KJP

Korean J Pain 2025;38(1):29-42
https://doi.org/10.3344/kjp.24290
pISSN 2005-9159, eISSN 2093-0569

Check for updates

Experimental Research Article

# The impact of central sensitization-related symptoms on subacromial steroid injection outcomes in patients with subacromial impingement syndrome: an observational study

**Feyza Nur Yücel[1], Semiha Özgüç[1], Yeliz Bahar-Özdemir[2], and Emre Ata[1]**

[1]Department of Physical Medicine and Rehabilitation, Health Science University, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkiye
[2]Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine, Istanbul, Turkiye

ABSTRACT

**Background:** Evidence indicates that central sensitization (CS) plays a role in subacromial impingement syndrome (SIS). Reduced treatment response has been associated with pretreatment pain sensitization features, such as CS-related symptoms.
**Methods:** Patients who received subacromial steroid injection were evaluated before the injection, at the first and third months. CS-related symptoms were investigated through the central sensitization inventory (CSI), and pain hypersensitivity was investigated by pressure pain threshold (PPT). Patients were evaluated using the visual analog scale (VAS), Quick Disabilities of the Arm, Shoulder, and Hand, Hospital Anxiety and Depression Scale, and Short Form-36.
**Results:** With the injection, all participants had a significant reduction in shoulder pain ($P < 0.05$). In all follow-ups, VAS values did not differ significantly between the groups, and patients with CSI ≥ 40 had higher levels of disability, anxiety, depression, and worse quality of life before treatment ($P < 0.05$). Post-injection disability decreased significantly in the CS group and reached similar levels in both groups at the third month ($P > 0.05$). Although both groups' PPT values were comparable pre-treatment and at the third month, the CS group's affected shoulder showed a notable PPT decline at the first month ($P < 0.05$).
**Conclusions:** Pre-treatment CS-related symptoms had no effect on SIS patients' responsiveness to steroid injections.

**Keywords:** Central Nervous System Sensitization; Chronic Pain; Pain Threshold; Rotator Cuff; Shoulder Pain; Shoulder Impingement Syndrome.

Received August 30, 2024; Revised November 20, 2024; Accepted November 22, 2024

Handling Editor: Ki Tae Jung

Correspondence: Feyza Nur Yücel
Department of Physical Medicine and Rehabilitation, Health Science University, Sultan Abdulhamid Han Training and Research Hospital, Selimiye, Tıbbiye Cad, Uskudar, Istanbul 34668, Turkiye
Tel: +902165422000, Fax: +902164717408, E-mail: dr.fny28@gmail.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © The Korean Pain Society

## INTRODUCTION

Shoulder impingement syndrome (SIS) is the primary cause of shoulder pain and, if overlooked, can result in chronic pain and disability [1]. A variety of pathologies, from subacromial bursitis to full-thickness rotator cuff tears (RCTs), are included in the SIS spectrum [2]. There are many treatment options for SIS, and subacromial steroid injection is frequently preferred due to its effectiveness and ease of application [3]. Many variables influence the treatment response and pain relief in SIS patients, and almost half of them still report pain one year later [4]. Studies based on this clinical problem draw attention to the role of central sensitization (CS) in unilateral persistent shoulder pain, including SIS [5].

The central nervous system's enhanced nociceptive neuronal response to subthreshold or normal afferent inputs is defined as CS. CS impairs pain modulation systems; it also activates pain-facilitating pathways, which results in the patient experiencing prolonged and intense pain [6]. Consequently, compared to those without pain sensitization, patients with CS exhibit worsening in an array of clinical parameters, including treatment response. It has been reported that in patients undergoing cervical epidural steroid injection for cervical disc herniation, the presence of pretreatment CS negatively affects pain scores, disability, and quality of life [7]. Similarly, preoperative sensitization findings in patients undergoing shoulder arthroplasty have been reported to be associated with one-year disability [8].

As of yet, there is no method to detect CS in humans directly. Even though it's not the gold standard, revealing the sensitization findings in a patient's somatosensory profile with quantitative sensory testing (QST) offers important insights into the diagnosis of CS [6]. Pressure pain threshold (PPT) is one of the most commonly used QST elements and provides useful information on pain sensitization in clinical research. However, the lack of standardized protocols for certain locations limits the generalizability of PPT results [9]. Alternatively, by quantifying the severity of symptoms associated with CS, CSI offers information about different aspects of pain sensitization. CSI, which enables classification according to CS-related symptoms, is also associated with treatment response in several patient groups, such as PPT [7,10]. CSI also correlates with functional and psychological parameters such as disability, which are also associated with treatment outcomes [11]. Due to these features, it is argued that CSI can be used as a screening tool and treatment outcome measure in patients with chronic spinal pain [12].

Because surgical therapies are advised in more severe and chronic cases of SIS, studies on this topic do not include milder cases [13]. Clinicians should be aware of how CS affects patients undergoing injections because, in these cases, a conservative approach is more commonly preferred than surgery. To the authors' knowledge, there is no study investigating the response of pre-treatment pain sensitization to injection therapy in this patient group. Additionally, the majority of existing studies report data on this relationship only as present or absent and usually do not report what changes occur after treatment. Based on these gaps regarding CS in shoulder pain, this study aimed to examine the impact of pre-treatment CS-related symptoms in SIS on the response to subacromial steroid injection. The second objective was to investigate the association between these symptoms and PPT measurements longitudinally.

## MATERIALS AND METHODS

### 1. Design and study population

This is a prospective and observational study. The authors evaluated patients with SIS who received US-guided subacromial corticosteroid injection between May 2023 and January 2024, taking into account inclusion and exclusion criteria. To avoid bias, patients on centrally acting pain drugs (such as myorelaxants, opioids, duloxetine, or pregabalin) were not included in the study. The data collection process was completed without any dropout, and 44 patients who satisfied the criteria were followed prospectively (**Fig. 1**). The patients were assessed three times in total: before the injection, and at 1 and 3 months. The same practitioner evaluated and documented the patients at each visit, including pain intensity (visual analog scale, VAS) for the affected shoulder, bilateral goniometric shoulder active range of motion (AROM) and PPT measurements, and all questionnaires.

