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Original Experimental

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Abstract

Objectives: The aim of the current study was to examine the convergent validity of the Central Sensitization Inventory by quantifying the correlation with experimental measures of pain sensitivity and self-reported psycho-social questionnaires, in a low back pain population.
Methods: All participants were recruited from an outpatient hospital spine care clinic (Spine Centre of Southern Denmark). Participants underwent a standardized experimental pain test protocol and completed the Central Sensitization Inventory (CSI) along with additional self-reported questionnaires to assess psycho-social constructs across different domains. The association between the CSI, experimental pain measures and other self-reported psycho-social questionnaires were analyzed using correlation and contingency tests. ROC-curve analysis was used to determine sensitivity and specificity for CSI.
Results: One hundred sixty-eight (168) participants were included. The CSI was weakly correlated with nine out of 20 variables in the experimental pain test protocol (rho range −0.37 to 0.22). The CSI was more closely correlated with psycho-social factors such as work ability, disability, and symptoms of exhaustion disorder. ROC-analysis identified an optimal cut-point of 44 on CSI (Sn=39.1% Sp=87.4%). The CSI had an area under the ROC curve of 0.656. Fisher's exact test demonstrated a statistically significant association between participants scoring ≥40 on CSI and participants categorized as sensitized by experimental pain tests (p-value=0.03).
Conclusions: Our findings are consistent with previous studies, indicating that the CSI is related to psycho-social constructs. However, the convergent validity with experimental pain measures is small and probably not clinically meaningful.

Keywords: central sensitization; central sensitization inventory; low back pain; psycho-social measures; quantitative sensory testing.

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Introduction

Central sensitization (CS) is defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input" [1]. Several mechanisms involved in the development of CS have been suggested, including an altered sensory processing in the brain [2], and a dysregulation in both ascending pain facilitatory [2, 3] and descending pain inhibitory pathways [4]. Central sensitization has been described in a number of chronic conditions, including chronic low back pain (LBP) [5–8], and generally manifests as pain hypersensitivity in the form of lower pain thresholds, higher pain responses, and perturbations of pain modulation [9]. Despite extensive research into this phenomena, there is no general

consensus on the definition of clinical criteria for CS, and a gold standard for assessing CS is lacking.

While direct physiological detection of CS in pain patients is not possible, psycho-physical measures of pain sensitivity, such as Quantitative sensory testing (QST), can be used to assess and evaluate the function of the somatosensory nervous system [10, 11], and is often used to infer perturbations in pain modulation, such as those seen in patients affected by CS [9, 11, 12]. Examples of such changes are lowered pain thresholds and elevated pain ratings for patients subjected to standardized painful stimuli in experimental pain testing [13, 14]. Limitations to QST are their time-consuming nature and requirement of expensive equipment, as well as expertise and adherence to a rigorous testing protocol. While standardization of QST has been proposed and implemented [15, 16], there is currently no universally accepted protocol for experimental pain testing for clinical subgroups, such as patients with LBP.

To aid clinicians in identifying CS, the Central sensitization inventory (CSI) was developed in 2011. The CSI is a self-reported questionnaire aiming to screen for symptoms related to CS [17]. The CSI has been shown to be associated with other self-reported instruments aimed at measuring psychological constructs, such as pain catastrophizing, fear avoidance, and anxiodepressive symptoms [18–22]. However, it remains uncertain whether CSI scores also correlate with more direct measures of pain sensitivity, such as QST. Only a few studies have examined the correlation between CSI and QST, and results have varied [18, 20, 23, 24]. Kregel et al. [23] examined PPT and CPM in a chronic spinal back pain cohort in a primary care setting, and found a weak correlation between CSI and PPT, but no correlation between CSI and CPM. The authors suggested that the CSI "does not reflect a direct measure of CS, yet is a representation of general distress, possible originating from CS symptoms". Gervais-Hupé et al. [20] studied PPT, CPM and TS in a group of knee osteoarthritis (KOA) patients and found only weak or non-significant correlations between CSI and QST. They found that the CSI was "more strongly associated with psychological factors than psychophysical test results". Coronado and George [18] examined the correlation between CSI and pain sensitivity in a shoulder pain population and reported similar findings. Furthermore, in a study by Mibu et al. [24], the association between CSI scores with PPT and TS was investigated in patients with either chronic LBP or KOA, finding no significant correlations in either group. In a more recent study, Zafereo et al. [25] investigated the association of CSI scores with thermal and pressure pain thresholds in patients with chronic musculoskeletal pain, finding only low-to-negligible correlations between CSI scores and QST variables.

Thus, when summarizing the literature, the correlation between QST and CSI remains uncertain. But does not appear strong. Previous studies have applied limited QST protocols and studied different pain populations, making conclusions less certain. Arguably, applying a broad QST battery consisting of relevant QSTs to a large group of LBP patients, all seen in the secondary care sector, could potentially shed further light on the association between CSI and QST.

The aim of the present study was to examine the convergent validity of the CSI questionnaire, by exploring the correlation of CSI with QST (construct validity) and self-reported psycho-social measures (concurrent validity), in a cohort of secondary-care sector patients with LBP. Furthermore, we explored the correlation between QST and self-reported psycho-social measures. A secondary objective was to examine the sensitivity and specificity of CSI when categorizing participants as sensitized or non-sensitized by QST. Thirdly, we determined the optimal cut-point on CSI for sensitized/non-sensitized categorizations in the present study population.

Methods

Study design

The study was designed as a cross-sectional study. Participants were recruited from the patient population of the Spine Centre of Southern Denmark, Lillebaelt Hospital, a large regional outpatient hospital spine care unit. All patients referred to the spine care unit between February and August (2019) with LBP as the primary complaint, were invited to participate in the study. Invitations, along with written information about the study, were posted electronically. Patients were included through two parallel channels:

(i) Patients responding to electronic invitations were assessed for inclusion and exclusion criteria through telephone interview, before presenting for clinical consultation at the spine care unit. Eligible patients were invited to participate in the study on the day of their clinical consultation, or at a date in close conjunction thereto.
(ii) Patients presenting for initial consultations at the hospital spine care unit and identified by the examining clinician as eligible for inclusion.

Inclusion and exclusion criteria

The patients were eligible if they fulfilled the inclusion and exclusion criteria. Inclusion criteria for participants were: 18 years of age or above; able to understand, speak, and read Danish; primary complaint of LBP (defined as lumbar dorsal pain, muscle tension, or stiffness localized between the lower costal margin and the inferior gluteal folds, with or without sciatica); had completed a clinical

questionnaire and provided written consent for the use of data in research.

Participants were excluded from the analysis if: they withdrew their consent for participation during the study; the experimental procedure was discontinued, due to technical difficulties or participant compliance issues; the participant had severe psychiatric disorders. Furthermore, participants presenting with a clinical history of cardiovascular disease (CVD) were excluded in parts of the QST protocol.

Data collection

Once enrolled, participants were asked to complete baseline questionnaires as described below. Subsequently, participants were assessed by a research assistant (LH) trained in performing a predefined QST protocol. Testing was conducted at the Experimental Pain Laboratory at the medical research department of the Spine Centre. Demographic variables were obtained through an online questionnaire [26] 1–2 days prior to inclusion. Additional questionnaires (described in Sections SpineData clinical registry: psychological domain, Oswestry disability index (ODI), Karolinska exhaustion disorder scale (KEDS)) were completed immediately prior to QST testing.

Demographic variables

Demographic variables were obtained for all participants using the SpineData clinical registry [26], a clinical online system designed to capture current patient data electronically. Variables obtained were age, sex, BMI, duration of the current pain episode, current low back and leg pain intensity, as well as typical- and worst pain intensity during the last 14 days.

