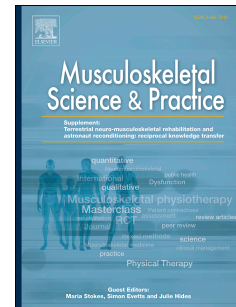


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TITLE PAGE**People with musculoskeletal shoulder pain demonstrate no signs of altered pain processing**

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People with musculoskeletal shoulder pain demonstrate no signs of altered central pain processing

ABSTRACT

Background: Central sensitisation may contribute to persistent musculoskeletal shoulder pain. Few studies have provided a comprehensive sensory and psychosocial evaluation of this population.

Objective: To comprehensively assess whether sensory function and psychosocial aspects are impaired in people with shoulder pain and whether age, gender and clinical outcomes are related to impaired sensory function.

Study design: Observational case-control study

Methods: Twenty-three participants with musculoskeletal shoulder pain and 23 age- and gender-matched healthy participants were included. Static (pressure and thermal pain thresholds) and dynamic (temporal summation) quantitative sensory testing was performed bilaterally at the shoulder and remote tibialis anterior muscle. Conditioned pain modulation was measured at the affected/matched shoulder. Shoulder function (SPADI), depression, anxiety and stress (DASS-21) and health-related quality of life (EQ-5D-5L) were also measured. Comparisons were performed between body regions and groups. Age and gender were included as factors in analyses. Clinical outcomes were tested for correlation with sensory measures.

Results: Shoulder pain group had higher local pressure pain threshold (i.e., hypoalgesia; $p = 0.03$; $Z = 0.5.04$), higher SPADI score ($p < 0.01$; $Z = -5.76$) and higher EQ-5D-5L ($p < 0.01$; $Z = 5.23$) compared to the control group. There was no difference between groups for thermal pain sensitivity, dynamic sensory testing or psychological measures.

Conclusion: People with shoulder pain demonstrated mechanical hypoalgesia, increased upper limb disability and poorer quality of life compared with healthy controls. Central sensitisation seems not be a characteristic of musculoskeletal shoulder pain although it could be present in a subgroup of patients.

Keywords: central nervous system; CNS sensitisation; quantitative sensory testing; shoulder pain

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sensitisation seems not be a characteristic of musculoskeletal shoulder pain although it could be present in a subgroup of patients.

INTRODUCTION

Musculoskeletal shoulder pain is the third most frequent reason people seek treatment from a healthcare professional (McBeth and Jones, 2007), and while there is evidence that suggests conservative interventions can reduce pain and improve function (Camargo et al., 2015; Haik et al., 2016), 50% of patients report persistent pain at six months and 40% still have pain at one year (Bot et al., 2005; Croft et al., 1996; Kuijpers et al., 2006). There is debate regarding the most effective management strategies for patients with shoulder pain, as the underlying pathophysiology may involve more than local tissue pathology (Littlewood et al., 2013; Noten et al., 2017; Sanchis et al., 2015). That is, similar to other persistent musculoskeletal conditions, both peripheral and central pain processes may contribute to the clinical presentation of persistent shoulder pain (Borstad and Woeste, 2015; Noten et al., 2017; Sanchis et al., 2015).

Central sensitisation is defined as an *amplification of neural signalling within the central nervous system (CNS) that elicits pain hypersensitivity* (Woolf, 2011), and is clinically observed as aberrant sensory processing in the CNS, malfunctioning of the diffuse noxious inhibitory system, and/or enhanced activity of pain facilitation pathways (Nijs et al., 2014; Woolf, 2011). Neurophysiological changes in central sensitisation are related to alterations in the cortical network that modulate pain processes through neurological, psychosocial and local tissue factors (Fryer, 2017; Nijs et al., 2014; Wijma et al., 2016) and have been found in different shoulder conditions (Gwilym et

al., 2011; Hidalgo-Lozano et al., 2010; Paul et al., 2012). Although there is no gold standard for diagnosis, quantitative sensory testing (QST) is being employed to identify characteristics thought to be related to central sensitisation and to assist in monitoring of chronic pain processes (Wilder-Smith, 2011; Yarnitsky et al., 2014).

