

Central sensitization in CRPS patients with widespread pain: A cross-sectional study

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Running title: Signs of central sensitization in CRPS

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Abstract

Objective: Widespread pain hypersensitivity and enhanced temporal summation of pain (TSP) are commonly reported in patients with complex regional pain syndrome (CRPS) and discussed as proxies for central sensitization. This study aimed to directly relate such signs of neuronal hyperexcitability to the pain phenotype of CRPS patients. **Methods:** Twenty-one CRPS patients and 20 healthy controls (HC) were recruited. The pain phenotype including spatial pain extent (assessed in % body surface) and intensity were assessed and related to widespread pain hypersensitivity, TSP, and psychological factors. Quantitative sensory testing (QST) was performed in the affected, the contralateral and a remote (control) area. **Results:** CRPS patients showed decreased pressure pain thresholds in all tested areas (affected: $t(34)=4.98$, $p<0.001$, contralateral: $t(35)=3.19$, $p=0.005$, control: $t(31)=2.65$, $p=0.012$). Additionally, patients showed increased TSP in the affected area ($F(3,111)=4.57$, $p=0.009$) compared to HC. TSP was even more enhanced in patients with a high compared to a low spatial pain extent ($F(3,51)=5.67$, $p=0.008$), suggesting pronounced spinal sensitization in patients with extended pain patterns. Furthermore, the spatial pain extent positively correlated with the Bath Body Perception Disturbance Scale ($\rho=0.491$; $p=0.048$). **Conclusion:** Overall, we provide evidence that the pain phenotype in CRPS, i.e., spatial pain extent, might be related to sensitization mechanism within the central nociceptive system. This study points towards central neuronal excitability as a potential therapeutic target in patients with more widespread CRPS.

Keywords

complex regional pain syndrome, spatial pain extent, central sensitization, quantitative sensory testing, temporal summation of pain

Introduction

Complex regional pain syndrome (CRPS) is characterized by persisting pain disproportionate to the initiating event [1]. Pain can be accompanied by a variety of other symptoms such as vasomotor, sudomotor, motor and trophic changes [2] and thus several pathomechanisms are thought to be involved in CRPS (for review see Bruehl 2015 [3]).

CRPS patients commonly present with allodynia and hyperalgesia to mechanical stimuli which are not necessarily restricted to the affected area [4,5]. Such hypersensitivities beyond the affected area are features of central sensitization [6] and have previously been assessed contralaterally to the affected area or in a remote area such as the face [4,5,7,8]. Central sensitization is defined as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” [9]. A surrogate marker of central sensitization is exaggerated temporal summation of pain (TSP) [10], the human correlate of wind-up in animal studies, representing an increased excitability of dorsal horn neurons in the cat or rat spinal cord [11–13]. A plethora of studies have reported increased TSP in chronic pain patients (e.g., back pain or neuropathic pain after spinal cord injury) in affected as well as remote body areas [14–18]. A further, rather clinical characteristic of sensitization within the central nervous system is a spread of pain beyond the expected anatomical region of pathology [6]. This has been observed in various

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3 chronic pain conditions such as neuropathic pain after spinal cord injury [19], chronic
4 pelvic pain [20], osteoarthritis [21], low back pain [22] and CRPS [23]. In particular,
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6 CRPS patients showed three different patterns of pain distribution, i.e., continuous
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8 spreading, independent spreading and mirror-image spreading [23]. The extent of
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10 the pain distribution has been related to other surrogate markers of central
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12 sensitization such as widespread pain hypersensitivities in patients with osteoarthritis
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14 [21]. However, to our knowledge such a relationship has not yet been assessed in
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16 CRPS patients. Lastly, psychological factors were associated with more severe pain,
17
18 disability and poorer long-term recovery in CRPS [24–27]. A review by Park and
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20 colleagues [28] discussed that psychological factors may modulate the pain intensity
21
22 of CRPS patients by altered neural circuits in the cortico-limbic system and
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24 increased nociceptive firing due to enhanced circulating catecholamine levels.
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26 Whether also the spatial pain extent is related to psychological factors remains
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28 unexplored. Therefore, the aim of this study was to investigate the relationship of
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30 different signs of central sensitization with the clinical pain phenotype in terms of the
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32 spatial pain extent in patients with CRPS. We hypothesized that an extended pain
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34 pattern will be associated with (1) widespread pain hypersensitivities and increased
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36 TSP, as well as (2) enhanced psychological distress in CRPS patients.
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46 Methods

47 Study population

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49 This study was part of a larger study including patients with CRPS,
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51 neuropathic pain after spinal cord injury, and low back pain, as well as age- and sex-
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53 matched healthy controls (HC), which were recruited between November 2019 and
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55 April 2022. The results presented in this manuscript are based on a consecutive
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3 sample of all patients with CRPS (N = 21) and 20 age-matched HC. CRPS patients
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5 were recruited at the Department of Physical Medicine and Rheumatology of the
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7 Balgrist University Hospital in Zurich, Switzerland and diagnosed by an experienced
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9 rheumatologist (FB). All patients needed to fulfill the clinical Budapest Criteria [1] at
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11 inclusion and had experienced pain for more than 3 months. Patients were excluded
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13 in case of neurological (e.g., polyneuropathy, disk herniation), systemic (e.g.,
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15 autoimmune disease, diabetes) or clinically diagnosed psychiatric diseases or in
16
17 case of pregnancy. HC had the same exclusion criteria with the addition of not
18
19 having acute pain or a history of chronic pain (>3 months). Written informed consent
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21 was obtained from each participant and all experimental procedures were in
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23 accordance with the Declaration of Helsinki. The study was approved by the local
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25 ethics board 'Kantonale Ethikkommission Zürich, KEK' (EK-04/2006, PB_2016-
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27 02051, clinicaltrial.gov number: NCT02138344).
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33 Study protocol

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36 As previously stated, this study was part of a larger study, which comprised a
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38 comprehensive test battery (2 visits of 3 hours each) including the evaluation of
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40 clinical pain characteristics, neurophysiological assessments, experimental pain
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42 paradigms, and psychological and pain questionnaires. The presented data in this
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44 manuscript are based on (1) psychological questionnaires (i.e., Pain Catastrophizing
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46 Scale (PCS) [29], the Hospital Anxiety and Depression Scale (HADS) [30] and the
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48 Bath Body Perception Disturbance Scale (BBPDS) [31]), (2) assessment of the
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50 spatial pain extent, intensity and intake of pain medication, and (3) quantitative
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52 sensory testing (QST) including (4) TSP. The psychological questionnaires were
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54 completed electronically while QST (visit 1) and TSP (visit 2) were part of the test
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56 battery mentioned above.
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Psychological questionnaires