Questionnaires

Central sensitization inventory: The CSI is a two-part questionnaire. Part A consists of 25-items regarding the frequency and severity of symptoms assumed related to CS. Part B lists 10 diagnoses, allowing participants to note whether they have previously been diagnosed with CS-related disorders. For the purpose of this study, participants only completed Part A.

Participants were asked to rate each of the 25 items on a 5-point Likert scale, ranging from 0 (“never”) to 4 (“always”), with a total possible score of 100. A cut-off score of ≥40 is indicated to best discriminate between patients with suspected CS and healthy participants, with a strong level of sensitivity (81%) and acceptable level of specificity (75%) [27], as well as to indicate the presence of CS [17, 27, 28]. The suggested 40-point cut-point has shown similar results in studies conducted on an LBP population [29]. The original English CSI has showed excellent test-retest reliability and internal consistency (intraclass correlation coefficient=0.817; Cronbach’s α=0.879, respectively) [17, 27].

Prior to use in the present study, we translated the CSI into Danish (CSI-Dan) using guidelines for cross-cultural adaption of questionnaires [30]. Initially, the CSI was forward translated independently by two translators fluent in Danish, creating two translated versions of the questionnaire, *T1* and *T2*. Secondly, a synthesis of both versions (*T-12*) was created through a consensus process between the two translators and a recording observer. Thirdly, the synthesized *T-12* version was backward-translated to the original language independently by two different translators fluent in English. Lastly, all translations were reviewed at a consensus meeting by a committee consisting of three health professionals and all four translators, where a consensus was reached on any discrepancies between translations. This resulted in a ‘pre-final’ version of the translated questionnaire. Finally, the pre-final version was pilot-tested through cognitive interviews with five participants from the target population to test for relevance, comprehensiveness and comprehensibility [31]. No further changes were made to the pre-final version of the questionnaire after the pilot test. The CSI has been cross-culturally adapted into several languages [32–36], and the CSI has been reported to be a valid and psychometrically sound screening tool for its purposes. A recent systematic review of 14 articles on the measurement properties of CSI concluded that it generates reliable and valid data to quantify the severity of CS-related symptoms [37].

SpineData clinical registry: psychological domain: The psycho-social domain of the SpineData Clinical Registry uses brief one-item and two-item screening questions [38] to assess the constructs of anxiety, risk of persistent pain, social isolation, pain catastrophizing, depression and fear avoidance beliefs. The brief screening questions are derived from the full-length reference standard questionnaires [39–43], and their concurrent validity has been shown to be acceptable [38].

Oswestry disability index (ODI): The oswestry disability index (ODI) is a 10-item self-reported questionnaire commonly used to assess disability in LBP [44]. The items have six response alternatives in a Likert-format (0=no disability, 5=the greatest disability), with a scale range of 0–50.

Karolinska exhaustion disorder scale (KEDS): Karolinska Exhaustion Disorder Scale (KEDS) [45] is a 9-item self-reported questionnaire used to assess symptoms of stress-induced exhaustion disorder (ED). Each item is scored on a 7-point Likert scale, with higher scores indicative of greater severity of ED symptoms, with a scale range of 0–54.

A cut-off score of 19 has been shown to have high sensitivity and specificity (each above 95%) in the discrimination between healthy subjects and patients with ED. Furthermore, the internal consistency of KEDS has been shown to be acceptable, with Cronbach’s alpha of 0.94 in the full sample, 0.74 in patients, and 0.81 in controls [45].

Work ability index (WAI): item one: The work ability index (WAI) is a 7-item questionnaire used to assess work ability. For the present study, a short-measure version of WAI (WAI-1) was used. The WAI-1 has been shown to correlate moderately with the full length version of WAI [46]. The WAI-1 consists of a single-item which addresses current work ability compared to the life-time best. The item is measured on a 11-point numeric scale (0=completely unable to work, 10=work ability at its best), with a scale range of 0–10.

Experimental protocol

The QST procedure was optimized to examine LBP. An overview of tests included in the QST protocol can be seen in Appendix 1. The order of testing in the experimental protocol was optimized as to minimize the risk of interaction between the tests, and tests were performed as described in the sections below (Sections Cuff-algometry, Weighted

pinprick pressure, Pressure algometry, Spring-loaded probe, Cold pressor test). Participants had a minimum of 2 min rest between each test in order to avoid interaction between tests.

Cuff-algometry

Cuff algometry: pressure pain detection threshold and pressure pain tolerance threshold: A Computer-controlled cuff algometry system (CCA) (NociTech, CPAR, Denmark) was used to determine heterotopic pressure pain detection threshold (CPPT), heterotopic pressure pain tolerance threshold (CPTT), temporal summation (TS) and conditioned pain modulation (CPM) [47]. Two 13-cm wide cuffs were placed around the dominant and non-dominant gastrocnemicus muscle 8 cm distal to the tibial tuberosity. Deep-tissue pain sensitivity was assessed as a stimulus-response curve. The cuff pressure increased with 1 kPa/s, with a pressure limit of 100 kPa. The participant was instructed in the use of an electronic visual analogue scale (VAS) ("No pain"=0 cm to "Worst pain imaginable"=10 cm). Participants were instructed to continuously rate the induced pressure pain intensity from the initial pain onset. The first pressure perceived as painful by the participant was noted as PPT (CPPT), and the pressure at the time of termination was noted as PTT (CPTT). In cases where no pain was elicited by 100 kPa, 100 kPa was recorded as the CPTT, and the cuffs were instantly deflated. This test was performed initially on the dominant leg and subsequently on the non-dominant leg.

Cuff algometry: temporal summation and conditioned pain modulation: To determine cuff temporal summation (CTS), the CCA was programmed to apply a series of 10 repeated stimulations of the participant's dominant leg. The pressure used for each stimulation was equivalent to the individual's CPTT of the dominant leg at a rate of 1 Hz (i.e. 1 s of inflation to target pressure followed by 1 s of deflation). Before the start of the test, participants were instructed in the use of the VAS to continually score the perceived pain intensity with repeated stimulations as it changed over time. The average pain intensity scores for the first three and last three stimulations were calculated, and CTS was recorded as the difference between these.

To determine cuff conditioned pain modulation (CCPM), the procedure described in Section Cuff algometry: pressure pain detection threshold and pressure pain tolerance threshold was repeated, with a concomitant conditioning stimulus applied to the non-dominant leg. The conditioning stimulus consisted of 70% of the individuals CPTT and was maintained constantly on the non-dominant leg, whilst test stimuli consisted of gradually increasing pressure applied to the dominant leg. Starting at 0 kPa, the test stimuli increased with a rate of 1 kPa/s. Participants scored dominant leg pain intensity continuously using the VAS. Pressure stimulus was increased until either (i) a maximum pressure of 100 kPa was reached, or (ii) the pressure stimulus became unbearable for the participant, indicated by pressing a button, immediately after which the cuff was deflated. This was recorded as the CPPT. The difference in CPPT between the Sections Cuff algometry: pressure pain detection threshold and pressure pain tolerance threshold and Cuff algometry: temporal summation and conditioned pain modulation protocols was recorded as the CCPM.

