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Central sensitization and functioning in patients with chronic low back pain: A cross-sectional and longitudinal study

Jone Ansuategui Echeita[1,*], Henrica R. Schiphorst Preuper[1], Rienk Dekker and Michiel F. Reneman
Department of Rehabilitation Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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Abstract.
BACKGROUND: Central sensitization (CS) is present in a subgroup of patients with chronic low back pain (CLBP). Studies on the relationship between CS and functioning have limited operationalizations of CS and functioning.
OBJECTIVE: To determine whether CS was related to functioning in patients with CLBP (cross-sectional); and to determine whether changes in CS were related to changes in functioning (longitudinal).
METHODS: An observational prospective cohort study with data collected at baseline and discharge of an interdisciplinary pain rehabilitation program was executed. CS indicators: CS Inventory part A (CSI-A), quantitative sensory testing (QST), root mean square of successive differences of heart-rate variability (RMSSD). Functioning measures: lifting capacity, physical functioning subscale of Rand36 (Rand36-PF), Work Ability Score (WAS), Pain Disability Index (PDI). Main analyses included correlation and multiple regression controlling for confounders; cross-sectional with baseline data and longitudinal with deltas (Δ).
RESULTS: 76 patients with primary CLBP participated at baseline and 56 at discharge. Most associations were weak (cross-sectional $r_{partial} = -0.30$–0.24; longitudinal $r_{partial} = -0.37$–0.44). Cross-sectional multiple regression significant associations: mechanical pain threshold-QST and lifting capacity ($r_{partial} = -0.39$), parasympathetic/vagal tone-RMSSD and physical functioning–Rand36-PF ($r_{partial} = 0.26$). Longitudinal multiple regression significant associations: Δ parasympathetic/vagal tone-RMSSD and Δ lifting capacity ($r_{partial} = 0.48$), ΔCSI-A and Δdisability-PDI ($r_{partial} = 0.36$). Cross-sectional and longitudinal final regression models explained 24.0%–58.3% and 13.3%–38.0% of total variance.
CONCLUSION: CS was weakly related to functioning, and decreases in CS were weakly-moderately related to increases in functioning.

Keywords: Hyperalgesia, lifting, physical functioning, disability, work ability

1. Introduction

Worldwide, chronic low back pain (CLBP) is the leading condition of years lived with disability [1]. The functioning of individuals with CLBP can be limited in daily live activities [2,3]. Patients with limited functioning are more likely to utilize healthcare [4], but treatment outcomes are only moderate [5]. An important strategy to improve treatment efficacy is to better understand the mechanisms associated with functioning limitations in patients with CLBP.

A mechanism underlying the pain experience in patients with CLBP is central sensitization (CS). CS reflects a hypersensitive state of the central nervous system due to: an increase in the signaling of neu-

[1]J. Ansuategui Echeita and H.R. Schiphorst Preuper are co-first authors.

*Corresponding author: Jone Ansuategui Echeita, Department of Rehabilitation Medicine, University Medical Center Groningen, P.O. Box 30.002, 9750 RA Haren, The Netherlands. E-mail: j.ansuategui.echeita@umcg.nl.

ronal responsiveness to nociceptive stimuli in firing frequency and intensity, a decrease in nociceptive activation threshold, a reduction in nociceptive inhibition mechanisms, and a reduced vagal nerve activity [6–9]. These indicators have most frequently been assessed with the Central Sensitization Inventory (CSI) –a screener questionnaire–, the quantitative sensory testing (QST) –threshold determination and stimulus-response assessments of sensory processing–, and the heart-rate variability (HRV) –autonomous nervous system function assessment, including vagal activity.

CS can be present in a subgroup of patients with CLBP [10]. Because pain experience is enhanced if CS is present, and because pain is consistently related to limitations in functioning in patients with CLBP [11], the presence and/or more CS indicators in patients with CLBP may be expected to be associated with lower functioning. Consequently, if this association exists, a decrease in the presence of CS indicators could be associated with improved functioning.