Depression and anxiety have also been found to mediate central sensitisation and predict prognosis in musculoskeletal conditions (Orenius et al., 2012; Schafer et al., 2017; Wong et al., 2014). Specifically at the shoulder, there seems to be a higher prevalence of depression and anxiety in people with shoulder pain when compared to healthy controls (Cho et al., 2013). Also, high levels of depression and anxiety have been correlated to shoulder disability in patients with chronic shoulder pain (Badcock et al., 2002; Cho et al., 2013), which illustrates a possible interaction between psychological status and shoulder pain. Therefore, these psychological factors may play a key role in the explanation as to why musculoskeletal pain becomes chronic (Vranceanu et al., 2009).

Signs and symptoms of central sensitisation have been found in 65-90% of people with shoulder pain (Coronado et al., 2014, 2015; Gwilym et al., 2011; Paul et al., 2012), and its presence may contribute to poor treatment outcomes and prognosis (Gwilym et al., 2011; Kuijpers et al., 2006; Noten et al., 2017; Paul et al., 2012). This notion is supported by two systematic reviews that concluded that central sensitisation might be a feature of chronic shoulder pain (Noten et al., 2017; Sanchis et al., 2015). However, most of the studies included in these reviews only included one or two sensory modalities and mainly locally at the affected shoulder. Only one study has recently examined sensory function in participants with unilateral shoulder pain compared with

healthy controls using a comprehensive QST protocol, including static and dynamic assessment methods (Kuppens et al., 2017). This study found no features of central sensitisation in the shoulder pain group based on the absence of local or remote alterations in pressure pain, vibration or sharp detection thresholds, in dynamic pain modulatory mechanisms, nor psychological aspects related to pain vigilance and catastrophising (Kuppens et al., 2017). However, local measures of sensory function were performed only at the upper trapezius muscle belly and only mechanical pain sensitivity was assessed. Therefore, more comprehensive testing is required to better understand the role of central sensitisation in shoulder pain.

The primary aims of this study were to investigate whether musculoskeletal shoulder pain is related to impaired sensory function and to investigate whether musculoskeletal shoulder pain is related to psychosocial behaviours. The secondary aims were to assess whether age, gender and clinical outcomes influence sensory function. The hypotheses were that participants with shoulder pain will exhibit local and widespread hyperalgesia as well as afferent facilitation to noxious stimuli, increased anxiety and stress states, and poorer quality of life compared to healthy participants. Also, we hypothesised that high anxiety and depression states and poor quality of life would be associated with widespread hyperalgesia in participants with shoulder pain.

MATERIALS AND METHODS

Participants

Twenty-three participants (mean age \pm SD 35.6 ± 11.8 years; 9 women) with unilateral musculoskeletal shoulder pain (shoulder pain group) and 23 healthy control (33.7 ± 10.7 years) volunteers were consecutively recruited from the general community between

January and March 2015. Participants were recruited via email and print advertising at local community centres, orthopaedic clinics, and university buildings. Eligibility for inclusion in the shoulder pain group included pain at the proximal anterolateral aspect of the shoulder that was aggravated by arm elevation, and of at least six weeks duration together with positive findings on at least three of the following tests (Michener et al., 2009): Neer (Neer, 1972), Hawkins-Kennedy (Hawkins and Kennedy, 1979), Jobe (Jobe and Moynes, 1982), painful arc (Kessel and Watson, 1977), and external rotation resistance (Park et al., 2005). Tests were performed by a qualified physiotherapist with 8 years' experience in musculoskeletal physiotherapy. Participants were excluded from the shoulder pain group if they had any form of treatment for the shoulder in the past six months or for any other musculoskeletal pain in the past three months. Healthy control participants were age, gender, weight, height and dominance matched to their shoulder pain counterparts. Eligibility for enrolment into the healthy group included no history of shoulder pain or any other pain lasting more than four weeks.

Exclusion criteria for both groups included history of cancer, cardiac, systemic or neurological disorders, use of medication known to affect sensory sensitivity (e.g., opioids, gabapentin), surgery or significant shoulder injuries (e.g., dislocations or fractures) (McClure et al., 2006). This study was approved by the XXX University Human Research Ethics Committee and was conducted according to the Declaration of Helsinki. Participants gave written informed consent prior to their enrolment in the study.