Weighted pinprick pressure: Pinprick pressure pain threshold (WPPT) was assessed using a custom-made weighted probe. The pinprick was applied using a common metal needle (23G, 4G) for sterile intravenous injection, which had been blunted by grinding off the tip. The hollow pin thus presented a non-sharp contact area with an outer diameter of 0.64 mm. The pin was mounted inside a metal tube with a guide that permitted the pin to move freely up/down along the needle axis. By loading the pin with a variable number of spherical weights of 8 g inside the tube, pin prick of varying and controlled pressure could be applied. Pinprick pressure pain threshold (WPPT) was assessed at the dorsal thenar space on the dominant hand ($WPPT_{hand}$), as well as on the lumbar paraspinal muscle mass ($WPPT_{lower\ back}$).

Pinprick pressure pain threshold was assessed using a split-middles method, with six different weights applied: 4 g, 12 g, 20 g, 28 g, 44 g and 55 g. Initially, a pinprick was applied using the 20 g probe, and the participant was asked to verbally indicate if the applied stimuli was perceived as painful or non-painful. If the initial stimulus was perceived as non-painful, the largest (55 g) probe was applied. If this stimulus was perceived as non-painful, this was determined as the WPPT. If, on the other hand, the stimulus was perceived as painful, the 28 g probe was applied, and if non-painful, followed by the larger 44 g probe. Conversely, if the initial (20 g) pinprick was perceived as painful, the smallest probe (4 g) was applied. If this stimulus was perceived as non-painful, the middle of the smaller probes (12 g) was applied. Using this approach, the WPPT was determined as the smallest weight perceived as painful by the participant. Three trials were performed at each test site alternating between test sites. The mean was calculated and recorded for each test site ($WPPT_{hand}$ and $WPPT_{lower\ back}$ respectively).

Pressure algometry: Using a custom-made handheld electronic pressure algometer, pressure pain threshold (APPT) was assessed at the extensor muscles of the dominant forearm ($APPT_{forearm}$) and the lumbar paraspinal muscle ($APPT_{lower\ back}$). Increasing pressure was applied at a near-constant rate of 50 kPa/s, until the pressure was perceived as painful by the participant; this pressure was determined as the APPT. Three trials were performed at each test site alternating between test sites, and mean values were calculated and recorded for each test site.

Spring-loaded probe

Spring-loaded probe: pressure pain threshold and pressure pain intensity: Using a series of ten custom-made, spring-loaded pressure probes [48], pressure pain threshold (SPPT) was assessed at the extensor muscles of the dominant forearm ($SPPT_{forearm}$), and on the lumbar paraspinal muscle ($SPPT_{lower\ back}$). Using pressures ranging from 1 to 10 kg in steps of 1 kg, pressure was applied perpendicular to the skin and maintained for 1 s, before being released. Using a split-middles method similar to that described in Section Weighted pinprick pressure, the smallest pressure perceived as painful by the participant was recorded as the SPPT. Initially, the 5 kg probe was applied, and the participant was asked to verbally indicate if the applied stimuli was perceived as painful or non-painful. The smallest pressure perceived as painful by the participant was determined as the SPPT. Two trials were performed at each test site, alternating between sites, and mean values where calculated for each test site. Lastly, a final pressure of SPPT + 2 kg was applied at each test site, and pressure pain intensities (SPPI) were recorded at both sites by having the participant score pain intensity on the VAS.

Spring-loaded probe: temporal summation: Temporal summation by spring-loaded pressure probe (TS_1) was assessed at the lumbar paraspinal muscle contralateral to the side assessed in the tests described

in Section Spring-loaded probe: pressure pain threshold and pressure pain intensity. Using pressures of SPPT + 1 kg, a single pressure stimulus was applied, and, after a short pause (10 s), 10 consecutive stimulations were applied. The participant was asked to record pain intensity for the first and last stimulation, with temporal summation (TS_1) calculated as the difference in pain intensity between the 10th and first stimulation.

Cold pressor test: To further examine conditioned pain modulation, Cold pressor test (CPT) was used as a conditioning stimulus in a CPM paradigm [49], with the temporal summation test paradigm described in Section Spring-loaded probe: temporal summation used as test stimuli. Participants were instructed to immerse their left, non-clenched hand to the wrist in circulating cold water, refrigerated to a temperature of 0–2 °C. Participants were encouraged to keep their hand immersed for 2 min, or until the pain became unbearable, and to continually score their subjective pain experience using the VAS. Maximum cold pain intensity (CPI_{CPT}), time to achieve maximum cold pain intensity (T_{CPT}) and area under the curve (AUC_{CPT}) were recorded. Immediately after the completion of the CPT, temporal summation was once again assessed at the lower back (TS_2) using the procedure described in Section Spring-loaded probe: temporal summation, and the CPM effect ($CPM_{lower\ back}$) was calculated as the difference in TS before (TS_1) and after (TS_2) participants were exposed to the conditioning stimulus. We included the CPT in addition to the Cuff Algometry CPM protocol described in Section Cuff-algometry, since it has been shown that frequency of responders and non-responders show large variations across CPM protocols [50], and that there is considerable intra-individual variation in CPM testing [50].

Statistical methods

Variables of interest and data transformation: For the purpose of the statistical analysis, CSI scores were dichotomized using an *a priori* cut-point of ≥40 [27]. In order to dichotomize QST scores, we created a composite variable [51] that combined the score in each psychophysical variable obtained from QST. Before calculating the composite variable, psychophysical test scores were normalized using a min-max standardization, rescaling all data points to a value between 0 and 1 ($0 \leq x \leq 1$). Test variables which were inversely related to the degree of sensitization, such as pressure pain thresholds (i.e., the larger the pressure pain threshold, the lesser degree of sensitization), were assigned a negative value, ensuring higher test scores were indicative of sensitization. After scores were normalized, we calculated the composite variable, the QST total score, as a sum score of each normalized psychophysical variable. The QST total score was then divided by the total number of psychophysical tests, so that the scale range of the QST total score was 0–1. Subsequently, QST total scores were dichotomized using an *a priori* cut-point of the mean QST total score + 1 SD, with participants scoring above the cut-point categorized as having signs of CS in QST.

Similarly, to gauge the overall psycho-social profile of participants according to their scores in self-reported measures, a psycho-social composite variable was created and calculated as a sum of the total scores in each self-reported measure, excluding the CSI; Spine-Data Clinical Registry, ODI, KEDS, and WAI-1. Scores from self-reported measures were normalized similar to the procedure described for the QST total score, and a higher psycho-social composite score was indicative of a participant displaying more symptoms of psychosomatic disorder.

Statistical analysis: Descriptive statistics for demographic and experimental pain test variables are presented as means and standard deviations. Data distribution was assessed using Shapiro-Wilk's test. Bivariate correlation analysis was used to investigate the association between CSI, QST, and psycho-social variables. Pearson's (r) and Spearman's (r_s) correlation was used for parametric and non-parametric variables, respectively. Results from the correlation analyses are presented as correlation coefficients [52], and significant correlations are visualized as scatterplots. Due to the factor structure of the CSI [17, 53], we hypothesized that CSI and QST would have weak correlations in the present cohort, and that CSI would have stronger correlations with self-reported psycho-social measures. A 2×2 contingency table was created from which we calculated a sensitivity and specificity score for CSI, with the absence or presence of CS defined by the QST. Fisher's exact test was used to assess group difference in CS categorization. Lastly, receiver operator characteristic (ROC) curves were used to assess the discriminatory accuracy of CSI when compared with QST, and ROC-curve analysis was used to identify the optimal cut-point on CSI. The optimal cut-point was determined as the cut-point achieving an equally balanced sensitivity and specificity [54].

Statistical analyses were performed using the statistical software R (version 3.5.1 "Feather Spray", MacOS, El Capitan).