There is some evidence of the association between CS and limited functioning [12–20], however, these studies utilized limited and diverse CS indicators and functioning measures. Specifically, more self-reported CS-related symptoms [12,13,18,20], decreased parasympathetic/vagal activity [14,15] , or altered somatosensory responses [16,17,19], were associated with higher self-reported pain-related disability and/or lower physical function. But the indicators of CS varied in the associations; also if somatosensory responses were assessed the associations varied per body site of testing, stimuli and type of tests performed; and functioning was mostly measured with self-reported measures. The combined use of different methods to assess CS will give complementary information and a more comprehensive overview of CS phenomenon. Similarly, a comprehensive overview of the functioning status of the individual is better obtained with performance and self-reported measures combined [21,22]. To our knowledge, no study has been performed where a comprehensive set of methods to assess CS and functioning were used.

One of the main objectives of pain rehabilitation is to help patients to improve their functioning and resume to their usual daily living, including work. Better understanding of factors associated with functioning limitations in CLBP is needed to improve effectiveness of pain rehabilitation. The aim of the present study was to analyze the association between CS indicators and functioning in patients with CLBP, cross-sectional and longitudinally. The research questions were: 1) Is CS associated to functioning in patients with CLBP? It was hypothesized that a stronger presence of CS indicators would be inversely associated to functioning measures; 2) Are changes in CS associated to changes in functioning in patients with CLBP? The hypothesis was that a decrease in the presence of CS indicators would be associated to increases in functioning measures.

2. Materials and methods

2.1. Design

An observational prospective cohort study was conducted from September 2017 to September 2019 in the center for rehabilitation of a university medical center in the Netherlands. This study is part of a larger project, Dutch national trial register (NTR7167/NL6980), and a detailed description of the study protocol is published elsewhere [23].

Ethical approval was obtained (METc 2016/702), and the study procedures followed the ethical standards of the Declaration of Helsinki of 1975, revised in 2013 [24]. The STROBE statement was used for the report of observational studies [25] (Appendix 1).

2.2. Participants

Consecutive patients between 18 and 65 years referred to the Pain Rehabilitation Department because of primary CLBP ($\geqslant$ 3 months; ICD-11 code MG30.02) [26]. Main exclusion criteria, based on patient's file, were: (suspicion of) a specific diagnosis that would better account for the symptoms (e.g. cancer, osteoporosis and/or spinal fractures), neuralgia or radicular pain in the legs, major disorder or comorbidity substantially interfering with functioning (e.g. affecting their physical and/or mental functioning such as severe psychiatric disorders or severe cardiopulmonary problems), or pregnancy. Exclusion criteria belonging to specific tests, were: for the lifting test hypertension ($\geqslant$ 100/160 mmHg) [27]; for the QST the presence of nerve or tissue damage affecting the measurement locations, or a blood vessel disorder such as Raynaud's disorder; and for the HRV the use of medication (for example beta blockers) or a cardiac disease that could influence heart-rate. All participants provided written informed consent.

2.3. Measurements

The assessment of patients was part of care as usual during baseline and discharge of an interdisciplinary pain rehabilitation program. This is a personalized out-

patient program that lasts on average 12 weeks with 2 visits per week. For the assessments a biopsychosocial framework is used and patients actively participate in the content and planning of their treatment. The assessments and program are delivered by a team specialized in pain rehabilitation, consisting of physical therapists, occupational therapists and psychologists working together.

2.3.1. Functioning

Lifting capacity was assessed with the floor-to-waist lifting test [28]. Patients were asked to lift a crate with standardized weights from a shelf at 75 cm to the floor and vice versa. The weight in the crate is progressively increased every five repetitions until patients reach the endpoint. The maximum weight lifted patient-reported and clinician-observed efforts with Borg's category ratio scale (CR-10; 0–10) [29,30] were recorded. The lifting test has acceptable test–retest in patients with CLBP [31] and predictive ability in work participation [32].

Physical functioning was measured with the subscale of the Rand36 (Rand36-PF) [33]. The subscale assesses the health-related limitations patients experience during daily activities. A higher total mean score (0–100) is associated with fewer limitations in performing daily activities. Dutch translation of Rand36 has acceptable psychometric qualities in the general population [34].

Disability was measured with the Pain Disability Index (PDI). The PDI consists of seven questions which assess the interference of pain during several daily activities: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity [35]. A higher total sum score (0–70) is associated with higher interference in daily life activities. The Dutch language version has acceptable psychometric qualities in patients with musculoskeletal pain including CLBP [36].

