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Investigation of central pain processing in shoulder pain: converging results from two musculoskeletal pain models

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Abstract

Recent reports suggest deficits in conditioned pain modulation (CPM) and enhanced suprathreshold heat pain response (SHPR) potentially play a role in the development of chronic pain. The purpose of this study was to investigate whether central pain processing was altered in 2 musculoskeletal shoulder pain models. The goals of this study were to determine whether central pain processing: 1) differs between healthy subjects and patients with clinical shoulder pain, 2) changes with induction of exercise induced muscle pain (EIMP), and 3) changes 3 months after shoulder surgery. Fifty eight patients with clinical shoulder pain and 56 age and sex matched healthy subjects were included in these analyses. The healthy cohort was examined before inducing EIMP, and 48 and 96 hours later. The clinical cohort was examined before shoulder surgery and 3 months later.

CPM did not differ between the cohorts, however; SHPR was elevated for patients with shoulder pain compared to healthy controls. Induction of acute shoulder pain with EIMP resulted in increased shoulder pain intensity but did not change CPM or SHPR. Three months following shoulder surgery clinical pain intensity decreased but CPM was unchanged from pre-operative assessment. In contrast SHPR was decreased and showed values comparable with healthy controls at 3 months. Therefore, the present study suggests that: 1) clinical shoulder pain is associated with measurable changes in central pain processing, 2) exercise-induced shoulder pain did not affect measures of central pain processing, and 3) elevated SHPR was normalized with shoulder surgery. Collectively our findings support neuroplastic changes in pain modulation were associated with decreases in clinical pain intensity only, and could be detected more readily with thermal stimuli.

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Disclosures

The authors have no financial relationships that might lead to a conflict of interest.

Keywords

Conditioned pain modulation; suprathreshold heat pain response; shoulder pain; shoulder surgery; exercise induced muscle pain

Introduction

Few definitive factors mark the transition from “normal” acute pain after surgery to chronic pathological pain. Pre-operative elevated pain sensitivity, which may be attributed to central pain dysregulation (e.g. central sensitization), may increase risk for the development of chronic pain after surgery¹⁹. There are multiple ways of determining central pain dysregulation and this study examined two specific approaches; conditioned pain modulation and suprathreshold heat pain response.

Conditioned pain modulation (CPM) is one type of endogenous modulation of pain^{18, 24, 36}, which is typically induced by a painful stimulus applied to a remote area of the body (conditioning stimulus), which causes inhibition of pain in response to a different painful stimulus (test- stimulus)³⁶. A reduction in the magnitude of the test-stimulus in response to the conditioning stimulus is considered as “conditioned pain modulation”³⁶, and this measure is believed to be an indication of the potential for endogenous pain inhibition. In this study we are using CPM as an “inhibitory” measure, and we included CPM because previous studies show its predictive utility in chronic post-operative pain development^{16, 37}.

Evidence also supports enhanced suprathreshold heat pain response (SHPR) for involvement in a variety of chronic pain disorders^{10, 26, 32, 35}, via altered central pain processing²⁹. SHPR results in the perception of increased pain despite constant or even reduced peripheral afferent input³². We included SHPR in this study because it is considered a perceptual manifestation of enhanced central excitability.^{20, 27–29, 31}, therefore we are using SHPR as a “facilitatory” measure. Furthermore, SHPR is derived from a dynamic quantitative sensory testing protocol and dynamic measures are thought to better capture the pain modulatory ability of the central nervous system in comparison with static measures (e.g. threshold and tolerance)². Finally we included SHPR in the current study because our previous study suggested that this particular measure had clinical relevance by contributing additional variance to reports of shoulder pain intensity³³.

Together these data suggest that patients with continued pain after surgery may have a dysregulation in central pain processing similar to that seen in other chronic pain disorders^{1, 10, 20, 27, 28, 32}. However, it remains unclear whether this dysregulation in central pain processing could be detected pre-operatively or whether central pain processing changes over time as a consequence of continued post-operative pain. The primary purpose of this study was to investigate whether central pain processing (as measured by CPM and SHPR) was altered in 2 different musculoskeletal shoulder pain models.