Results

Descriptive statistics of participants

During the period of inclusion, 669 patients were invited to participate in the present study. A total of 168 participants responded to invitations and fulfilled inclusion criteria. Twenty-one participants did not complete cuff algometry due to known CVD. Demographic and clinical data are presented in Table 1.

Correlation between central sensitization inventory and quantitative sensory tests

Significant but weak correlations were found for six out of 21 variables included in the QST protocol, while two variables showed moderate correlation with CSI total score (*see* Table 2). No strong correlations were found. Furthermore, a weak correlation was found between CSI and QST total scores (r=0.22, p-value=0.008). Scatterplots visualizing significant correlations are illustrated in Figure 1. Distribution of experimental pain test variables can be seen in Appendix 2. Only CSI, TS, CPM and QST total score were normally distributed.

Table 1: Descriptive statistics, n=168. For variables where missing data is present, n is reported.

Variables	Mean ± SD	n
Descriptive variables		
Age, years	55.8 ± 14.9	
Gender, N (%) male	103 (60.9%)	
BMI, kg/m^2	27.6 ± 5.1	147
Self-reported pain-related measures		
Duration of pain, months	45.7 ± 73.3	147
Back pain, current [NRS 0–10]	5.2 ± 2.5	147
Back pain, last 14 days [NRS 0–10]	5.9 ± 2.4	144
Leg pain, current [NRS 0–10]	4.3 ± 2.9	146
Leg pain, last 14 days [NRS 0–10]	5.1 ± 2.9	144
Self-reported psycho-social measures		
CSI [0–100]	30.9 ± 12.7	
ODI [0–50]	31.7 ± 14.4	133
KEDS [0–54]	17.0 ± 8.6	
WAI-1 [0–10]	5.4 ± 2.5	
Anxiety [0–10]	3.9 ± 3.2	134
Risk of persistent pain [0–10]	7.0 ± 2.7	142
Social isolation [0–10]	1.4 ± 2.1	144
Catastrophizing [0–20]	7.8 ± 6.1	
Depression [0–20]	7.0 ± 6.1	
Fear avoidance [0–20]	6.8 ± 6.2	
Psycho-social composite score [0–9]	2.9 ± 1.5	110

BMI, body mass index; CSI, central sensitization inventory; ODI, oswestry disability index; KEDS, karolinska exhaustion disorder scale; WAI-1, work ability index: item 1; […], scale range.

Correlation between central sensitization inventory and psycho-social measures

The CSI was significantly correlated with five out of ten psycho-social variables (*see* Table 3), with the largest correlation found between CSI and KEDS-scores (r_s=0.74, p-value<0.001), constituting a strong correlation [52]. Furthermore, a moderate correlation was found between CSI and psycho-social composite scores (r_s=0.48, p-value<0.001).

Correlation between quantitative sensory test and psycho-social factors

We found significant correlations between several QST variables and psycho-social factors; however, correlations were negligible in strength. No significant correlations were found between the QST total score and the same psycho-social factors. Results from the correlation analysis can be seen in Appendix 3.

Table 2: Bivariate correlations between Central Sensitization Inventory and experimental pain test variables in the Quantitative Sensory Pain Test protocol.

	n	Pearson's (r) and Spearman's (r_s) correlation coefficient	p-value
Cuff algometry			
$CPPT_{dominant\ leg}$	148	r_s=−0.01	0.927
$CPTT_{dominant\ leg}$	148	r_s=0.04	0.670
$CPPT_{non\text{-}dominant\ leg}$	148	r_s=−0.02	0.839
$CPTT_{non\text{-}dominant\ leg}$	148	r_s=0.03	0.718
CTS	148	r=0.17*	0.043
CCPM	145	r=0.08	0.351
Weighted pinprick pressure			
$WPPT_{lower\ back}$	167	r_s=−0.13	0.104
$WPPT_{hand}$	167	r_s=−0.18*	0.018
Pressure algometry			
$APPT_{lower\ back}$	167	r_s=−0.33***	<0.001
$APPT_{forearm}$	167	r_s=−0.24**	0.002
Spring-loaded probe			
$SPPT_{lower\ back}$	167	r_s=−0.37***	<0.001
$SPPT_{forearm}$	167	r_s=−0.22**	0.005
$SPPI_{lower\ back}$	167	r_s=0.22**	0.004
$SPPI_{forearm}$	167	r_s=0.09	0.244
TS_1	167	r_s=0.10	0.222
TS_2	167	r_s=0.09	0.224
Cold pressor test			
$CPM_{lower\ back}$	167	r_s=−0.02	0.804
CPI_{CPT}		r_s=0.17*	0.032
T_{CPT}		r_s=−0.13	0.101
AUC_{CPT}	167	r_s=0.02	0.823
Quantitative sensory test			
Total score	142	r=0.22**	0.008

CPPT, cuff algometry pressure pain detection threshold; CPTT, cuff algometry pressure pain tolerance threshold; CTS, cuff algometry temporal summation; CCPM, cuff algometry conditioned pain modulation; WPPT, pinprick pain threshold; APPT, algometry pressure pain threshold; SPPT, spring-loaded probe pressure pain threshold; SPPI, spring-loaded probe pressure pain intensity; TS_1, temporal summation before cold pressor test; TS_2, temporal summation after cold pressor test; $CPM_{lower\ back}$, conditioned pain modulation in the cold pressor test; CPI_{CPT}, maximum cold pain intensity in the cold pressor test; T_{CPT}, time to achieve maximum cold pain intensity in the cold pressor test; $AUC_{CPT,}$ area under the curve for the cold pressor test. **Significance Levels**: *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). ***Correlation is significant at the 0.001 level (2-tailed).

ROC-curve analysis and Fisher's exact test

Excluding observations containing missing data, 142 complete observations were available for Fisher's exact test