Work ability was measured with the Work Ability Score (WAS), a single-item question from the Work Ability Index (WAI). The WAS assesses the current work ability compared to the lifetime best (0–10) The WAS is highly correlated to the full WAI questionnaire [37–39].

2.3.2. Central sensitization

CSI part A (CSI-A) is a questionnaire designed to estimate the severity of the symptoms related to CS. The presence of CS-related somatic and emotional symptoms are scored on a five-point Likert-scale (from 0 (never) to 4 (always)). A higher total sum score (0–100) is associated with more severe symptomatology [40]. The Dutch version of CSI has good psychometric qualities in controls and in patients with chronic musculoskeletal pain [41].

QST has a battery of standardized sensory tests to quantify the function of the somatosensory system. The QST consisted of five tests based on the German Research Network on Neuropathic Pain (DFNS) protocol [42]: sharp cutaneous pain sensation (mechanical pain threshold-MPT), blunt pressure pain sensation (pressure pain threshold-PPT), allodynia (dynamic mechanical allodynia-DMA), touch sensation (mechanical detection threshold-MDT) and temporal summation (wind-up ratio-WUR). These five tests were assessed in six body locations (most painful location in the low back, mirror to the most painful location, ipsi- and contralateral muscle trapezius and ipsi-and contralateral rectus femoris of muscle quadriceps) after being acquainted with the tests in a training location [23]. Additionally, the descending pain modulation (conditioned pain modulation–CPM) was tested according the Nijmegen-Aalborg Screening QST (NASQ) protocol [43]. The detailed description of the QST assessment is presented in Appendix 2.

HRV is a non-invasive assessment to measure the function and balance of the sympathetic tone and the parasympathetic/vagal tone of the autonomic nervous system [44,45]. The HRV was performed by trained assessors and followed the five minute protocol [45]. HRV was assessed with an ear pulse sensor, while patients were seated and breathing normally [46]. The HRV time and frequency domain data was recorded with emWave PC software (emWave®, HeartMath Inc., USA), and was processed by an experienced clinician to eliminate potential noise if needed. The parasympathetic/vagal tone in individuals with chronic pain is low. In HRV, the parasympathetic/vagal tone is reflected by both root mean square of successive differences (RMSSD) and high frequency (HF, 0.15–0.40 Hz); although RMSSD is preferred because it is less influenced by respiratory rates [47].

2.3.3. Participants' characteristics

Age, sex, height, weight, pain duration, use of pain medication, educational level, occupation, and work status data were collected with a questionnaire developed for the study.

Clinical data was collected: pain intensity with the Visual Analogue Scale (VAS pain, 0–10) [48]; catastrophizing with the Pain Catastrophyzing Scale (PCS, 0–52) [49,50]; injustice with the Injustice Experience

Questionnaire (IEQ, 0–48) [51,52]; and distress with the Brief Symptom Inventory (BSI, global severity index t-score (GSIT), 0–100) [53,54]. All these questionnaires have sufficient test-retest reliability (r or ICC 0.71–0.94) [48,50,52,53].

2.4. Statistical analyses

Data was prepared for analyses. Body mass index was calculated. Occupation was converted into work physical demands categories per the Dictionary of Occupational Titles (DOT) [55]. Means of each QST test (MPT, PPT, DMA, MDT and WUR) were calculated from the body locations, with the exception of the training location and provided that a minimum of four locations had data. The mean DMA was calculated from the DMAs whose stimulus (brush swipe) was felt and subsequently categorized into: no DMA, DMA pain score 0–1, and DMA pain score 1–100 [56]. For variables entering longitudinal analyses deltas (Δ) were computed, expressed as the percentage change from baseline: $\Delta =$ [(Discharge–Baseline)/Baseline]*100; if a score of 0 was at baseline, delta was alternatively computed as: $\Delta =$ (Discharge–Baseline)*100. Higher values of Δ indicate greater differences from baseline; and positive Δs mean higher values at discharge compared to baseline.

