Do "central sensitisation" questionnaires reflect measures of nociceptive sensitisation or psychological constructs? A systematic review and meta-analyses

Do "Central Sensitisation" Questionnaires Reflect Measures of Nociceptive Sensitisation or Psychological Constructs? a Systematic Review and Meta-Analyses:

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Abstract

Central sensitization (CS) is defined as an increased nociceptive responsiveness due to sensitization of neurons in the central nervous system, usually the result of prolonged nociceptive input or a disease state associated with noxious inputs (e.g., polyarthritis). The concept of CS has recently been adopted in clinical assessments of chronic pain, but its diagnosis in humans may now includes a wide range of hypervigilant responses. The purpose of this review is to ascertain whether self-report questionnaires linked with CS are associated with enhanced nociceptive responses, or whether they measure sensitivity in a broader sense (i.e., emotional responses).

According to our published, PROSPERO-registered review protocol (CRD42021208731), a predefined search of studies that involve the Central Sensitization Inventory (CSI) and/or Pain Sensitivity Questionnaire (PSQ) correlated with either nociceptive sensory tests or emotional hypervigilance was conducted on MEDLINE, PsychINFO and Web of Science. Correlations between the CSI/PSQ with our primary outcomes were extracted and meta-analysed.

A Review of 66 studies totalling 13,284 participants found that the CSI (but not the PSQ) strongly correlated with psychological constructs: Depression, anxiety, stress, pain catastrophising, sleep and kinesiophobia. The CSI and PSQ showed weak/no correlations with experimental measures of nociceptive sensitivity: pain thresholds, temporal summation or conditioned pain modulation. The PSQ did however correlate strongly with phasic heat and tonic cold pain tests.

The studies reviewed did not provide sufficient evidence that self-report measures reflect a canonical understanding of CS. The CSI more closely reflects psychological hypervigilance than increased responsiveness of nociceptive neurons.

Introduction

Central sensitisation (CS) is defined by the International Association for the Study of Pain (IASP) as "increased responsiveness of nociceptive neurons in the central nervous system to either normal or subthreshold afferent input," [25,53,131]. CS has been linked with a multitude of chronic pain disorders in humans [62,70,79,105,110,144], with 'Central Sensitivity Syndrome (CSS)' being a recently developed diagnosis for several 'medically unexplained' pain disorders (e.g. fibromyalgia and temporomandibular disorder) for which CS is thought to play an etiological role [143]. As of yet, there is no conclusive method of accurately establishing the presence of CS in humans [100], although quantitative sensory testing (QST) is used to assess the dynamic modulation of nociceptive signals, which can suggest the presence of CS [6,137]. QST measures include pain threshold tests, temporal summation (a measure of "wind-up" or enhancement of pain with prolonged nociceptive exposure [31]) and conditioned pain modulation (said to quantify the efficiency of endogenous inhibition of pain [27]).

Although QST allows for a comprehensive assessment of pain sensitivity profiles, it often involves select training, expensive lab equipment and additional patient burden, which limits its use in clinical settings[104]. Self-report questionnaires would make a pragmatic alternative assessment of CS in clinics, allowing for quick and convenient assessment at little cost. To serve this purpose, however, these questionnaires would need to demonstrate acceptable associations with known measures of CS to show sufficient construct validity.

A self-report questionnaire that is widely used in the assessment of central sensitisation is the Central Sensitisation Inventory (CSI). The CSI was designed as a self-report screening measure to help identify patients who might have a CSS, such as fibromyalgia, neck injury,

temporomandibular joint disorder or migraine/tension headaches [89]. It has been shown to be a reliable and valid psychometric instrument for identifying individuals vulnerable to pain [74].

The Pain Sensitivity Questionnaire (PSQ), however, may more directly measure the sensory facilitation involved in CS [107]. The PSQ is a valid and reliable measured designed to investigate self-reported pain sensitivity as a supplement or alternative to experimental pain testing [80,108]. It focuses more on respondents imagining situations that involve nociceptive input and predicting how they would react. The questions are posed to measure sensitisation to sensory input, but the degree to which it reflects a top-down component influenced by personality type or disposition remains open. More specifically, whether it reflects these psychological profiles to the same degree as the CSI is a germane question in terms of understanding how closely related and psychometrically distinct these measures are.

It would appear that the term "central sensitization" has undergone construct drift from its canonical (pre-clinical) use describing enhanced responsivity of central nociceptive neurons [64,139,140] to a broader usage including psychological profiles. This construct drift may reflect a noble desire to legitimize poorly explained pain by providing a putative central mechanism, but the degree to which this broader construct reflects mechanisms outlined in animal models of central sensitization is unclear. As such, we are interested in exploring the degree to which the CSI and PSQ reflects CS as an 'increased responsiveness of nociceptive neurons'. The meta-analyses of available studies examined whether self-report measures (the PSQ and/or CSI) aligned more closely with QST measures/experimental measures of nociceptive sensitivity or psychological questionnaires such as anxiety, depression, stress

etc. In doing so, we aim to assess and compare the two questionnaires in terms of the degree to which they assess nociceptive sensitisation or emotional sensitisation.

Methods

The review protocol has been previously published [1], and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=208731) prepared in accordance with recommendations specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [95].

Sources of Evidence

We searched MEDLINE, PsychINFO and WebofScience from their inception until June 2021. Two separate searches were conducted including both the CSI and PSQ. One search reviewed these questionnaires for sensory correlates (e.g., Quantitative sensory testing). The second search reviewed their correlations with psychological questionnaires (e.g., anxiety, depression, pain catastrophising etc). Any duplicates within both searches were removed.

Search Terms

Search 1 terms:

("Quantitative Sensory Testing" or "wind-up" or "temporal summation" or "conditioned pain modulation" or " pain threshold" or "pain ratings" or "hyperalgesia" or "allodynia" or "offset analgesia" or "widespread pain" or “evoked pain” or “experimental pain” or “pain tolerance”) AND ("central sensitization inventory" or "central sensitisation inventory" or "pain sensitivity questionnaire")

Search 2 terms:

("depression" or "anxiety" or "stress" or "catastrophizing" or "rumination" or "neuroticism" or "personality" or "abuse" or "trauma") AND ("central sensitization inventory" or "central sensitisation inventory" or "pain sensitivity questionnaire")

Inclusion Criteria

Only human studies were eligible for inclusion. They must have been written in English and an original peer-reviewed experiment (i.e., not a dissertation, case study or review article). Finally, studies must have included at least one of the CSI or PSQ instruments. The CSI and/or PSQ must have been correlated against at least one psychological or sensory measure of interest.