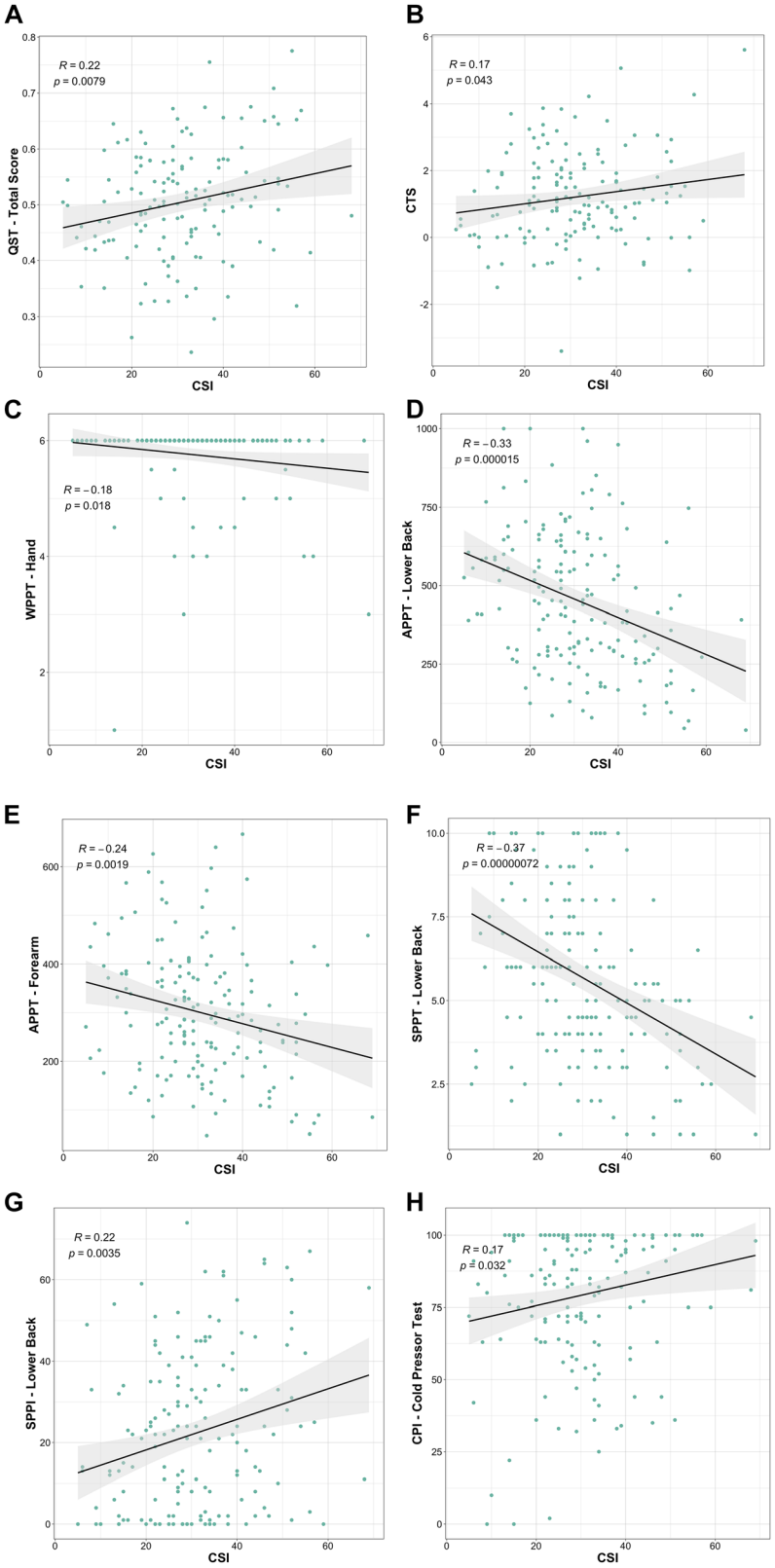

Figure 1: Scatterplots visualizing bivariate correlations of CSI total scores with experimental pain test variables included in the QST-protocol. A: QST Total Score; B: CTS; C: $WPPT_{Hand}$; D: $APPT_{lower\ back}$; E: $APPT_{forearm}$; F: $SPPT_{lower\ back}$; G: $SPPI_{lower\ back}$; H: CPI_{CPT}. A linear regression line as well as 95% confidence interval is displayed in all scatterplots. CSI=central sensitization inventory. R=correlation coefficient.

Table 3: Bivariate correlations between Central Sensitization Inventory total score and psycho-social factors.

	n	Pearson's (r) and Spearman's (r_s) correlation coefficient	p-value
Psycho-social factors			
ODI	132	r_s=0.52***	<0.001
KEDS		r_s=0.74***	<0.001
WAI-1		r_s=−0.42***	<0.001
Anxiety	134	r_s=0.16	0.062
Risk of persistent pain	142	r_s=0.16	0.055
Social isolation	144	r_s=0.28***	<0.001
Catastrophizing		r_s=0.09	0.268
Depression		r_s=0.23**	0.003
Fear-avoidance		r_s=0.03	0.671
Psycho-social composite score	110	r_s=0.49***	<0.001

ODI, oswestry disability index; KEDS, karolinska exhaustion disorder scale; WAI-1, work ability index: item 1.
Significance Levels: **Correlation is significant at the 0.01 level (2-tailed). ***Correlation is significant at the 0.001 level (2-tailed).

and ROC-curve analysis. Dichotomizing CSI and QST scores, 24.6% (n=35) of the participants were categorized with CS by the CSI (score ≥40), and 16.2% (n=23) by QST (mean + 1SD). Fisher's exact test demonstrated a statistically significant association between participants scoring ≥40 on CSI and participants categorized as sensitized by experimental pain tests (p-value=0.03) (Table 4). The positive predicative value of CSI using a cut-point of 40 points was low (PPV=28.6%), while the negative predicative value was high (NPV=87.9%).

Furthermore, ROC-curve analysis revealed the CSI had a low sensitivity (Sn=43.5%) and acceptable specificity (Sp=76.5%) in identifying CS. The CSI resulted in an ROC-AUC of 0.656 in the present population. The ROC-curve of CSI and QST total scores suggested an optimal cut-point of 44 (Sn=39.1% Sp=87.4%) in the present population (Table 4 and Figure 2).

Table 4: Receiver Operator Characteristic (ROC) values and Fisher's Exact Test for suggested cut-points.

	AUC	Cut-point (sensitivity, specificity %)	Positive and negative predicative value	Fisher's exact test p-value
CSI	0.656	40 (Sn=43.5%, Sp=76.5%)	PPV=28.6%, NPV=87.9%	0.033
		44 (Sn=39.1%, Sp=87.4%)	PPV=37.5%, NPV=88.1%	0.045

The Fisher's exact test p-value denotes the significance of the deviation from the null hypothesis in the Fisher's exact test of independence. Results of the Fisher's exact test using different CSI cut-points is shown in the rightmost column of the table.
Abbreviations: CSI, central sensitization inventory; AUC, area under curve; Sn, sensitivity; Sp, specificity; PPV, positive predicative value; NPV, negative predicative value.

Post hoc analysis of between group difference

Due to exclusion criteria for some of the QST tests, there was a large number of missing data in the cuff algometry test. To assess potential between group differences, we divided participants in a 'complete observation group' and 'non-complete observation group'. Subsequently, between group mean was examined through univariate testing using appropriate methods. There were no statistically significant differences between group means in either CSI or QST scores when comparing participants with complete observations to participants with incomplete observations.

Post hoc exploratory analysis of correlations between QST variables and psycho-social factors in the low- and high-CSI-score groups

To further assess the correlation between QST and psycho-social variables, we examined the coefficients for participants with high and low CSI scores, respectively. For this purpose, participants were dichotomized into a low-CSI-score and high-CSI-score group using (i) a cut-point of ≥40, and (ii) the optimal cut-point of 44, as identified by the ROC-curve analysis. For both cut-points, correlations were generally negligible in the low-CSI-score group, and weak in the high-CSI-score group. All significant correlations can be seen in Appendix 4.

Discussion

This is the first study investigating the convergent validity of CSI with experimental pain measures obtained through an extensive QST protocol, and psycho-social factors, in a cohort of LBP patients. It is only the second study to report ROC-characteristics of CSI when compared to psychophysical tests in determining the presence of CS in a study sample [20]. We found significant correlations between nine out of 21 experimental pain tests and the CSI score, but coefficients were mostly weak. Furthermore, when