With the approval of the local ethics committee (protocol number: 23-20, approval date: 3.16.23), all participants provided verbal and written consent for the study. This study protocol was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT06404125) and performed following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

### 2. Injection procedure

All injections were performed by an experienced practi-

 https://doi.org/10.3344/kjp.24290

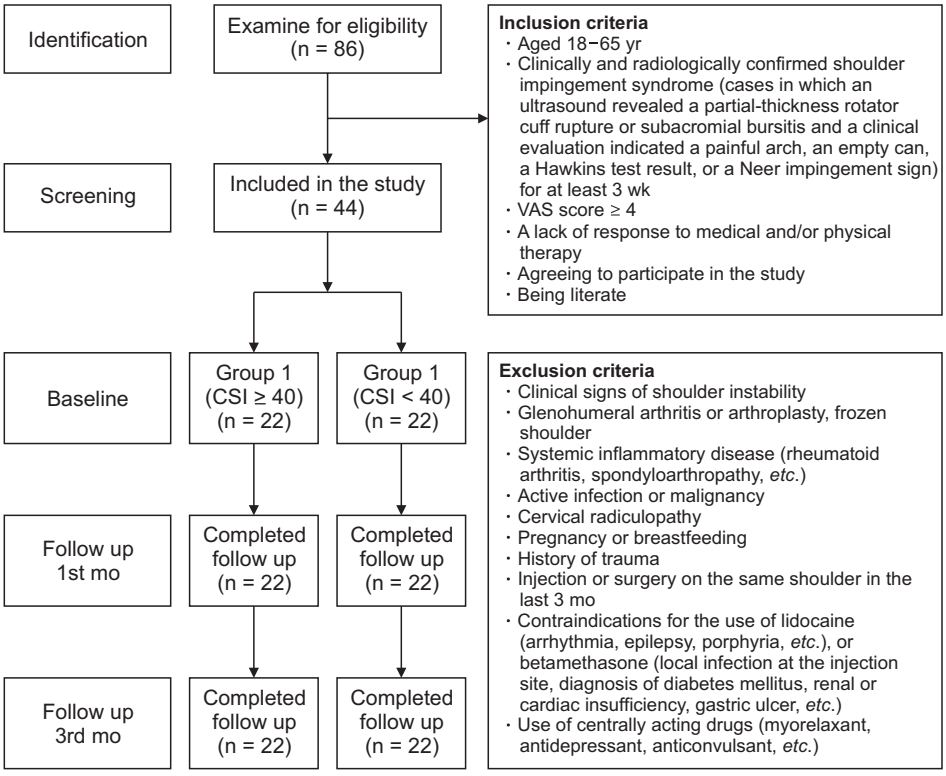



**Fig. 1.** STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram of participant flow through three months. CSI: central sensitization inventory, VAS: visual analog scale.

tioner (EA) under ultrasound guidance (Sonosite-M Turbo). With the patient in a sitting position, the palmar side of the hand was placed on the superior iliac crest, with the elbow in semi-flexion, and the subacromial space and rotator cuff were visualized with a linear probe. Targeting the area where the subacromial bursa is most prominent under the deltoid muscle, the entry site was cleaned with povidone-iodine and an 80% alcohol solution. With an in-plane approach, a 21 g 38 mm needle was advanced from lateral to medial, being careful to place the needle tip inside the bursa. After bleeding control, 1 mL betamethasone dipropionate + betamethasone sodium phosphate and 4 mL 2% prilocaine mixture were injected by visualizing their equal distribution in the bursa. In case there were complications, the patient was monitored for twenty minutes following the injection.

## 3. Clinical variables

Demographic variables including age, sex, body mass index (BMI), and clinical variables including painful side, duration, of pain and hand dominance were recorded.

## 4. Outcome measures

### 1) VAS

In epidemiological and clinical research, the VAS is one of the most commonly used pain rating instruments to assess the intensity of pain. The 10-centimeter VAS has anchor statements on the left (no pain) and right (severe pain). During the assessment, patients are asked to mark on the line how much pain they are experiencing. This number serves as a numerical representation of the patient's pain severity, and higher scores correspond to more intense pain [14].

### 2) Shoulder AROM measurement

A standard two-arm goniometer was used to assess the shoulder's AROM, which includes flexion (FL), extension (EX), abduction (AB), external rotation (ER), and internal rotation (IR).

### 3) PPT

With a Wagner manual pressure algometer (1 $cm^2$ probe, 10 kg/20 lb), bilateral PPT measures were taken on the shoulders and trapezius. Because a decrease in PPT re-

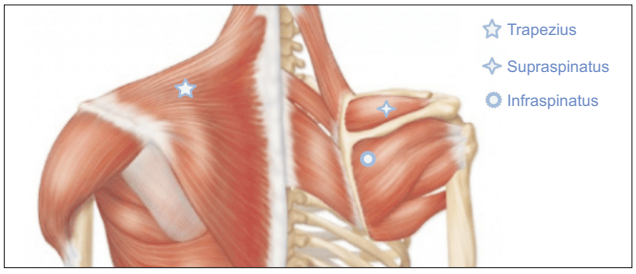



**Fig. 2.** Locations of pressure pain threshold measurement points around the shoulder.

lated to its involvement has been observed in individuals with shoulder pain, the trapezius muscle was additionally assessed [15]. The volar side of the unaffected forearm was selected for remote site PPT measurement.

PPT measurement sites [4,16] (**Fig. 2**):

1. Supraspinatus muscle: 1 cm cranial to the midpoint of the spina scapula
2. Infraspinatus muscle: medial edge of the scapula (intersection of the spina scapula, and the lower scapular angle)
3. Trapezius muscle: midpoint of the line connecting the acromion and the C7 spinous process
4. Unaffected forearm volar side midpoint

To ensure that patients understood the test, a demonstration was done on the left forearm volar side prior to the procedure starting. The 1 $cm^2$ algometer probe was placed vertically at each selected point, and the pressure was increased by 0.1 kg/sec until the participant reported pain. The pressure terminated when the patient reported of pain, and this value was noted as PPT. The PPT value for each measurement site was calculated as the average of two applications 30 seconds apart. All measurements were taken with the patient in a sitting position. Lower PPT values in the region of the pain indicate peripheral sensitization, whereas low PPT values at the remote site indicate CS [17]. PPT was not regarded as the main criteria in the patient classification according to pain sensitization in this study since the measurements in patients with subacromial impingement could not be standardized.