Healthy subjects were examined before inducing pain by exercise induced muscle pain (EIMP) at the shoulder. EIMP refers to muscular pain produced during active contractions or passive stretch of a muscle after eccentric exercise, which typically peaks 24–48 h after the exercise³. This experimental model was chosen because as per our previous studies it provided a controlled method for inducing clinically relevant shoulder pain^{7, 8}; thus, it is an appropriate model to study acute pain mechanisms. In addition, this study examined patients with acute and sub acute shoulder pain preparing to undergo shoulder surgery. We chose this model of clinical pain, since patients can be assessed before surgery and reassessed 3

months post surgery to detect changes in central pain processing, as has been previously observed in total knee arthroplasty¹⁶.

The specific goals of this study were to determine whether: 1) central pain processing differs between healthy subjects and patients with clinical shoulder pain, 2) induction of exercise induced muscle pain produces central pain processing changes over 4 days, and 3) central pain processing changes 3 months after shoulder surgery.

Methods

Subjects

The University's institutional review board for human participants approved this study. This prospective design includes two groups of participants, a clinical cohort of patients having shoulder surgery, and an age and sex matched healthy control cohort (subjects without pain) (see Figure 1). All participants provided informed consent before participating in this study.

Healthy cohort—This study includes data from individuals recruited from undergraduate and graduate courses from University of Florida and surrounding community areas. The inclusion criteria for being a participant in the healthy cohort were: healthy subjects (without any pain or psychological condition) between 18 and 85 years of age, and English speaking. The exclusion criteria were: history of neck or shoulder injury, sensory or motor impairment of the shoulder, regular participation in high or low intensity upper-extremity weight training, or currently taking pain medication^{7, 8}.

Clinical cohort—This study includes data from consecutive patients seeking treatment of shoulder disorder, which were recruited from University of Florida's Orthopaedics Sports Medicine Institute (OSMI). The inclusion criteria for being a participant in the clinical cohort were: patient between 18 and 85 years of age, complaints of pain limited to anterior, lateral, or posterior shoulder, rotator cuff tendinopathy, adhesive capsulitis, SLAP (Superior Labrum from Anterior to Posterior) lesion, and scheduled for arthroscopic surgery. Exclusion criteria for the prospective clinical cohort were: current complaints of pain greater than the past 3 months involving neck, elbow, hand, low back, hip, knee, or ankle, massive or complete rotator cuff tear, shoulder OA or RA, prior shoulder surgery within the past year, current shoulder fracture, tumor, or infection, previously diagnosed chronic pain disorder, current psychiatric management, and gastrointestinal or renal illness³³.

Measures and procedure

Demographic Information—Study participants completed a standard intake information form. Demographic data collected at initial evaluation included gender, age, race, ethnicity, employment status, marital status, and educational level.

Quantitative Sensory Testing—Quantitative sensory testing measures from previously established protocols were used in this study. Dynamic measures such as SHPR and CPM were included because are thought to better capture the pain modulatory capacity of the central nervous system^{2, 33}.

A) Suprathreshold Heat Pain Response (SHPR)—Suprathreshold Heat Pain Response was tested in both cohorts at the thenar eminence of both sides, the surgical and non-surgical sides (side of shoulder surgery and opposite side of shoulder surgery) for the clinical cohort, and dominant and non dominant sides for the healthy cohort, with a thermode of 2.5 cm² surface area, by a Contact Heat Evoked Potential Stimulator (CHEPS) (Medoc Advanced Medical Systems, Ramat Yishai, Israel). The CHEPS was programmed to

deliver 5 consecutive heat pulses that rapidly rise from an adapting temperature (41°C) to a peak temperature at a rate of 30°C/s, remain at this level for 0.5 second, and then return to baseline at a rate of 30°C/s, with an interpulse intervals of 2.5 s^{5, 6, 23, 33}. Subjects verbally rated the intensity of each thermal pulse on a numerical rating scale from 0 = “no pain” to 100 = “the worst pain imaginable”⁶. The procedure was performed three times in a consecutive order, using three different peak temperatures (46°C, 48°C, and 50°C) for the thermal stimuli, and waiting 60 seconds between trials to avoid any potential accommodation.