Descriptive statistics were performed and data distribution was assessed. Missing data of main measures (functioning and CS) were inspected and sensitivity analyses comparing patients were performed when $>$ 10% was missing. Sensitivity analyses were also performed to ensure that the characteristics of the group measured at baseline and at discharge (patients ceasing participation) did not differ from the group measured at baseline only. The sensitivity analyses were performed on dependent variables and participants' characteristics: lifting capacity, physical functioning, disability, work ability, age, sex, physical work demands, and pain intensity. Continuous variables with independent t-tests– or Mann-Whitney U if not normally distributed – and categorical variables with chi-squared tests.

For research question 1, cross-sectional analyses with baseline data were performed. First, Spearman partial correlation analyses were performed, corrected for sex and age due to known differences in lifting capacity, HRV and QST [47,57,58]. Second, multiple regression analyses were performed, with each functioning measurement separately as dependent variable, one variable representative of each CS indicator as fixed independent variables, and participants' characteristics as potential confounders (including the correction for age and sex). The variables representative of CS indicators were: CSI-A, the QST test with the highest correlation coefficient (per first step), and RMSSD for HRV. Confounders with a correlation coefficient $\geqslant 0.1$ (from the first step) were entered to the regression model one at a time in a descending order until the model was fit (10 cases per variable [59]). Confounders were retained if their addition was significant ($p < 0.05$).

Table 1
Participants' demographic characteristics at baseline

	n	Median	IQR (25–75) or %
Age (years)	76	40.0	(31.3–50.8)
Sex	76		
Men	31		40.8%
Women	45		59.2%
Body mass index (kg/m^2)	76	26.7	(24.2–30.6)
Pain duration (years)	76	2.2	(1.3–4.2)
Use of medication	74		
Use pain medication	55		74.3%
No use of pain medication	19		25.7%
Educational level	71		
Primary	2		2.8%
Secondary	41		57.7%
Bachelor or higher	28		39.4%
Physical work demands (DOT)	76		
Sedentary	18		23.7%
Light	33		43.4%
Medium	21		27.6%
Heavy	4		5.3%
Working status	76		
Working	28		36.8%
Reduced/Adapted work	17		22.4%
Sick-leave	9		11.8%
Disability pension	8		10.5%
Not working	10		13.2%
Other	4		5.3%

Abbreviations: DOT, Dictionary of Occupational Titles.

For research question 2, longitudinal analyses with Δs were executed. Correlation analyses were performed; Pearson if data was normally distributed and Spearman otherwise. Multiple regression analyses were performed anew for each functioning measurement, with one variable representative of each CS indicator as independent variables, and participants' characteristics as potential confounders. CS indicators entering these models were again CSI-A, the QST test with the highest correlation coefficient (per first step), and RMSSD for HRV. Confounders entered regression models in a descending order, from highest to lowest coefficient of correlation, if $r \geqslant 0.1$, and until the model was fit [59]. Confounders were retained if their addition was significant ($p < 0.05$).

Correlations were interpreted as weak if < 0.3, moderate if 0.3–0.5, and strong if > 0.5 [60]. The significance level for multiple correlation and sensitivity

analyses was established at $p < 0.01$, to account for the risk of type I errors. Results from multiple regression analyses were considered significant if $p < 0.05$. The regression assumptions were checked and results were expressed in unstandardized betas and 95% confidence intervals, partial correlations, p-values and adjusted explained variance. All correlation and regression analyses were performed with pairwise deletion. SPSS software version 22.0 (IBM Corp., NY) was used.

3. Results

Patients' demographic characteristics are presented in Table 1. Seventy-six patients participated, mean age 40.6 years (SD:12.2), 59% were women, 40% used pain medication regularly and another 34% on demand. Of them, 73 performed the lifting capacity, 75 filled in the physical functioning and work ability questionnaires, and 73 the disability questionnaire. Sensitivity analyses for missing data was needed in only one variable, WUR (from QST), due to its computation (see Appendix 2).The characteristics of participants with missing data in the variable WUR showed no significant differences ($p > 0.157$) from participants without missing data in it.