The PCS consists of 13 items, where participants have to reflect on past painful experiences and choose from different negative thoughts and feelings which are presented on a numerical scale from 0 (not at all) to 4 (all the time) [29]. The minimum and maximum scores of the PCS are therefore 0 and 52, respectively. The HADS consists of 14 items, where seven items particularly assess a general state of anxiety and seven items the general state of a depressive mood [30]. The minimum and maximum scores for the items assessing anxiety and depression separately are 0 and 21, respectively. Scores less than seven indicate non-cases, scores between 8-10 indicate mild anxiety/depression, scores between 11-14 indicate moderate anxiety/depression, and scores between 15-21 indicate severe anxiety/depression. Lastly, the BBPDS was developed to capture and quantify body perception disturbances in patients with CRPS [32]. Here, some questions have to be rated on a scale from 0 (minimum) to 10 (maximum), whereas other questions are yes (1 point) or no (0 points) questions. The last question considers the description of the patients' affected limb while keeping the eyes closed. The examiner draws the affected limb based on the patients' description and evaluates the degree of distortion (0 = no distortion, 1 = moderate distortion, 2 = severe distortion). The score of the BBPDS ranges from 0-57, where a higher score means more disturbed body perception.

Pain characteristics and intake of pain medication

Pain characteristics included the spatial pain extent and the pain intensity. CRPS patients were asked to mark their painful areas by shading the corresponding area on two standardized body charts (dorsal and frontal view) on A4 papers. Here, only painful areas associated with CRPS were considered for further analysis. The borders of each area were marked manually by the investigator and run through a

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3 custom-made analysis software calculating the percentage of the marked body area
4 (pixels) in relation to the entire body surface [19]. Additionally, the average pain
5 intensity of the last 4 weeks was specified. Moreover, to better describe the CRPS
6 cohort, the duration of CRPS pain was specified. Further, the regular intake of pain
7 medication was surveyed and classified into categories of anti-inflammatory and
8 antirheumatic products (M01A), analgesics (opioidergic (N02A) and non-opioidergic
9 (N02B)), anticonvulsants (N03), psycholeptics (N05), and psychoanaleptics (N06)
10 according to the ATC/DDD classification by the World Health Organization
11 [http://www.whocc.no/atc_ddd_index/].
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23 Measurement areas

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26 The participants were measured in three different areas: their affected area,
27 the contralateral homologous body site and in a remote, pain-free body area (control
28 area). The contralateral and control area were measured to detect possible spinal
29 and supraspinal sensitization, respectively [10]. If the hand was affected the
30 contralateral shoulder was used as control area whereas if the foot was affected, the
31 contralateral hand was used as control area. If the shoulder was affected, no control
32 area was measured. If multiple body regions were affected by CRPS or extended
33 pain areas were present, the area with the momentarily highest pain rating within the
34 affected area was measured. Individually age- and sex-matched HC were measured
35 in the exact same areas as their corresponding CRPS patient.
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50 Quantitative sensory testing

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52 The QST protocol was performed by trained experimenters based on the
53 German Research Network on Neuropathic Pain (DFNS) [33]. It consists of the
54 following measurements: cold detection threshold (CDT), warm detection threshold
55 (WDT), thermal sensory limen (TSL, including paradoxical heat sensation (PHS)),
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3 cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection
4 threshold (MDT), mechanical pain threshold (MPT), stimulus-response function (SR-
5 function, including mechanical pain sensitivity (MPS) and dynamic mechanical
6 allodynia (DMA)), wind-up ratio (WUR), vibration detection threshold (VDT), and
7 pressure pain threshold (PPT). Because the contralateral and the control area were
8 primarily measured to examine central sensitization, only measures reflecting gain of
9 function were assessed (i.e., CPT, HPT, MPT, SR-function, WUR, and PPT). Due to
10 time constraints, the SR-function assessed in the contralateral and control area
11 consisted of only two (instead of five) stimulations of each pinprick (i.e., 8mN, 16mN,
12 32mN, 64mN, 128mN, and 256mN) and dynamic light touch stimulation (i.e., brush,
13 cotton wool, and Q-tip). For the SR function, each stimulus was rated in terms of
14 perceived pain on an NRS from 0 to 100 (0: no pain, 100: most pain tolerable). In
15 accordance with the DFNS, the control area was always assessed first and the order
16 of the affected and contralateral area was randomized. QST measures were z-
17 transformed for each participant using the eQuiSTA software provided by the DFNS.

Temporal summation of pain

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TSP was assessed in response to twelve consecutive pinprick stimulations (MRC Systems, Heidelberg, Germany) applied at a frequency of 0.33Hz only to the affected and control area. The order of measurement area was randomized. The stimulation intensity was set individually at an intensity of 4 on a numeric rating scale (NRS) from 0 to 10 (0: no pain, 10: most tolerable pain). The intensity of NRS 4 was assessed by a staircase method just before the TSP paradigm, with an upper limit of stimulation intensity at 512mN. During the TSP protocol, participants were instructed to rate each stimulation on the NRS.

Statistical analysis

All statistical tests were performed at an α level of 0.05 in R Studio statistical software (R version 4.1.2 for Windows). Missing data was excluded from further analysis (N/A).

Demographics, pain characteristics, and psychological factors

Demographics and questionnaire scores were tested for normality by a Shapiro Wilk test. The sex proportion within CRPS patients and HCs was compared by a Chi-squared test. Age, height, weight, and psychological factors (i.e., HADS and PCS scores) were compared between CRPS patients and HCs using an unpaired t-test or Wilcoxon signed-rank test in the case of normal or non-normal distributed data, respectively. Additionally, the pain characteristics (i.e. pain intensity and spatial pain extent) and psychological factors (i.e., PCS, HADS, and BBPDS score) of CRPS patients were analysed using Pearson (for normally distributed data) or Spearman (for not normally distributed data) correlations with the `corrplot()` function from the `corrplot` package in R studio. Multiple comparison correction was applied using the Benjamini-Hochberg method.