## 4) Questionnaires

### (1) Central sensitization inventory (CSI)

The CSI was used to assess symptoms related to CS. CSI consists of two parts, Part A and B. Part A consists of 25 items scored on a scale from 0 to 100, with higher scores being associated with an increase in CS-related symptom burden. In Part B, diagnoses of central sensitivity syndromes are questioned, and this part is not included in the scoring. According to the severity of CS-related symptoms, patients were classified into two groups: those with and those without clinical central sensitization syndrome (CSS), using a cut-off value of 40, which is suggested by the authors who developed the CSI [18]. Patients with a CSI score of 40 or higher were accepted as CSS based on previous studies because there is no established cut-off value for shoulder patients [19,20]. The CSI has been demonstrated to be a reliable and valid tool in the Turkish population with chronic pain (test-retest reliability = 0.92, Cronbach's alpha = 0.93) [21].

### (2) Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH)

Shoulder pain-related disability was investigated using QuickDASH, a shortened 11-item version of the 30-item DASH outcome measure. To calculate a score, a minimum of 10 out of the 11 items need to be completed. The scores vary from 0 (no disability) to 100 (the most severe disability). The Turkish version of this scale has been reported to be valid and reliable (Cronbach's alpha: 0.84) [22].

### (3) Hospital Anxiety and Depression Scale (HADS)

The 14-item HADS is a tool designed to assess anxiety and depressive symptoms in individuals with physical illness. HADS consists of two subgroups of 7 questions, each ranging from 0 to 21 points: anxiety (HADS-A) and depression (HADS-D) [23]. A score of more than 10 for anxiety and more than 7 for depression is considered significant, and the scale's validity and reliability in Turkish have been established (Cronbach's alpha: 0.90–0.77) [24].

### (4) Short Form 36 (SF-36)

The SF-36 is a self-reported outcome measure assessing the impact of health on an individual's quality of life. There are 36 questions on this scale covering eight different areas of health. These domains are divided into two primary categories: mental and physical health. The SF-36v2 scoring software is frequently used to calculate the SF-36. The subscores range from 0 to 100, with higher scores being associated with better health status [25]. This study will solely report on the general health domain. The Turkish adaptation of the SF-36 has been established as


https://doi.org/10.3344/kjp.24290

**Table 1.** Patients' variables according to CSS

| Variable | Total (n = 44) | CSS | | *P* value |
|---|---|---|---|---|
| | | Yes (n = 22) | No (n = 22) | |
| Age (yr) | 52.5 (31–65) | 50 (31–64) | 58.5 (32–65) | 0.930 |
| BMI (kg/m$^2$) | 28.12 (20–38) | 28.65 (21–35) | 27.16 (20–38) | 0.496 |
| Symptom duration (wk) | 17 (1–324) | 24 (4–270) | 16 (1–324) | 0.311 |
| Sex (female/male) | 27/17 | 14/8 | 13/9 | > 0.999 |
| Marital status (married/single) | 36/8 | 18/4 | 18/4 | > 0.999 |
| Dominant extremity (R/L) | 43/1 | 21/1 | 22/0 | > 0.999 |
| Affected side (R/L) | 24/20 | 11/11 | 13/9 | 0.763 |
| VAS baseline | 7 (4–10) | 7 (4–10) | 6.5 (4–10) | 0.981 |
| CSI | 38.73 (15.88)[a] | 47.5 (40–70) | 25 (2–39) | < 0.001 |
| CSI severity levels (subclinic-mild-moderate/severe/extreme) | 15/19/10 | 0/12/10 | 15/7/0 | < 0.001 |

Values are presented as number, median (min–max), or mean (standard deviation)[a].
CSS: central sensitization syndrome, BMI: body mass index, R/L: right/left, VAS: visual analog scale, CSI: central sensitization inventory.

valid and reliable (Cronbach's alpha: 0.80–0.88) [26].

### 5. Data analysis

In order to achieve an error alpha of 0.05 and a power of 0.95 for a 95% confidence interval (CI), a minimum sample size of 14 patients per group was determined to be 19 with a 25% loss and 38 patients overall with G-power (v3.1.9.4; University of Dusseldorf) [27].

Using histogram plots, skewness, kurtosis, and Kolmogorov–Smirnov, the normality of the data was examined. In descriptive statistics, patient variables were summarized as median (interquartile range, IQR) and min-max values due to a non-parametric distribution.

In cross-sectional analysis, the Mann–Whitney *U*-test was used for continuous variables (age, BMI, pain duration, AROM, VAS, questionnaires, and PPT measurements) for comparison between groups before and after the injection according to CSI. To compare the qualitative data the Pearson's chi-squared test was used. For intragroup analysis, the Friedman test was used for temporal change within groups and the Wilcoxon signed-rank test was performed with a Bonferroni correction for *post-hoc* comparisons.

The linear relationship between CSI and VAS, HADS, QuickDASH, SF-36, and PPT measurements at pre-treatment and 1st and 3rd month post-treatment assessments was examined with Pearson and Spearman correlations according to the distribution pattern of the variables. $P < 0.05$ is considered statistically significant with a 95% CI using SPSS, version 26.0 (IBM Corporation).

## RESULTS

### 1. Participant characteristics

Of the 44 participants, 27 (61.4%) were female and 17 (36.8%) were male, and the median (IQR) age was 52.5 (17.5). Patients with a CSI score of ≥ 40/100 were considered to have CSS, and twenty-two of the participants had CSS. Patient characteristics are summarized in **Table 1**, and no significant difference was observed in terms of sociodemographic data ($P > 0.05$). Regarding shoulder pathologies, both groups showed comparable results; however, individuals without CSS had a higher rate of supraspinatus tendinitis ($P = 0.015$), and patients with CSS had a higher rate of partial rupture ($P = 0.033$) (**Table 2**).

### 2. Assessment of clinical scales

As seen in **Table 3**, where the treatment results are examined, the VAS scale decreased significantly in both groups, and no significant difference was detected between the groups. While no significant difference was observed between the groups after treatment in the follow-up of anxiety and depression, anxiety was high between groups at all times, and depression was significantly higher in Group 1 (CSS+) at baseline and in the 1st month after treatment (HAD-Anxiety *P* values: T0 < 0.001, T1 = 0.008, T2 = 0.006, and HAD-Depression *P* values: T0 = 0.019, T1 = 0.004).