Procedure

Fifty-two volunteers with shoulder pain were screened, and 29 did not meet the

inclusion criteria because of one of the following reasons: shoulder pain from cervical origin, upper trapezius pain, shoulder fracture or dislocation, bilateral shoulder pain, recent cortisone injection, associated chronic elbow or low back pain, or unable to attend the data collection session. Twenty-three participants completed the testing session. Following collection of demographic and clinical data, outcome measures were recorded in a single session using a test order designed to avoid systemic provocation of hyperalgesia after thermal stimuli (Gröne et al., 2012): 1) active shoulder range of motion (ROM); 2) temporal summation (TS); 3) pressure pain threshold (PPT); 4) cold (CPT) and heat pain thresholds (HPT); and 5) conditioned pain modulation (CPM).

Outcome Measures

Questionnaires

Worst shoulder pain experienced over the past 24 hours was measured using a 0-10 point numerical rating scale (NRS; 0 = no pain at all, 10 = worst pain experienced), a valid and reliable measure of pain severity (Gallagher et al., 2001). We interpreted the NRS scores to be mild (1-3), moderate (4-6) or severe (7-10). Pain and disability were measured using the Shoulder Pain and Disability Index (SPADI), a validated condition-specific questionnaire with a total score ranging from 0 (no pain or disability) to 100 (maximal pain and disability) (Ekeberg et al., 2008; Roach et al., 1991). Psychosocial behaviours were assessed with the following questionnaires: the Depression Anxiety Stress Scale (DASS-21; score 0 - 21) (Henry and Crawford, 2005), Quality of Life (EQ-5D-5L with UK value set -0.285 to 1) (Devlin et al., 2018; McCaffrey et al., 2016; Rabin and Charro, 2001), and the single global rating of self-perceived health (EQ-VAS, range: 0 to 100).

Physical Measures

In standing, participants were asked to actively raise their arm (elbow extended and forearm in mid pronation) in the plane of the scapula until they first felt pain in the affected shoulder (Kolber et al., 2011). A measure of pain-free ROM was taken three times at 30-second intervals with a universal goniometer (Kolber and Hanney, 2012) and the average used in further analyses.

Temporal summation (TS) was measured using an 180 g von Frey filaments as pinprick stimuli (North Coast Medical, San Jose, California) (Rolke et al., 2006). The monofilament was applied as a single stimulus (pinprick stimulus) to the painful shoulder (mid-deltoid region, halfway between the lateral border of the acromion and deltoid insertion), and also the contralateral tibialis anterior (upper one third of the muscle belly) in a random order. A measure of pain severity was recorded using a 0-100 mm visual analogue scale (PVAS, 0 = no pain, 100 = worst pain imaginable). After a 15-seconds interval, 10 pinprick stimuli were applied within 1cm² of the same area with a 1-second inter-stimulus interval (ProMetronome App, Xiao Yisiang, Apple store). Participants were again asked to rate pain intensity immediately following the 10th stimulus. This process was repeated 5 times within a 5-minutes interval and the difference in PVAS between the first and 10th stimuli was averaged and defined as 'temporal summation' for further analyses. Temporal summation is a valid method to assess excitability of spinal cord neurons that reaches a plateau after five stimuli (Rolke et al., 2006).

Pain thresholds (PPT, CPT, HPT) were measured bilaterally over the shoulder and contralateral tibialis anterior muscle in a random order. PPT, defined as the minimum

amount of pressure that provoked the first onset of pain, was assessed using a pressure algometer (Somedic AB, Farsta, Sweden) with 1cm² probe tip. Triplicate measures were taken at each point (30 s inter-stimulus interval), and the average calculated for use in further analyses (Chesterton et al., 2007).

CPT/HPT were measured using the Neurosensory Analyzer TSA-II (Medoc, Israel) with a 9 cm² contact thermode. The baseline temperature was set at 32°C and the skin was cooled (CPT) or heated (HPT) at a rate of 1°/sec until the instant the participant indicated the first sensation of cold/heat-with-pain (minimum temperature 0°C; maximum temperature 50°C) (Coombes et al., 2012). The probe then returned to 32°C at a rate of 5°/sec, with a 30-second rest interval prior to the next test. Each test was repeated three times and the results averaged to obtain the mean threshold value.