Types of studies

The review included studies that correlate the PSQ/CSI with sensory and/or psychological measures. In studies that involved an intervention, measures were only considered if they were assessed at baseline.

Data collection, extraction and management

Two independent reviewers assessed studies for eligibility (GA and WG). Initially, titles and abstracts were screened using excel, and full-text screening was performed on citations felt to be potentially eligible. Both Authors were required to agree for inclusion. We excluded studies that did not satisfy our inclusion criteria. Discrepancies between the reviewers were resolved by discussion and consensus, with a third reviewer being consulted in cases of disagreement. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of this process is provided (Fig.1).

Outcome Measures

Our primary outcomes were correlations between the CSI total score and/or the PSQ total score with sensory measures associated with CS. These include QST measures; temporal summation, pain thresholds and tolerance, and any measure related to nociceptive hypersensitivity or widespread pain. We were also interested in exploring the extent to which self-report questionnaires may be

predictive of descending aspects of modulation (impaired inhibition), therefore including conditioned pain modulation as a measure of interest.

The second outcome measure was correlations between the CSI and/or the PSQ and psychological factors. These included questionnaires that assess depression, anxiety, stress, pain catastrophizing, abuse, trauma, mindfulness, neuroticism or personality and any other measure related to emotional hypersensitivity.

Data Extraction and Management

One reviewer (GA) extracted relevant data from each study (correlation coefficient *r*, and number of participants *n*). If these values were not given within the paper, authors were contacted to provide the relevant correlation coefficient. A second reviewer checked the extracted data (DW-A). Data extracted from each citation included information about the study design, the correlation coefficients age, sex and number/type of participants.

Data Items

Psychological Measures

Psychological correlates with PSQ or CSI that were provided for at least 3 studies were included in meta-analyses; these were depression, anxiety, pain catastrophising, stress, sleep, and kinesiophobia. The questionnaires used to assess depression were the Depression Anxiety Stress Scale (DASS-21) [67], the four-dimensional Symptom Questionnaire (4DSQ)[125], the Hospital Anxiety and Depression Scale (HADS-D) [146], the Symptom Checklist 90 depression subscale (SCL90-D) [14], Beck's Depression Inventory (BDI) [114], the Depression Scale (DEPS) [97], the Centre for Epidemiologic Studies Depression Scale (CES-D) and the Geriatric Depression Scale (GDS-15) [101] and the Hamilton Depression Rating Scale (HAM-D) [71]. The questionnaires used to assess anxiety were DASS21 [67], 4DSQ [125], HADS-A [146], the Symptom Checklist 90 anxiety subscale (SCL90-A) [14], the State and Trait Anxiety Inventory (STAI) [81], the Brief Symptom Inventory (BSI) [34], the

Beck Anxiety Inventory (BAI) and the Hamilton Anxiety Rating Scale (HAM-A) [71]. The questionnaire used to assess pain catastrophising was the pain catastrophising scale (PCS) [94]. The questionnaires used to assess stress were the DASS-21 [67], the Perceived Stress Scale (PSS) [68], 4DSQ [125]and the Brief Measure of Emotional Preoperative Stress (B-MEPS) [138]. The questionnaires used to assess sleep were the Medical Outcomes Study Sleep Scale (MOS) [3], the Basic Scale of Insomnia Complaints and Quality of Sleep (BaSIQs) [2], and the Insomnia Severity Index (ISI) [87]. The questionnaire used to assess kinesiophobia was the Tampa Scale of Kinesiophobia (TSK) [126].

Other questionnaires that reported correlations with CSI/PSQ in fewer than 3 studies were included for narrative review but not for meta-analyses; these were the Brief Resilience Scale (BRS) [120], the Patient Health Questionnaire (PHQ-15) [59], the Adolescent/Adult Sensory Profile (AASP) [15], the Sensory Responsiveness Questionnaire (SRQ) [10], the Difficulties in Emotion Regulation Scale (DERS) [13], the Positive and Negative Affect Schedule (PANAS) [24], the Pain Anxiety Sensitivity Scale (PASS) [75], the Childhood Trauma Questionnaire (CTQ) [11] and the Child Abuse and Trauma questionnaire (CATS) [111].

Nociceptive Sensory Measures

Sensory correlates suitable for meta-analyses included Pressure Pain Threshold (PPT), Heat Pain Threshold (HPT), Conditioned Pain Modulation (CPM), Temporal Summation (TS) and Widespread Pain. Methods that were not carried out regularly enough for meta-analyses (i.e., fewer than 3 studies reported correlations for these measures) included suprathreshold (pain rating associated with the 5th heat pulse out of a series of 5 heat pulses (46°C)) [23], offset analgesia [119], pain tolerance [33,55,60,99,128,129,138] (electrical, pressure or thermal), area/number of pain sites [70,86], cold pain threshold [38], electrical pain threshold [103], and tonic heat [107]. Correlations for the CSI/PSQ with these measures can be found in Supplementary Tables 1a-d.

The methodologies for the nociceptive measures included in the meta-analyses were considered standardised and generally consistent, although they did show slight variations in some cases, as outlined below:

Pressure Pain Threshold

In most cases for PPT, a digital or handheld mechanic pressure algometer was used to apply pressure through a 1cm² probe. The main variation in PPT was in the rate of pressure applied being between 0.1kg/s to 1kg/s. The body site for which the PPT was applied varied across studies, though it was consistently applied to muscles. Participants were asked to report the moment that the increasing pressure became painful or unpleasant.

Heat Pain threshold

For Heat Pain threshold, a thermode was applied to various body sites depending on the study, consistently applied to muscles. In all studies, the thermode started at a baseline temperature (commonly 32°C) and was increased at a varied rate between 0.5°C/s to 2°C/s across studies. Participants were asked to report the moment that the increasing heat became painful or unpleasant.

