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Experimental Pain Responses Support Peripheral and Central Sensitization in Patients with Unilateral Shoulder Pain

Rogelio A. Coronado, PT, CSCS, FAAOMPT[1], **Corey B. Simon, PT, DPT, FAAOMPT**[1], **Carolina Valencia, PT, PhD**[2], and **Steven Z. George, PT, PhD**[1,3]

[1]Department of Physical Therapy, College of Public Health and Health Professions, University of Florida

[2]Department of Applied Medicine and Rehabilitation, Indiana State University

[3]Center for Pain Research and Behavioral Health, University of Florida

Abstract

Objective—The aims of this study were to 1) examine the pattern of experimental pain responses in the affected and non-affected extremities in patients with shoulder pain and 2) explore the intra-individual association between sensitization states derived from experimental pain testing.

Methods—Experimental pain responses from 58 patients with shoulder pain (17 females, ages 18 to 52) were compared to those from 56 age- and sex-matched healthy volunteers (16 females, ages 21 to 58). Experimental pain responses included pressure pain threshold (PPT), thermal pain threshold and tolerance, and suprathreshold heat pain response (SHPR). Comparisons were made between the affected and non-affected extremity of clinical participants and the average response of extremities in healthy participants. Peripheral and central sensitization indexes were computed for clinical participants using standardized scores and percentile cut-offs based on the data from the healthy control sample. Experimental pain responses in clinical participants observed beyond the 25th and 75th percentile of healthy control sample responses were used for investigation of intra-individual association of sensitization states.

Results—PPT on the affected side acromion and masseter of clinical participants were diminished compared to their non-affected side ($p < 0.015$). Bilateral sensitivity in clinical participants was noted for PPT at the acromion and SHPR ($p < 0.015$). Peripheral and central sensitization indexes demonstrated that individuals with shoulder pain present with variable patterns of peripheral and central sensitization.

Conclusions—Collectively, experimental pain responses supported peripheral and central sensitization in response to pressure and thermal stimuli. No clear association was made between individuals exhibiting peripheral or central sensitization and suggests heterogeneity in pain processing in this clinical population.

Keywords

central sensitization; musculoskeletal pain; pain sensitivity; quantitative sensory testing; shoulder pain

Send correspondence and request for reprints to: Rogelio A. Coronado, PT, CSCS, FAAOMPT, Box 100154, UFHSC, Gainesville, FL 32610-0154, Phone: 352-273-6085, Fax: 352-273-6109, rcoronado@phhp.ufl.edu. Steven Z. George, PT, PhD, Box 100154, UFHSC, Gainesville, FL 32610-0154, Phone: 352-273-6432, Fax: 352-273-6109, szgeorge@phhp.ufl.edu.

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INTRODUCTION

Shoulder pain is among the top musculoskeletal conditions which lead individuals to seek healthcare.[1] Recovery of shoulder pain can be problematic with approximately 40% of individuals reporting continued pain after 12 months.[2,3] Croft et al[4] reported that approximately 50% of individuals report incomplete recovery of function at 18 months. Recently, authors have begun to investigate whether alterations in pain sensitivity are factors of relevance underlying patient recovery.[5,6] Authors have used experimental pain testing as a proxy for measuring peripheral and central sensitization, which are proposed contributors to the development and maintenance of chronic pain.[7–9] Alterations consistent with either peripheral or central sensitization processes can be detected by measuring psychophysical responses following exposure to standard experimental stimuli in both patient and healthy populations. Sensitization is identified by findings such as reductions in pain threshold or enhanced pain ratings at suprathreshold levels (e.g. temporal summation of pain) when compared to healthy controls. Further differentiation of peripheral and central sensitization has been proposed by comparing experimental pain responses within subjects (e.g. affected vs. unaffected sides) and across multiple body regions.[7,9,10]

Central sensitization has been observed in individuals with chronic pain conditions such as fibromyalgia and arthritis and is characterized by generalized (widespread) hypersensitivity and enhanced temporal summation of pain.[11–16] Several authors have termed these conditions “central sensitivity syndromes” since they exhibit similar underlying pain mechanisms.[17–19] Pain processing alterations consistent with central sensitization have also been observed in conditions with less obvious connections to chronic pain states, such as unilateral extremity conditions. For example, Fernandez-Carnero et al[20] assessed experimental pain responses in patients with unilateral lateral epicondylalgia and found these patients exhibited generalized hypersensitivity to a mechanical stimulus compared to healthy control participants. Similarly, Arendt-Nielsen et al[16] observed enhanced pressure sensitivity and temporal summation of pressure pain at multiple anatomical sites in patients with unilateral knee pain.