The Cold Pressor Test was used as the conditioning stimulus for assessment of CPM. Firstly, the participants' unaffected (healthy control = matched) hand was immersed in a recirculating water bath (Polyscience model 912; Niles, IL) at a constant temperature of 2° ± 0.5°C. Participants were instructed to verbally report the moment when they first felt pain during immersion, with this time recorded as the cold pain threshold. Cold pain tolerance was reached either when the participant withdrew the hand due to pain intolerance or at the maximal time limit of 2 minutes' water immersion. Participants rated their worst pain during the water immersion (PVAS) immediately upon removal of their hand from the water. The test stimuli used during the CPM paradigm were PPTs. PPTs were measured every 30 seconds over the mid-deltoid muscle on the affected (healthy control = matched) side during water immersion, immediately following withdrawal, and 30 and 60 seconds post-withdrawal from the water. The

average and peak PPT during- and post-Cold Pressor Test were calculated separately and used in further analyses. Average PPT during Cold Pressor Test was defined as the mean recorded PPTs measured until 90 seconds of immersion. Average PPT post-Cold Pressor Test was defined as the mean recorded PPTs measured following removal of the hand from immersion. Absolute and relative CPM values were calculated as recommended (Yarnitsky et al., 2015). Absolute CPM was the difference of the respective 'Peak PPT (during or post-Cold Pressor Test)' from the average of the triplicate baseline PPTs. Each of these CPM values was converted to a percentage (relative CPM) using the formula $[(PPT_{\text{Peak}} - PPT_{\text{Baseline}}) / PPT_{\text{Baseline}}] * 100$.

Sample size

Sample size was calculated based on an estimated difference in PPT of 98 (standard deviation, SD 137) kPa between shoulder pain and healthy control groups from previous studies (Albuquerque-Sendín et al., 2013; Paul et al., 2012). With two-tailed significance set at 0.05 and power at 90%, it was calculated that a minimum of 23 participants were required for each group.

Statistical analyses

The affected side in the shoulder pain group was matched in the control group based on limb dominance. The distributions of data were assessed using visual inspection, box plots and the Shapiro-Wilks test. Normally distributed data are reported as means and standard deviations (SD) or 95% confidence intervals (95% CI) in the text. Otherwise, data are reported as median and interquartile range [IQR]. Appropriate parametric or non-parametric statistics were calculated for unadjusted univariate comparisons between shoulder pain and control participants. Multilevel modelling, using the linear mixed

models (LMM) function in SPSS (V24, IBM, Chicago USA) (Welch et al., 2007), was used to account for the repeated responses given by each participant for analyses of PPT, CPT, HPT, TS and CPM. Individual trial data (rather than averages) for each stimulus were included in multilevel modelling. The models controlled for the repeated measures by including random effects for participant, either a random intercept or a random slope, as determined during model building. A variance components covariance structure and restricted maximum likelihood estimation (REML) were used. In addition, age and gender were initially included in all multivariable models as potential confounders, and were retained in the final model if $p < 0.05$.

Group differences in HPTs, CPTs and PPTs were investigated using LMM with a random slope accounting for repeated measures (three trials of each measure performed over the affected/non-affected shoulders and remote tibialis anterior region). The model investigated the effects of Region (affected shoulder/non-affected shoulder/remote tibialis anterior) and determined if the effects differed by Group (shoulder pain/control). Similarly, group differences in TS were investigated using LMM with a random slope accounting for repeated measures (five trials of each Epoch performed for each body region and individual variability). The model evaluated the effect of Epoch (single/repeated) and body Region (affected shoulder/tibialis anterior) on Pain Ratings (PVAS) and determined if the effects differed by Group (shoulder pain or control). A random intercept LMM model was constructed to investigate CPM and evaluate the effect of Time (pre-test or during immersion) on shoulder PPTs and determine if the effects differed by Group (shoulder pain or control). Bonferroni corrected *post hoc* tests were used to investigate group differences for both models. Spearman's rho correlation coefficients were calculated to assess the relationship between clinical (duration of

condition, SPADI, DASS, EQ-5D-5L, EQ-VAS, ROM) and dynamic pain modulation characteristics (relative CPM% and TS) for the shoulder pain participants only, with Bonferroni adjustment for multiple comparisons. Statistical significance was set at $p < 0.05$, with all analyses performed using Statistical Package for Social Sciences (version 24.0; SPSS Inc., Chicago, IL).