Conditioned Pain Modulation

For CPM the conditioning stimulus was most regularly a cold-water bath applied to the opposite hand of the test stimulus. One study used a thermode to elicit cold pain [37], and another used a hot water bath [103]. Most commonly the test stimulus was a pre-determined pressure applied to a body part on the opposite side of the conditioning stimulus using a pressure algometer. One study used a combination of pressure and heat pain [60] and another used electrical stimuli applied to the right sural nerve [103]. One study used PPT as the test stimulus and Ischemic compression using a Sphygmomanometer was used as the conditioning stimulus [98]. The average pain ratings for the test stimulus given during the conditioning stimulus condition (both test and conditioning stimulus

simultaneously administered) were subtracted from the average pain ratings of the test stimulus only condition to give a CPM score.

Temporal Summation

TS was often calculated by applying a pre-determined pressure intensity using a pressure algometer to a body site (body sites varied across studies) for several repetitions (commonly 10 consecutive stimulations) at a rate of 1/second. The first pain rating in the series was subtracted from the final pain rating to give a TS score. One study used this same paradigm, as well as a similar paradigm using electrical stimulation [60]. Another study applied a 60g von Frey filament to the forearm and knee for 4 stimulations, the stimulus was then applied for 30 stimulations at a rate of 1/second. The initial pain rating was subtracted from the second to give a TS score [37].

Widespread Pain

Widespread pain measures consisted of the Widespread Pain Index (WPI) [32] and the Michigan Body Map (MBM) [16], which are both questionnaires used to assess the number of painful body sites and area of pain across the body.

Phasic Heat

Phasic heat stimulation was administered at 47°C or 48°C for 5 seconds. The average of four ratings collected at the set temperature of 47/48°C was used as phasic pain rating. If Phasic Heat rating was carried out at two temperatures the average of these two scores was taken as the Phasic heat score.

Tonic Cold

A thermode surface oscillated around 3°C (0.5 Hz, amplitude: ±1°C) for 60s. The average of the ratings over the four-time points and four measurements (twice on each hand) was used as the tonic cold pain rating.

Pinprick Stimulation

Pain intensity ratings of pinprick stimuli were obtained from the volar forearm using a weighted pinprick stimulator (force: 512 mN).

Assessment of risk of bias in included studies

For each study included in the review a modified version of the quality appraisal process proposed by Hayden et al (2006) [40] was conducted by two independent authors (GA, WG/RH) to evaluate potential sources of bias across 5 domains: participation bias, publication bias, attrition, methodological quality and statistical analysis. We assessed the following for each study: (1) Were potential sources of participation bias considered and addressed? (2) Was there any missing data regarding the variables of interest (3) Was the methodology of the variable of interest of a standardized quality? (4) Was the desirable statistical analyses performed? (5) Was the sample size adequate? Each category was assigned a low, unclear, or high risk of bias and presented with a "Risk of bias" summary. Disagreements between reviewers were resolved by discussion and consensus. A third reviewer (WG/RH) was consulted where assessments could not be agreed upon.

Analysis of Participation Bias

Specific sources of participation bias (bias assessment category (1) were identified i.e., age and sex characteristics of the population sample, as well as population samples that excluded participants based on mental health, physical health or medication being taken.

Synthesis of Results

Data eligibility

Sample sizes (*n*) and correlation scores (*r*) on primary outcomes were extracted from papers or via responses collected from emailing corresponding authors and presented to show individual study characteristics. Only data that provided sample size and a correlation value were included. Only Spearman's rank and Pearson's correlation (r-values) were considered eligible so that meta-analyses could be conducted.

Data Preparation

CSI correlations were extracted for each construct separately; depression, anxiety, stress, pain catastrophising, kinesiophobia and sleep. Meta-analyses were conducted if at least 3 studies reported findings for a related construct. Each meta-analysis was made up of a combination of instruments for that construct e.g., correlates with CSI and anxiety will include CSI against STAI Trait and State, the Anxiety component of the Depression Anxiety stress scale (DASS-21), the anxiety component of the Hospital Anxiety and Depression Scale (HADS), etc.)

Meta-analyses for quantitative sensory measures were conducted for each measure separately: Pressure pain threshold, heat pain threshold, conditioned pain modulation, and temporal summation were separately meta-analysed against CSI. If studies reported two correlations for one construct (e.g., multiple body sites taken for pain threshold or trait and state anxiety scores were reported for anxiety), scores were averaged together.

Data Visualization

Data for individual studies were reported in Supplementary Tables 1a-d to show individual study characteristics. This table was presented in four sections; CSI with psychological constructs (Supplementary Table 1a), CSI with nociceptive measures (Supplementary Table 1b), PSQ with psychological constructs (Supplementary Table 1c), and PSQ with nociceptive measures (Supplementary Table 1d). Meta-analyses findings were presented in table format with a summary of the effect size on the right of the table. For visualisation purposes, Forrest plots were provided for some of the main findings (Forrest plots for all other meta-analyses can also be found in Supplementary Figures1a-n). Any other findings with insufficient data for a meta-analysis were reviewed narratively where appropriate.

Primary Analysis

Meta-analyses consisted of Sample sizes (*n*) and correlation scores (*r*) on primary outcomes extracted from papers or via response from emailing corresponding authors and will be presented in

a table. These values were then input into a meta-analysis to give a weighted mean correlation using the Hunter-Schmidt method[113]. Statistical Software StatsDirect version 3.3.5 was used to calculate weighted mean correlations, to test for heterogeneity and to perform subgroup analysis [122]. Weighted mean correlations were calculated to measure the overall strength of a correlation between the PSQ/CSI and each construct. A sub-group analysis was performed where applicable to assess and compare the relative strength of our correlations of interest for chronic pain patients versus healthy controls.

Tests for Heterogeneity

The Chi-squared (X^2) test was used to measure statistical heterogeneity across studies. Significant heterogeneity (p<0.05) is an indicator of clinical and methodological heterogeneity. The I^2 statistic was calculated to report heterogeneity as a percentage [29,43]. A value of 0% implies no observed heterogeneity, 1 to 40% indicates low heterogeneity, 30% to 60% suggests moderate heterogeneity, 50% to 90% signifies substantial heterogeneity, and 75% to 100% is considered heterogeneous [43]. Moderator analyses were conducted when heterogeneity scores were above 50% to examine whether certain factors contributed towards heterogenous findings (e.g. age or sex) [43].