After treatment, Group 1 showed a decrease in their QuickDASH score ($P = 0.003$), whereas Group 2 showed

**Table 2.** Patients' ultrasound findings according to CSS

| Ultrasound finding | Total (n = 44) | CSS | | *P* value |
|---|---|---|---|---|
| | | Yes (n = 22) | No (n = 22) | |
| Subacromial bursitis | 36 | 18 | 18 | > 0.999 |
| Bicipital tenosynovitis | 18 | 9 | 9 | > 0.999 |
| Suprapinatus tendinitis | 11 | 2 | 9 | 0.015 |
| Supraspinatus rupture-partial | 25 | 16 | 9 | 0.033 |
| Glenohumoral effusion | 2 | 1 | 1 | > 0.999 |

CSS: central sensitization syndrome.

no discernible change. In comparison between groups, baseline and 1st month disability scores were found to be higher in Group 1 compared to Group 2 ($P$ = 0.044 and 0.040, respectively).

## 3. Assessment of shoulder AROM

Participants' pre- and post-injection AROM measurements showed no significant difference between the groups in terms of CSS ($P$ > 0.05). Only in shoulder flexion was a significant increase seen in both groups' pre- and post-treatment measurements in the within-group longitudinal follow-up ($P$ for Group 1 = 0.032; Group 2 = 0.023). The median (IQR) flexion angle, which was 170.5 (25.2) for Group 1 before treatment, increased to 178.9 (3.8) at the 3rd month visit. In Group 2, the flexion angle was 164.6 (33.6) before treatment and was calculated as 180 (0) in the 3rd month. There was no significant difference between the assessments in the *post-hoc* analysis ($P$ > 0.05).

## 4. Assessment of PPT values

### 1) Affected side

When the intra-group change in PPT values of the supraspinatus muscle was examined, the decrease in Group 1 was found to be significant ($P$ = 0.031). *Post-hoc* analysis showed that the change was significant between 1-month and 3-months ($P$ = 0.005). In the intergroup evaluation, the PPT score in the first month was found to be significantly lower in Group 1.

In the trapezius muscle, a significant decrease in PPT value was observed after the treatment in Group 1 and an increase in Group 2 ($P$ = 0.028, $P$ = 0.014, respectively). When compared between groups, Group 1 values were significantly lower than Group 2 in the baseline and 1-month ($P$ = 0.019, 0.004, respectively).

A significant increase was detected in the infraspinatus muscle after treatment in Group 1 ($P$ = 0.029). In the *post-hoc* evaluation, it was observed that the increase was between the 1 and 3 months ($P$ = 0.011). In the intergroup evaluation, the 1-month PPT value was statistically significantly higher in Group 2 ($P$ = 0.025). A statistically significant increase in forearm PPT after treatment was observed in Group 2 ($P$ = 0.006). In the intergroup evaluation, the value of Group 2 was found to be significantly higher ($P$ = 0.030).

### 2) Unaffected side

While no significant difference was detected within and between the groups in the unaffected side supraspinatus muscle after treatment in Group 1, significant changes were detected in the PPT values in the trapezius and infraspinatus muscles ($P$ = 0.020, 0.006, respectively). According to *post-hoc* analysis, it was found that there was a significant increase in the PPT, between 1 and 3 months, in the infraspinatus muscle ($P$ = 0.006). Although a similar increase was observed in the trapezius muscle, it was not statistically significant in the *post-hoc* analysis ($P$ = 0.040) (**Table 4**).

## 5. Bivariate correlation analysis

The correlation coefficients calculated to assess the linear relationship between pre-treatment CSI and HAD-Anxiety (r = 0.586, $P$ < 0.001), HAD-Depression (r = 0.390, $P$ = 0.009), QuickDASH (r = 0.454, $P$ < 0.001), and SF-36 (r = –0.372, $P$ = 0.013) were statistically significant. But for this assessment, no significant relationship was detected between the VAS and PTT values and the CSI ($P$ > 0.05). At the 1st month evaluation, all variables examined, except the trapezius PPT value on the unaffected side, were found to be significantly correlated with the CSI ($P$ > 0.05). **Table 5** shows the correlation coefficients of the CSI and

 https://doi.org/10.3344/kjp.24290

**Table 3.** Comparison of patients' clinical characteristics according to CSS and *post-hoc* results

| Variable | CSS | | *P* value |
|---|---|---|---|
| | Yes (n = 22) | No (n = 22) | |
| VAS | | | |
| T0 | 7 (5–8) | 6.5 (5–8) | 0.981 |
| T1 | 2 (1.75–3.13) | 2 (1–3) | 0.347 |
| T2 | 2 (1–3) | 2 (1–3.6) | 0.912 |
| *P* value[a] | < 0.001 | < 0.001 | |
| T0-T1 | < 0.001 | < 0.001 | |
| T0-T2 | < 0.001 | < 0.001 | |
| T1-T2 | 0.372 | 0.398 | |
| HAD-Anxiety | | | |
| T0 | 11 (6.75–12.25) | 4 (1–7) | < 0.001 |
| T1 | 8 (6.5–11.5) | 3.5 (0.75–9) | 0.008 |
| T2 | 8 (6–10.25) | 4 (1–9) | 0.006 |
| *P* value[a] | 0.209 | 0.351 | |
| HAD-Depression | | | |
| T0 | 8 (4–12) | 4 (0.75–7) | 0.019 |
| T1 | 8 (5–10.25) | 4.5 (0–0.25) | 0.004 |
| T2 | 8 (5–9) | 5 (1.5–8.5) | 0.073 |
| *P* value[a] | 0.592 | 0.422 | |
| QuickDASH | | | |
| T0 | 59.09 (43.18–77.84) | 43.73 (34.09–60.23) | 0.044 |
| T1 | 50 (36.36–61.93) | 35.22 (12.5–55.66) | 0.040 |
| T2 | 38.63 (32.95–55.68) | 40.9 (20.45–46.59) | 0.263 |
| *P* value[a] | 0.003 | 0.345 | |
| T0-T1 | 0.001 | | |
| T0-T2 | 0.004 | | |
| T1-T2 | 0.145 | | |
| SF36-GH | | | |
| T0 | 40 (25–51.25) | 45 (35–70) | 0.059 |
| T1 | 42.5 (30–60) | 55 (43.75–66.25) | 0.037 |
| T2 | 47.5 (33.75–55) | 55 (45.5–70) | 0.087 |
| *P* value[a] | 0.118 | 0.844 | |
| CSI | | | |
| T0 | 47.5 (16.5) | 25 (12) | < 0.001 |
| T1 | 42 (19.5) | 24 (17.5) | < 0.001 |
| T2 | 37 (22) | 27 (16) | 0.005 |
| *P* value[a] | < 0.001 | 0.729 | |
| T0-T1 | 0.022 | | |
| T0-T2 | < 0.001 | | |
| T1-T2 | 0.013 | | |

Values are presented as median (min-max).
CSS: central sensitization syndrome, VAS: visual analog scale, HAD: hospital anxiety depression, QuickDASH: Quick Disability of Arm, Shoulder and Hand, SF36-GH: Short Form 36 general health, CSI: central sensitization inventory.
[a]Friedman test, *post-hoc* paired comparisons: Wilcoxon rank-sum test.