Quantitative sensory testing

QST z-scores were tested for normality by the Shapiro Wilk test and compared between CRPS patients and HCs (unpaired t-test or Wilcoxon signed-rank test). The t-tests or Wilcoxon signed-rank tests were corrected for testing in multiple areas by the Benjamini-Hochberg method. Within the CRPS patients only, the z-scores of the different measurement areas were compared using a repeated measure ANOVA or Friedman test for either normally or not normally distributed data, respectively. Paired t-tests served as post-hoc test and were corrected for multiple comparisons using the Bonferroni method. Lastly, the relationship between widespread pain hypersensitivities (significant gain of function in control area) and

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3 pain characteristics (i.e., pain intensity and spatial pain extent) or psychological
4 factors (i.e., PCS, HADS, and BBPDS score) was investigated. The pain intensity
5 and the psychological factors were normally distributed and thereby analyzed using
6 Pearson correlations. The spatial pain extent was not normally distributed and after
7 inspection of the descriptive statistics, two phenotypic subgroups were identified
8 (high spatial pain extent >5% total body surface, N = 9; low spatial pain extent <5%
9 total body surface, N = 11). A histogram of the spatial pain extent can be found in
10 Figure 1A. Accordingly, the spatial pain extent was related to widespread pain
11 hypersensitivities by comparing the two phenotypic subgroups using an unpaired t-
12 test. Multiple testing within pain characteristics or psychological factors was
13 corrected using the Benjamin-Hochberg method. In addition, a possible confounding
14 effect of pain medication on widespread pain hypersensitivities was investigated by
15 dividing patients into two subgroups according to whether they regularly take pain
16 medication (yes/no). For this purpose, QST measures with a significant gain of
17 function in the control area were compared between the pain medication subgroups
18 by an unpaired t-test.

40 **Temporal summation of pain**

41 The differences in TSP between CRPS patients and HC was analyzed by
42 general linear mixed models in order to keep the information of temporal aspect of
43 TSP. The twelve stimulations of the TSP protocol were divided into four subblocks of
44 three stimulations each to reduce the model's dimensionality. The models were set
45 up using the R package lme4 [34] with the averaged pain ratings across a subblock
46 as dependent variable, the four stimulation subblocks as independent variable, and
47 participant as random effect. Study cohort (CRPS or HC) was included as interaction
48 effect with the stimulation subblock (subblock*cohort). The model p-value was
49 corrected for testing in multiple areas by the Benjamini-Hochberg method. Next, the
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3 association of pain characteristics (i.e., pain intensity and spatial pain extent) and
4 psychological factors (i.e., PCS, HADS, and BBPDS score) with TSP was tested
5 within the CRPS patients by including these factors as interaction effect with the
6 stimulation subblock (subblock*pain-characteristic or subblock*psychological-factor).
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8 Pain intensity and psychological factors were included as numeric vector, whereas
9 the spatial pain extent was included as phenotypic subgroup (high and low spatial
10 pain extent). Testing within multiple areas and pain characteristics or psychological
11 factors was corrected using the Benjamin-Hochberg method. Lastly, a potential
12 confounding effect of pain medication on TSP was investigated by including the pain
13 medication subgroup (yes/no) as factor into the model (subblock*medication). As
14 previously, the p-value was corrected for testing in multiple areas using the
15 Benjamin-Hochberg method.
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32 Results

33 Demographics, pain characteristics, and psychological factors

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35 The demographics of the study population and information regarding
36 psychological factors are shown in Table 1. CRPS patients had significantly higher
37 HADS-anxiety ($t(33) = 4.34, p < 0.001$), HADS-depression ($t(23) = 4.42, p < 0.001$)
38 and PCS scores ($t(33) = 4.88, p < 0.001$) compared to HC. CRPS-specific
39 characteristics are presented in Table 2. Table S1 in the supplementary information
40 section illustrates the intake of pain medication in detail. Examples of different pain
41 patterns observed in CRPS patients are shown in Figure 1B-E. The correlation
42 between pain characteristics and psychological factors of CRPS patients revealed
43 that patients with a higher BBPDS scores presented with a larger spatial pain extent
44 ($\rho = 0.491, p = 0.048$). The HADS and PCS, however, did not correlate with the
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3 spatial pain extent (HADS: $\rho = 0.006$, $p = 0.979$; PCS: $\rho = -0.116$, $p = 0.740$).
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5 Patients with a higher HADS and PCS score reported higher spontaneous pain
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7 intensities (HADS: $r = 0.601$, $p = 0.021$; PCS: $r = 0.571$, $p = 0.021$). The BBPDS
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9 score did not correlate with the pain intensity ($r = 0.168$, $p = 0.701$).
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12 Difference in sensory profiles between patients with CRPS and HC

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15 There were a few dropouts due to non-tolerance of the protocol encountered
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17 (full QST, WUR (N = 2), PPT (N = 1)). Furthermore, in two CRPS patients no control
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19 area could be assessed because it was either affected by pain (independent
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21 spreading pattern) or a frozen shoulder condition.
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25 CRPS patients showed a significant gain of function by means of decreased
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27 PPT and increased mechanical pain sensitivity (MPS) in the affected area compared
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29 to HC (PPT: $t(34) = 4.98$, $p < 0.001$, MPS: $t(34) = 2.54$, $p = 0.048$, Figure 2A).
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31 Additionally, CRPS patients showed significant loss of function in the affected area
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33 by means of an increased VDT compared to HC ($t(30) = -3.37$, $p = 0.002$). A gain of
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35 function in the contralateral (Figure 2B) as well as the control area (Figure 2C) of
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37 CRPS patients was measured by decreased PPT compared to HC (contralateral
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39 area: $t(35) = 3.19$, $p = 0.005$, control area: $t(31) = 2.65$, $p = 0.012$). There was no
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41 statistical difference between CRPS patients and HC for the remaining QST
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43 parameters ($p > 0.05$).
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47 QST across measurement areas in patients with CRPS

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50 Within the CRPS cohort, PPT and MPT were different between the three
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52 measurement areas (PPT: $F(2,19) = 7.13$, $p = 0.009$; MPT: $F(2,30) = 4.89$, $p =$
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54 0.015). Post-hoc analyses revealed that PPT was lower in the affected compared to
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56 the contralateral ($t(17) = 2.99$, $p = 0.025$) and control area ($t(15) = 3.39$, $p = 0.012$).
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58 In addition, MPT was lower in the affected compared to the control area ($t(16) =$
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2.88, $p = 0.033$). There was no statistical difference between the stimulation areas for the remaining QST parameters ($p > 0.05$).