Results

After excluding duplicates, the initial literature search identified 175 articles (Figure 1). 49 of these articles were eligible after full screening. A further 74 corresponding authors were emailed for specific correlations (either the PSQ or CSI with our variables of interest) as data were collected but not reported within their publication. 20 authors responded and provided the correlates of interest. Therefore, a total of 69 studies were eligible for quality appraisal/bias assessment (see Figure 1 for further details).

Risk of Bias

All 69 studies included in the review went through an assessment of quality and risk of bias. The results are presented in Figure 2. An additional breakdown of participation bias is presented in Figure 3.

1. Participation Bias – Many studies showed participation bias. This reflects some common exclusion criteria that occur in studies that measure pain sensitivity e.g., neuropathic pain patients are often excluded as well as individuals with any mental health disorders or people taking any medication as this may affect their responsivity to stimuli. We ran a separate assessment to showcase the common characteristics which were excluded from study populations. The 'other' column was primarily made up of participants being excluded due to cognitive deficits (see Figure 3).
2. Missing data- A few studies reported missing data. This was in part due to incomplete questionnaires or participation dropout. Data not being reported for all the participants (e.g., reporting for pain patients but not healthy controls) was reflected in their bias assessment.
3. Standardized method - Most studies conducted a standardized method. The questionnaires were standardized for CSI, PSQ and psychological correlates and if sensory measures were taken, the method was of standardised quality. We could check this by assessing whether studies employed protocols from previously published work, or how homogenous protocols were across studies. Two studies were excluded due to a lack of methodological standardization [76,133]
4. Desirable statistics- Most studies provided Pearson's correlations for our variables of interest, but a few provided Spearman's rank correlations. If the study had undergone the relevant methodology but did not provide Pearson's or Spearman's correlations, we contacted the authors to provide data for one of these correlations. Synthesised results could then be analysed comparatively and included in meta-analyses. One study gave partial correlations and was therefore excluded [80].

5. Sample Size- 63 out of 69 studies had an adequate sample size- a power calculation based on *r*=0.3 indicated that the sample size should have been 43 or over. Anything lower than n=43 was flagged. However, all studies were included for weighted meta-analyses. Low sample sizes simply reflected less influence in a weighted meta-analysis. However, these small sample sizes may be relevant when reviewing less frequent correlations that were not suitable for meta-analysis i.e., narrative review.

Overall, the quality assessment for studies selected for this study showed that the studies were of good quality with a low risk of bias. 3 studies were excluded due to a non-standardised method being used or data not being given in the required format for correlational meta-analyses [76,80,133].

There were some concerns over participation bias (Figure 3) due to certain types of chronic pain patients being excluded in several studies (n=46) based on their medical condition e.g., neuropathy. Patients on pain medication were excluded in several studies (n=19), patients with mental health or psychiatric disorders were excluded in studies (n=24), and individuals with cognitive deficits were excluded in a number of studies (n=12). This exclusion criteria may appear biased but it is typical across studies that examine pain populations as medical conditions, medication, cognitive deficits and mental health can all interfere with the pain processing/Interpretation of pain. [51,65,130]. Similarly, due to the typical nature of chronic pain populations, some study populations were predominantly female, and the mean age was high (over 60).

Only one study was identified as high risk in any of the assessed domains on participation bias. The reasons for this were that in one study of a Chinese population, women taking contraception were excluded [99]. However, this study was still included for further analysis as the potentially affected representation of females was balanced against having an international sample.

Excluded studies

Two studies were excluded due to a lack of methodological standardization [76,133] and one study gave partial correlations and was therefore excluded [80].

Summary

All studies included in this review were assessed for methodology and were considered standardized by at least two reviewers. Though it should be noted that, in general, there was a certain level of heterogeneity in methodology across studies involving nociceptive sensory measures, particularly with CPM.

Primary Outcomes

The surviving 66 studies included a total of 13,284 participants. 7,470 participants took the Central Sensitisation Inventory across 37 different studies and 5,531 took the Pain Sensitivity Questionnaire across 30 different studies (one study included both questionnaires [23]). 31 studies containing a total of 6,885 participants provided correlations for the CSI with at least one psychological primary outcome. 16 studies consisting of 1,857 participants provided correlations for the CSI with at least one sensory primary outcome. 25 studies consisting of a total of 4,482 participants provided correlations for the PSQ with at least one psychological primary outcome. 16 studies consisting of a total of 3,375 participants provided correlations for the PSQ with at least one primary sensory measure. All extracted correlations can be seen in Supplementary Tables 1a-d.

Supplementary Tables 1a-d show the extracted data for each of these studies (Supplementary Table 1a shows all extracted correlations for CSI with psychological primary outcomes, Supplementary Table 1b for CSI with sensory primary outcomes, Supplementary Table 1c for PSQ with psychological primary outcomes and Supplementary Table 1d for PSQ with sensory primary outcomes). All tables provide data for age, sex and subject population for each study if it was provided. Note that if multiple correlations of the same or very similar constructs were provided for a study, which only occurs when trait anxiety and state anxiety are reported within the State and Trait Anxiety Inventory

(STAI), the values were averaged together as these two measures have high intercorrelation [102]. Similarly, if measures for multiple body sites were recorded for PPT, HPT, CPM etc., the multiple correlations per study were averaged together to give a mean correlation score for that construct, given that intraclass correlations for pain measures across different body sites have been found to be high (Cronbach's alpha values >.80) [63,72]. This meant that one correlation score for each construct was provided for each population which could be used for meta-analysis.

Meta analyses:

The results of the meta-analyses are reported in Table 1. Studies reporting data for sub-set samples instead of a total (e.g., patients and healthy controls) were entered into the meta-analyses as separate correlations as they reflected separate populations. In a separate sub-analysis, they were divided appropriately to compare findings for pain patients with healthy participants (see Table 2). Data for some of the main findings are presented as Forrest plots in Figures 4a-h, Forrest plots for all other meta-analyses can be found in Supplementary Figures 1a-n.