**Table 4.** Comparison of patients' PPT values according to CSS and *post-hoc* results

| PPT | CSS | | *P* value |
|---|---|---|---|
| | Yes (n = 22) | No (n = 22) | |
| Supraspinatus $PPT_{Affected\ side}$ | | | |
| T0 | 3.05 (2.4–3.43) | 3 (2.43–3.56) | 0.725 |
| T1 | 2.53 (2.05–3.09) | 3.13 (2.38–4.38) | 0.042 |
| T2 | 2.8 (2.6–3.31) | 3.1 (2.55–4.18) | 0.224 |
| *P* value[a] | 0.031 | 0.212 | |
| T0-T1 | 0.053 | | |
| T0-T2 | 0.778 | | |
| T1-T2 | 0.005 | | |
| Supraspinatus $PPT_{Unaffected\ side}$ | | | |
| T0 | 2.85 (2.3–3.56) | 2.80 (2.55–4.11) | 0.372 |
| T1 | 2.65 (2.15–3.2) | 3.15 (2.34–5.06) | 0.152 |
| T2 | 3.08 (2.7–3.4) | 2.95 (2.53–4.88) | 0.481 |
| *P* value[a] | 0.102 | 0.549 | |
| Trapezius $PPT_{Affected\ side}$ | | | |
| T0 | 2.35 (2.13–2.56) | 2.45 (2–2.94) | 0.557 |
| T1 | 2.18 (1.91–2.45) | 2.30 (2.2–3.69) | 0.028 |
| T2 | 2.33 (2.09–2.68) | 2.55 (2.2–3.1) | 0.111 |
| *P* value[a] | 0.028 | 0.014 | |
| T0-T1 | 0.186 | 0.057 | |
| T0-T2 | 0.283 | 0.033 | |
| T1-T2 | 0.076 | 0.311 | |
| Trapezius $PPT_{Unaffected\ side}$ | | | |
| T0 | 2.58 (1.99–2.85) | 2.85 (2.14–3.55) | 0.076 |
| T1 | 2.25 (2–2.65) | 2.50 (2.14–3.38) | 0.088 |
| T2 | 2.33 (2.1–2.95) | 2.55 (2.28–3.4) | 0.093 |
| *P* value[a] | 0.020 | 0.588 | |
| T0-T1 | 0.153 | | |
| T0-T2 | 0.823 | | |
| T1-T2 | 0.040 | | |
| Infraspinatus $PPT_{Affected\ side}$ | | | |
| T0 | 2.93 (2.15–3.28) | 2.78 (2.15–3.58) | 0.851 |
| T1 | 2.4 (2.19–3.16) | 2.85 (2.4–4.03) | 0.025 |
| T2 | 2.98 (2.68–3.23) | 3.2 (2.48–4.58) | 0.610 |
| *P* value[a] | 0.029 | 0.471 | |
| T0-T1 | 0.237 | | |
| T0-T2 | 0.066 | | |
| T1-T2 | 0.011 | | |
| Infraspinatus $PPT_{Unaffected\ side}$ | | | |
| T0 | 2.93 (2.35–3.34) | 2.90 (2.36–3.85) | 0.557 |
| T1 | 2.6 (2.24–3.13) | 2.78 (2.6–4.11) | 0.063 |
| T2 | 2.95 (2.63–3.33) | 3.2 (2.65–4.63) | 0.263 |
| *P* value[a] | 0.006 | 0.401 | |
| T0-T1 | 0.117 | | |
| T0-T2 | 0.661 | | |
| T1-T2 | 0.006 | | |

 https://doi.org/10.3344/kjp.24290

**Table 4.** Continued

| PPT | CSS | | *P* value |
|---|---|---|---|
| | Yes (n = 22) | No (n = 22) | |
| Forearm PPT | | | |
| T0 | 2.92 (2.35–3.56) | 2.95 (2.49–3.86) | 0.879 |
| T1 | 2.73 (2.09–3.21) | 3.2 (2.68–4.6) | 0.030 |
| T2 | 3.08 (2.69–3.43) | 3.4 (2.7–4.8) | 0.177 |
| *P* value[a] | 0.102 | 0.006 | |
| T0-T1 | | 0.051 | |
| T0-T2 | | 0.022 | |
| T1-T2 | | 0.578 | |

Values are presented as median (min-max).
CSI: central sensitization inventory, PPT: pressure pain threshold.
[a]Friedman test, *post-hoc* paired comparisons: Wilcoxon rank-sum test.

**Table 5.** Correlation analysis results of CSI, clinical scales, and PPT measurements pre-treatment and 1st and 3rd months after treatment

| Variable | | CSI | | |
|---|---|---|---|---|
| | | T0 | T1 | T2 |
| VAS | r | 0.109[a] | 0.316[a] | 0.332[a] |
| | *P* value | 0.483 | 0.039 | 0.030 |
| HAD-Anxiety | r | 0.586 | 0.518 | 0.583 |
| | *P* value | < 0.001 | < 0.001 | < 0.001 |
| HAD-Depression | r | 0.390[a] | 0.420 | 0.331 |
| | *P* value | 0.009 | 0.005 | 0.030 |
| QuickDASH | r | 0.454 | 0.595 | 0.576 |
| | *P* value | < 0.001 | < 0.001 | < 0.001 |
| SF36-GH | r | –0.372[a] | –0.519 | –0.690 |
| | *P* value | 0.013 | < 0.001 | < 0.001 |
| Supraspinatus $PPT_{Affected\ side}$ | r | –0.167 | –0.367 | –0.354[a] |
| | *P* value | 0.279 | 0.015 | 0.020 |
| Supraspinatus $PPT_{Unaffected\ side}$ | r | –0.272 | –0.498 | –0.328[a] |
| | *P* value | 0.074 | 0.001 | 0.032 |
| Trapezius $PPT_{Affected\ side}$ | r | –0.211 | –0.363 | –0.291[a] |
| | *P* value | 0.169 | 0.017 | 0.059 |
| Trapezius $PPT_{Unaffected\ side}$ | r | –0.293 | –0.181 | –0.066[a] |
| | *P* value | 0.053 | 0.245 | 0.676 |
| Infraspinatus $PPT_{Affected\ side}$ | r | –0.168 | –0.498 | –0.342[a] |
| | *P* value | 0.275 | 0.001 | 0.025 |
| Infraspinatus $PPT_{Unaffected\ side}$ | r | –0.266 | –0.396 | –0.341[a] |
| | *P* value | 0.081 | 0.009 | 0.025 |
| Forearm PPT | r | –0.156 | –0.388 | –0.259 |
| | *P* value | 0.313 | 0.010 | 0.094 |