B) Conditioned Pain Modulation (CPM)

Test stimulus (SHPR): SHPR was delivered to the thenar eminence of the non surgical side for the clinical cohort, and non dominant side for the healthy cohort, using CHEPS. Sequences of 5 consecutive heat pulses were delivered as was previously described^{5, 6}. The temperature used for the test stimulus (SHPR) was determined from the previous SHPR assessment by selecting the temperature that reached a moderate level of pain (pain rating of 50 or closer to 50 from 0 to 100 on numerical rating scale) as an average of five heat pulses. Subjects verbally rated the intensity of each thermal pulse on a numerical rating scale from 0 = “no pain” to 100 = “the worst pain imaginable”⁶. We selected SHPR as the test stimulus because evidence suggests that CPM effects are largest for C-fiber mediated pain^{11, 24}

Conditioning stimulus (Cold-pressor pain): Subjects were instructed to immerse their surgical side hand (for the clinical cohort), and dominant hand (in healthy cohort) up to the wrist into a cold water bath for up to one minute. The water was maintained at a constant temperature of 8°C, and was constantly circulated to prevent warming around the hand.

CPM Procedure: Participants from both cohorts underwent the CPM assessment with the application of the test stimulus (described above) on the non-surgical side for the clinical cohort, and non dominant side for the healthy cohort. After 30s from the last heat stimulus, subjects were instructed to immerse their surgical side hand (for the clinical cohort), and dominant hand (in healthy cohort) up to the wrist into the cold water bath (conditioning stimulus). Thirty seconds after hand immersion, subjects were asked to rate the pain from the immersed hand, and were instructed to maintain their hand in the water bath for as long as they could tolerate for a maximum of one minute. One minute after the immersion of the hand, a new test stimulus was delivered on the non-surgical side for the clinical cohort, and non dominant side for the healthy cohort. The protocol was created with consecutive stimuli (test stimulus, then conditioning stimulus, hand removed from water, and then test stimulus)

Exercise Induced Muscle Pain (EIMP)—Pain was induced in subjects from the healthy cohort with a shoulder fatigue procedure using a Kin-Com (Chattanooga, TN) isokinetic dynamometer. In this cohort the shoulder from the dominant side was induced utilizing previously established protocols which provide more detail on the exact procedures^{7, 8}.

Clinical Pain Intensity—These data were not directly related to our specific goals, but were included to describe the effects of EIMP and shoulder surgery on clinical pain reports. Clinical pain intensity was assessed with the Brief Pain Inventory (BPI) questionnaire⁴, which includes a numerical rating scale (NRS) for pain intensity. Subjects from the clinical cohort and from the healthy cohort (after EIMP protocol) rate their pain intensity over three conditions, the present pain intensity, the worst pain intensity over the past 24 h, and the best pain intensity over the past 24 h. These 3 ratings were summed and divided by three because that measure was most consistent with the purposes of this study. Other studies have also shown that this aggregate measure has sufficient psychometric strengths¹³¹².

Testing Sequence

Subjects from the healthy cohort had a baseline examination to collect demographic data, clinical pain intensity, and quantitative sensory testing (QST) before inducing EIMP. Collection of QST and clinical pain intensity was repeated after 48 hours and after 96 hours from EIMP induction. Patients from the clinical cohort had a baseline examination to collect demographic data, clinical pain intensity, and QST 72 to 24 hours before the surgery. Collection of QST and clinical pain intensity was repeated 3 months after surgery (Figure 1).

Data analysis

Data analysis was performed in SPSS, Version 17.0 at alpha level of 0.05. Descriptive statistics (mean, standard deviation) were calculated for all variables. The distributions of variables were tested by visual examination and with Kolmogorov-Smirnov test before use in analysis. For analysis purposes measurements from both arms were averaged into one score, because paired t-test shows non significant differences ($p > 0.05$) between measures in the surgical and non-surgical sides for the clinical cohort, and dominant and non dominant sides for the healthy cohort.