Central Sensitization Inventory

When Cohen's standards for effect sizes are applied [22], the CSI showed moderate to strong correlations with psychological questionnaires. Depression *(r=0.58, 95% CI [0.54-0.62])*, anxiety *(r=0.60, 95% CI [0.56-0.63])*, pain catastrophizing *(r=0.48, 95% CI [0.43-0.54])*, stress *(r=0.63, 95% CI [0.56-0.69])*, sleep *(r=0.40, 95% CI [0.29-0.51])* and kinesiophobia *(r=0.46, 95% CI [0.40-0.53])* all showed moderate-strong weighted correlations with the CSI. There wasn't sufficient data for a meta-analysis on childhood trauma, somatization, and personality type (sensory profile and brief resilience scale) and negative affect but they all showed moderate-strong correlations with CSI [20,21,23,41,50,73,77]. Overall, these findings suggest that the CSI correlates strongly with psychological factors (see Supplementary Table 1A and Figures 4a-b).

CSI shows a weak negative correlation with PPT *(r=-0.22, 95% CI [-0.28 to -0.17])*, no correlation with HPT *(r=-0.01, 95% CI [-0.12-0.09])* and a weak/negligible correlation with CPM *(r=0.10, 95% CI [0.01-0.19])* and TS *(r=0.09, 95% CI [0.01-0.16])*. This suggests that CSI scores are a weak/negligible predictor of how an individual might respond to nociceptive sensory testing (see Supplementary Table 1B and Figures 4c-d). The correlations between the CSI and sensory measures PPT, HPT, CPM and TS are substantially weaker than their correlations with psychological constructs. Widespread pain was moderately correlated with the CSI *(r=0.39, 95% CI [0.23-0.50])*. Area of pain, number of pain sites and manual tender point count were also moderately correlated with the CSI *(r= 0.46, p<0.01; r=0.45 p<0.01; r=0.43 p<0.01; respectively)*.

Pain Sensitivity Questionnaire

The PSQ showed weak correlations with psychological questionnaires; depression *(r=0.11, 95% CI [0.08-0.15])*, anxiety *(r=0.16, 95% CI [0.14-0.19])* and stress *(r=0.23, 95% CI [0.15-0.30])*, and a moderate correlation with pain catastrophising *(r=0.32, 95% CI [0.25-0.40])* (see Supplementary Table 1c and Figures 4e-f). Regarding measures that did not provide sufficient data for meta-analyses - the Brief Resilience Scale (BRS) showed a moderate negative correlation with PSQ in one study [23]. Negative affect neuroticism aversiveness, past negativity and sensory responsiveness showed weak-moderate positive correlations with the PSQ [8,9,23,36].

The PSQ showed a weak negative correlation with PPT *(r=-0.17, 95% CI [-0.22 to -0.12])* and HPT *(r=-0.11, 95% CI [-0.25 to 0.02])* a negligible correlation with TS *(r=0.08, 95% CI [-0.00 to 0.17])* and no correlation with CPM *(r=-0.04, 95% CI [-0.15 to 0.07])* (see Supplementary Table 1d and Figures 4g-h). The PSQ was however strongly correlated with Phasic heat *(r=0.64, 95% CI [0.54-0.73])* and tonic cold *(r=0.64, 95% CI [0.51-0.77])* and moderately correlated with pin prick stimulation *(r=0.39, 95% CI [0.38-0.40])*. This suggests that the PSQ does assess what it is designed for and can predict how people might respond to painful stimulations.

Comparison of the PSQ and CSI

The correlations between the CSI and depression *(Z= 23.10, p<0.001)*, anxiety *(Z= 20.74, p<0.001)*, pain catastrophizing *(Z= 6.90, p<0.001)* and stress *(Z= 7.64, p<0.001)* were significantly stronger than their correlations with the PSQ. There was no significant difference between the CSI and PSQ correlations for nociceptive sensory measures; PPT *(Z= -1.50, p= 0.066)*, HPT *(Z= 1.08, P= 0.141)* and TS *(Z= 0.19, P= 0.425)*. CPM showed weak/no correlations with both the CSI *(r=0.10, 95% CI [0.01-0.19])* and PSQ *(r=-0.04, 95% CI [-0.15 to 0.07]).*

Moderator analyses

For meta-analyses where high heterogeneity was found [43] (i.e. I^2 was above 50%) a moderator analysis was performed to assess whether correlations were influenced by the varied populations in each study. A weight-least squares regression was carried out to assess if the correlations were influenced by age, sex, type of assessment used (e.g., different variations of depression questionnaires), whether the data were published or retrieved by email and type of population (chronic pain patients or healthy participants). A weighted least-squares regression analysis was used because this method tends to be the most accurate method for identifying moderator variables [124]. The correlation between sleep and CSI (our highest score of heterogeneity at 92.8%) was moderated by Sex (F=26.22, B=0.964, p=0.036) and publication/retrieval of data *(F=27.62, p=0.034)*. The retrieved data (weighted mean = 0.24, SD = 0.04) had a substantially lower mean compared to the published data (weighted mean = 0.47, SD = 0.02). Correlations between CSI and Anxiety *(F=5.59, p=0.032)* and Depression (F= 4.45, p=0.053) were moderated by type of population (chronic pain or healthy participants). The correlation between the PSQ and pressure pain threshold *(F=4.94, p=0.053)* was also moderated by type of population. The PSQ's correlation with CPM was moderated by Age *(F= 65.87, B=-0.985, p=0.015)*. CPM, TS and tonic cold correlations with the PSQ may have also been subject to high heterogeneity [43] due to the small number of studies incorporated in the

meta-analysis[44]. The heterogeneity for CSI with stress, sleep and kinesiophobia may also be inflated due to the small number of studies being included for meta-analysis [44].

Healthy Controls vs Pain Patients

There was insufficient data to run meta-analyses to compare healthy controls against chronic pain patients for the CSI. Only 2 studies involving healthy participants correlated CSI with psychological constructs, and anxiety was the only measure taken by both studies [83,96] *(r=0.43, p<0.01 and r= 0.14*, p=0.50 respectively), with the latter study having a small sample size (n=26). The two lowest correlations for anxiety across all studies were for these two with healthy populations. Similarly, Midenfjored et al (2021) reported a correlation for CSI with Depression *(r=0.32, p<0.01)* which is considerably lower than the meta-analytic average *(r=0.58, 95% CI [0.54-0.62])* [83]. This suggests that correlations for the CSI with psychological questionnaires may be stronger in pain patients compared to healthy participants although due to the low number of studies along with their small sample sizes this is inconclusive. More studies involving healthy participants are required to confirm this finding. The small sample sizes for healthy controls reporting lower correlations could help account for some of the high heterogeneity in our findings [44].