A total of 56 patients were measured again at discharge. Of the initial sample, 13 patients did not follow the rehabilitation program, three did not show for discharge and four cancelled participation in the study. Patients' functioning, CS indicators and clinical characteristics at baseline, discharge and deltas are presented in Table 2. Improvements were observed in lifting capacity, physical functioning and disability; but not in work ability. Improvements were also observed in CSI-A, QST thresholds (MPT, PPT and MDT) and parasympathetic/vagal tone (RMSSD and HF); but the dynamic measures of QST (WUR and CPM) did not improve. In the sensitivity analyses, the characteristics of participants measured at both time points was not different ($p > 0.012$) from those measured at baseline only.

Cross-sectional associations between CS indicators and functioning measurements were weak ($r_{partial} = -0.30$–0.24) and none was significant (Appendix 3).

The regression models of lifting capacity, physical functioning and disability included seven variables, whereas work ability six (Table 3). The model with the most total variance explained was lifting capacity ($r^2 = 58.3\%$; $p < 0.001$), followed by physical functioning ($r^2 = 41.7\%$; $p < 0.001$), disability ($r^2 = 34.8\%$; $p < 0.001$) and work ability ($r^2 = 24.0\%$; $p = 0.003$). MPT was significantly associated with lifting capacity ($r_{partial} = -0.39$), and RMSSD with physical functioning ($r_{partial} = 0.26$). No other CS measurements were associated with functioning. The residuals of the lifting capacity model were not normally distributed; consequently, the model was rerun with the square root of the lifting capacity (sq_lifting) as dependent variable. Both models were similar; no changes in the significance occurred after the transformation with the exception of age, which became significantly associated. Based on the results from sq_lifting and provided data of each of the variables included in the model is known, the lifting capacity (kg) can be calculated by squaring the outcome coefficient (see Appendix 4 for an example).

Longitudinal associations between CS and functioning measurements were mostly weak and largely not significant (Appendix 5). Moderate significant associations were observed between: Δ lifting capacity and Δ RMSSD ($r = 0.41$); and Δ disability and Δ CSI-A ($r = 0.44$). All other associations were weak ($r_{partial} = -0.37$–0.32) and not significant.

Regression models were partial; lifting capacity, disability and work ability models did not fulfill the assumption of normality in the distribution of residuals. Therefore, the results of the regression analyses should be considered as exploratory. The models included four variables, with the exception of disability which included three (Table 4). Δ Lifting capacity was the model with the most total variance explained ($r^2 = 38.0\%$; $p < 0.001$), followed by Δ work ability ($r^2 = 25.0\%$; $p = 0.005$), Δ physical functioning ($r^2 = 17.3\%$; $p = 0.027$) and Δ disability ($r^2 = 13.3\%$; $p = 0.068$). Of the CS measurements only Δ RMSSD and Δ CSI-A remained significantly associated respectively with Δ lifting capacity ($r_{partial} = 0.48$) and Δ disability ($r_{partial} = 0.36$).

4. Discussion

Some weak-to-moderate and heterogeneous associations were identified between CS indicators and functioning. In the cross-sectional analyses, CS indicators were associated weakly with functioning in patients with CLBP; and after correcting for confounders, MPT was associated with lifting capacity and RMSSD with physical functioning. In the longitudinal analyses, decreases in CS indicators were associated weakly-moderately to increases in functioning; and after correcting for confounders, Δ RMSSD was associated with Δ lifting capacity, and Δ CSI-A with Δ disabil-

Table 2
Participants' functioning, CS and clinical characteristics from baseline, discharge and deltas