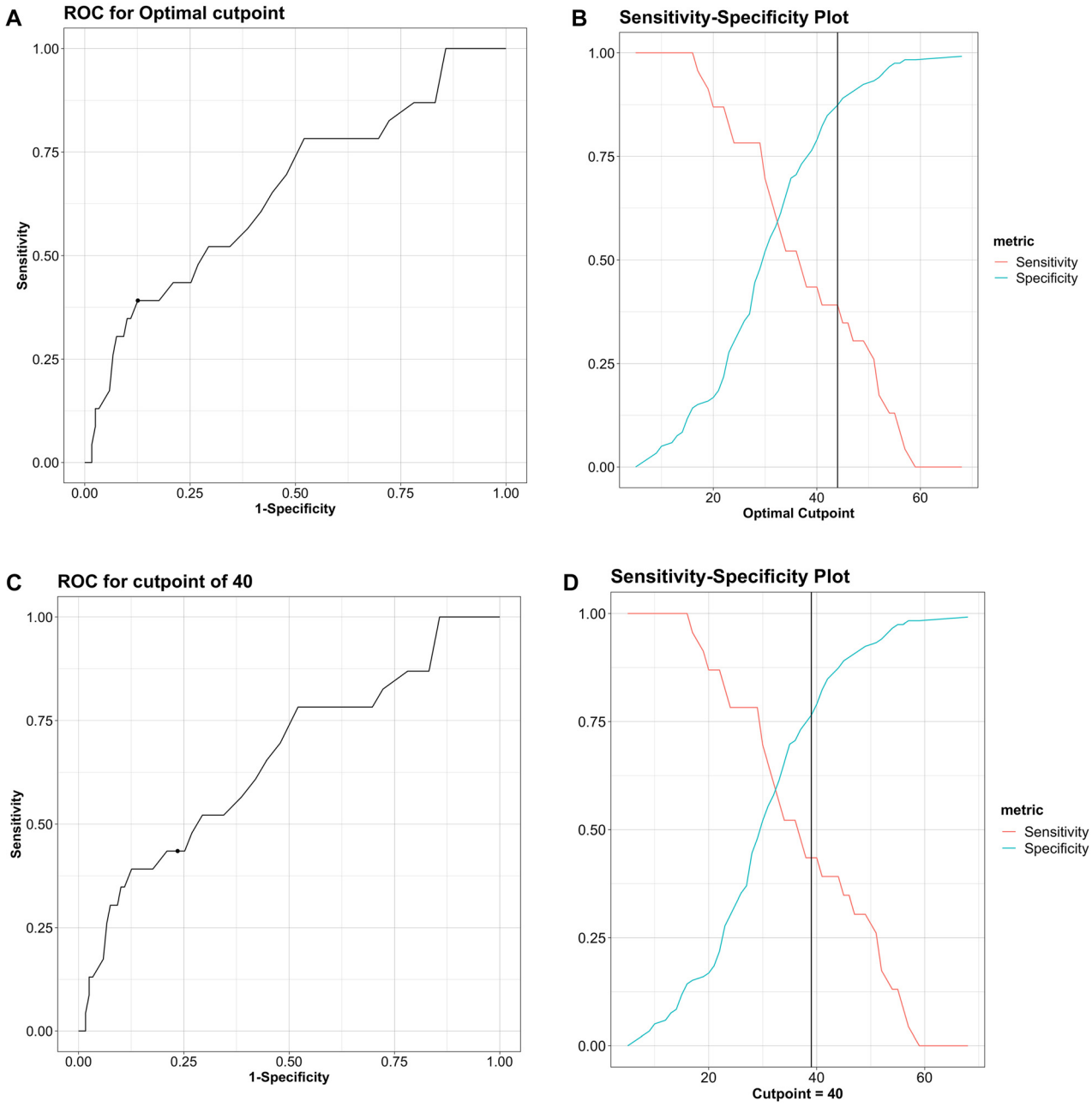

Figure 2: ROC-curves and sensitivity-specificity plots for cut-points on CSI.
A: ROC-curve for the optimal cut-point on CSI, B: Sensitivity-Specificity plot for the optimal cut-point on CSI, C: ROC-curve for cut-point of ≥40 on CSI, D: Sensitivity-specificity plot for cut-point of ≥40 on CSI.

categorizing participants as centrally sensitized as identified by QST, probability of agreement between CSI and QST was low. These findings suggest that the CSI and experimental pain testing quantify different underlying constructs. For significant correlations, p-values were generally very small, suggesting that the weak correlations were unlikely to be a chance finding. Conversely, when statistical significance was not reached, correlation coefficients were generally of magnitude ~0.1, suggesting that it is unlikely that strong correlation coefficients were missed by chance. While it is possible that different experimental pain tests measure different domains of pain sensitivity, no clear pattern was observed between the types of QST procedures and correlations with CSI scores.

We explored the association between CSI and other psycho-social measures and found CSI to be significantly

correlated with six out of ten psycho-social variables, with strength of correlations ranging from weak-to-strong. It is noteworthy that CSI correlated strongly with symptoms of exhaustion disorder (KEDS). Exhaustion disorder would expectedly impact other psycho-social measures, and it is thus hardly surprising that moderate correlations were also seen with disability (ODI). While psycho-social variables were associated with CSI scores, only negligible associations were found with QST scores. Our findings thus contrast those of Zafereo et al. [25], who found moderate correlations between QST and pain interference, and low correlations between QST and anxiety, fatigue and depression.

Our findings are consistent with results from an earlier study [51] examining the correlation between a comparable QST composite score and psycho-social profile, finding no significant correlations. As such, our findings support the notion that the CSI most likely quantifies an underlying psychological or social construct, as opposed to perturbations in the function of the somatosensory nervous system.

Psycho-social and cognitive factors have been suggested as a contributing factor to the development and persistence of CS [55], and the CSI has been shown to correlate with both social and cognitive behavioral factors in patients with chronic pain [21, 22]. The authors of the CSI have in fact made it clear that the aim of the CSI is not to assess CS as a neurophysiological phenomenon, but rather to clinically screen for CS-related symptoms [56]. In other words, the CSI is intended to measure symptoms theorized to stem from CS, but which may in fact result from a combination of psychological, social and physiological factors. The association between CSI and psycho-social measures found in the present study align with findings of earlier studies [18, 20, 23] showing the CSI to be more closely related to psycho-social measures than experimental pain tests. This raises questions regarding the construct validity of the CSI: do CSI scores relate meaningfully to an individual's neurophysiological changes in pain modulation, or rather, does it measure a different construct, such as psycho-social factors which may (or may not) be related to chronic pain? Furthermore, questions can be raised regarding the content validity of the CSI, i.e., whether items on the CSI are fully representative of all relevant aspects of central sensitization. Our results would suggest that the CSI does not adequately capture unique signs of pain sensitization or changes in pain modulation.

Our findings echo those of previous studies of the convergent validity of CSI and experimental measures of pain sensitivity. Thus, when summarizing the literature, it seems that the clinical use of CSI as an indicator of CS as a neurophysiological phenomenon should be challenged. This should come as no surprise, as the individual questions which make up the CSI, at least on face validity, are concerned with psychological and social factors [17, 53]. Seeing as the CSI and QST appear to measure different constructs, the use of CSI as a self-report instrument to infer the presence of CS as a neurophysiological phenomenon is thus questionable.

Strengths of the present study include the large sample size, no inter-rater variability (one QST tester), and a relatively extensive QST protocol used, in line with current recommendations [57]. Methodological limitations include the use of several short-item questionnaires. While these short-item questionnaires have shown acceptable concurrent validity [38] when compared to the full-length reference standard from which they are derived [39–43], there is inherently a degree of uncertainty regarding their content validity. Another limitation to this study is that, while the CSI was cross-culturally adapted to Danish prior to this study, the Danish version of CSI is yet to be validated in a Danish context. However, the CSI-Dan was translated following guidelines [30] for cross-cultural adaptation of self-report measures, and the CSI has previously been cross-culturally adapted to a range of languages whilst maintaining its psychometric properties and validity [32–36]. As such, we expect the CSI-Dan to perform similar to the original and other adapted versions of the CSI.

A further limitation is the fact that there is no universally accepted cut-point for CS as indicated by QST. As such, we chose an arbitrary cut-point of one standard deviation above the sample mean. This cut-point was chosen as it has been shown that, while healthy human subjects have a bell-shaped distribution of pain sensitivity on QST [16], patients suffering from chronic pain conditions tend to fall on the right side of the curve, displaying significant secondary hyperalgesia and allodynia [12, 58, 59].