Association between widespread hypersensitivity and pain characteristics or psychological factors

Widespread pain hypersensitivity, assessed by a significant gain of function (decrease in PPT) in the control area, did not correlate with pain intensity ($r = 0.56$, $p = 0.066$) or any of the psychological questionnaire scores (HADS: $r = 0.52$, $p = 0.406$; PCS: $r = 0.42$, $p = 0.132$; BBPDS: $r = 0.06$, $p = 0.482$). In addition, there was no difference in widespread pain hypersensitivity between CRPS patients with a high ($> 5\%$) compared to a low ($< 5\%$) spatial pain extent ($t(14) = 0.68$, $p = 0.510$). Lastly, there was no difference in widespread pain hypersensitivity whether the patients regularly took pain medication or not ($t(10) = 0.01$, $p = 0.993$).

Temporal summation of pain

One patient with CRPS did not tolerate the TSP protocol and had to be excluded from the TSP analysis. In addition, two patients did not have a control area as mentioned in the previous subsection.

TSP was observed for both CRPS patients (affected area: $F(3,54) = 16.25$, $p < 0.001$; control area: $F(3,54) = 13.30$, $p < 0.001$) and HCs (affected area: $F(3,57) = 5.51$, $p = 0.002$; control area: $F(3,57) = 5.62$, $p = 0.002$). Figure 3 shows increased TSP in CRPS patients compared to HCs in the affected ($F_{\text{subblock*cohort}}(3,111) = 4.57$, $p = 0.009$), but not in the control area ($F_{\text{subblock*cohort}}(3,111) = 2.08$, $p = 0.107$). Post-hoc tests within the affected area are illustrated in Figure 3. There was no significant difference in TSP between the control and affected area of CRPS patients ($F_{\text{subblock*area}}(3,126) = 0.38$, $p = 0.769$).

Relation between TSP and pain characteristics or psychological factors

All results regarding the interaction effect between the TSP-subblock and pain characteristics or psychological factors are illustrated in Table 3. Importantly, CRPS patients with a high spatial pain extent (>5% of total body surface) showed more pronounced TSP in the affected area compared to patients with a low spatial pain extent (<5%) (Figure 4). Post-hoc tests within the affected area are illustrated in Figure 4. TSP tested in the control area was, however, not significantly different between the high and low spatial pain extent group. Pain intensity was neither related to TSP assessed in the affected area, nor to TSP assessed in the control area. Moreover, psychological factors did not significantly relate to both TSP measures. The intake of pain medication did not influence TSP regardless of the tested area.

Discussion

The aim of this study was to better characterize the clinical pain phenotype of CRPS patients and relate it to signs of central sensitization and psychological distress. In line with previous work, this study provides additional evidence that central sensitization might contribute to the pathophysiology of CRPS [3] indicated by mechanical hyperalgesia in remote pain-free body regions (widespread pain hypersensitivity) and increased TSP compared to HC. Strikingly, CRPS patients with an extended pain pattern showed more pronounced TSP in the affected area as well as higher disturbance of body perception compared to patients with a more focal pain phenotype.

Signs of central and peripheral sensitization

Central sensitization is proposed to be a pathophysiological mechanism in CRPS [35] and has previously been indicated by assessments of widespread pain hypersensitivities [36]. Especially mechanical hyperalgesia in contralateral and remote areas was shown to be a hallmark of CRPS [4,7,8,36]. Our finding of reduced PPT in the control area supports previous studies and indicates a general disturbance in central pain processing which might be due to hyperexcitable neurons in the central nervous system or deficient endogenous pain control. The latter was previously shown in patients with CRPS [8,37], and proposed as a main underlying mechanism of widespread pain hypersensitivity because of its spatially non-restricted nature [38]. Alternatively, the observed widespread pain hypersensitivity might be induced by spinal sensitization through glial activation. Such widespread spinal sensitization was previously observed in rats with spinal cord injury, where astrocyte and microglia activation was present even 10 segments rostrally to the injury [39]. Del Valle and colleagues supported this finding in a clinical CRPS case report [40]. Post-mortem histology and immunochemistry were performed at different segmental levels of this chronic CRPS patient and revealed increased numbers of astrocytes and microglia in the dorsal horn of the CRPS patient compared to control subjects. Although the increase of microglia and astrocytes was most prominent at the segmental level of the affected area, it was present throughout the entire spinal cord.

Regardless of probable central hyperexcitability, a potential co-existence of peripheral sensitization, such as irritable primary nociceptive neurons, might additionally lower pain thresholds in the affected area [41]. When comparing the sensory profiles of the different measurement areas within the CRPS patients we

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3 found lower MPTs in the affected compared to the contralateral or control area. This
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5 difference highlights a potential cumulative contribution of peripheral and central
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7 hypersensitivities in CRPS.
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10 In addition to mechanical hyperalgesia, mechanical hypoesthesia was present
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12 in the affected area of CRPS patients (by means of reduced VDT). The combination
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14 of mechanical gain and loss of function was previously described in patients with
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16 CRPS [42]. Previous literature suggested that such hypoesthesia results from
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18 cerebral reorganization due to continuous activation of the nociceptive neuraxis and
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20 is referred to as pain-induced hypoesthesia [43]. The contribution of central plasticity
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22 to mechanical hypoesthesia in CRPS patients without any definable nerve lesion
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24 was previously supported by Pleger and colleagues [44]. They showed reduced
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26 activity of the somatosensory cortex in response to electrical stimulation of the
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28 affected area which correlated with an increased two-point discrimination threshold.
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30 Additionally, neglect-like symptoms have been previously reported in CRPS patients
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32 [45], potentially contributing to the observed mechanical hypoesthesia in the affected
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34 limb [46].
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40 Exaggerated TSP as sign of spinal sensitization

