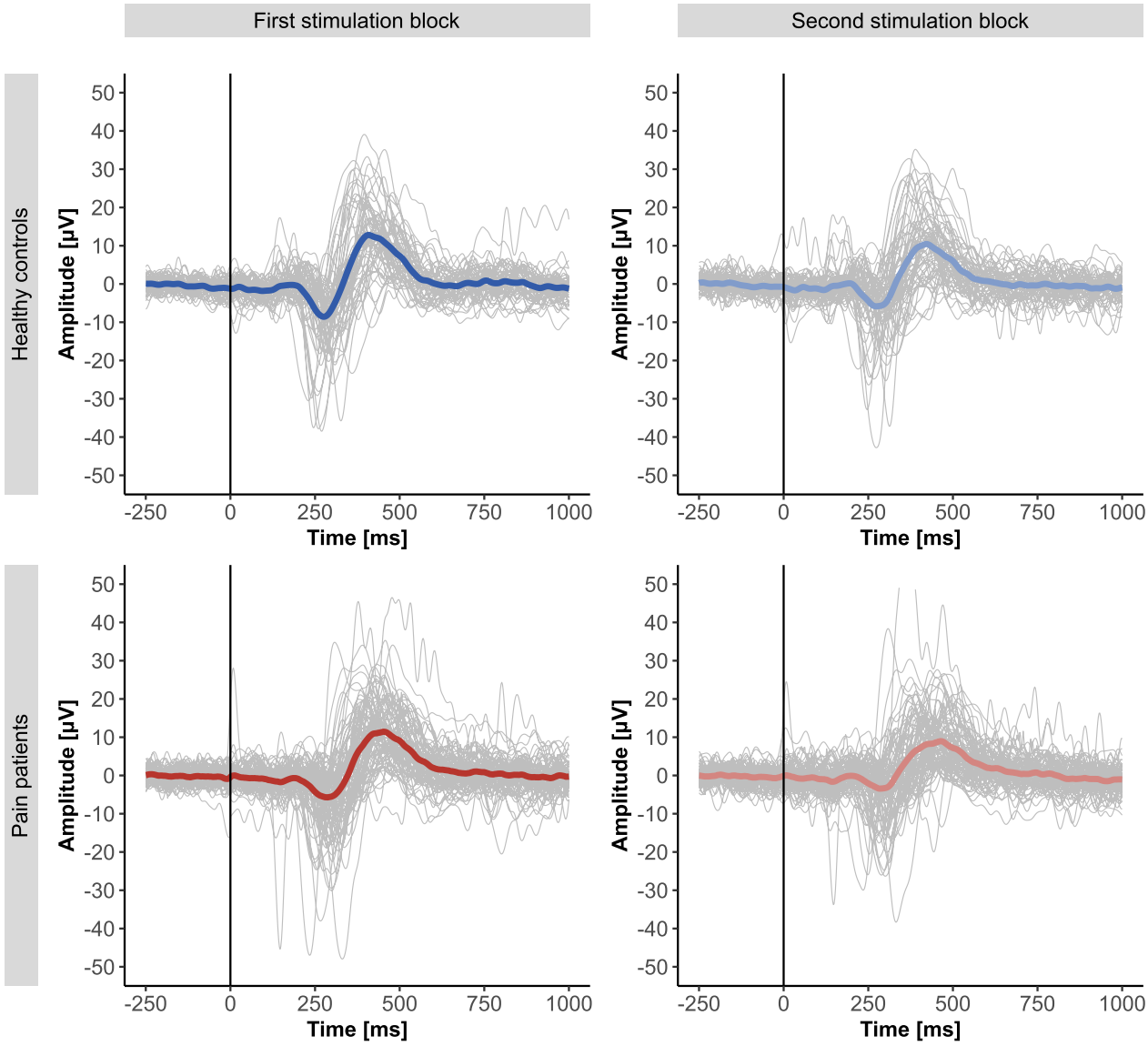

Fig. 3. Grand average of contact-heat evoked potentials (CHEP). Illustrated are the block averages of each participant (gray lines) for the first and second stimulation block. The grand average for each stimulation block is shown by a thick line for pain patients (red) and healthy controls (blue) separate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Scheuren et al., 2022). It is possible that our study design including two stimulation blocks was not able to reveal potential differences in pain habituation compared to HC. Moreover, the stimulation modality could be a factor to consider. This study specifically focused on noxious thermal stimulation, which may not be directly comparable to some previous studies that have shown reduced habituation following noxious mechanical stimulation (Scheuren et al., 2022, 2020). Lastly, the observed variations between our findings in conjunction with previous research could also be due to the choice of the stimulation area. While some studies have focused on non-painful body areas, a significant portion have explored painful body regions (van der Miesen et al., 2023b)). Reduced experimental habituation in these regions, could indicate peripheral or spinal sensitization. The focuse on a remote, pain-free area in the current study may have limited the ability to adequately capture localized sensitization within the spinal circuitry. In other words, "normal" habituation in the remote, pain-free area may not accurately reflect the entire central nervous system.

In addition to attributing the lack of significant findings to potential methodological differences or sensitivity issues inherent to experimental pain habituation paradigms, we would also like to consider a physiological explanation for our results. Commonly, chronic pain is accompanied by an imbalance between pro- and anti-nociceptive processing (Yarnitsky, 2015), shifting towards increased pro-nociceptive modulation. This shift potentially leads to an overall amplification of pain signals, which may be related to changes in cortical excitability (Lefaucheur et al., 2020). Although most studies investigated CHEP amplitudes in painful regions to evaluate the integrity of the nociceptive neuraxis (Casanova-Molla et al., 2011; Caty et al., 2013; Huynh et al., 2021; Lagerburg et al., 2015; Lütolf et al., 2021; Parson et al., 2013), increased CHEP amplitudes in remote areas could be a surrogate marker of enhanced pro-nociceptive modulation. Amplified pain-related evoked potentials in remote body regions were previously illustrated in experimental human models of central sensitization (Iannetti et al., 2013; Scheuren et al., 2020) and patients