Only 3 studies [96,98,119] correlated the CSI with nociceptive sensory correlates for healthy participants. Of these, PPT was the only sensory measure recorded in more than one study *(r=-0.33, p=0.09; and r=-0.06, p=0.60,* respectively) [96,98], with both of these studies having a small sample size *(n=28 and n=31,* respectively). There was insufficient data to make any clear conclusions about whether healthy participants and pain populations differed in their correlations for CSI and nociceptive sensory measures (QST).

There was sufficient data to run meta-analyses comparing chronic pain patients versus healthy participants for the PSQ's correlations with several of our primary outcomes. The meta-analyses for these comparisons can be seen in Table 2.

Overall, correlations between the PSQ and psychological and sensory measures were stronger for chronic pain patients compared to healthy participants, though not always significantly so. The only measure where the healthy participants showed a stronger correlation was TS, however, these correlations were not significantly different *(Z = -0.36, p= 0.360)*. Pain catastrophizing *(Z= 2.72, p= 0.003)* and PPT *(Z= -1.81, p= 0.035)* showed significantly stronger correlations for chronic pain patients than healthy controls. Depression *(Z= 1.51, P= 0.065)*, Anxiety *(Z= 0.40, p= 0.346)*, HPT *(Z= -1.28, p= 0.100)* and CPM *(Z= -0.42, p= 0.338)* did not show significantly different correlations between chronic pain and healthy subject populations.

In regards to heterogeneity, with the exception of TS which only had 2 studies that assessed healthy controls and was therefore vulnerable to high heterogeneity due to a small number of studies being used in the meta-analyses [44], heterogeneity was below the suggested benchmark for substantial heterogeneity in healthy controls (I^2=50%) [43]. The overall higher heterogeneity found in the chronic pain group suggests that type of pain may be an important factor that moderates our correlations. To conclude, high heterogeneity in some of our findings appears to be down to different target populations being used across studies with characteristics such as age, sex and type of pain having a moderating influence on correlations.

Discussion

We found that the CSI was strongly correlated with psychological measures (anxiety, depression, pain catastrophising, stress, sleep, and kinesiophobia). In contrast, it was not or only weakly correlated with QST measures; Pain thresholds, TS and CPM were all found to be low in their correlation to the CSI (all r's<0.3). Only the extent of widespread pain as a sensory measure reached a moderate correlation with the CSI, which differs in methodology from the other 'sensory' measures as it does not involve experimental lab testing of nociception. Compared to the CSI, the PSQ showed significantly lower correlation coefficients with psychological constructs. For their correlations with sensory measures (QST), there was no significant difference between the two

questionnaires. The PSQ was however associated with measures of pain where participants were asked to rate a set painful stimulus; phasic heat, tonic cold and pinprick stimulation. Therefore, there is evidence to suggest that PSQ does measure what it was designed for i.e., sensitivity to pain. But there is little evidence from QST correlations to suggest either questionnaire is a useful tool for identifying enhanced nociceptive sensitivity or altered pain modulation. These findings concur with a previous small empirical report [23].

There is a lack of data that assesses the association between the CSI and human surrogate models of CS (measures specifically designed in an attempt to quantify the 'increased responsiveness of nociceptive neurons in the central nervous system to either normal or subthreshold afferent input,' [47]). Quesada et al. (2021) provided a review and practical guide of different models of CS in humans finding that there were more than a dozen methods used to induce hyperalgesia and allodynia (characteristics of CS), including intradermal or topical capsaicin, low or high-frequency electrical stimulation and thermode induced heat injury. Duration and area of hypersensitivity were subsequently measured to examine the presence of CS [100]. We found none of these measures of CS to be assessed alongside the CSI or PSQ in this review. More studies should be conducted to directly examine correlations between the CSI and these measures of CS. While we acknowledge that QST measures are not direct measures of CS, for this review they were the best measures available for identifying pain facilitatory mechanisms of a pro-nociceptive phenotype that are associated with chronic pain [141], which might suggest the presence of CS [137]. Several studies, for instance, use QST measures to indicate central sensitization [5,121,127,135]. As a result, this review is limited to QST measures (TS, CPM and pain thresholds) as the primary form of physical assessment for CS. QST is a largely standardised method used to evaluate sensory profiles in response to stimuli, assessing the functional integrity of small and large nerve fibre afferents and central somatosensory pathways [25,53,131]. One of these measures that is particularly considered an indication of CS is TS [5,123]. TS assesses the windup that occurs from repetitive stimulation of peripheral c-fibres and is thought to reflect summation mechanisms of dorsal horn neurons [69,123].

We would therefore expect self-report assessments related to CS (such as CSI) to be strongly correlated with TS. However, this review has revealed that the CSI and TS show only a very weak correlation *(r=0.09)* which is likely to be of low clinical relevance. The PSQ shows a similarly weak correlation with TS *(r=-0.08)*. Low correlations between CPM and the two questionnaires were found. CPM is said to quantify the efficiency of endogenous inhibition of pain based on the concept of 'pain inhibits pain' derived from diffuse noxious inhibitory control in animal studies [27,66,93]. There is no evidence to suggest either of these questionnaires could be used to help identify underlying mechanisms of pain facilitation or inhibition in humans.