Further limitations include the use of custom-made tools in the experimental pain test protocol. While the custom-made spring-loaded probes used in the present study have been shown to be reliable in measuring pressure pain thresholds [60], the weighted pin pricks used are new and yet to be validated. The use of such tools limits the comparability of our results with data reported in studies using similar experimental pain measurements.

Lastly, due to exclusion criteria for some of the QST tests, there was a large number of missing data in the cuff algometry test. While missing data in the QST protocol limits the statistical strength of our analysis, we found there were no significant between group differences in CSI scores (Welch Two Sample *t*-test score=−0.08,

p-value=0.9) when comparing participants who had complete QST data to participants with missing data. Furthermore, there was no significant between group mean difference in each of the experimental pain test variables. This suggests that the characteristics of participants with missing data was not significantly different from participants with no missing data, and that the inclusion of participants with missing data did not have a significant impact upon our statistical analysis.

To complement the psycho-social measures used in our study, we created a psycho-social composite variable, aiming to gauge the overall psycho-social profile of participants. This composite variable was created by combining scores across all psycho-social questionnaires, excluding the CSI. It should be noted that, while the intention of the composite variable was to reflect the psycho-social profile of participants, it is uncertain if in fact the composite variable adequately reflects this. However, the composite variable showed moderate correlation to CSI scores, and the strength of this correlation was similar to the strength of correlation between CSI and the other psycho-social measures (ODI and KEDS), suggesting the psycho-social profile of participants was reflected adequately by the psycho-social composite variable. Similarly, to gauge the overall performance of participants in the QST protocol, we created a composite variable by combining scores in each QST test. As with the psycho-social composite variable, to what extent the QST composite variable reflects the function of the somatosensory nervous system of participants, is uncertain.

To our knowledge, only one previous study [20] has reported sensitivity and specificity of CSI when categorizing participants as sensitized or not sensitized, as determined by QST. The optimal cut-points identified by Gervais-Hupé and colleagues yielded sensitivity levels ranging from 75.0 to 87.2%, while specificity ranged from 34.2 to 63.4%. In the present study, using the cut-point of ≥40 on CSI, only 43.5% of participants categorized as sensitized by CSI, were also categorized as sensitized by QST. Conversely, of the participants categorized as not sensitized by CSI, 76.5% were concordantly categorized as not sensitized by QST.

In our analysis, the ROC-AUC was used to assess the convergence between CSI and QST in categorizing participants as "CS" and "no CS" patients. The observed AUC of 0.656 in our study would suggest that the convergence of CSI and QST was low. It should be noted that only "Part A" of the CSI was used for the ROC-analysis. For this reason, we were not able to subgroup participants using "Part B" of CSI, and as such, did not know whether the participants were known with CSS, and if so, in what proportion and how this affects our reported correlations.

Conclusions

This study examined the convergent validity of CSI. We found small and not clinically meaningful correlations between CSI and QST, demonstrating poor convergent validity. The CSI was more closely correlated with psycho-social factors such as symptoms of ED and disability. These findings are consistent with previous studies, indicating that while the CSI is related to psycho-social factors associated with chronic pain conditions, CSI scores do not directly relate to perturbations in the function of the somatosensory nervous system. In the present cohort, only negligible correlations were found between QST variables and psycho-social factors, contrasting the findings of a previous study. Our findings suggest that the CSI and experimental pain testing quantify different underlying constructs, and clinicians should be cautious when drawing conclusions regarding CS in patients based solely on CSI scores.

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Competing interests: Authors state no conflict of interest.

Informed consent and ethical approval: Oral and written consent was obtained in all cases. The study was approved by The Regional Committee on Health Research Ethics for Southern Denmark (ref. number *S-20180098)*.

Appendix

Appendix 1 Overview of tests in experimental pain testing and the psychophysical variables obtained

QST test Psychophysical variables	Test site	Unit of measure	Pressure intensity	Repeated at intervals
Cuff algometry				
Pressure pain threshold	Lower leg	kPa	Increasing, 1 kPa/s	No
Pressure pain tolerance	Lower leg	kPa	Increasing, 1 kPa/s	No
Temporal summation	Lower leg	ΔVAS	100% of CPTT	No
Conditioned pain modulation	Lower leg	ΔCPPT	70% of CPTT	No
Weighted pinprick pressure				
Pressure pain threshold	Paraspinal muscle	Weight, g	Fixed, 4–55 g	x3
Pressure pain threshold	Dorsum of thenar space	Weight, g	Fixed, 4–55 g	x3
Pressure algometry				
Pressure pain threshold	Paraspinal muscle mass	kPa	Increasing, 50 kPa/s	X3
Pressure pain threshold	Extensors of forearm	kPa	Increasing, 50 kPa/s	x3
Spring-loaded pressure probe				
Pressure pain threshold	Paraspinal muscle mass	kg	Fixed, 1–10 kg	x2
Pressure pain threshold	Extensors of forearm	kg	Fixed, 1–10 kg	x2
Pressure pain intensity	Paraspinal muscle mass	VAS	SPPT + 2 kg	No
Pressure pain intensity	Extensors of forearm	VAS	SPPT + 2 kg	No
Temporal summation	Paraspinal muscle mass	$\Delta SPPI_{lower\ back}$	SPPT + 1 kg	No
Temporal summation	Paraspinal muscle mass	$\Delta SPPI_{\ lower\ back}$	SPPT + 1 kg	No
Cold pressor test				
Conditioned pain modulation	Paraspinal muscle mass	ΔTS	Cold, 0–2 °C	No
Cold pain intensity	Hand	VAS	Cold, 0–2 °C	No
Time to maximum cold pain intensity	Hand	Time, sec	Cold, 0–2 °C	No
Area under the curve	Hand	Area	Cold, 0–2 °C	No

kPa, kilopascal; ΔVAS, difference in VAS after a cuff algometry temporal summation protocol; CPPT, heterotopic pressure pain detection threshold; ΔCPPT, difference in pressure pain detection threshold before and after conditioning stimulus; ΔSPPI, difference in pressure pain intensity before and after a temporal summation protocol; ΔTS, difference in temporal summation before and after a conditioning stimulus in the cold pressor test; SPPT, pressure pain threshold.

Appendix 2 Distribution of experimental pain test variables in the Quantitative Sensory Pain Test protocol

	n	Median	Mean	Standard deviation	1st quartile	3rd quartile	Interquartile range
Cuff algometry							
Pressure pain threshold	148	22.4	25.4	11.8	16.9	33.3	16.5
Pressure pain tolerance threshold	148	52.2	54.1	20.4	38.4	66.1	27.6
Pressure pain threshold	148	25.5	26.4	11.9	16.9	33.8	17.0
Pressure pain tolerance threshold	148	48.6	50.0	17.2	38.0	59.7	21.7
Temporal summation	148	1.1	1.2	1.4	0.2	2.0	1.8
Conditioned pain modulation	145	5.5	5.8	12.7	−1.6	13.7	15.3
Weighted pinprick pressure							
Pressure pain threshold	167	6.0	5.2	1.4	4.5	6.0	1.5
Pressure pain threshold	167	6.0	5.8	0.7	6.0	6.0	0.0
Pressure algometry							
Pressure pain threshold	167	440.0	452.4	219.0	282.3	607.5	325.2
Pressure pain threshold	167	288.3	300.0	130.9	206.7	380.7	174.0
Spring-loaded probe							
Pressure pain threshold	167	5.5	5.6	2.5	4.0	7.5	3.5