Distinguishing between peripheral and central pain processing alterations in patients with musculoskeletal pain is important as central sensitization is considered a potential influence in the development and maintenance of chronic pain.[21] Several studies have examined experimental pain responses in patients with shoulder pain; however, a majority of studies have not included a comparison group of healthy controls.[10,22–25] In our previous work,[10] we identified enhanced sensitivity to pressure stimuli on the affected versus non-affected extremity for patients with unilateral shoulder pain. This was interpreted as being consistent with a peripherally-sensitized state, however a distinction between peripheral and central sensitization could not be made due to a lack of an asymptomatic comparison group. We also noted that responses from pressure and thermal stimuli were distinct as only pressure pain threshold (PPT) showed side-to-side differences. The discrepancy in findings based on stimulus modality supports the use of multiple stimulus modality testing when assessing experimental pain responses. Incorporation of either mechanical or thermal stimulus for testing experimental pain sensitivity, but not both, has been most frequently reported in experimental pain studies involving patients with shoulder pain.[22–28] Use of multiple modality stimuli is important as there is not a strong correlation between responses to different stimuli.[29,30]

Detecting the presence of peripheral or central sensitization can be achieved by comparing responses to multiple experimental pain stimuli taken at various anatomical regions in patients with unilateral musculoskeletal pain and healthy participants. Thus, the primary aim of this study was to examine whether differences in experimental pain responses in the

affected and non-affected side of patients with unilateral shoulder pain differed in comparison to responses from healthy age- and sex-matched participants. For this study, we used pressure and thermal stimuli applied to the local shoulder region and areas remote to the shoulder. We hypothesized that the patient sample would exhibit characteristics of central sensitization as evidenced by bilateral hypersensitivity to pressure and thermal stimuli. Hypersensitivity in the patient sample would be indicated by 1) reductions in pain threshold (amount of force or temperature) or tolerance (temperature) values or 2) elevations in pain ratings associated with the different stimuli as compared to responses from the healthy participant sample. Additionally, we hypothesized that hypersensitivity would be evident at sites local and remote to the primary area of injury (e.g. beyond the shoulder). A secondary aim of this study was to explore intra-individual association of peripheral and central sensitization using indices derived from the healthy participant group. Specifically, we were interested in examining whether there was an association between peripheral and central sensitization states. We hypothesized that individuals with shoulder pain would have a strong association between peripheral and central sensitization states, such that those with evidence of peripheral association would be more likely to also show evidence of central sensitization. As an exploratory follow-up, we also examined the relationship between derived sensitization indexes with relevant demographic, clinical, and psychological characteristics as a way to assess potential confounding of these factors with the sensitization states.

MATERIALS AND METHODS

Participants

Clinical participants—This study involves recruitment of clinical and healthy participants. Clinical participants were age- and sex-matched to healthy participants. Participants with unilateral shoulder pain were recruited during routine pre-operative physician visits at the University of Florida Orthopaedics and Sports Medicine Institute. Participants were considered eligible for this study if they were between the ages of 18 – 85 years, had a current complaint of pain in the anterior, lateral, or posterior shoulder, and were scheduled for arthroscopic surgery. Additionally, evidence (e.g. clinical examination and/or imaging) of 1) rotator cuff tendinopathy or tear, 2) Superior Labrum Anterior to Posterior (SLAP) lesion, or 3) adhesive capsulitis was required

Participants were excluded from enrollment if they met any of the following criteria: 1) current complaint of pain for more than the past 3 months in the neck, elbow, hand, low back, hip, knee, or ankle region, 2) diagnosed neurological disorder, 3) history of shoulder osteoarthritis or rheumatoid arthritis or current shoulder fracture, tumor, infection, or cancer, 4) prior shoulder surgery within the past year or currently complaint of pain from a prior shoulder surgery, 5) previously diagnosed chronic pain disorder (including, but not limited to irritable bowel syndrome, fibromyalgia, temporomandibular disorder, chronic low back pain), 6) current psychiatric management (from patient history or medication usage involving multiple psychiatric drugs), and 7) current gastrointestinal or renal illness.

Healthy participants—Healthy participants were recruited from the University of Florida campus and surrounding community via posted flyers and general advertisements. Participants were considered eligible for this study if they were between the ages of 18 – 85 years and not currently performing resistance exercise for the upper extremity. Participants were excluded based on the following criteria: 1) currently experiencing neck or shoulder pain, 2) reporting any neurological impairments of the upper extremity, such as loss of sensation, muscle weakness, or reflex changes, 3) currently taking pain medication, and 4) reporting a previous history of shoulder surgery.