RESULTS

Questionnaires

Shoulder pain participants demonstrated moderate levels of pain (NRS), mild levels of disability (SPADI) and poorer quality of life (EQ-5D-5L and EQ-VAS) compared to controls (Table 1).

Table 1: Baseline characteristics of study participants

	Healthy control (n=23) Mean (95% CI) Median [IQR]	Shoulder pain (n=23) Mean (95% CI) Median [IQR]	Test Statistic Z	p Value
NRS (0-10)	N/A	4.6 (3.5, 5.7)		
Symptoms duration (weeks)	N/A	149.3 (68.2, 230.7)		
SPADI – Pain (/50)	0 [0, 0]	23 [12, 29]	-5.82	< 0.001*
SPADI – Disability (/80)	0 [0, 0]	14 [6, 26]	-5.50	< 0.001*
SPADI - Total (/130)	0 [0, 0]	38 [26, 57]	-5.76	< 0.001*
Depression (0-21)	1 [0, 2]	2 [0, 4]	-1.09	0.28
Anxiety (0-21)	0 [0, 3]	1 [0, 4]	-1.22	0.22
Stress (0-21)	3 [0, 4]	4 [2, 8]	-1.68	0.09
EQ-5D-5L (-0.285-1)	1 [0.93, 1]	0.84 [0.76, 0.87]	-5.23	< 0.001*
EQ-VAS (0-100)	85 [75, 95]	78 [70, 85]	-2.62	0.009*

Legend: CI = confidence interval; IQR = interquartile range; NRS = numerical pain

rating scale; SPADI = Shoulder Pain and Disability Index; EQ-5D-5L and EQ-VAS = quality of life; N/A = Not Applicable, indicating that these measures were not collected in the healthy control group.

Physical Measures

Range of motion

The shoulder pain group presented with a significant reduction of active pain-free scaption ROM compared to healthy controls (Table 3).

Temporal summation

Results from univariate analysis of temporal summation (TS) showed higher pain ratings in the shoulder and tibialis anterior for repeat (x10) pinprick stimuli in the shoulder pain group, resulting in significantly greater temporal summation in the shoulder pain group for both body regions compared to the control group (Table 2).

Table 2: Unadjusted participant pain ratings for #1 and #10 stimuli in the painful shoulder and lower limb during temporal summation.

Region	Epoch	Pain scores (NRS 0-100)		Test Statistic	
		Healthy control (n=23)	Shoulder pain (n=23)	Mann-Whitney U	
		Median [IQR] (/100)	Median [IQR] (/100)	Z	p
Affected shoulder	#1	0 [0,1.8]	0 [0, 3.4]	-0.55	0.59
Affected shoulder	#10	2.6 [0.4, 8]	6.0[3, 9.8]	-1.76	0.08
Affected shoulder difference	#10 - #1	1.2 [0.4, 6.6]	4.2 [1.4, 6.8]	-1.96	0.05*
Tibialis anterior	#1	0 [0, 1.6]	0.8 [0, 3.4]	-1.78	0.08
Tibialis anterior	#10	1.6 [0, 5]	5.6 [3, 9.6]	-2.88	0.004*
Tibialis anterior difference	#10 - #1	0.8 [0, 3.4]	5.0 [1.8, 8.4]	-2.50	0.012*

Legend: IQR = interquartile range; #1 = first epoch for single pinprick stimulus; #10 =

tenth epoch for 10 pinprick stimuli train. **Bolded** * $p \leq 0.05$.

The multilevel model revealed a significant main effect of Epoch ($F_{1,46.0} = 53.6$, $p < 0.001$) with post hoc testing showing that pain ratings were higher for the #10 applied

stimuli, irrespective of body region or group. There was no significant Group*Epoch effect ($F_{1,46.0} = 2.89$, $p = 0.10$) or main effect of Group ($F_{1,46} = 3.79$, $p = 0.058$), indicating that pain ratings for #1 or #10 applied stimuli did not significantly differ by group.