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42 Increased TSP was seen in the affected area of CRPS compared to HC,
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44 supporting the hypothesis of a sensitized central nervous system in CRPS. TSP is
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46 considered to indicate increased excitability of second-order neurons located in the
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48 dorsal horn of the spinal cord [11–13]. Consequently, we would argue that the
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50 observed increase in TSP in the affected area implies a hyperexcitability of these
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52 second-order neurons. Several potential mechanisms of spinal hyperexcitability have
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54 been previously discussed such as long term potentiation of second-order neurons,
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56 disinhibition due to the loss of inhibitory interneurons, and glial-neuronal interactions
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(for review see Basbaum et. al., 2009 [47]). Previously, treatment with Ketamine (NMDA-receptor antagonist) [48] and Baclofen (GABA-receptor agonist) [49], have been shown to reduce CRPS specific symptoms by reducing the excitability of second-order neurons. These findings support the assumption that spinal hyperexcitability contribute to the pathophysiology of CRPS. When assessing the control area, however, TSP in CRPS patients was not increased compared to HC. On the one hand, this might be due to the greater variability in TSP when stimulating the control area of CRPS patients (SD = 2.20) compared to HC (SD = 1.59). On the other hand, a seminal preclinical study in rats has shown that dorsal horn neurons receiving input from deep muscle afferents (such as tested with PPT) are under more descending inhibitory control than spinal neurons receiving input from superficial cutaneous afferents [50]. Therefore, it can be assumed that the increased hypersensitivity to painful pressure stimuli in the control area might better resemble a potential lack of descending inhibition, i.e., net increase in spinal excitability, in CRPS patients than measures testing superficial cutaneous nociceptors (TSP).

Association between experimental and clinical signs of central sensitization

Since some pain characteristics (e.g., spatial pain extent) might indicate central sensitization [38], we hypothesized that these pain characteristics relate to psychophysical signs of central sensitization, e.g., widespread pain hypersensitivity and increased TSP. In line with our hypothesis, patients with a high spatial pain extent had increased TSP in the affected area compared to patients with a low spatial pain extent. This strengthens the assumption that extended pain patterns in CRPS patients might occur due to hyperexcitable neurons within the central nervous system [23]. The relationship between TSP and spatial pain extent was, however, not confirmed when studying TSP in the control area. This result might therefore

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3 further indicate that a large spatial pain extent is mainly a result of use-dependent
4 plasticity within the spinal cord (i.e., neurogenic inflammation, glial activation, and
5 long term potentiation) [38], which induces hyperexcitability within restricted body
6 regions (i.e., within the affected area).
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12 Both spatial pain extent and pain intensity did not relate to widespread pain
13 hypersensitivity (i.e., reduced PPT in control area). Regarding spatial pain extent,
14 these findings are in line with studies investigating patients with fibromyalgia and
15 knee osteoarthritis [16,51]. However, regarding pain intensity, these studies found
16 that patients with higher pain intensity showed more signs of hypersensitivity [16,51].
17 Although this tendency was also observed in our study, it could not be confirmed
18 after correction for multiple comparisons. One possibility as to why no correlation
19 was observed between the widespread pain hypersensitivity and pain intensity or
20 spatial pain extent could be that underlying mechanisms are cumulative rather than
21 congruent.
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36 Psychological factors are differently related to pain intensity and spatial pain 37 extent 38 39

40 The spontaneous pain intensity correlated with psychological factors such as
41 depression, anxiety, and pain catastrophizing whereas the spatial pain extent
42 correlated with perceptual disturbances of the affected area. In line with these
43 findings, previous systematic reviews in chronic pain conditions discussed the
44 association between psychological factors and greater pain intensity [52–55]. In
45 particular with regard to patients with CRPS, Feldman and colleagues [27]
46 investigated in a prospective study the influence of depression and anxiety on pain
47 intensity and vice versa. They found that pain led to increases in depression, anxiety
48 and anger the next day, but also that depressed mood contributed to more pain the
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3 next day. Similarly, Farzad and colleagues [26] found that psychological factors
4 including, depression, anxiety and pain catastrophizing were associated with greater
5 pain intensity in patients with CRPS. However, the causality between psychological
6 factors and pain intensity remains elusive.
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12 Further, a relationship between CRPS severity and body perception
13 disturbances has previously been reported [56]. These body perception disturbances
14 were related to maladaptive cortical plasticity of the somatosensory cortex [44].
15 Hence, such a cortical reorganization might contribute to the observed expansion of
16 the spatial pain extent in our CRPS patients. This, however, is just speculative and
17 should be investigated in further studies.
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26 Limitations

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29 The sample size of patients with CRPS was rather small with a large
30 variability in terms of pain characteristics (i.e., pain intensity and spatial pain extent)
31 and CRPS duration. On the one hand, this heterogeneity made it possible to
32 investigate possible differences in terms of underlying mechanisms between these
33 patients; on the other hand, it also limits the generalizability of the observed results.
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35 It would be of great interest to investigate whether these results are consistent in a
36 larger patient sample reporting more homogeneous pain characteristics. Further, the
37 data presented is a subset of a larger test battery. The additional tests performed on
38 the participants may have influenced the results presented by, for example,
39 sensitizing the tested areas. Moreover, this study comes with the limitation that
40 patients maintained their intake of pain medication during the period of study
41 participation, potentially confounding our primary readouts. Nevertheless, we found
42 no significant effect of pain medication on pain sensitivities assessed by QST or
43 TSP. Lastly, previous literature has mainly reported a pronounced ipsilateral spread
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3 of sensitization in patients with CRPS [4,7]. Based on the measured control area in
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5 this manuscript, no conclusion can be drawn as to whether widespread sensitization
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7 mechanisms are more pronounced on the ipsilateral compared to the contralateral
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9 side of the affected area.
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11 12 Conclusion

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15 To conclude, CRPS patients showed widespread pain hypersensitivity as
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17 means of decreased PPT in the control area and increased TSP in the affected area,
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19 corroborating previous studies indicate a potential presence of central sensitization
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21 in these patients. Most importantly, patients with high spatial pain extent showed
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23 increased TSP and body perception disturbances compared to patients with low
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25 spatial pain extent. Hence, the spatial pain extent itself might provide a clinically
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27 relevant measure for signs of sensitization mechanism within the central nervous
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29 system and may provide a marker for therapeutic success.
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37
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46 (CRPP) Pain of the University of Zurich. There is no conflict of interest to declare.
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Figure legends

Figure 1: Spatial pain extent reported by the complex regional pain syndrome (CRPS) patients. (A) Histogram of the spatial pain extent. Illustrated are four different examples of CRPS patients with (B) continuous pain spread, (C) mirror-image pain spread, (D) independent pain spread and (E) focal pain.