Demographic and Clinical Characteristics

All study participants completed standard questionnaires for obtaining demographic (age, sex, hand dominance) and psychological information. Clinical participants completed clinical questionnaires related to the current shoulder pain episode. Information obtained included duration of pain and clinical pain intensity. Clinical pain intensity was assessed with the Brief Pain Inventory (BPI).[31] The BPI includes an 11-point numeric rating scale for pain where participants rate their pain from 0 “no pain” to 10 “pain as bad as you can imagine”. Participants provide a rating for current pain intensity, pain intensity at its least within the past 24 hours and pain intensity at its worst within the past 24 hours. The BPI is an appropriate measure of pain intensity for patients with musculoskeletal pain.[32]

Psychological characteristics were measured with three commonly-used questionnaires: Fear of Pain Questionnaire (FPQ-9), Pain Catastrophizing Scale (PCS) and Tampa Scale of Kinesiophobia (TSK-11). The FPQ-9 is a shortened version of the original 30-item FPQ and consists of 9 items that measure pain-related fear.[33,34] Questions on the FPQ-9 are answered on a 5-point scale with total scores ranging from 9 to 45. Higher summed scores on the FPQ-9 indicate higher levels of pain-related fear. The FPQ-9 is a reliable measure of pain-related fear in patients with musculoskeletal pain.[35] The PCS is a 13-item self report questionnaire that assesses thoughts associated with various pain experiences. Questions on the PCS are answered on a 5-point rating scale with total scores ranging from 0 to 52. Higher summed scores on the PCS indicate greater levels of pain catastrophizing. The PCS has shown good reliability, internal consistency, construct validity, and concurrent validity.[36–38] The TSK-11 is a shortened version of the original 17-item tool and consists of 11 items that measure fear of movement.[39] Questions on the TSK-11 are answered on a 4-point rating scale with total scores ranging from 11 to 44. Higher scores on the TSK-11 indicate higher levels of fear of movement. The TSK-11 has demonstrated good reliability and validity and has been examined in patients with shoulder pain.[40]

Experimental Pain Sensitivity Testing

Pressure Pain Sensitivity—PPT measurements were collected using a hand-held Fischer pressure algometer with a 1-cm diameter probe (Pain Diagnostics and Thermography Inc, Great Neck, NY) in both healthy and clinical participants. PPT was assessed bilaterally at the acromion and masseter at an applied rate of 1kg per second. The participant was instructed to inform the assessor when they first perceived a sensation of pain. The amount of pressure in kilograms (kg) at which point pain was perceived was recorded. This process was repeated three times bilaterally at each site and the average of these measures was used in the data analysis. The test-retest reliability of PPT measurements has been established in previous studies.[41–43]

Thermal Pain Sensitivity: Threshold and Tolerance—Thermal threshold temperatures and thermal tolerance temperatures and pain ratings were obtained in clinical and healthy participants. Thermal stimuli were applied to the volar surface of the participant’s forearm using a 30 × 30 mm thermode connected to a PATHWAY Model Advanced Thermal Stimulator (ATS) (Medoc Advanced Medical Systems, Ramat Yishai, Israel). For thermal threshold, the participant was instructed to inform the assessor when they first perceived a sensation of pain. For thermal tolerance, the participant was instructed to inform the assessor when the heat sensation became intolerable. The temperature, in degrees Celsius (°C), associated with thermal threshold and tolerance and pain intensity rating associated with thermal tolerance were recorded. Pain intensity was measured on a scale of 0 to 100 with 0 meaning “no pain” and 100 “worst pain imaginable”. Two trials were conducted bilaterally for thermal threshold and tolerance and the average of the trials for temperature and pain intensity was used in the data analysis.

Thermal Pain Sensitivity: Suprathreshold Heat Pain Response—Suprathreshold heat pain response (SHPR) was obtained in both groups by applying a thermal stimulus to the participant's thenar eminence with a contact thermode with 2.5 cm^2 surface area connected to a PATHWAY Model Contact Heat Evoked Potential Stimulator (CHEPS) (Medoc Advanced Medical Systems, Ramat Yishai, Israel). The CHEPS was programmed to apply a series of 5 consecutive heat pulses at a rate of 30°C per second with an interstimulus interval of 2.5 seconds. Participants were instructed to rate the pain intensity associated with each pulse on a scale of 0 to 100 with 0 meaning "no pain" and 100 "worst pain imaginable". SHPR was identified as the pain intensity rating of the 5^{th} pulse in the train of heat pulses. The peak temperature of the heat pulse used for this analysis was 50°C. SHPR was selected as we have used this measure in prior studies and have demonstrated that this measure is linked with clinical pain.[25,27]

Procedures

This study was a cross-sectional analysis of data collected prospectively from March 2009 to January 2011. The study protocol was approved by the University of Florida Institutional Review Board. Clinical and healthy participants provided informed consent for the study and commenced with questionnaires and experimental pain sensitivity testing. The order of experimental pain sensitivity testing was standardized as follows: PPT, thermal threshold, thermal tolerance, and SHPR. For all experimental pain sensitivity tests, the participant's right upper extremity was assessed first for standardization purposes. After one trial of experimental pain sensitivity testing on the right extremity, testing proceeded immediately on the left upper extremity. All experimental pain sensitivity testing was conducted with an alternating pattern between right and left extremities, allowing adequate time between subsequent trials on the same extremity.