Pressure and thermal pain thresholds

The shoulder pain group demonstrated higher PPTs than the healthy control group for the affected shoulder (Table 3). There were no other significant thermal or pressure pain threshold group differences demonstrated for any body region (Table 3).

Table 3: Thermal and pressure pain threshold for shoulder pain and control groups.

	Healthy control (n=23) Median [IQR]	Shoulder pain (n=23) Median [IQR]	Test Statistic Mann-Whitney U	
			Z	p
Scaption ROM (°)	177 [173.0, 181.0]	134 [93.0, 163.0]	-5.04	< .001*
PPT (kPa)				
Affected shoulder	193 [156.0, 320.0]	276 [207.0, 366.0]	-2.16	0.03*
Non-affected shoulder	210 [147.0, 328.0]	264 [191.0, 367.0]	-1.67	0.10
Tibialis anterior	295 [189.0, 414.0]	289 [237.0, 425.0]	-0.61	0.54
CPT (°C)				
Affected shoulder	8.3 [2.9, 17.3]	19.2 [1.0, 25.8]	-0.92	0.36
Non-affected shoulder	5.3 [0.1, 19.1]	13.5 [0.6, 25.2]	-0.66	0.51
Tibialis anterior	4.8 [0, 22.7]	12.8 [3.1, 25.5]	-1.94	0.052
HPT (°C)				
Affected shoulder	46.6 [43.8, 48.6]	45.9 [42.0, 46.6]	-0.40	0.69
Non-affected shoulder	46.7 [43.9, 48.1]	45.6 [43.6, 47.0]	-0.97	0.33
Tibialis anterior	45.5 [44.5, 48.1]	45.0 [42.4, 46.5]	-1.56	0.12

Legend: ROM = range of motion; PPT = pressure pain threshold; kPa = kilopascal;

CPT/HPT = cold/heat pain thresholds; IQR = interquartile range; **Bolded** * $p \leq 0.05$

After controlling for gender, multilevel modelling for PPTs demonstrated significant main effects for region ($F_{2,87.7} = 9.88$, $p < 0.001$) and group ($F_{1,46.0} = 4.95$, $p = 0.031$).

There was no significant interactive region*group effect. Post hoc tests demonstrated

that PPTs were higher in the tibialis anterior when compared to the affected ($p < 0.001$) or non-affected ($p < 0.001$) shoulder, and there was no significant difference between shoulders ($p = 0.69$). The shoulder pain group demonstrated higher PPTs than the control group ($p = 0.031$) independently of the region (main effect of group).

After controlling for age, multilevel modelling for HPTs and CPTS demonstrated a significant main effect for age (HPT: $F_{1,46.2} = 7.17$, $p = 0.01$; CPT: $F_{1,46.2} = 4.31$, $p = 0.044$), with post hoc tests showing that increasing age resulted in increased HPT and CPT. There were no significant interactive region*group effects (HPT: $F_{2,88.7} = 1.13$, $p = 0.33$; CPT: $F_{2,88.6} = 0.24$, $p = 0.79$), region (HPT: $F_{2,88.7} = 0.20$, $p = 0.82$; CPT: $F_{2,88.6} = 0.39$, $p = 0.68$), or group (HPT: $F_{1,45.8} = 3.00$, $p = 0.09$; CPT: $F_{1,45.9} = 3.15$, $p = 0.08$) for either HPT or CPT, indicating that thermal pain thresholds did not differ across body regions or between groups.

Conditioned pain modulation

Apart from a significantly increased peak PPT during immersion for the shoulder pain group, the results from conditioned pain modulation showed no significant differences between the healthy control and shoulder pain groups (Table 4). One participant in each group was unable to immerse their hand for the full 120 seconds.

Table 4: Unadjusted conditioned pain modulation results for shoulder pain and healthy control groups.