The CSI is a self-report questionnaire designed to identify patients who might have a central sensitivity syndrome (CSS), for which central sensitization is thought to be an aetiological cause, such as fibromyalgia, temporomandibular disorder or migraine/tension headaches [88,89]. The CSI consists of two parts. Part A includes 25 questions related to common CSS symptoms such as fatigue, depression, poor sleep, lack of concentration and general sensitivity. Part B determines if the patient has been diagnosed with certain CSS disorders or related disorders, such as chronic fatigue syndrome, migraines, fibromyalgia etc [74]. A 2015 study by Neblett et al found the CSI accurately aligned with a CSS diagnosis in 82.8% of participants whereas 54.8% of participants were correctly identified as not having a CSS diagnosis [89]. It appears that the CSI can be useful in diagnosing CSS, but the diagnosis of CSS is not scientifically precise itself, particularly with respect to its relationship to central sensitization. Neblett et al (2015) stated that a diagnosis of CSS relied on tender point evaluations being conducted on people suspected of having fibromyalgia and trigger point evaluations for patients suspected of having myofascial pain syndrome [89]. There are therefore some assumptions made about the presence of CS in these cases to begin with, with tender and trigger point evaluations being used to confirm the presence of CS– these measures would not be sufficient to accurately identify an 'increased responsivity of nociceptive neurons'. The CSI asks if the patient has been diagnosed with certain CSS disorders and/or shows associated symptoms, thus, intercorrelation between the two would be expected to be high. Although the CSI aligns with

diagnosis of CSS, questions remain about whether either diagnostic accurately identifies 'an increased responsiveness of nociceptive neurons' [47].

The CSI has strong correlations with other validated self-report measures of psychological constructs (e.g., anxiety, depression, stress etc.), which has previously been given as evidence for convergent validity [88]. A recent review, however, recommends that data using the CSI should be interpreted with caution as so far there is no scientific evidence to suggest that the CSI is a valid indicator of CS [115]. No self-report questionnaire can identify the physiological mechanism of CS. It appears that there has been expansion of the term "central sensitization" from its initial use in pre-clinical studies to the term used in this inventory. It may be that CS and emotional sensitivity are closely linked [26,30], but as this systematic review demonstrates, the CSI loads almost exclusively on emotional sensitivity rather than on measures of nociceptive response. It appears that a form of construct drift regarding the definition of CS has occurred across disciplines where patients in clinics have been assumed to be suffering from CS based on their psychological difficulties that occur alongside pain. One practical reason for this drift is that it allows a clinician to finally diagnose a 'medically unexplained' condition in a patient in a way that suggests a known physiological mechanism. From the patient's perspective, this is comforting and may legitimizes their pain. This review raises questions, however, about the degree to which such a diagnosis actually indicates a known physiological mechanism

Due to the large scope of the study, one limitation is that only single extraction was carried out, with extracted correlations being checked by a second author. One interesting observation and another possible limitation is the lack of data that assesses the CSI with electrical and thermal stimuli. Similarly, few studies explore the relationship between CSI and psychological or nociceptive sensitivity in healthy participants. This suggests that the questionnaire is largely used in clinical populations with only certain mechanical instruments available to assess CS. More research is required in laboratory settings that can further assess the association between the CSI and CS. This

systematic review was largely restricted to QST, with no studies found assessing the CSI/PSQ against measured areas of allodynia/hyperalgesia. Future research should include the CSI with human surrogate models of CS using thermal, electrical and capsaicin models that induce measurable areas of hyperalgesia/allodynia [100], and the assessment of both healthy participants and pain patients. There is clearly a need for more data to assess the relevance of the CSI related to CS and on what basis of research the questionnaire was formulated. If the CSI was a good tool for identifying CS, we would expect high scores on the CSI to be reflected in neuropathic pain patients who have clinical signs of CS. Strikingly, however, we found that neuropathic pain patients are typically excluded from studies incorporating the CSI.

To conclude, there is not strong evidence in the literature to suggest that self-report instruments currently available (the CSI or PSQ) reflect CS. The CSI appears to identify people with a psychological vulnerability that is associated with pain, rather than CS itself. It may be valuable in identifying a hypervigilant state that is common in many chronic pain patients. However, on its own, we question its utility as a tool for identifying CS as defined by an increased responsiveness of nociceptive neurons [64]. More research is required to develop an optimal method for identifying CS in humans, with these models being used to assess the construct validity of the CSI as an accurate indicator of CS. The PSQ does appear to correlate with experimental measures of pain sensitivity, not QST, albeit these measures are conducted by one particular lab group [106–108]. More studies assessing the validity of the PSQ with experimental measures of nociception should be conducted by different lab groups. Overall, there is no evidence to suggest either self-report questionnaire is suitable for assessing CS in humans or identifying a pro-nociceptive phenotype, based on QST measures.

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Figure Legend

Figure 1

Flowchart to show the process of inclusion eligibility for Meta-analyses

Figure 2

Bias Assessment (Quality Assessment)

Figure 3

Bias Assessment (Participation Bias)

Figure 4

Forrest Plots to Show Meta-analytic Correlations for the CSI/PSQ with Outcome Measures

Table 1

Meta-analyses for CSI and PSQ with Psychological and Sensory Measures.

Outcome Measures	Studies	N of Populations	Total N of Participants	Weighted mean correlation [95% CI]	Heterogeneity	Strength of Correlation
	All Participants – CSI					
Depression	[4,19,23,41,48,50,73,83–85,90–92,117,118]	15	4,248	0.58 [0.54-0.62]	χ^2 = 52.66, df = 14 (P <0.001); I^2 = 61.3%	Strong
Anxiety	[4,19–21,23,41,50,73,83,84,90–92,96,117,118]	16	3,295	0.60 [0.56-0.63]	χ^2 = 58.35, df = 15 (P < 0.001); I^2 = 72%	Strong
Pain Catastrophizing	[4,12,18,28,37,48,54,56,58,84,92,96,116–118,134,136]	17	3,812	0.48 [0.43-0.54]	χ^2 = 82.56, df = 16 (P < 0.001); I^2 = 82.6%	Moderate-Strong
Stress	[4,23,41,132,138]	5	1,889	0.62 [0.56-0.69]	χ^2 = 27.79, df = 4 (P < 0.001); I^2 = 80.2%	Strong
Sleep	[4,54,90,91]	4	2,649	0.40 [0.29-0.51]	χ^2 = 44.57, df = 3 (P < 0.001); I^2 = 92.8%	Moderate
Kinesiophobia	[4,85,118,132,134]	5	1,865	0.46 [0.40-0.53]	χ^2 = 16.08, df = 4 (P = 0.003); I^2 = 80%	Moderate-Strong
Pressure Pain Threshold	[23,28,35,37,41,58,82,86,96,98,138]	14	1,272	-0.22 (-0.28 to -0.17)	χ^2 = 17.37, df = 13 (P = 0.183); I^2 = 24.2%	Weak
Heat Pain Threshold	[23,96]	3	132	-0.01 (-0.12 to 0.09)	χ^2 = 1.16, df = 2 (P = 0.558); I^2 = 0%	No Effect
Conditioned Pain Modulation	[37,58,86,98,138]	6	679	0.10 [0.01-0.19]	χ^2 = 9.09, df = 5 (P = 0.106); I^2 = 45.5%	Weak