Statistical Analysis

Data were analyzed with SPSS Statistics for Windows, version 20 (SPSS, Inc, Chicago, IL). Normality distribution was assessed with Kolmogorov-Smirnov test and observation of histograms and normal probability plots. Variables exhibiting a non-normal distribution were analyzed with distribution-free tests (Rank Sums and Wilcoxon signed-rank). These variables included PPT, thermal tolerance pain ratings, and SHPR.

The primary analysis involved comparison of experimental pain responses in the affected and non-affected side of clinical participants to the average of sides of the healthy participants (termed "control side"). An average of left and right sides in the healthy participants was used as the comparison because there was no side to side difference between these responses ($p > 0.05$). Primary analyses were conducted with independent and paired t-tests or Rank Sums and Wilcoxon signed-rank test. Independent tests were used when comparing either the affected or non-affected side of clinical participants to the control side of healthy participants, while paired tests were used when comparing between sides of the clinical participants. Effect size (r) was computed for significant differences.[44] An effect size was considered small (0.20), moderate (0.50), or large (0.80).[45] To adjust for multiple comparisons, an alpha level of 0.015 was used for all pairwise comparisons.

For the secondary analysis, we created index variables as indicators of peripheral and central sensitization. We took a conservative approach by using only experimental pain responses that demonstrated either side-to-side differences in the clinical participants (supporting peripheral sensitization) or bilateral differences between the clinical and healthy participants (supporting central sensitization). For peripheral sensitization, we computed a ratio of the experimental pain responses between 1) the clinical participant's affected and non-affected extremities and 2) the healthy participant's dominant and non-dominant extremities. We

computed a standardized score for each clinical participant based on a z-score using the healthy participant group's mean and standard deviation (see equation below).

$$\text{Standardized Score:}\frac{\text{Raw Score}_{\text{Clinical}}-\text{Mean}_{\text{Healthy}}}{\text{Standrard Deviation}_{\text{Healthy}}}$$

We identified whether a clinical participant's ratio response fell below the 25th percentile (for threshold or tolerance values) or above the 75th percentile (for pain ratings) among the healthy sample which would indicate peripheral sensitization. The 25th percentile has been suggested as a lower limit reference value for enhanced sensitivity.[46] We used similar reasoning in choosing the 75th percentile as a reference value for pain ratings as well. For central sensitization, we averaged the experimental pain responses for each extremity of the clinical participants as was initially computed for the healthy participants. We computed a similar standardized z-score for each clinical participant using the healthy participant's mean and standard deviation and identified whether clinical participant's averaged responses fell below the 25th percentile or above 75th percentile among the healthy sample, indicating central sensitization. Each standardized score, or index, was examined with Pearson's r correlation for its association with relevant baseline characteristics including demographic, clinical, and psychological variables. Finally, we compared our computed peripheral sensitization index (PSI) to our central sensitization index (CSI) using separate 2×2 tables to determine whether individual clinical participants demonstrated peripheral, central, a mixed-pattern or no sensitization. We analyzed association between indexes with Chi-square (χ^2) analysis. Key demographic, clinical, and psychological characteristics were also examined between sensitization subgroups. Comparisons between variables were examined using one-way analysis of variance and assessment of 95% confidence intervals (CI).

RESULTS

Demographic, Clinical and Psychological Characteristics

Data from 58 clinical participants with shoulder pain and 56 healthy participants were included in this analysis. Values for the relevant demographic, clinical, and psychological variables are presented in Table 1. The clinical participants were comprised of 41 males and 17 females with age ranging from 18 to 52 years. The healthy participants were comprised of 40 males and 16 females with age ranging from 21 to 58 years. The majority of participants were right hand dominant (clinical = 52/58, healthy = 54/56).

Pressure Pain Sensitivity

For PPT at the acromion, a small-to-moderate, significant difference was noted between sides with lower PPT values on the affected side as compared to the non-affected side in clinical participants ($T = 349$, $z = -3.53$, $r = -0.33$, $p < 0.015$) (Table 2). Additionally, PPTs at both affected ($U = 903$, $z = -3.98$, $r = -0.37$, $p < 0.015$) and non-affected side ($U = 1108$, $z = -2.80$, $r = -0.26$, $p < 0.015$) of the clinical participants were significantly lower compared to the control side of healthy participants (Table 2). These differences were also small-to-moderate in magnitude.

For PPT at the masseter, a small-to-moderate, significant difference was noted between the affected side of the clinical participants compared to the control side of healthy participants ($U = 1115$, $z = -2.77$, $r = -0.26$, $p < 0.015$), where lower PPT values were seen on the affected side (Table 2). No differences in PPT values at the masseter were observed between

sides of the clinical participants (T = 663, z = −1.11, p = 0.269) and between the non-affected and control sides (U = 1191, z = −2.33, p = 0.020).