	Baseline		Discharge		Delta	
	n	Median IQR (25–75)	n	Median IQR (25–75)	n	Median IQR (25–75)
Functioning						
Lifting capacity (kg)	73	13.5 (7.4–19.3)	52	16.3 (9.0–22.5)	52	13.6 (−16.1–38.3)
Patient's reported exertion (CR-10, 0–10)†	73	6.1 ± 1.9	52	5.4 ± 1.6	52	0.0 (−32.5–25.0)
Assessor's observed exertion (CR-10, 0–10)†	72	5.5 ± 2.1	52	5.3 ± 1.8	51	0.0 (−28.6–60.0)
Physical functioning (Rand36-PF, 0–100)†	75	50.9 ± 19.5	52	64.4 ± 22.4	51	20.0 (0.0–50.0)
Disability (PDI, 0–70)†	73	36.9 ± 12.0	53	23.1 ± 14.7	51	−42.0 (−61.8–15.6)
Work ability (WAS, 0–10)†	75	4.6 ± 2.4	52	5.8 ± 2.1	51	0.0 (0.0–66.7)
CS						
CSI						
CS-related symptoms (CSI-A, 0–100)	73	40.0 (31.0–49.8)	46	33.0 (27.8–45.0)	45	−12.1 (−30.3–5.9)
QST						
Sharp cutaneous pain sensation (MPT, mN)	71	72.0 (32.0–186.7)	53	77.3 (44.0–213.3)	53	8.3 (−43.2–123.8)
Blunt pressure pain sensation (PPT, N)	71	53.3 (41.2–72.6)	53	60.1 (43.2–82.5)	53	8.0 (−7.3–23.3)
Allodynia (DMA)	70	0.0%	53	1.9%		
Touch sensation (MDT, mN)	71	3.3 (1.6–8.0)	53	3.5 (1.5–8.7)	53	9.1 (−45.8–97.1)
Temporal summation (WUR, ratio)	60	2.4 (1.8–3.2)	44	2.6 (1.9–3.2)	41	3.7 (−35.2–40.2)
Descending pain modulation (CPM, %)	70	6.9 (−4.3–23.1)	52	6.2 (−7.2–16.2)	52	−80.7 (−171.5–6.6)
HRV						
Parasympathetic/vagal tone (RMSSD, ms)	70	40.7 (30.6–54.3)	52	42.8 (30.6–61.5)	52	8.1 (−18.2–41.4)
Parasympathetic/vagal tone (HF, ms^2/Hz)	70	101.4 (61.5–192.5)	52	127.6 (54.9–243.2)	52	6.0 (−45.8–122.3)
Mean inter-beat time interval (R-R interval, ms)	70	816.7 (748.7–917.5)	52	840.3 (770.0–905.9)	52	−0.2 (−6.0–9.7)
Standard deviation of R-R intervals (SDNN, ms)	70	56.8 (42.0–71.8)	52	72.4 (45.4–90.6)	52	21.7 (−6.6–63.4)
Clinical characteristics						
Pain intensity (VAS pain, 0–10)	75	5.1 (2.7–6.6)	52	3.2 (1.9–4.6)	51	−23.7 (−56.9–18.9)
Catastrophyzing (PCS, 0–52)	66	18.0 (11.0 – 27.0)	44	8.0 (5.0–14.0)	43	−54.5 (−73.7—20.4)
Injustice (IEQ, 0–48)	71	16.0 (10.0–23.0)	42	11.0 (5.0–15.3)	41	−29.4 (−55.8—4.8)
Distress (BSI-GSIT, 0–100)	66	38.1 (33.0–45.8)	42	33.8 (30.6–40.2)	41	−7.2 (−15.7–3.8)

†: variable normally distributed, mean and standard deviation (± SD) are shown. Abbreviations: BSI-GSIT, Brief Symptom Inventory Global Severity Index T-score; CPM, Conditioned Pain Modulation; CR, Category Ratio; CS, Central Sensitization; CSI-A, Central Sensitization Inventory part A; DMA, Dynamic Mechanical Allodynia; HF, High-Frequency; HRV, Heart-Rate Variability; IEQ, Injustice Experience Questionnaire; MDT, Mechanical Detection Threshold; MPT, Mechanical Pain Threshold; PCS, Pain Catastrophyzing Scale; PDI, Pain Disability Index; PF, subscale Physical Functioning; PPT, Pressure Pain Threshold; QST, Quantitative Sensory Testing; RMSSD, Root Mean Square of Successive Differences; SDNN, Standard Deviation of Normal-to-Normal range; VAS, Visual Analogue Scale; WAS, Work Ability Score; WUR, Wind-Up Ratio.

ity. Knowledge on the associations of factors related to functioning and on changes in those associations overtime, can assist in better personalization of the rehabilitation programs. Previous research has identified biopsychosocial factors contributing to the functioning of patients with CLBP [61]. Our study has been able to analyze the contribution of CS indicators to functioning measures beyond biopsychosocial factors, not only cross-sectionally but also longitudinally.