Temporal Summation	[37,41,82,86, 96]	7	600	0.09 [0.01 – 0.16]	χ^2 = 6.07, df = 6 (P = 0.415); I^2 = 0%	None-Weak (negligible)
Widespread Pain	[37,82,96,13 6]	6	455	0.39 [0.23-0.50]	χ^2 = 10.53, df = 5 (P = 0.061); I^2 = 54.9%	Moderate
	All Participants– PSQ					
Depression	[23,33,38,42, 46,57,61,61, 78,99,103,10 6,107,112]	17	2,985	0.11 [0.08-0.15]	χ^2 = 16.71, df = 17 (P = 0.474); I^2 = 0%	Weak
Anxiety	[23,33,38,42, 45,49,60,61, 78,99,103,10 6,107,142,14 5]	18	2,859	0.16 [0.14-0.19]	χ^2 = 9.65, df = 17 (P = 0.918); I^2 = 0%	Weak
Pain Catastrophisi ng	[7,9,33,45,46 ,52,60,61,78, 99,107,112,1 42]	15	1,980	0.32 [0.25-0.40]	χ^2 = 48.97, df = 14 (P < 0.001); I^2 = 82.6%	Moderate
Stress	[17,23,60]	3	261	0.23 [0.15-0.30]	χ^2 = 1.39, df = 2 (P = 0.49); I^2 = 0%	Weak
Pressure Pain Threshold	[23,33,38,42, 60,106,108,1 09,129]	10	2,464	-0.17 [-0.22 to -0.12]	χ^2 = 13.94, df = 9 (P = 0.124); I^2 = 35.6%	Weak
Heat Pain Threshold	[23,33,38,60, 106,108,128]	9	1,078	-0.11 [-0.25 to 0.02]	χ^2 = 46.77, df = 8 (P < 0.001); I^2 = 84.8%	Weak
Conditioned Pain Modulation	[60,61,103]	4	508	-0.04 [-0.15 to 0.07]	χ^2 = 7.00, df = 3 (P = 0.072); I^2 = 57.2%	No Effect
Temporal Summation	[33,60,61]	4	865	0.08 [-.00 to 0.17]	χ^2 = 6.36, df = 3 (P = 0.095); I^2 = 53.6%	None-Weak (negligible)
Phasic Heat	[106–108]	3	158	0.64 [0.54 to 0.73]	χ^2 = 3.03, df = 2 (P = 0.219); I^2 = 31.9%	Strong
Tonic Cold	[106–108]	3	158	0.64 [0.51 to 0.77]	χ^2 = 6.1, df = 2 (P = 0.047); I^2 = 63%	Strong
Pin Prick Stimulation	[106–108]	3	158	0.39 [0.38 to 0.40]	χ^2 = 0.02, df = 2 (P = 0.991); I^2 = 0%	Moderate

Table 2:

Comparison of Healthy controls and Chronic pain patients (PSQ)

Outcome Measures	Population	Studies	N of Populations	Total N of participants	Weighted mean correlation [95% CI]	Heterogeneity	Strength of Correlation
Depression	Chronic pain population	[23,33,38,46,61,61,103,106]	8	1,076	0.12 [0.06-0.18]	χ^2 = 8.21, df = 7 (P = 0.314); I^2 = 14%	Weak
	Healthy Participants	[33,38,46,61,78,99,107,112]	8	809	0.05 [-0.02 to 0.13]	χ^2 = 10.15, df = 7 (P = 0.180); I^2 = 31.8%	No-effect
Anxiety	Chronic pain population	[23,33,39,61,61,103,106]	7	940	0.15 [0.10 – 0.19]	χ^2 = 4.31, df = 6 (P = 0.634); I^2 = 0%	Weak
	Healthy Participants	[33,38,45,61,78,99,107,142]	8	633	0.13 [0.06 – 0.19]	χ^2 = 5.48, df = 7 (P = 0.601); I^2 = 0%	Weak
Pain Catastrophizing	Chronic pain population	[7,33,52,60,61]	7	929	0.36 [0.23 – 0.49]	χ^2 = 37.35, df = 6 (P < 0.001); I^2 = 90.7%	Moderate
	Healthy Participants	[9,33,45,46,61,78,99,107,112,142]	10	1097	0.25 [0.19 – 0.31]	χ^2 = 11.57, df = 9 (P = 0.239); I^2 = 27.4%	Weak-Moderate
PPT	Chronic pain population	[23,33,38,60,106,108]	6	688	-0.18 [-0.26 to -0.09]	χ^2 = 8.53, df = 5 (P = 0.129); I^2 = 42%	Weak
	Healthy Participants	[33,38,129]	3	429	-0.07 [-0.10 to -0.03]	χ^2 = 0.44, df = 2 (P = 0.803); I^2 = 0%	None-Weak (negligible)
HPT	Chronic pain population	[23,33,38,61,106,108]	6	688	-0.17 [-0.34 to 0.00]	χ^2 = 33.55, df = 5 (P<0.001); I^2 = 86.7%	Weak
	Healthy Participants	[33,38,78,128]	4	279	-0.08 [-0.22 to 0.05]	χ^2 = 5.41, df = 3 (P = 0.144); I^2 = 44.8%	None-Weak (Negligible)

CPM	Chronic pain population	[60,61,103]	3	428	-0.04 [-0.22 to 0.04]	χ^2 = 7.01, df = 2 (P=0.03); I^2 = 71.5%	No Effect
	Healthy Participants	[61]	1	80	r= -0.04		No-Effect
TS	Chronic pain population	[33,60,61]	3	562	0.07 [0.02 to 0.14]	χ^2 = 1.71, df = 2 (P = 0.42); I^2 = 0%	None-Weak (Negligible)
	Healthy Participants	[33,61]	2	192	0.10 [-0.13 to 0.33]	χ^2 = 5.29, df = 1 (P = 0.022); I^2 = 81.3%	Weak