Thermal Pain Sensitivity

No differences were noted in thermal threshold temperatures between sides of the clinical participants (t = −0.430, p = 0.669), between the affected side and control side (t = 1.199, p = 0.233), or between the non-affected side and control side (t = 1.360, p = 0.177). Similarly, no differences were observed for thermal tolerance temperatures between sides of the clinical participants (t = 0.468, p = 0.642), between the affected side and control side (t = −0.265, p = 0.792), or between the non-affected side and control side (t = −0.466, p = 0.642).

Similar findings were observed for thermal tolerance pain ratings. No differences were found between sides of clinical participants (T = 352, z = −0.278, p = 0.781), or between the affected (U = 1198, z = −1.59, p = 0.112) and non-affected side (U = 1203, z = −1.56, p = 0.119) as compared to the control side. A side-to-side difference in SHPR rating was not found in the clinical participants (T = 359, z = −1.804, p = 0.071). However, there were significant increases in SHPR of small-to-moderate magnitude between the affected side (U = 1001, z = −3.182, r = −0.30, p < 0.015) and non-affected side (U = 1116, z = −2.504, r = −0.24, p < 0.015) as compared to the control side (Table 2).

Peripheral Sensitization Index

PPT responses at the acromion demonstrated side-to-side differences in clinical participants and were therefore used to compute a peripheral sensitization index (PSI). Thirty-four participants (59.6%) with unilateral shoulder pain had a PSI value below the 25th percentile of the healthy sample and were considered peripherally sensitized based on this criterion. Correlation values between PSI and relevant baseline variables are listed in Table 3. There was no significant association between PSI and any of these variables (p > 0.015).

Central Sensitization Index

Central sensitization indices (CSI) were created with the averaged PPT responses at the acromion (CSI-PPT) and averaged SHPR (CSI-SHPR). These responses exhibited bilateral differences between the clinical participants compared to the healthy participants. Thirty-one participants (54.4%) with unilateral shoulder pain had CSI-PPT value below the 25th percentile of the healthy sample and were considered centrally sensitized based on this criterion. Twenty-one participants (38.2%) with unilateral shoulder pain had CSI-SHPR values above the 75th percentile of the healthy sample and were considered centrally sensitized based on this criterion. Only CSI-PPT showed a significant association with any baseline variable (Table 3) and these associations were similar to what has been previously reported.[24,47] CSI-PPT was negatively correlated with TSK-11 scores (r = −0.334, p < 0.015). Associations between CSI-PPT and sex (r = 0.320, p = 0.015) and PCS (r = −0.309, p = 0.021) approached statistical significance.

Comparison of Peripheral and Central Sensitization Indexes

No significant correlation was observed between PSI and CSI-PPT (r = 0.239, p = 0.074) or PSI and CSI-SHPR (r = −0.047, p = 0.731) (Table 3). Table 4 is an interpretive guide to the individual cell counts presented in Table 5. Table 5 is a 2×2 table of frequencies between the PSI and each of the central sensitization indices (CSI-PPT, CSI-SHPR). There was not a significant association between PSI and CSI-PPT ($\chi^2(1) = 0.669$, p = 0.413) or CSI-SHPR ($\chi^2(1) = 0.051$, p = 0.821). Exploratory follow-up analyses showed no differences between

subgroups based on relevant demographic, clinical, or psychological variables (Table 6). Descriptive data for each subgroup is depicted in Table 6.

DISCUSSION

In this study, we found a side-to-side difference in pressure sensitivity in participants with unilateral shoulder pain supporting a peripherally sensitized state. However, these same participants demonstrated bilateral pressure and thermal hypersensitivity at local and remote regions when compared to healthy age- and sex-matched participants, indicating central sensitization. A finding of bilateral hypersensitivity to pressure and thermal stimuli is consistent with prior studies examining the presence of central sensitization in patients with unilateral musculoskeletal pain. To advance this line of research we examined intra-individual associations between peripheral and central sensitization in the current paper. We found that individuals demonstrate variable sensitization processes without either 1) significant association between peripheral and central sensitization or 2) a predominant pattern of peripheral sensitization or central sensitization. This latter finding was surprising and suggests potential heterogeneity in the underlying pain processing for discrete musculoskeletal conditions like unilateral shoulder pain.