Calculations for CPM and SHPR—We followed recent recommendations on presenting results and calculation of CPM³⁶ using the absolute difference for CPM and the percent change. The “absolute difference” for CPM, was calculated by the difference between test stimulus before the application of conditioning stimulus (pre CPM), minus the test stimulus after the application of conditioning stimulus (post CPM). The “percent change” for CPM was calculated for each subject as follows:

$$[(\text{post CPM} - \text{pre CPM}) / \text{pre CPM}] * 100$$

For SHPR, the 5th pain rating at 48°C and 50°C were included in this analyses, because our previous study suggested that the 5th pain rating of a SHPR train accounted for a significant proportion of variance in shoulder pain intensity³³ and we wanted to include it as a potentially clinical relevant measure of pain sensitivity. A priori decision to not use 46 and preliminary analysis of current data led us to not use 5th pain rating at 46°C.

Baseline comparison between cohorts—One way ANOVA was performed to determine differences between groups at baseline on absolute difference of CPM, the percent of change of CPM, and the 5th pain rating of SHPR. Repeated measures ANOVA was used to assess the effect of pain inhibition (pre CPM, and post CPM) between groups.

Longitudinal analyses for the healthy cohort—Repeated measures ANOVA were used to assess the effect of condition (baseline, 48 hours post EIMP, 96 hours post EIMP) on CPM and SHPR. An accompanying descriptive analysis used repeated measures ANOVA to determine changes in “clinical” pain intensity (BPI) before and after EIMP.

Longitudinal analyses for the clinical cohort—Repeated measures ANOVA was used to assess the effect of condition (baseline, and 3 month after surgery) on the absolute difference of CPM, the percent change of CPM, and SHPR. In an accompanying descriptive analysis repeated measures ANOVA evaluated changes in clinical pain intensity (BPI) before and after the surgical procedure.

Results

Subjects

A total of 58 subjects from the clinical cohort, and 56 age and sex matched healthy subjects were included in this analysis. Age and gender were similar across cohorts (p 's > 0.05).

Descriptive statistics for the demographic and clinical measures from both cohorts are summarized in table 1 and table 2. All variables were found to approximate a normal distribution by visual examination and were appropriate for our planned ANOVA's analyses.

Because the 5th pain rating at 48°C and the 5th pain rating at 50°C were highly correlated in both samples (r 's between 0.89 and 0.97), only the 5th pain rating at 50°C was used in subsequent analyses.

Baseline comparison between cohorts

Simple ANOVAs showed no significant differences in the absolute difference of CPM [$F(1,100) = 0.414$; $p=0.522$; $\eta^2 = 0.04$] between cohorts (figure 2-a) even after controlling for baseline level of clinical pain. However the percent change of CPM significantly differed between cohorts [$F(1,101) = 9.922$; $p=0.002$; $\eta^2 = 0.59$], such that the clinical cohort had a lower percentage increase (mean = 17.09) compared to the healthy cohort (mean = 54.12) (figure 2-b).

The 5th pain rating at 50°C of SHPR showed significant differences between cohorts [$F(1,110) = 6.138$; $p=0.015$; $\eta^2 = 0.45$]; the clinical cohort had a higher mean rating (mean = 36.65; $sd = 24.16$) compared with the healthy cohort (mean = 24.98; $sd = 25.41$) (figure 2-c).

In a follow up analysis of these results, repeated measures ANOVA was used to assess group differences in pain inhibition (pre CPM, and post CPM). The interaction term CPM*group was not significant [$F(1,107) = 0.049$; $p=0.83$; $\eta^2 < 0.001$]; however, there was a significant main effect of CPM [$F(1,107) = 65.64$; $p < 0.001$; $\eta^2 = 0.51$], showing that conditioning stimulus produced a significant inhibitory effect in both groups (figure 2-d).

Longitudinal analyses for the healthy cohort

Clinical pain intensity changed significantly between baseline, 48 hours post EIMP, and 96 hours post EIMP [$F(2, 108) = 50.27$; $p < 0.001$; $\eta^2 = 0.48$] increasing significantly from baseline (mean = 0.43; $sd = 0.733$) to 48 hours post EIMP (mean = 2.22; $sd = 1.64$), and decreasing significantly from 48 hours to 96 hours post EIMP (mean = 1.00; $sd = 1.03$).