CLBP is multifaceted, patients suffering from it form a heterogeneous group, and have been reported to have contradictory results in the outcome measures of the assessment of the presence of CS [62]. Also, patient's state or situation is dynamic, continuously evolving, which would affect their perceptions and functioning as well as the factors associated with them. And, their coping strategy to pain is diverse, ranging from an avoiding behavior to a persisting/enduring behavior [63], where mixed and changing strategies may also be present. Therefore, even if the associations found in this study are weak and not unequivocal, they may be representative of the complex and individualized nature of pain and the adaptive strategies of patients with CLBP. In clinical practice, the inclusion of CS indicators along with known biopsychosocial factors contributing to the functioning of patients with CLBP during the initial evaluation, the rehabilitation program, as well as the

Table 3
Results of multiple regression analyses (cross-sectional)

	Lifting capacity ($n = 66$)†			Physical functioning ($n = 66$)			Disability ($n = 66$)			Work ability ($n = 56$)		
	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$
(Constant)	4.22	[2.80, 5.65]		56.67	[30.23, 85.11]		34.50	[15.99, 53.01]		1.04	[−3.12, 5.20]	
CSI												
CS-related symptoms (CSI-A)	0.00	[−0.02, 0.02]	0.00	0.11	[−0.19, 0.42]	0.10	0.12	[−0.08, 0.32]	0.15	−0.02	[−0.06, 0.03]	−0.11
QST												
Sharp cutaneous pain sensation (MPT)	−0.00	[−0.00, −0.00]	−0.39**		–			–			–	
Touch sensation (MDT)		–			–		0.34	[0.01, 0.69]	0.25		–	
Temporal summation (WUR)		–			–			–		0.26	[−0.11 , 0.63]	0.20
Descending pain inhibition (CPM)		–		−0.11	[−0.23 , 0.01]	−0.23		–			–	
HRV												
Parasympathetic/ vagal tone (RMSSD)	−0.00	[−0.01 , 0.01]	−0.02	0.19	[0.01, 0.37]	0.26*	0.06	[−0.06, 0.18]	0.12	−0.01	[−0.04, 0.02]	−0.11
Age	−0.02	[−0.04, −0.00]	−0.28*	−0.21	[−0.52, 0.11]	−0.17	−0.01	[−0.22, 0.20]	−0.01	0.02	[−0.03, 0.07]	0.10
Sex: Women	−1.10	[−1.53, −0.67]	−0.56***	−1.04	[−8.59, 6.51]	−0.04	−0.71	[−5.63, 4.22]	−0.04	−0.02	[−1.17, 1.13]	−0.01
Assessor's observed exertion (CR-10)	0.31	[0.21, 0.42]	0.63***		–			–			–	
Pain intensity (VAS pain)	−0.12	[−0.22, −0.03]	−0.32*		–		1.36	[0.18 , 2.54]	0.29*		–	
Disability (PDI)		–		−0.62	[−0.96, −0.27]	−0.42**		–			–	
Work ability (WAS)		–		2.86	[1.17, 4.55]	0.40**		–			–	
Physical functioning (Rand36-PF)		–			–		−0.25	[−0.39, −0.11]	−0.42**	0.07	[0.04 , 0.10]	0.52***

†: the model uses the square root of lifting performance (sq_lifting) as dependent variable. –: not tested. Significance level of the introduced variables in the final regression models: *, $p < 0.05$; **, $p < 0.01$; ***$p < 0.001$. Abbreviations: CPM, Conditioned Pain Modulation; CR, Category Ratio; CS, Central Sensitization; CSI-A, Central Sensitization Inventory part A; HRV, Heart Rate Variability; MDT, Mechanical Detection Threshold; MPT, Mechanical Pain Threshold; PDI, Pain Disability Index; PF, subscale Physical Functioning; QST, Quantitative Sensory Testing; RMSSD, Root Mean Square of Successive Differences; VAS, Visual Analogue Scale; WUR, Wind-Up Ratio.