(continued)

	n	Median	Mean	Standard deviation	1st quartile	3rd quartile	Interquartile range
Pressure pain threshold	167	3.5	3.7	1.6	2.5	4.5	2.0
Pressure pain intensity	167	21.0	22.3	19.5	2.5	35.0	32.5
Pressure pain intensity	167	36.0	36.3	21.7	21.0	54.0	33.0
Temporal summation	167	16.0	17.5	18.1	5.0	29.0	24.0
Temporal summation	167	9.0	11.9	15.6	0.0	19.0	19.0
Cold pressor test							
Conditioned pain modulation	167	−4.0	−5.6	16.8	−16.5	4.5	21.0
Cold pain intensity		87.0	79.4	23.7	64.0	100.0	36.0
Time to maximum cold pain intensity		49.0	55.3	34.7	24.8	83.2	58.5
Area under the curve	167	3445.0	3916.1	2856.6	1404.0	6298.0	4894.0
Quantitative sensory test							
Total score	142	0.5	0.5	0.1	0.4	0.6	0.1

Appendix 3 Correlation matrix showing significant correlations between Quantitative Sensory Pain test variables and psycho-social factors:

QST variables	Psycho-social factors	Spearman's correlation coefficient	p-value
$SPPI_{lower\ back}$	ODI	0.217	0.012
$SPPI_{lower\ back}$	KEDS	0.192	0.013
$SPPI_{lower\ back}$	Social isolation	0.221	0.008
$SPPI_{lower\ back}$	Depression	0.203	0.009
$SPPI_{forearm}$	ODI	0.174	0.045
$SPPI_{forearm}$	Depression	0.155	0.045
T_{CPT}	WAI-1	0.190	0.014
CCPM	Social isolation	−0.184	0.043
$WPPT_{hand}$	Fear-Avoidance	−0.173	0.025
$APPT_{lower\ back}$	ODI	−0.219	0.011
$APPT_{lower\ back}$	KEDS	−0.298	<0.001
$APPT_{lower\ back}$	WAI-1	0.180	0.020
$APPT_{lower\ back}$	Depression	−0.190	0.014
$APPT_{forearm}$	KEDS	−0.174	0.025
$APPT_{forearm}$	Risk of persistent pain	−0.167	0.048
$APPT_{forearm}$	Depression	−0.159	0.040
$SPPT_{lower\ back}$	ODI	−0.285	0.001
$SPPT_{lower\ back}$	KEDS	−0.278	<0.001
$SPPT_{lower\ back}$	WAI-1	0.188	0.015
$SPPT_{lower\ back}$	Catastrophizing	−0.160	0.039
$SPPT_{lower\ back}$	Depression	−0.180	0.020
TS_2	Risk of persistent pain	−0.179	0.034
TS_2	Catastrophizing	−0.169	0.029
$CPM_{lower\ back}$	Catastrophizing	−0.160	0.039

ODI, oswestry disability index; KEDS, karolinska exhaustion disorder scale; WAI-1, work ability index: item one; SPPI, spring-loaded probe pressure pain intensity; T_{CPT}, time to achieve maximum cold pain intensity in the cold pressor test; CCPM, cuff algometry conditioned pain modulation; WPPT, pinprick pain threshold; APPT, algometry pressure pain threshold; SPPT, spring-loaded probe pressure pain threshold; TS_2, temporal summation after cold pressor test; $CPM_{lower\ back}$, conditioned pain modulation in the cold pressor test.

Appendix 4 Correlations (Spearman's Correlation Coefficients) of QST variables and psycho-social factors in the Low- and High-CSI-Score Groups (CSI Cut-off Score=40):

QST variables	Psycho-social factors	Spearman's correlation coefficient	p-value
High CSI group			
$CPTT_{non\text{-}dominant\ leg}$	ODI	0.396	0.0370
$CPTT_{non\text{-}dominant\ leg}$	WAI-1	−0.372	0.0232
CCPM	Depression	−0.331	0.0484
$WPPT_{hand}$	WAI-1	0.358	0.0232
TS_2	Risk of persistent pain	−0.425	0.0136
Low CSI group			
$SPPI_{lower\ back}$	ODI	0.255	0.0098
$SPPI_{lower\ back}$	Social isolation	0.196	0.0398
$SPPI_{lower\ back}$	Depression	0.196	0.0270
$SPPI_{forearm}$	ODI	0.305	0.0018
$SPPI_{forearm}$	Anxiety	0.178	0.0458
CCPM	Risk of persistent pain	0.229	0.0283
$APPT_{forearm}$	Risk of persistent pain	−0.194	0.0447
$SPPT_{lower\ back}$	ODI	−0.195	0.0499
$CPM_{lower\ back}$	Catastrophizing	−0.205	0.0207

CPTT, cuff algometry pressure pain tolerance threshold; CCPM, cuff algometry conditioned pain modulation; WPPT, pinprick pain threshold; SPPT, spring-loaded probe pressure pain threshold; TS_2, temporal summation after cold pressor test; SPPI, spring-loaded probe pressure pain intensity; APPT, algometry pressure pain threshold; $CPM_{lower\ back}$, conditioned pain modulation in the cold pressor test; ODI, oswestry disability index; WAI-1, work ability index: item 1.

Correlations (Spearman's Correlation Coefficients) of QST variables and psycho-social factors in the Low- and High-CSI-Score Groups (CSI Cut-off Score=44):

QST variables	Psycho-social factors	Spearman's correlation coefficient	p-value
High CSI group			
$CPTT_{non\text{-}dominant\ leg}$	KEDS	0.411	0.0414
CCPM	ODI	0.472	0.0478
CCPM	KEDS	0.444	0.0298
$WPPT_{hand}$	Risk of persistent pain	−0.482	0.0171
$WPPT_{hand}$	WAI-1	0.370	0.0482
$SPPT_{lower\ back}$	WAI-1	0.374	0.0459
Low CSI group			
$SPPI_{lower\ back}$	ODI	0.235	0.0131
$SPPI_{lower\ back}$	Social isolation	0.193	0.0358
$SPPI_{lower\ back}$	Depression	0.207	0.0147
$SPPI_{forearm}$	ODI	0.296	0.0016
$SPPI_{forearm}$	Depression	0.173	0.0430
$SPPI_{forearm}$	Anxiety	0.170	0.0463
$CPPT_{non\text{-}dominant\ leg}$	Risk of persistent pain	0.197	0.0458
CCPM	Risk of persistent pain	0.198	0.0474
CCPM	Risk of persistent pain	−0.234	0.0181
$WPPT_{hand}$	Anxiety	−0.187	0.0283
$APPT_{forearm}$	Risk of persistent pain	−0.205	0.0269

(continued)

QST variables	Psycho-social factors	Spearman's correlation coefficient	p-value
$APPT_{forearm}$	Anxiety	−0.174	0.0415
$SPPT_{lower\ back}$	ODI	−0.217	0.0221
$CPM_{lower\ back}$	Catastrophizing	−0.216	0.0108
QST total score	Depression	0.190	0.0394

CPTT, cuff algometry pressure pain tolerance threshold; CCPM, cuff algometry conditioned pain modulation; WPPT, pinprick pain threshold; SPPT, spring-loaded probe pressure pain threshold; SPPI, spring-loaded probe pressure pain intensity; CPPT, cuff algometry pressure pain detection threshold; APPT, algometry pressure pain threshold; $CPM_{lower\ back}$, conditioned pain modulation in the cold pressor test; KEDS, karolinska exhaustion disorder scale; ODI, oswestry disability index; WAI-1, work ability index: item 1.

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