Figure 2: Sensory profiles of the affected, contralateral, and control area from complex regional pain syndrome (CRPS) patients and the corresponding areas in healthy controls (HC). Illustrated is the mean and standard error of measurement of z-scores and $\pm 1.96SD$ (gray area). Sensory profile of the (A) affected, (B) contralateral, and (C) control area. Abbreviations: CDT: cold detection threshold; CPT: cold pain threshold; DMA: dynamic mechanical allodynia; HPT: heat pain threshold; MDT: mechanical detection threshold; MPS: mechanical pain sensitivity; MPT: mechanical pain threshold; NRS: numeric rating scale; PHS: paradoxical heat sensation; PPT: pressure pain threshold; QST: quantitative sensory testing; TSL: thermal sensory limen; VDT: vibration detection threshold; WDT: warm detection threshold; WUR: wind-up ratio. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 3: Temporal summation of pain in the affected (left) and control area (right) of CRPS patients (purple) and HC (turquoise). Illustrated is the mean pain rating (y-axis) of the stimulation subblocks (x-axis). The purple and turquoise lines illustrate the linear fit of the corresponding boxplots. The error bars illustrate the standard deviation. Additionally, post-hoc tests for the interaction effect between stimulation subblock and cohort are shown. Abbreviations: CRPS: complex regional pain syndrome; HC: healthy controls; NRS: numeric rating scale. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 4: Temporal summation of pain (TSP) in the affected area of complex regional pain syndrome (CRPS) patients. The patient cohort is divided into two groups depending on their spatial pain extent (phenotypic subgroups). Patients with a high spatial pain extent are shown in red and patients with a low spatial pain extent in brown. Illustrated is the mean pain rating (y-axis) of the stimulation subblocks (x-axis). The burgundy and brown lines show the linear fit of the corresponding boxplots. The error bars illustrate the standard deviation. Abbreviations: NRS: numeric rating scale. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 1: Summary of the study population.

	CRPS	HC	p-value
	N = 21	N = 20	
Demographics			
Female [N] (%)	17 (81%)	14 (70%)	0.414
Age [y]	44 (12)	45 (14)	0.870
Height [cm]	170 (6)	170 (7)	0.966
Weight [kg]	73 (14)	68 (12)	0.300
Psychological questionnaires			
HADS-anxiety [score]	8.0 (3.7)	3.6 (2.5)	<0.001
HADS-depression [score]	6.7 (4.8)	1.6 (1.5)	<0.001
PCS [score]	22.2 (11.8)	7.2 (7.8)	<0.001

Categorical data is presented as number of occurrences and relative proportion of the total data set. Continuous data is presented as mean (standard deviation).

Abbreviations: CRPS: Complex Regional Pain Syndrome; HADS: Hospital Anxiety and Depression Scale; HC: Healthy Controls; PCS: Pain Catastrophizing Scale.