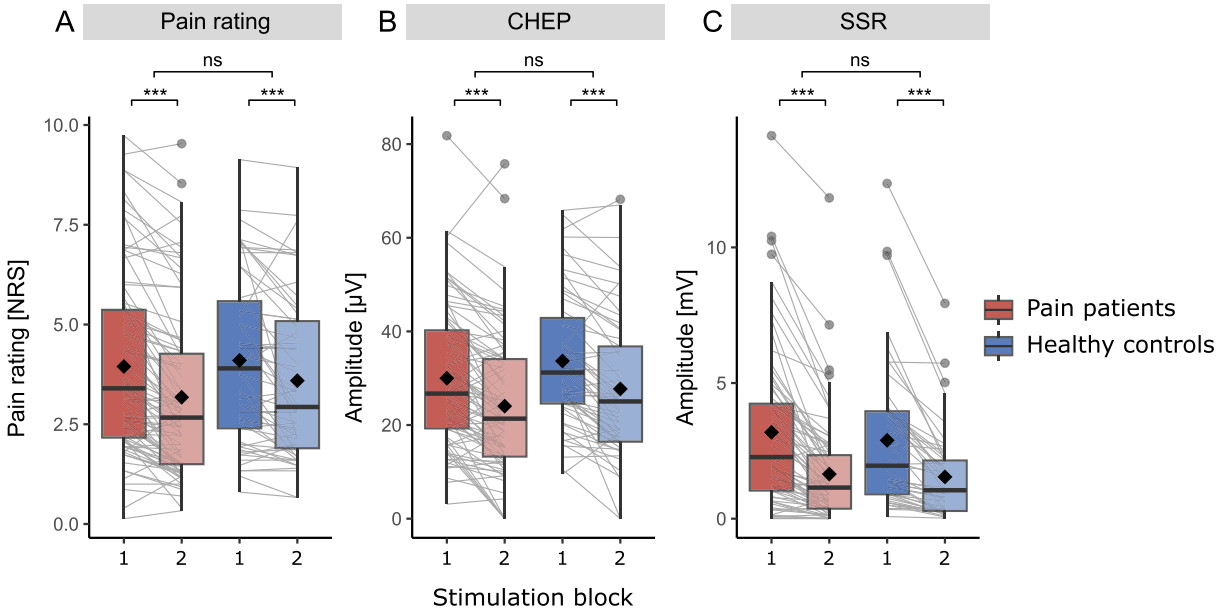

Fig. 4. Habituation of pain ratings, contact-heat evoked potential (CHEP) and sympathetic skin response (SSR) amplitudes. Illustrated are boxplots of the first (dark color) and second stimulation block (light color) of pain ratings (A), CHEP amplitudes (B), and SSR amplitudes (C). Measures from the same participant are connected by a grey line. The mean of each variable is illustrated by a rhombus. Patients are colored red and healthy controls (HC) blue. Remaining abbreviations: NRS: numeric rating scale, ns: not significant (habituation difference). ***p < 0.001. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Correlations between pain characteristics and habituation indices in patients.

Clinical readout	Habituation index	Spearman's rho	p-value
HADS	Pain ratings	0.01	0.849
	CHEP	0.06	0.459
	SSR	-0.14	0.410
PCS	Pain ratings	0.05	0.797
	CHEP	0.07	0.450
	SSR	-0.07	0.726
Pain intensity	Pain ratings	-0.09	0.387
	CHEP	0.13	0.252
	SSR	0.05	0.666
Pain extent	Pain ratings	-0.08	0.479
	CHEP	-0.06	0.583
	SSR	0.11	0.358
Pain duration	Pain ratings	-0.07	0.514
	CHEP	-0.07	0.524
	SSR	0.14	0.224

Abbreviations: CHEP: contact-heat evoked potential, HADS: hospital anxiety and depression scale, PCS: pain catastrophizing scale, SSR: sympathetic skin response.

with fibromyalgia (Gibson et al., 1994; De Tommaso et al., 2011). We, however, neither found amplified pain ratings nor increased CHEP and SSR amplitudes nor a reduction in pain habituation in our population of patients with chronic pain. Considering that differences in amplitudes of evoked potentials could reflect a change in cortical excitability (Bohotin et al., 2002; Fumal et al., 2006; Kumru et al., 2013), the apparent physiologically normal CHEP amplitude and habituation observed in the presence of chronic pain may indicate compensatory mechanisms on a cortical level. Such a compensatory endogenous pain inhibition