Previous investigations have examined experimental pain responses to mechanical stimuli in patients with unilateral musculoskeletal conditions.[16,20,26,28,48–51] Similar to our current study, prior studies have observed enhanced mechanical sensitivity at the affected local region,[20,26,48,49] as well as in bilateral local and remote regions.[20,28,49–51] We found converging evidence for bilateral hypersensitivity, or central sensitization, with the use of thermal stimuli, but only for SHPR. We did not find a difference in threshold or tolerance temperatures bilaterally which conflicts with previously reported findings.[52] Several studies have investigated inter-individual differences in pain hypersensitivity by examining thermal threshold or tolerance temperatures.[49,52,53] Furthermore, most studies examining experimental pain responses in patients with unilateral musculoskeletal conditions involve static measures of pain processing (e.g. threshold and tolerance) and fewer studies have incorporated dynamic measures like temporal summation of pain or suprathreshold responses.[10,27]

Dynamic measures such as SHPR are thought to provide additional information related to the endogenous modulation of pain.[7] In a previous study from our group, Valencia et al[25] advocated for the use of SHPR as a dynamic measure and was the reason we incorporated that measure into this study. Our finding of enhanced SHPR responses bilaterally in this patient group is indicative of alterations in the perception of pain and potentially a characteristic of enhanced central “facilitation”. Recently, Valencia et al[27] reported that SHPR decreased alongside clinical pain intensity in patients after 3 months following shoulder surgery, but conditioned pain modulation (“inhibition” measure) did not, indicating a neuroplastic change in central pain facilitation.

Collectively, our findings support alterations in both peripheral and central sensitivity converging with other recent reports involving subjects with musculoskeletal pain. In an attempt to further this work and determine the clinical relevance, we created indexes to determine whether peripheral and central sensitization were more likely to occur together than not. However, we did not find an association between sensitization indexes or a consistent pattern of one particular sensitization subgroup in this cohort of patients. From a theoretical perspective, our finding has potential implications regarding the measurement of pain sensitization for musculoskeletal pain conditions. For example, it is possible for an individual with unilateral shoulder pain to show signs of varying pain sensitization states (i.e. peripheral or central sensitization) or no pain sensitization at all. This suggests that,

despite having a similar presentation of shoulder pain, individuals may not have similar pain processing. Specifically, this study indicates that individuals with a unilateral shoulder pain may represent the full spectrum of experimental pain sensitivity, even though the overall spectrum may be elevated in comparison to healthy controls. This study also suggests that peripheral sensitization is not a prerequisite for the presence of central sensitization, and vice versa. The observed patterns of peripheral and central sensitization seem to occur independently from each other and from other factors relevant to the pain experience, such as psychology. Furthermore, in the current study we did not find evidence that the pattern of sensitization is reflective of the degree of severity of the clinical condition as measured by clinical pain intensity. The only potential clinical link observed was between individuals with central sensitization reporting the longest pain duration and those with no sensitization reporting the shortest pain duration (Table 6). This finding may indicate the importance of symptom duration in developing central sensitization, which is consistent with the basic literature on this topic. Although it should be noted that even symptom duration was not a definitive predictor of sensitization state, so other factors must be involved. Finally, we acknowledge the limitations of our measurement approach for determining sensitization and are unable to confirm whether these responses are indicative of actual changes in pain neurophysiology. Therefore, the lack of a clear link between peripheral and central sensitization could be a reflection of the current measurement limitations of pain processing in humans. The relation between our findings of mixed patterns of sensitization and their underlying neurophysiological mechanisms is beyond the scope of this paper, but should be considered in subsequent studies.

From a clinical perspective, our finding of mixed presentations of sensitization patterns within a given clinical population is potentially meaningful for clinical practice, especially if these patterns are related to differential recovery or treatment strategies. Shoulder rehabilitation is influenced by treatment paradigms focused primarily on alleviating peripheral sensitization by reducing inflammation and pain within the region of injury and these paradigms are typically guided by pathoanatomical or biomechanical principles.[54–57] Translation of alternative approaches to management, which focus on pain mechanisms, for example, has not been seen as widely as in low back pain[58–60] where central sensitization is more accepted as a pain mechanism of relevance. Similar focus on central sensitization has not been attempted in extremity conditions and reflects a management model focused primarily on peripheral pain generation. Given that the patient sample in the current study exhibited variability in patterns of sensitization, we speculate that involvement of central pain processes may be a potential reason some individuals with shoulder pain fail to recover following a standard bout of conservative management directed at peripheral targets.

Recommendations have been made for basing management decisions on underlying pain mechanisms in musculoskeletal conditions.[61–66] Central sensitization is highlighted often and authors have emphasized a need for treatment modifications in the presence of central sensitization.[64,67] We present preliminary evidence for heterogeneity in altered pain processes as measured by experimental pain responses and encourage future efforts to identify whether individuals demonstrating different patterns of sensitization respond selectively to specific treatment approaches. It may be the case that individuals presenting with a primary pattern of peripheral sensitization respond best to treatment approaches directed at reducing inflammation and improving peripheral deficits. Conversely, individuals with a primary pattern of central sensitization may require more centrally-focused interventions. Those with a mixed pattern of sensitization may require a multi-modal approach including interventions to reduce peripheral and central sensitization. This conclusion is entirely speculative, but hopefully will provide direction for future studies in this area.