Table 4
Results of multiple regression analyses (longitudinal)

	ΔLifting capacity ($n = 42$)†			ΔPhysical functioning ($n = 40$)			ΔDisability ($n = 32$)†			ΔWork ability ($n = 41$)†		
	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$	B	[95% CI]	$r_{partial}$
(Constant)	13.81	[−10.32, 37.93]		12.73	[−3.18, 28.63]		−18.70	[−40.13, 2.74]		13.36	[−31.07, 57.80]	
CSI												
ΔCS-related symptoms (CSI-A)	−0.26	[−1.10, 0.58]	−0.10	−0.15	[−0.73, 0.43]	−0.09	0.77	[0.01, 1.53]	0.36*	−1.46	[−2.99, 0.08]	−0.30
QST												
ΔSharp cutaneous pain sensation (MPT)	−0.03	[−0.13, 0.07]	−0.11		–			–			–	
ΔBlunt pressure pain sensation (PPT)		–			–			–		1.31	[−0.51, 3.13]	0.23
ΔTouch sensation (MDT)		–		−0.01	[−0.10, 0.08]	−0.03		–			–	
ΔTemporal summation (WUR)		–			–		−0.21	[−0.53, 0.10]	−0.25		–	
HRV												
ΔParasympathetic/ vagal tone (RMSSD)	0.60	[0.24, 0.96]	0.48**	−0.02	[−0.22, 0.19]	−0.03	−0.07	[−0.37, 0.24]	−0.08	−0.57	[−1.32, 0.18]	−0.25
ΔAssessor's observed exertion (CR-10)	0.37	[0.00, 0.73]	0.32*		–			–			–	
ΔCatastrophizing (PCS)		–		−0.42	[−0.76, −0.07]	−0.38*		–			–	
ΔLifting capacity		–			–			–		0.75	[0.16, 1.35]	0.39*

†: the model does not fulfill all the regression assumptions. –: not tested. Significance level of the introduced variables in the final regression models: *, $p < 0.05$; **, $p < 0.01$; ***$p < 0.001$. Abbreviations: CS, Central Sensitization; CSI-A, Central Sensitization Inventory part A; HRV, Heart Rate Variability; MDT, Mechanical Detection Threshold; MPT, Mechanical Pain Threshold; PCS, Pain Catastrophizing Scale; PPT, Pressure Pain Threshold; QST, Quantitative Sensory Testing; RMSSD, Root Mean Square of Successive Differences; WAS, Work Ability Score; WUR, Wind-Up Ratio.

regular follow-ups, is encouraged. It may be beneficial for better personalizing and regularly adjusting goal settings and treatment approaches, which would lead to improved treatment efficacy.

This research is the first of its kind as it has been performed with a comprehensive set of methods to assess CS phenomenon and functioning in patients with CLBP, both cross-sectionally and longitudinally. The measurements are implemented within the usual care and CS indicators are assessed with state of the art methods-considered best available. Additionally, the functioning assessment in this study included a lifting test to complement the self-report outcomes, thus, better resembling usual care. The selection of one QST test (per highest correlation coefficient) to enter the regression models as representative, was a choice made to suit better the functioning outcome, although results could not be compared to other studies [16]. Nevertheless, the most informative somatosensory measure for each functioning measure was obtained and, seeing the heterogeneity in the models, it is assumed the loss of comparability is outweighed.

There are some limitations to consider in this study. The amount of patients participating was not sufficient to include confounders to the regression models for longitudinal analyses. The study had two measurement points which was insufficient for insights on the evolution of the association between CS and functioning. Delta calculation is vulnerable to regression to the mean; other options are available but have shortcomings as well. Three longitudinal models did not fulfill all the assumptions for regression analyses; although results are less robust, valuable insights on the diversity of the associations are obtained.

Future research can build on the strengths and overcome the limitations of this study, to replicate and assist in the ongoing unravelling of the relation between CS and functioning. It is recommended that studies do not rely on a single CS indicator or functioning measure, and use both self-report and performance-based. Studies should consider prospective cohort designs with more measurement points and larger study samples, whereby it might be possible to distinguish subgroups in patients with CLBP for whom different treatment approaches may be needed and different evolutions can be expected.

5. Conclusion

Some CS indicators were related to functioning in patients with CLBP and associations were weak-to-moderate and heterogeneous; they differed between CS indicators and functioning measures and from cross-sectional to longitudinal analyses. Because of this, the rehabilitation evaluation should include the assessment of underlying pain mechanisms, and the program goals may need regular adjustments to the current state of the patient.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

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