However, the analysis revealed that the absolute difference in CPM [$F(2,106) = 0.252$; $p=0.778$; $\eta^2 = 0.01$], the percent change on CPM [$F(1.43, 65.6) = 1.116$; $p=0.317$; $\eta^2 = 0.12$], and the 5th pain rating at 50°C [$F(1.43,75.58) = 0.640$; $p=0.479$; $\eta^2 = 0.01$], did not change significantly over time.

The reported p -value(s) associated with the F statistic(s) for percent change on CPM, and 5th pain rating at 50°C, are adjusted via Greenhouse-Geisser.

Longitudinal analyses for the clinical cohort

Analysis revealed that the clinical pain intensity decreased significantly [$F(1, 41) = 48.67$; $p < 0.001$; $\eta^2 = 0.54$] from the pre surgical time point (mean = 3.01; $sd = 1.94$) to 3 months post surgery (mean = 1.33; $sd = 0.18$).

The absolute difference on CPM [$F(1,40) = 1.812$; $p=0.186$; $\eta^2 = 0.05$], and the percent change of CPM [$F(1, 39) = 1.584$; $p=0.216$; $\eta^2 = 0.04$], did not change significantly between pre surgical and post surgical stages.

However, the 5th pain rating at 50°C decreased significantly [$F(1, 42) = 5.199$; $p=0.028$; $\eta^2= 0.11$] from the pre surgical (mean = 36.65; sd = 24.16) to the post surgical stage (mean = 27.95; sd = 22.98).

An independent t-test was performed to further explore whether the 5th pain rating from 3 months after surgery was equivalent to baseline state from the healthy cohort. Results showed that there was not a difference [$t(97) = -0.60$; $p=0.55$] in SHPR between the clinical cohort tested 3 months after surgery and the baseline from healthy cohort for the 5th pain rating.

Discussion

This study investigated whether central pain processing (measured by CPM and SHPR) was altered by changes in 2 different musculoskeletal shoulder pain models. These are potentially novel data to report because few longitudinal studies have reported whether central pain processing (measured by CPM as an “inhibitory” measure and by SHPR as a “facilitatory” measure) changes when associated reports of pain intensity increase or decrease. Overall this study revealed that: 1) absolute change in CPM did not differ between healthy and surgical cohorts, however; SHPR did and was elevated for those seeking surgery for their shoulder pain, 2) induction of acute shoulder pain with EIMP resulted in increased pain reports but did not affect CPM or SHPR over 4 days of monitoring, and 3) shoulder surgical procedure decreased clinical pain report and SHPR at 3 month, but did not affect CPM. Overall this study suggests that preoperative shoulder pain is associated with measurable changes in central pain processing. In addition, the novel longitudinal exploration of 2 musculoskeletal pain models provides specific evidence that: 1) induced muscle pain did not have immediate effects on our measures of central processing, and 2) the elevated SHPR in a clinical cohort may be sensitive to changes in CNS processing of pain during the first 3 month post-operative period.

The purpose of the baseline comparison between cohorts was to determine if central pain processing differed between healthy subjects and patients with clinical shoulder pain. The data showed that the SHPR differed between cohorts with evidence of altered pain sensitivity for the clinical cohort before having shoulder surgery. Central sensitization has been defined as an increase in the excitability of nociceptive neurons in the dorsal horn of the spinal cord as a result of continuous nociceptor input³⁵. Even though we did not measure directly nociceptor responsiveness, we measured CPM and SHPR as proxy measures of central pain processing². The 5th pain rating is a measure derived from a dynamic QST (temporal summation of heat pain stimuli) protocol, but it does not directly reflect the pain modulatory ability of the central nervous system (as calculation of the commonly reported slope of temporal summation would). However, previous findings from our lab³³ indicated that the 5th pain rating after 5 consecutive heat pulses showed better predictive ability than the traditional slope of temporal summation, being a potentially clinically relevant measure of pain sensitivity, and a potentially significant indicator of central pain processing. In this study there were indications of central pain dysregulation for 2 of our measures (figure 2- b and 2-c). These findings are in agreement with other studies in clinical populations showing that continued nociceptive input from musculoskeletal structures is related with enhance pain perception^{15–17, 32, 34}.