CSI: central sensitization inventory, VAS: visual analog scale, HAD: hospital anxiety depression, QuickDASH: Quick Disability of Arm, Shoulder and Hand, SF36-GH: Short Form 36 general health, PPT: pressure pain threshold, r: correlation coefficient.
[a]Spearman's rho.

selected clinical parameters for each assessment with corresponding *P* values.

## DISCUSSION

In this study, the effect of the pre-treatment CS-related symptoms on treatment results and its relationship with functional parameters and PPT were examined. While subacromial injection proved beneficial in both groups, shoulder pain before and after the injection was unaffected by CSS. The CSI is the most commonly used scale to investigate CS-related symptoms, and higher pretreatment CSI scores have been reported to be associated with reduced treatment response in a variety of musculoskeletal disorders [28]. Patients with a CSI score of ≥ 40 are reported to have a 39-fold increased risk of persistent pain and, consequently, dissatisfaction following total knee arthroplasty [29]. Similarly, higher pre-treatment CSI scores were associated with reduced physical therapy response in patients with knee osteoarthritis [30]. Contrary to these findings and somewhat surprisingly, treatment response in the present study did not differ based on pre-treatment CSS. The continuum feature of CS will make this result easier to understand. CS is not a phenomenon that can be classified as present or absent; rather, it is a dynamic process that unfolds from minimal to extreme [31]. In this case, the time period in which the patient is evaluated is important because pain sensitization becomes more evident over time in the majority of patients under the influence of certain factors. In a study conducted with 404 RCT patients, higher CSI scores were found to be associated with higher age, duration of symptoms for more than six months, and the presence of anxiety and depression [32]. In the present study, the median pain duration of the patients was four months, and the median CSI score was 47.5, corresponding to the moderate CS level [33]. The absence of variations in treatment responses between the groups in this study may possibly be attributed to the moderate level of CS-related symptoms among the patients. This explanation can be somewhat supported by the consistent correlation found between the CSI and pain ratings following treatment. However, the lack of analysis of the patients' treatment response based on the severity of their CS-related symptoms precludes any direct conclusions from this study.

Another possible reason is that the majority of existing studies are based on patients who underwent surgery rather than conservative treatment. As with other musculoskeletal disorders, the general approach for shoulder pathologies is to refer patients who do not improve with conservative care to surgery [13]. These patients often have longer pain duration, more severe pain, and disability; these are also factors associated with higher CSI scores and thus a poorer treatment response [11].

In addition, these results may also be associated with issues arising from the use of the questionnaire. For CSI, the most effective cut-off score for distinguishing individuals with CSS from the non-patient group was reported to be 40; however, this score was not considered diagnostic [18]. As an alternative, it is recommended to use specific CSI cut-off values calculated for particular patient categories, such as low back pain [31]. To the authors' knowledge, there is no more reliable, specific cut-off value recommended for shoulder patients yet. Another preference for the authors was that the CSI's validated cut-off score of 40/100 made the results comparable to existing data.

On the other hand, some argue that there is insufficient evidence to support a negative effect of CS on treatment outcomes. According to a systematic review, individuals with shoulder pain associated with the rotator cuff pathology should have particular attention paid to the nociceptive component of pain, as there is insufficient and conflicting information regarding the central pain processes [34]. A case-control study of patients with shoulder pain found mechanical hypoalgesia around the shoulder, increased upper extremity disability, and poor quality of life in the patient group. The authors pointed out that CS is not a feature of shoulder pain but may be present in a subset of patients [35]. The variability observed in the literature regarding this subject matter appears to be associated with differences in the methods employed to assess CS in patients with shoulder pain. Measures of nervous system sensitization, with the exception of cold hyperalgesia, CSI, and the fibromyalgia survey questionnaire, did not support an independent predictive relationship between response to surgical and conservative interventions for musculoskeletal disorders, according to a systematic review [36]. Therefore, it is a more rational approach to interpret the effect of CS on treatment response according to the underlying disease and chosen assessment method, as well as the severity of sensitization findings.

The nature and extent of the underlying disease become significant when considering that both structural and functional factors impact CS [31]. The CSI score has been reported to be higher in patients with glenohumeral osteoarthritis than in patients with RCT [19]. The results of this study indicate that patients with CSS had a higher rate of partial rupture in the supraspinatus and a lower

 https://doi.org/10.3344/kjp.24290

rate of tendinosis. One possibility is that patients with supraspinatus rupture may be more likely to trigger and maintain sensitization mechanisms due to higher levels of inflammation and nociceptive input [37].

The expected response in individuals with effective pain modulation is an improvement in QST, including PPT, as an indicator of the desensitization process, concurrent with pain relief following treatment [38]. Different from healthy participants, patients with chronic fatigue syndrome, one of the CS-related disorders, showed a post-exercise PPT decrease, which the authors explained away as aberrant central pain processing [39]. This study reveals that SIS patients with CSS have a comparable dysfunction in pain modulation, as seen by the paradoxical decrease in PPT at one month following treatment. In the third month, PPT increased to the level of those without CSS.