may counteract the state of nociceptive gain underlying the clinical pain condition and in turn be reflected as seemingly normal pain habituation. The assumption of a pronounced compensatory antinociceptive drive may be further supported by the observation of prolonged baseline latencies (stimulation block 1) in our pain patients. Most previous studies investigated CHEPs when stimulating painful areas and found that, for example, the CHEP latency positively correlated with the epidermal fiber density in patients with small and mixed fiber neuropathy (Casanova-Molla et al., 2011; Lagerburg et al., 2015; Parson et al., 2013). Here we found prolonged CHEP (and also SSR) latencies when stimulating a remote, pain-free area, in which clinical testing revealed normal somatosensory function. Previous literature has shown that QST might not be sensitive to reveal subtle sensory dysfunctions (Courtin et al., 2020) and thereby subclinical peripheral neurological alterations might pose a potential alternative explanation for observing prolonged CHEP and SSR latencies.

With regards to SSR, previous studies including patients with fibromyalgia also reported prolonged latencies (De Tommaso et al., 2017; Ulas et al., 2006) and autonomic dysfunctions were considered as an explanation thereof. However, by observing prolonged SSR in addition to prolonged CHEP in a remote pain-free area, which also positively correlated, we assume that this finding is mainly driven by abnormal central processing of noxious contact-heat stimuli. We therefore rather hypothesize that the prolonged CHEP and SSR latencies can be explained by changes in synaptic relay of afferent input. In animal models, inhibitory mechanisms in central nociceptive processing have been shown to change membrane properties, delaying synaptic transmission and could therefore be a physiologically plausible mechanism (Li and Zhuo, 2001; Ohashi et al., 2019).