Limitations

There are limitations to note in this study. First, this study is a cross-sectional analysis and does not include data related to clinical outcome. Our results are best interpreted as a baseline examination of differences in patterns of pain responses that may or may not influence subsequent outcome. There is, however, preliminary evidence that experimental pain responses are important factors to consider in clinical management.[6,27,68] Second, We developed indexes to identify sensitization patterns and used a reference value based on prior author suggestions. The initial step in deriving these indexes was to examine differences between sides (in clinical participants) and between groups (clinical and healthy). The differences observed, while significant, were also accompanied by small effect sizes and should be considered when interpreting these results. In determining sensitization, we chose the 25th and 75th percentiles as cutoffs for identifying hypersensitivity. There are other means to determining sensitization states (e.g. based on 95% confidence intervals) and we acknowledge our results are appropriate only to this sample and this specific form of analyses. Further investigation into the validity of the derived indexes of sensitization is warranted. Third, we matched clinical and healthy participants by age and sex, but not psychological distress. Matching based on psychological distress may be difficult due to differences between these two populations. Further, it was beyond the scope of this analysis to examine influence of psychological distress on our findings and should be investigated in future analyses. We attempted in this analyses to examine whether our sensitization indexes or the derived sensitization subgroups were influenced by potential confounding factors (e.g. duration of pain, psychology), however, as this was not the primary intent of this paper, and previous research has addressed similar questions, we refrained from conducting more advanced statistical analyses. Additionally, we were unable to include data related to shoulder diagnoses in our analyses. We did not, however, have a specific hypothesis on how shoulder diagnoses are related to experimental pain findings. Future analyses should consider whether shoulder diagnoses differentially influence experimental pain responses. Finally, our results are limited to a patient population scheduled for surgery for shoulder pain. Future research should examine experimental pain responses in a more general population of patients with shoulder pain.

Conclusions

These findings suggest patients with unilateral shoulder pain present with variable patterns of peripheral and central sensitization. Contrary to our expectations, no association was observed between patterns of peripheral and central sensitization. Future research will determine the importance of distinguishing between peripheral and central sensitization for management of patients with shoulder pain.

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Table 1

Demographic, clinical, and psychological characteristics of the clinical and healthy participants.

	Clinical Participants (n = 58)	Healthy Participants (n = 56)
Age (years)	32.3 ± 11.6	28.7 ± 8.4
Sex (N of females)	17	16
Pain duration (weeks)	75.1 ± 81.9	-
Pain intensity (x/10)		
Current	2.9 ± 2.4	-
Least	1.6 ± 1.8	-
Worst	5.4 ± 2.6	-
FPQ-9	20.9 ± 5.5	23.1 ± 6.5
PCS	12.2 ± 8.8	8.6 ± 7.6
TSK-11*	24.8 ± 5.4	18.3 ± 5.2

Values represented as N or mean ± SD.

*Significant difference between clinical and healthy participants ($p < 0.015$).

Abbreviations: FPQ-9 – Fear of Pain Questionnaire, PCS – Pain Catastrophizing Scale, TSK-11 – Tampa Scale of Kinesiophobia.

Table 2

Pressure and thermal pain sensitivity values for the affected and non-affected side of clinical participants with unilateral shoulder pain and the control side in healthy participants.

	Clinical Participants		Healthy Participants
	Affected Side	**Non-affected Side**	**Control Side**
Pressure Pain Sensitivity			
PPT at acromion*#† (kg)	4.7 ± 2.9	5.1 ± 3.0	5.8 ± 1.9
PPT at masseter# (kg)	1.7 ± 0.9	1.8 ± 1.0	1.9 ± 0.5
Thermal Pain Sensitivity			
Thermal threshold (°C)	43.9 ± 2.3	44.0 ± 2.3	43.4 ± 2.3
Thermal tolerance (°C)	47.8 ± 1.9	47.7 ± 1.9	47.9 ± 2.0
Thermal tolerance (NRS)	66.7 ± 19.9	66.8 ± 19.5	59.1 ± 24.9
SHPR#† (NRS)	38.3 ± 24.4	35.0 ± 25.3	25.0 ± 25.4

Values represented as mean ± SD

*Significant difference between affected and non-affected side ($p < 0.015$)

#Significant difference between affected and control side ($p < 0.015$)

†Significant difference between non-affected and control side ($p < 0.015$)

Abbreviations: PPT – pressure pain threshold, SHPR – suprathreshold heat pain response, kg – kilograms, °C – degrees Celsius, NRS – numeric rating scale

Table 3

Correlations between sensitization indexes and relevant demographic, clinical, and psychological variables.

	PSI	CSI-PPT	CSI-SHPR
CSI-PPT	.239		
CSI-SHPR	−.047	−.214	
Age	−.257	−.198	−.055
Sex	.138	.320	−.230
Pain duration	−.018	−.064	.019
Pain intensity	−.229	−.217	.116
FPQ-9	−.252	−.204	−.033
PCS	−.172	−.309	−.015
TSK-11	−.235	−.334*	.022

Values are Pearson's correlation.