CPM	Healthy	Shoulder pain	Test Statistic	
	control (n=23)	(n=23)	Mann-Whitney U	
	Median [IQR]	Median [IQR]	Z	p
	Mean (95% CI)	Mean (95% CI)		

Cold pressor threshold (s)	8 [5, 10]	8 [6, 11]	-1.51	0.13
Cold pressor tolerance (s)	120 [120, 120]	120 [120, 120]	-0.59	0.56
Cold pressor maximum pain (NPRS/10)	8.5 [7.2, 9.1]	8.8 [8.0, 10]	-1.65	0.10
Shoulder PPT pre-Cold Pressor Test (kPa)	193 [156, 320]	277 [207, 366]	-1.29	0.20
Average shoulder PPT during Cold Pressor Test (kPa)	324 [278, 476]	425 [333, 512]	-1.70	0.09
Peak shoulder PPT during Cold Pressor Test (kPa)	365 [330, 528]	545 [378, 579]	-2.00	0.046*
Average shoulder PPT post-Cold Pressor Test (kPa)	296 [212, 404]	388 [258, 502]	-1.88	0.06
Peak shoulder PPT post-Cold Pressor Test (kPa)	331 [255, 466]	397 [314, 545]	-1.73	0.085
Absolute CPM during Cold Pressor Test (kPa)	184 [140, 263]	217 [132, 295]	-0.88	0.38
Relative CPM during Cold Pressor Test (%)	96 (73, 119)	85 (63, 108)	$t_{44} = 0.68$	0.50
Absolute CPM post-Cold Pressor Test (kPa)	135 [60, 157]	140 [64, 208]	-0.80	0.42
Relative CPM post-Cold Pressor Test (%)	61 (41, 81)	56 (34, 79)	$t_{44} = -1.85$	0.07

Legend: CPM = Conditioned pain modulation; IQR = Interquartile Range; CI =

Confidence interval; NPRS = Numerical pain rating scale; PPT = Pressure pain threshold; kPa = kilopascal; **Bolded** * $p \leq 0.05$.

After controlling for the effect of gender, the multilevel model revealed that CPM (i.e., difference between pre-Cold Pressor Test PPT and peak PPT during Cold Pressor Test) was similar for both study groups (Group*Time interaction: $F_{1,44} = 0.65$, $p = 0.42$).

There was a significant main effect of Group ($F_{1,43} = 5.37$, $p = 0.025$) and Time (i.e. Pre/During Cold Pressor Test) ($F_{1,44} = 39.8$, $p < 0.001$), indicating that PPTs were higher overall in the shoulder pain group (irrespective of immersion status) and higher during immersion in 2°C water compared to pre-Cold Pressor Test for both groups.

Association between clinical characteristics and pain modulation

There were no significant correlations (Bonferroni corrected for multiple comparisons) demonstrated between duration of symptoms ($p > 0.51$), self-reported pain ($p = 1.00$), disability ($p = 1.00$), Total DASS scores ($p > 0.06$), EQ-5D-5L ($p = 1.00$) or ROM ($p = 1.00$), and either dynamic measure (i.e. TS or relative CPM%) of pain modulation.

DISCUSSION

This study investigated whether sensory function was altered in people with shoulder pain compared to healthy controls using static and dynamic measures of pain processing. The study also assessed whether clinical outcomes were related to dynamic sensory function. The results partially supported our hypotheses. Compared to healthy controls, people with shoulder pain presented with local mechanical hypoalgesia. However the hypoalgesia effects were small and not clinically meaningful. Increased mechanical hypoalgesia was also observed in the shoulder pain group during the cold pressor test. Upper limb function and quality of life were significantly impaired in this population while depression, anxiety and stress states were not. We also found that clinical outcomes were not related to dynamic sensory function.

Our findings do not support the hypothesis that central sensitisation is a feature of musculoskeletal shoulder pain. While the shoulder pain group exhibited significant local mechanical *hypoalgesia* (i.e., increased PPTs at the affected shoulder) compared to the control group, the between-group difference was not clinically important (Bisset et al., 2015; Fisher, 1990). A recent study reported similar findings of no difference in PPT, TS or CPM in participants with shoulder pain compared to healthy controls (Kuppens et al., 2017). However, this conflicts with other studies that reported widespread mechanical hyperalgesia (Coronado et al., 2014; Paul et al., 2012), increased local

temporal summation of thermal pain (Coronado et al., 2014; Valencia et al., 2012) and decreased descending inhibition (Valencia et al., 2012) in people with shoulder pain.