From a neurophysiological point of view, CHEP latency readouts may also be influenced by changes in dipole source activity. Under physiological conditions, the main dipole sources contributing to the vertex potential are the operculo-insular and anterior cingulate cortices (Garcia-Larrea et al., 2003). However, because of cortical reorganization in chronic pain (McCarberg and Peppin, 2019), these dipole sources may be shifted, which could lead to slight latency shifts. For instance, Lelic and colleagues (Lelic et al., 2014) reported a posterior shift of the operculo-insular source and an anterior shift of the cingulate source after contact-heat stimulation of the pancreatic area in patients with chronic pancreatitis. Generally, it is well documented that there is structural and functional cortical reorganization in patients with chronic pain as reviewed by McCarberg and Peppin (McCarberg and Peppin, 2019). This cortical reorganization might lead to an enhanced

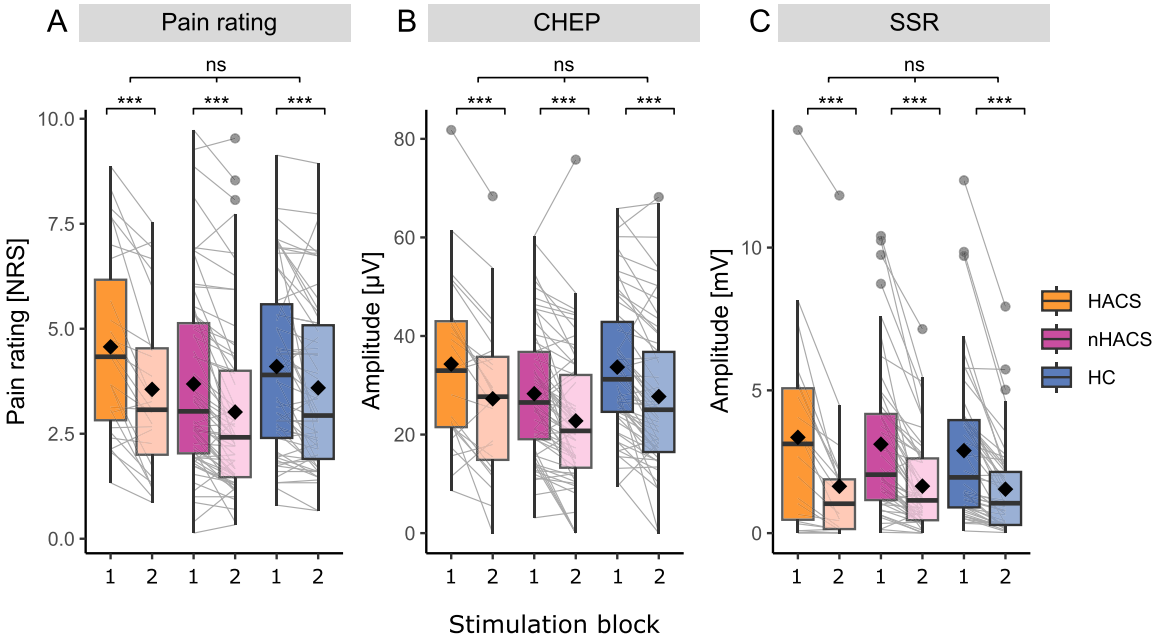

Fig. 5. Differences in pain habituation in patients with/without "human-assumed" central sensitization. Illustrated are the first (dark color) and second stimulation block (light color) of pain ratings (A), contact-heat evoked potential (CHEP) amplitudes (B), and sympathetic skin response (SSR) amplitudes (C). Measures from the same participant are connected by a grey line. The mean of each boxplot is illustrated by a rhombus. Patients with "human-assumed" central sensitization (HACS) are colored orange, patients without "human-assumed" central sensitization (nHACS) pink, and healthy controls (HC) blue. Remaining abbreviations: NRS: numeric rating scale, ns: not significant. ***p < 0.001. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