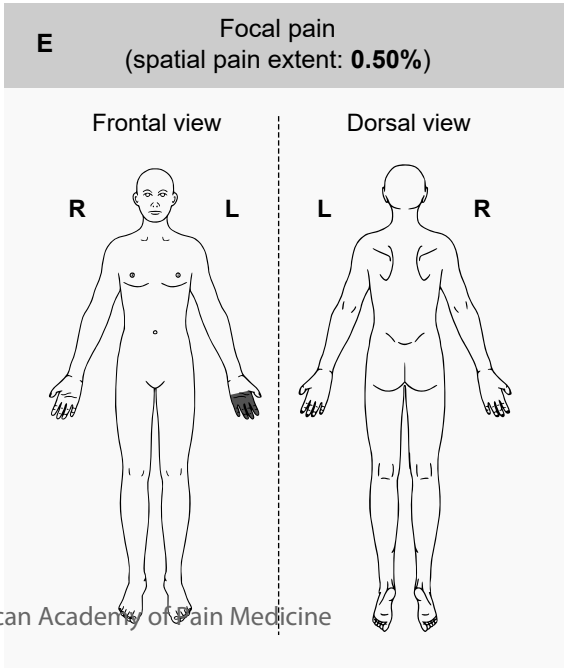
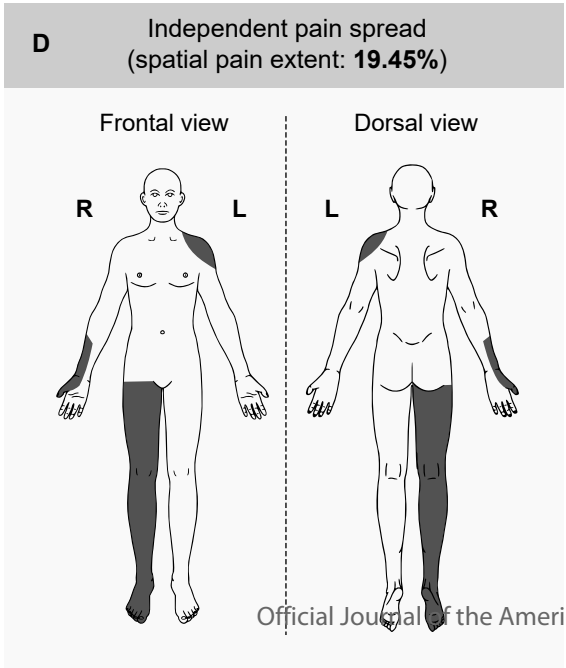
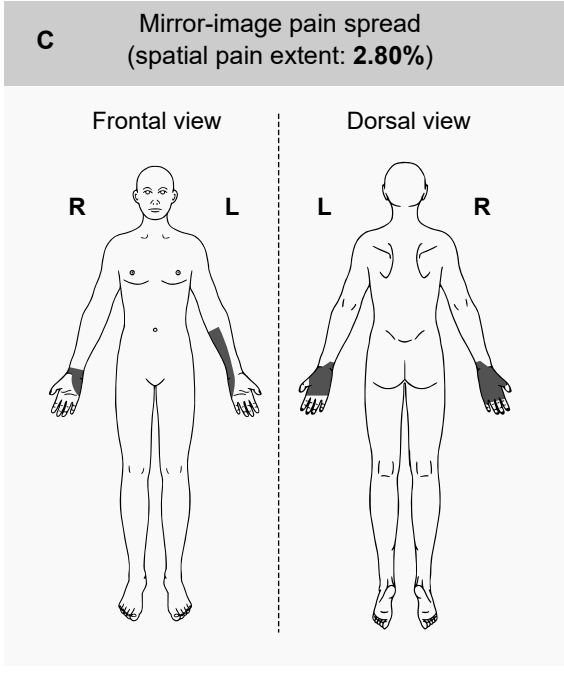
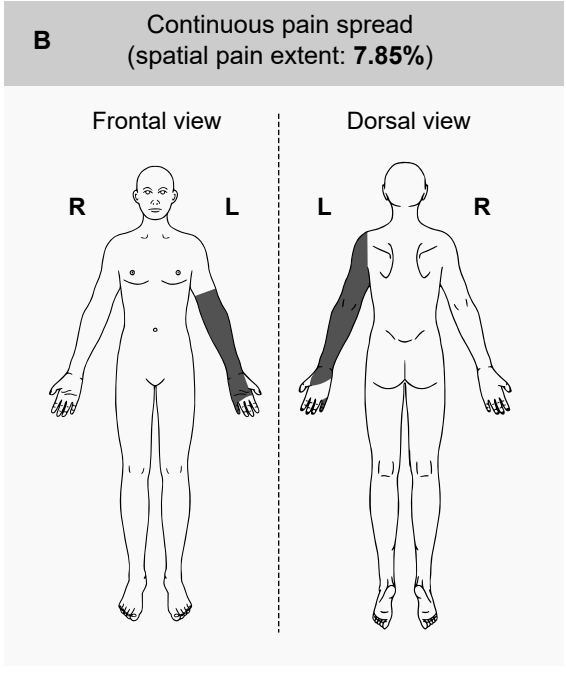
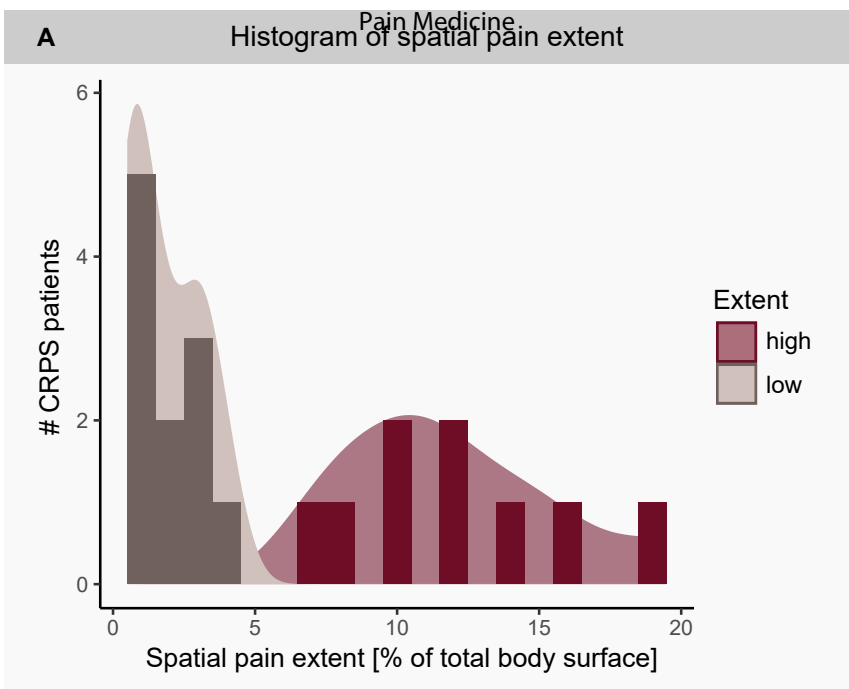
Table 2: CRPS-specific characteristics.