* Significant association between variables ($p < 0.015$). Pain intensity is the average of pain reported currently, at least, and at worst.

Abbreviations: CSI-PPT – Central Sensitization Index (averaged pressure pain threshold at acromion), CSI-SHPR – Central Sensitization Index (averaged suprathreshold heat pain response), FPQ-9 – Fear of Pain Questionnaire, PCS0000 – Pain Catastrophizing Scale, PSI – Peripheral Sensitization Index, TSK-11 – Tampa Scale of Kinesiophobia.

Table 4

Interpretation of cell counts within the 2×2 frequency distribution table.

Peripheral vs. Central Sensitization Index		
	Central Sensitization Index	
Peripheral Sensitization Index	Yes	No
Yes	*Peripheral and Central Sensitization*	*Peripheral Sensitization*
No	*Central Sensitization*	*No Sensitization*

Table 5

Comparison of frequencies between those meeting/not meeting the peripheral sensitization index (PSI) and central sensitization index (CSI) based on PPT response (CSI-PPT) and SHPR (CSI-SHPR).

PSI x CSI-PPT*

	CSI-PPT		
PSI	Yes	No	Total
Yes	20 (35.1)	14 (24.6)	34 (59.7)
No	11 (19.3)	12 (21.0)	23 (40.3)
Total	31 (54.4)	26 (45.6)	

PSI x CSI-SHPR*

	CSI-SHPR		
PSI	Yes	No	Total
Yes	13 (23.6)	20 (36.4)	33 (60.0)
No	8 (14.5)	14 (25.5)	22 (40.0)
Total	21 (38.1)	34 (61.9)	

Values are individual counts (percentages).

*Non-significant association between indexes ($p > 0.015$).

Table 6

Demographic, clinical, and psychological characteristics of sensitization groups based on index comparison methods.

	Peripheral Sensitization	Central Sensitization	Peripheral and Central Sensitization	No Sensitization	p-value
Method 1					
Age (years)	32.1 [26.1; 38.1]	32.4 [25.3; 39.4]	34.6 [28.3; 40.9]	27.3 [21.6; 33.0]	0.389
Sex (%females)	14.3 [2.8; 41.2]	45.5 [21.3; 72.0]	35.0 [18.0; 56.8]	16.7 [3.5; 46.0]	0.239
Pain duration (weeks)	82.3 [20.4; 144.4]	108.4 [48.4; 168.3]	67.7 [45.3; 90.1]	28.9 [6.6; 51.2]	0.080
Pain intensity (x/10)	3.0 [1.7; 4.3]	3.8 [2.2; 5.5]	3.5 [2.6; 4.5]	2.5 [1.3; 3.6]	0.392
FPQ-9	19.5 [16.7; 22.3]	19.3 [16.4; 22.2]	23.3 [20.2; 26.4]	20.1 [17.0; 23.1]	0.120
PCS	9.3 [5.6; 13.0]	13.8 [6.8; 21.0]	13.3 [19.0; 17.5]	11.2 [5.6; 16.7]	0.503
TSK-11	23.7 [20.3; 27.2]	25.5 [23.1; 27.8]	26.0 [23.6; 28.3]	23.6 [19.2; 28.0]	0.537
Method 2					
Age (years)	32.8 [27.2; 38.3]	28.4 [21.1; 35.7]	33.5 [25.9; 41.1]	31.4 [25.3; 37.4]	0.762
Sex (%females)	20.0 [7.5; 42.2]	50.0 [21.5; 78.5]	30.8 [12.4; 58.0]	21.4 [6.8; 48.3]	0.401
Pain duration (weeks)	83.6 [41.8; 125.3]	110.4 [30.4; 190.3]	56.3 [22.8; 89.8]	46.5 [14.2; 78.8]	0.212
Pain intensity (x/10)	3.0 [2.1; 3.9]	3.6 [1..2; 6.0]	3.4 [2.1; 4.8]	2.8 [1.7; 3.9]	0.785
FPQ-9	22.1 [19.4; 24.7]	21.1 [18.7; 23.5]	20.5 [16.5; 24.6]	18.9 [15.9; 22.0]	0.449
PCS	12.1 [8.6; 15.5]	14.0 [3.5; 24.5]	9.2 [4.8; 13.5]	12.0 [7.6; 16.4]	0.592
TSK-11	25.5 [23.1; 27.9]	26.8 [22.2; 31.3]	23.7 [20.3; 27.3]	23.4 [20.3; 26.6]	0.442

Values presented as % (for sex) or mean with [95% CI]. Method 1 is based on classification of PSI x CSI-PPT. Method 2 is based on classification of PSI x CSI-SHPR. Pain intensity is the average of pain reported currently, at least, and at worst.

Abbreviations: FPQ-9 – Fear of Pain Questionnaire, PCS – Pain Catastrophizing Scale, TSK-11 – Tampa Scale of Kinesiophobia.