activity in emotional and motivational cortical-limbic circuitries following noxious stimulation (for review see (Mansour et al., 2014)). Further evidence that increased emotional processing during noxious stimulation could change the dipole source stems from studies conducted in HC. Functional remapping from the posterior to anterior insula (Stancak et al., 2013) and changes in evoked potential latencies (Ring et al., 2013) were observed after noxious stimulation in combination with negative emotional stimuli. Although there is an inherent uncertainty of EEG source reconstruction and these findings should be interpreted with caution, this line of argumentation could potentially also explain the observed prolongation of SSR latencies. Previous studies in patients with fibromyalgia showed that the SSR latency positively correlated with the patients' anxiety level, meaning that more anxious patients had longer SSR latencies (Ozgocmen et al., 2006; De Tommaso et al., 2017). These findings support the hypothesis that emotional factors such as, for example, anxiety, and potentially also emotional and motivational cortical-limbic circuitries following noxious stimulation can modulate SSR latencies.

4.1. Limitations

The intake of pain medication was not discontinued during the period of study participation due to ethical reasons which might have confounded our primary pain habituation readouts. For instance, the intake of pain medication, such as topiramate (an anticonvulsant), has been previously shown to enhance pain habituation in patients with migraine (Di Clemente et al., 2013). We did, however, statistically control for the potential effect of pain medication on our parameters of interest and found no significant difference between patients with or without regular intake of pain medication. Further, there was a slight overlap in stimulation area of consecutive contact-heat stimuli. As the extent of this overlap was not controlled for, differences in overlap between stimuli might have obscured peripheral adaptation and central habituation. Additionally, some variability in response amplitudes might have been introduced by different numbers of trials included in the averaged response. Nevertheless, we ensured that the two stimulation blocks of each participant included the same number of trials. Finally, contact-heat application was limited to two blocks of stimulation, potentially impeding the observation of a complete habituation pattern. However, the application of up to 40 contact-heat stimuli is in line with the majority of previous studies investigating pain habituation following contact-heat stimulation (for review see (van der Miesen et al., 2023a, 2023b)). Moreover, the relative amount of CHEP habituation in studies applying a larger number of contact-heat stimuli (50 to 93 contact-heat stimuli, which is clinically not feasible, especially if tested in multiple areas) is comparable to the present study (~20% reduction between blocks) (Lev et al., 2013, 2010; Olesen et al., 2013). A within-block habituation analysis, as previously performed (Kumru et al., 2012), was not performed due to low SNR for single trials of CHEP. Regarding SSR, habituation was commonly investigated using even less (only 5–20) stimuli (Cariga et al., 2001; Donadio et al., 2005; Lütolf et al., 2022; Schestatsky et al., 2007; Scheuren et al., 2022, 2020; Shunzo et al., 1997; De Tommaso et al., 2017).

4.2. Conclusion

Based on the findings of preserved pain habituation in chronic pain patients, a state of generalized central sensitization in these patients as previously hypothesized cannot be assumed. Even in chronic pain patients with overt signs of "human-assumed" central sensitization, pain habituation capacity was normal and might therefore not be an appropriate marker for central sensitization. Moreover, the variability of pain habituation could not be explained by differences in pain intensity, extent, or duration nor by variations in anxiety, depression, or pain catastrophizing. These seemingly normal levels of pain habituation might be attributed to methodological issues and imprecise assessment of the specific sites of nociceptive gain along the central neuraxis. Another potential explanation might be a compensatory antinociceptive mecha-

nisms normalizing the nociceptive gain within central networks. This assumption is supported by the findings of prolonged baseline latencies (stimulation block 1) not only of pain-related brain potentials, i.e., CHEP, but also autonomic responses, i.e., SSR, in patients with chronic pain.

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Declarations of interest

There are no conflicts of interest to declare.

Data availability statement

Data and programming codes are available upon request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.07.007.

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