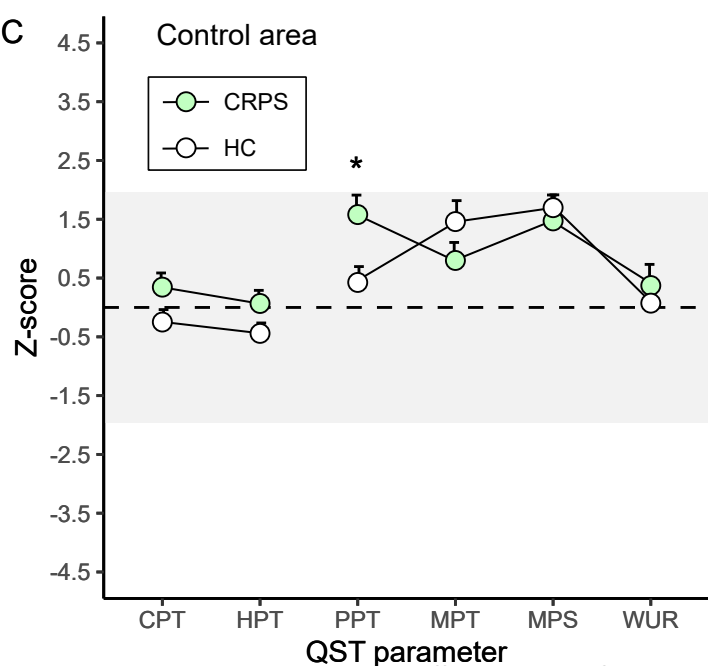
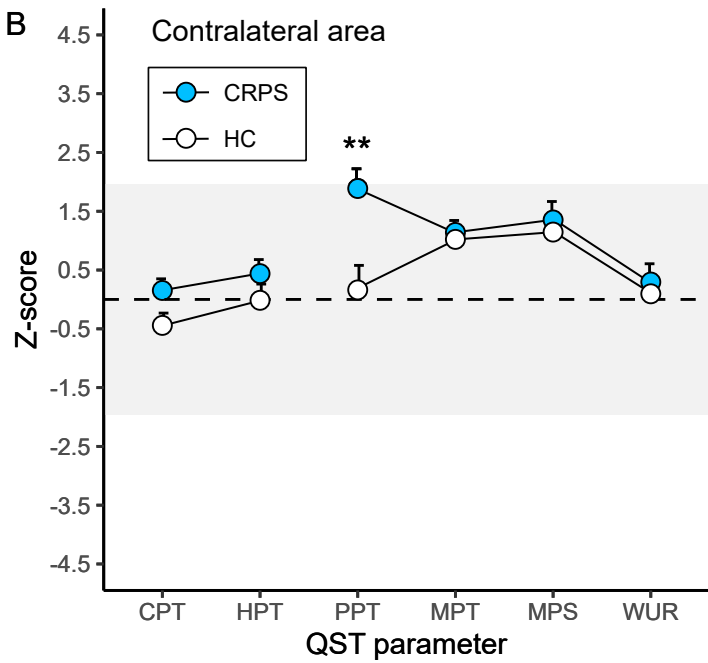
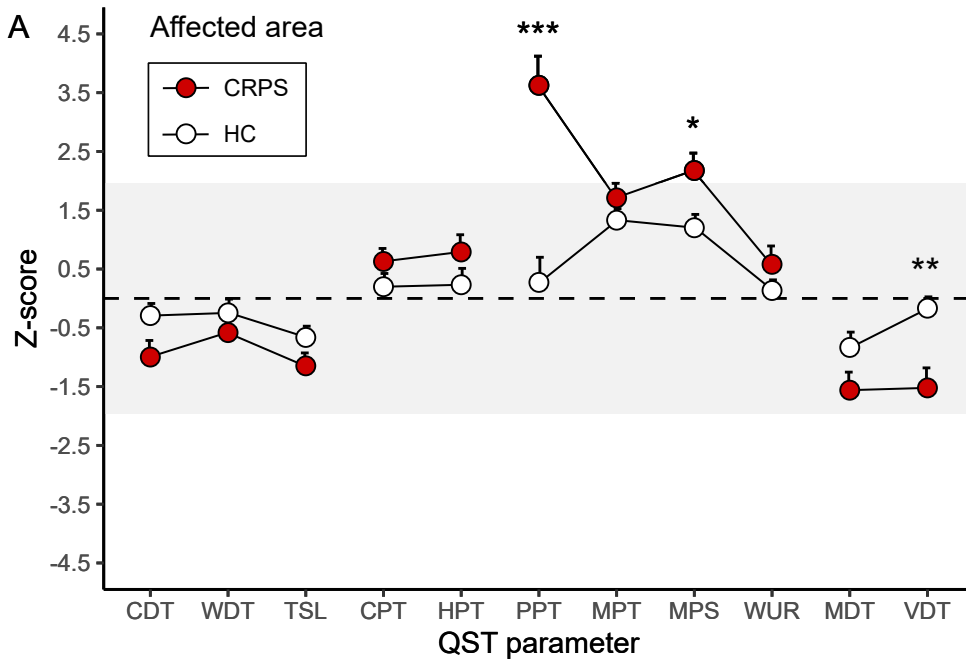
CRPS-specific characteristics (N=21)			
CRPS type I [N]	20	Continuous pain spreading [N]	11
CRPS type II [N]	1	Mirror-image pain spreading [N]	3
Etiology	16	Independent pain spreading [N]	2
		Focal pain [N]	5
		Spatial extent [% body surface]	4.1 (0.5-24.9)
Initial trauma [N]	16	Intensity [NRS]	5.5 (2.4)
followed by surgery [N]	7		
Initial surgery [N]	5		
Affected hand [N]	13	Duration [months]	35 (6-159)
Affected foot [N]	7		
Affected shoulder [N]	1		
Pain medication intake	14	BBPDS [score]	19.3 (8.1)
No [N]	7		

Normally distributed data is presented as mean (standard deviation) and not normally distributed data is presented as median (range). Abbreviations: BBPDS: Bath Body Perception Disturbance Scale; CRPS: Complex Regional Pain Syndrome.

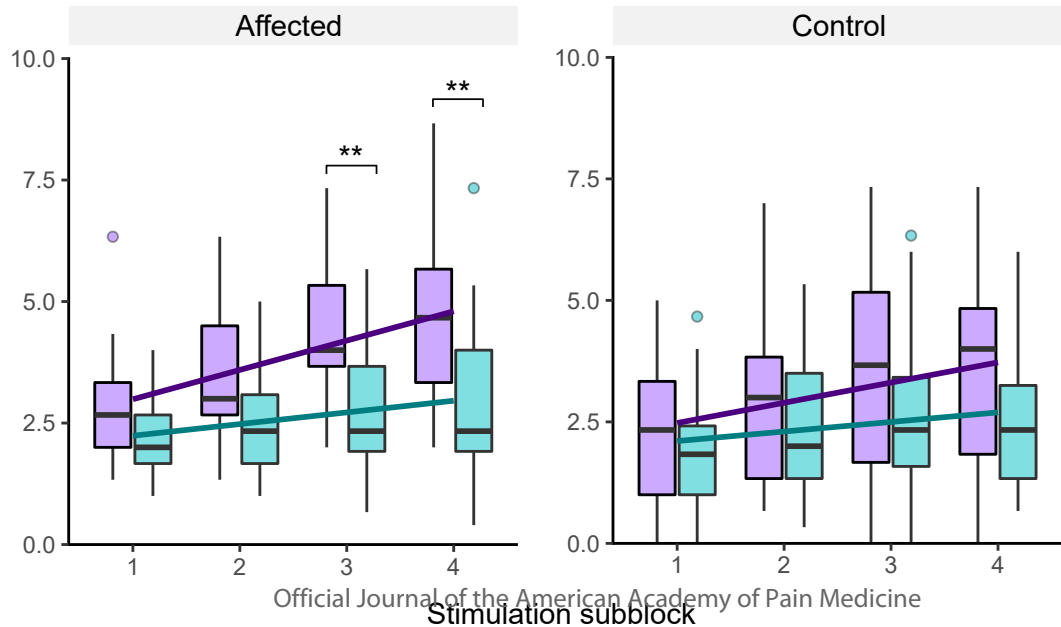
Table 3: Interaction effects between TSP-subblock and other factors.

Interaction effect with subblock	Affected area		Control area	
	F(3,51)	p-value	F(3,51)	p-value
Spatial pain extent	5.67	0.008	1.78	0.217
Pain intensity	0.97	0.415	3.11	0.068
HADS	0.39	0.920	0.17	0.920
PCS	0.53	0.920	0.52	0.920
BBPDS	0.25	0.920	0.37	0.920
Pain medication	0.49	0.935	0.14	0.935





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Pain Medicine