Differences in findings between studies may be explained by methodological differences and by clinical differences in studied populations. For example, CPM methods reported in the literature incorporate different conditioning stimuli (e.g., contact thermode (Kuppens et al., 2017) or cold pressor test at varying intensities of 8°C (Valencia et al., 2012) compared to 2°C in our study), and different test stimuli such as algometry (Kuppens et al., 2017) or suprathreshold heat pain (Valencia et al., 2012).

Differences in study populations may also influence results. For example, the mean duration of shoulder pain in our study was approximately 3 years, compared to 6-70 months (Coronado et al., 2014; Kuppens et al., 2017; Paul et al., 2012). Although a longer duration of the condition correlates with higher prevalence of peripheral and/or central sensitisation processes both in individuals with shoulder pain (Coronado et al., 2014) or other musculoskeletal pain conditions such as low back pain (Corrêa et al., 2015) our findings did not demonstrate such a correlation. Given the chronicity of shoulder pain in our cohort, the mechanisms and contributing factors underpinning musculoskeletal shoulder pain currently remain unclear. Moreover, our population presented with low levels of shoulder disability and shoulder pain had to be provoked during arm elevation. In contrast, Valencia et al. (2012) and Coronado et al. (2014) included people with shoulder pain also associated with adhesive capsulitis and people who were scheduled to undergo arthroscopic surgery, which may suggest participants had greater degrees of shoulder disability in these other studies compared to our cohort. Therefore, symptom severity might play an important role in influencing the

development and maintenance of central sensitisation, since people with subacromial and/or internal impingement may only experience pain intermittently while those with adhesive capsulitis may have constant pain and dysfunction.

Central sensitisation is characterised by impaired endogenous pain inhibition, overactive endogenous pain facilitation or temporal summation (Nijs et al., 2014; Woolf, 2011). Increased temporal summation has previously been identified in conditions such as chronic fatigue (Collin et al., 2017), fibromyalgia (Arendt-Nielsen and Graven-Nielsen, 2003; Staud et al., 2007) and phantom limb pain following amputation (Vase et al., 2011). While the present study did not find evidence of altered temporal summation in the shoulder pain group after controlling for baseline score and body region, it is possible that some individuals within the cohort displayed increased temporal summation. The study was not powered to allow exploration of sub-groups within the shoulder pain group. As such, a larger cohort study is necessary to understand whether some individuals with shoulder pain are more likely to present with, or develop, afferent facilitation mechanisms related to central sensitisation processes.

There are some limitations that must be considered in the present study. The small sample size and cross sectional study design limits the generalisability of the results. A longitudinal study is needed to assess the causal relationship between sensory and clinical characteristics and also the influence of sensory changes on treatment outcomes. Pain inhibition or facilitation may be influenced by other biological and psychosocial factors that were not fully investigated in this study, such as optimism and pain catastrophising (Goodin et al., 2013, 2009). Volunteers with comorbidities were excluded in the current study, so the results may not be generalisable to individuals with

concomitant musculoskeletal disorders such as neck pain or even to those with more severe shoulder pain symptoms such as early stages of adhesive capsulitis, which might be incorporated in future studies. Lastly, the outcome assessor was not blind to the participant group, which may lead to a risk of bias. However, he was blind to all the sensorial measures, as a second assessor read and recorded these measures out of the primary assessor's vision. It is important to highlight that, when dealing with physical measures, blinding of relevant parties is often extremely difficult (Boutron et al., 2004). Also, although trials with inadequate blinding of assessor or participants tend to overestimate group differences, a recent systematic review of clinical trials did not find differences in treatment effects between studies that did use a blinded assessor and/or participants and studies that did not (Armijo-Olivo et al., 2017). Notwithstanding this, the lack of between-group differences in our study suggests that there was minimal bias from the unblinded outcome assessor.

CONCLUSION

People with musculoskeletal shoulder pain did not demonstrate clinically meaningful differences in sensory function compared to healthy controls. Central sensitisation may not characterise musculoskeletal shoulder pain, although it may be present in a subgroup of patients. In addition, clinical and psychological outcomes were not associated with changes in sensory function in this population.

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