The close association of CSI with various patient-based outcome measures, including disability, quality of life, and psychological comorbidities in chronic musculoskeletal pain, is now well established in the literature [11]. However, the majority of available results are from cross-sectional studies, and data on changes in this association with treatment are limited. In a prospective study investigating the effects of CS-related symptoms on surgical outcomes in patients with lumbar spinal stenosis, CSI scores were reported to have significant correlations with all outcome measures, including pain and disability, preoperatively and at 12 months postoperatively. These results were interpreted by the authors as evidence for the sustained effect of CS [40]. In this study, all clinical scales except pre-injection pain intensity showed a significant relationship with the CSI score before and after the procedure. It is noteworthy that the post-treatment visits revealed an association between pain intensity and CSI, which was not apparent before treatment. This implies that the patients' pain sensitization dynamics may have been altered by the treatment. Due to the complex and variable structure of CS, understanding these dynamics requires detailed and long-term follow-up.

Because PPT and CSI measurements are influenced by the same parameters, albeit addressing CS from different perspectives, a significant relationship is expected between them [41]. A meta-analysis examining the CSI-PPT correlation reports that low CSI scores may not show an association with PPT because of the reduced probability of CS [28]. In contrast, this study found that CSI at lower values showed a correlation with pain intensity and PPT that was not present at higher pretreatment levels. Among the QST measures, PPT has the highest reported association with CSI; this relationship is explained by shared physiological and psychological factors that affect both sensitization metrics [28]. It is possible that in SIS patients, when the painful peripheral stimulus is removed by injection, these factors reorganize and make the CSI-PPT correlation evident. To the authors' knowledge, this is the first study to repeatedly examine the relationship between CS-related symptoms and PPT measurements at different time points before and after treatment. The authors of a study on patients with low back pain suggest that early CS might be a "normal" adaptive response that resolves for many people, but it could be exacerbated and/or sustained by additional factors [42]. The changes observed in the PPT and CSI scores of SIS patients, both within themselves and in their correlation with each other, may be a manifestation of this resolving process. These findings also imply that the CSI-PPT association may change based on the assessment period, making it potentially misleading to evaluate the PPT association with CS-related symptoms based on a single assessment. The dynamic association of measures indicating sensitization from different perspectives, such as CSI and PPT, requires additional exploration using longitudinal examinations.

This study also found that pre-treatment disability was higher in patients with CSS, while disability scores were similar between groups at the 3-month visit. In this case, it is noteworthy that while there was no significant difference in pain ratings, there was a difference in the groups' levels of disability. It has been documented that, in addition to pain, CS also contributes to disability through psychological mediators such as anxiety and depression [11]. Depression has been associated, in individuals with unilateral shoulder pain, to an increase in the CSI score and disability [43]. In the cohort of the present study, HADS scores were significantly higher in patients with CSS, and this difference was maintained in longitudinal analysis.

One of the potential limitations of this study is that the patients were analysed using their CSI scores rather than their QST. QST-based classification cannot be used in the present study due to the lack of standard measurement points in shoulder patients and their implementation at multiple sites. The authors adopted an approach in which they categorized individuals based on their CSI score and examined the way the PPT and clinical parameters change with regard to CS symptoms. The limited number of patients, relatively short follow-up period, and absence of patient analgesic use documentation are further limitations of the study. This is one of the pioneer studies examining the effect of pre-treatment CS-related symptoms on shoulder injection response. Furthermore, the authors

believe that repeated, bilateral PPT measurements taken at multiple locations have an important role in providing insightful data regarding sensitization process.

This study showed that the treatment response to subacromial steroid injection in individuals with SIS was not significantly affected by CS-related symptoms. PPT measurements of patients with CSS reveal a different pattern from that of individuals without CSS, suggesting a dysfunction in pain modulation. It makes more sense to assess how CS-related symptoms affect treatment response in light of the underlying diseases, the selected therapeutic strategy, the maturation of sensitization, and other factors.

## DATA AVAILABILITY

The datasets of the current study are available from the corresponding author on reasonable request.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## FUNDING

No funding to declare.

## AUTHOR CONTRIBUTIONS

Feyza Nur Yücel: Writing/manuscript preparation; Semiha Özgüç: Writing/manuscript preparation; Yeliz Bahar-Özdemir: Writing/manuscript preparation; Emre Ata: Writing/manuscript preparation.

## ORCID

Feyza Nur Yücel, https://orcid.org/0000-0001-7438-6047
Semiha Özgüç, https://orcid.org/0000-0002-5887-6828
Yeliz Bahar-Özdemir, https://orcid.org/0000-0003-2253-3767
Emre Ata, https://orcid.org/0000-0002-8923-4158

## REFERENCES

1. Horowitz EH, Aibinder WR. Shoulder impingement syndrome. Phys Med Rehabil Clin N Am 2023; 34: 311-34.
2. Harrison AK, Flatow EL. Subacromial impingement syndrome. J Am Acad Orthop Surg 2011; 19: 701-8.
3. Messina C, Banfi G, Orlandi D, Lacelli F, Serafini G, Mauri G, et al. Ultrasound-guided interventional procedures around the shoulder. Br J Radiol 2016; 89: 20150372.
4. Coronado RA, Simon CB, Valencia C, George SZ. Experimental pain responses support peripheral and central sensitization in patients with unilateral shoulder pain. Clin J Pain 2014; 30: 143-51.
5. Paul TM, Soo Hoo J, Chae J, Wilson RD. Central hypersensitivity in patients with subacromial impingement syndrome. Arch Phys Med Rehabil 2012; 93: 2206-9.
6. Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. Handb Exp Pharmacol 2015; 227: 79-102.
7. Sacaklidir R, Sanal-Toprak C, Yucel FN, Gunduz OH, Sencan S. The effect of central sensitization on interlaminar epidural steroid injection treatment outcomes in patients with cervical disc herniation: an observational study. Pain Physician 2022; 25: E823-9.
8. Kadum B, Inngul C, Ihrman R, Sjödén GO, Sayed-Noor AS. Higher preoperative sensitivity to pain and pain at rest are associated with worse functional outcome after stemless total shoulder arthroplasty: a prospective cohort study. Bone Joint J 2018; 100-B: 480-4.
9. Rankin J, Rudy-Froese B, Hoyt C, Ramsahoi K, Gareau L, Howatt W, et al. Quantitative sensory testing protocols to evaluate central and peripheral sensitization in knee OA: a scoping review. Pain Med 2022; 23: 526-57.
10. Kim MS, Kim JJ, Kang KH, Lee JH, In Y. Central sensitization and neuropathic pain cumulatively affect patients reporting inferior outcomes following total knee arthroplasty. J Bone Joint Surg Am 2024; 106: 102-9.
11. Dahmani D, Taik FZ, Berrichi I, Fourtassi M, Abourazzak FE. Impact of central sensitization on pain, disability and psychological distress in patients with knee osteoarthritis and chronic low back pain. BMC Musculoskelet Disord 2023; 24: 877.
12. Neblett R, Hartzell MM, Williams M, Bevers KR,

Mayer TG, Gatchel RJ. Use of the central sensitization inventory (CSI) as a treatment outcome measure for patients with chronic spinal pain disorder in a functional restoration program. Spine J 2017; 17: 1819-29.
13. Lewis J. Rotator cuff related shoulder pain: assessment, management and uncertainties. Man Ther 2016; 23: 57-68.
14. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11: S240-52.
15. Go SU, Lee BH. Effects of manual therapy on shoulder pain in office workers. J Phys Ther Sci 2016; 28: 2422-5.
16. Doménech-García V, Peirotén AR, Imaz ML, Palsson TS, Herrero P, Bellosta-López P. Not just sensitization: sympathetic mechanisms contribute to expand experimental referred pain. Korean J Pain 2022; 35: 240-9.
17. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010; 6: 599-606.
18. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract 2012; 12: 276-85.
19. Iio R, Manaka T, Nakazawa K, Hirakawa Y, Ito Y, Ogura A, et al. Assessment of prevalence and risk factors for central sensitization related to shoulder osteoarthritis and rotator cuff tears using the central sensitization inventory: a cross-sectional study in shoulder surgery patients. J Clin Med 2023; 12: 5633.
20. Akeda K, Yamada J, Takegami N, Fujiwara T, Murata K, Kono T, et al. Evaluation of central sensitization inventory in patients undergoing elective spine surgery in a multicenter study. Global Spine J 2023; 13: 1716-27.
21. Düzce Keleş E, Birtane M, Ekuklu G, Kılınçer C, Çalıyurt O, Taştekin N, et al. Validity and reliability of the Turkish version of the central sensitization inventory. Arch Rheumatol 2021; 36: 518-26.
22. Koldas Dogan S, Ay S, Evcik D, Baser O. Adaptation of Turkish version of the questionnaire Quick Disability of the Arm, Shoulder, and Hand (Quick DASH) in patients with carpal tunnel syndrome. Clin Rheumatol 2011; 30: 185-91.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-70.
24. Paker N, Bugdayci D, Midik M, Celik B, Kesiktas N. Reliability of the Turkish version of the hospital anxiety and depression scale in the people with traumatic spinal cord injury. NeuroRehabilitation 2013; 33: 337-41.
25. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000; 25: 3130-9.
26. Demiral Y, Ergor G, Unal B, Semin S, Akvardar Y, Kivircik B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. BMC Public Health 2006; 6: 247.
27. Walankar PP, Panhale VP, Patil MM. Psychosocial factors, disability and quality of life in chronic shoulder pain patients with central sensitization. Health Psychol Res 2020; 8: 8874.
28. Neblett R, Sanabria-Mazo JP, Luciano JV, Mirčić M, Čolović P, Bojanić M et al. Is the central sensitization inventory (CSI) associated with quantitative sensory testing (QST)? A systematic review and meta-analysis. Neurosci Biobehav Rev 2024; 161: 105612.
29. Kim MS, Koh IJ, Sohn S, Kang BM, Kwak DH, In Y. Central sensitization is a risk factor for persistent postoperative pain and dissatisfaction in patients undergoing revision total knee arthroplasty. J Arthroplasty 2019; 34: 1740-8.
30. Yüzügüldü SB, Kutlay Ş, Gök H. The relationship between inadequate response to physical therapy and central sensitization in patients with knee osteoarthritis: A prospective cohort study. Turk J Phys Med Rehabil 2023; 69: 266-74.
31. Mibu A, Nishigami T, Tanaka K, Manfuku M, Yono S. Difference in the impact of central sensitization on pain-related symptoms between patients with chronic low back pain and knee osteoarthritis. J Pain Res 2019; 12: 1757-65.
32. Peng R, Yang R, Ning N. Central sensitization syndrome in patients with rotator cuff tear: prevalence and associated factors. Postgrad Med 2023; 135: 593-600.
33. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing clinically relevant severity levels for the central sensitization inventory. Pain Pract 2017; 17: 166-75.
34. Lo CN, Leung BPL, Sanders G, Li MWM, Ngai SPC.

The major pain source of rotator cuff-related shoulder pain: a narrative review on current evidence. Musculoskeletal Care 2023; 21: 285-93.
35. Haik MN, Evans K, Smith A, Henríquez L, Bisset L. People with musculoskeletal shoulder pain demonstrate no signs of altered pain processing. Musculoskelet Sci Pract 2019; 39: 32-8.
36. O'Leary H, Smart KM, Moloney NA, Doody CM. Nervous system sensitization as a predictor of outcome in the treatment of peripheral musculoskeletal conditions: a systematic review. Pain Pract 2017; 17: 249-66.
37. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152(3 Suppl): S2-15.
38. Andersen LL, Andersen CH, Sundstrup E, Jakobsen MD, Mortensen OS, Zebis MK. Central adaptation of pain perception in response to rehabilitation of musculoskeletal pain: randomized controlled trial. Pain Physician 2012; 15: 385-94.
39. Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, et al. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. J Intern Med 2010; 268: 265-78.
40. Akeda K, Yamada J, Takegami N, Fujiwara T, Murata K, Kono T, et al. Central sensitization as a predictive factor for the surgical outcome in patients with lumbar spinal stenosis: a multicenter prospective study. Eur Spine J 2023; 32: 4200-9.
41. Coronado RA, George SZ. The central sensitization inventory and pain sensitivity questionnaire: an exploration of construct validity and associations with widespread pain sensitivity among individuals with shoulder pain. Musculoskelet Sci Pract 2018; 36: 61-7.
42. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Are signs of central sensitization in acute low back pain a precursor to poor outcome? J Pain 2019; 20: 994-1009.
43. Bilika P, Nijs J, Fandridis E, Dimitriadis Z, Strimpakos N, Kapreli E. In the shoulder or in the brain? Behavioral, psychosocial and cognitive characteristics of unilateral chronic shoulder pain with symptoms of central sensitization. Healthcare (Basel) 2022; 10: 1658.

 https://doi.org/10.3344/kjp.24290