Several studies have reported differences in magnitude of conditioned pain modulation between patients having chronic pain and healthy controls^{14, 15, 17, 26, 30}. Our study showed that the percent change of CPM (relative amount of endogenous inhibition) differed between cohorts, which corroborated our previous finding for thermal stimuli as an indication of altered central pain processing for the clinical cohort. The most likely explanation for the

differences in relative inhibition was that, as expected, the clinical cohort had elevated responses to the experimental pain used in the CPM protocol. However, it is also important to note that the amount of change in CPM did not differ between cohorts, meaning that both cohorts have the same absolute baseline capacity for endogenous inhibition. The differences in CPM were only present when the relative change was considered. Because the cohort differences in CPM were dependent on the analytic method, replication of these findings is needed before drawing conclusions regarding altered central pain inhibitory function in this clinical population. Our results further confirm the necessity of reporting both calculations for CPM; absolute and percent change³⁶. In our opinion, if the purpose of the analysis is to detect baseline differences between cohorts, the percent change of CPM should be considered the best indicator of group differences. If the goal of the analysis is to detect potential deficits in inhibitory mechanisms it is our opinion that the absolute change of CPM may be the appropriate indicator of inhibition. Whichever method is used, future research is necessary to determine which measure shows the best predictive validity as evidenced by its association with clinical outcome measures.

We used an EIMP model because we wanted to explore whether central pain processing (measured by CPM and SHPR) would change when individuals convert from a pain free state to a state of induced acute musculoskeletal pain as has been previously reported^{1, 21, 22}. This part of pain transition is not possible for measurement in clinical populations and a novel part of this study was the investigation of CPM and SHPR during this transition in this healthy cohort. Interestingly, the present study showed no changes in CPM or SHPR between baseline and 48 and 96 hours following EIMP induction. These results suggest that there are not immediate changes in central pain processing in the early stages of musculoskeletal pain, even when pain intensity reports increase and then decrease in the 96 hours after EIMP. The pain from EIMP is caused by disruption of connective and contractile tissue reflecting events typically seen in acute inflammation³. However, our data suggest that the acute noxious stimulation induced by EIMP over 4 days is not enough to induce measurable changes in central pain processing through CPM and SHPR.

One study has explored the predictive ability of CPM, indicating the potential for CPM to predict the development of chronic post operative pain³⁷. Another study found baseline differences on CPM between patients with painful osteoarthritis of the hip and healthy controls, and CPM normalized in arthritis patients after their pain was successfully treated¹⁶. The present study adds to this relatively small literature and shows equivocal differences at baseline on CPM between healthy and surgical cohorts, no changes on CPM 3 months after surgery in the clinical cohort, and no changes in CPM in the healthy cohort following EIMP induction. This could indicate that CPM dysfunction is detectable only during chronic pain stages and may be associated with the chronicity of pain. A potential alternate explanation is that our study included a 3 month follow up and this may not be a sufficient time period to reveal neuroplastic changes in the CNS as have been described by Kosek et al.¹⁶ 6 months post surgery. Sample differences could be another potential explanation, where patients with CNS abnormalities in pain processing (i.e inclusion of subjects with chronic pain) prior the intervention may be more susceptible to changes after the intervention. In addition, we should consider that many efforts have been made to have a consistent CPM measure as there are considerable test specific factors involved with application of CPM^{25, 36}. However different laboratories still use different parameters to evoke the CPM effect, limiting the comparison among studies.

The fact that the SHPR decreased between baseline assessment and 3 months after surgery in the clinical cohort, indicates that the decreased pain intensity after 3 months from shoulder surgery, potentially induced changes in CNS processing of pain. Interestingly, at 3 months after surgery SHPR was comparable with that observed in the baseline state in the

healthy cohort, indicating the “normalization” of SHPR 3 months after shoulder surgery. This change in SHPR, followed the same pattern as those described for CPM by Kosek et al¹⁶, where normal CPM function was seen when patients were re-assessed 6 months after surgery in a pain free stage. These are convergent findings even though two completely different operative models and measures of central pain processing were used. Our findings further suggest that the SHPR could be more sensitive to immediate changes in clinical pain severity among patients with shoulder pain when compared to CPM, but further research is necessary to validate this statement.

Some important limitations of this study will need to be addressed by future research. First, our study included a three month follow up time after surgery; it will be important in future studies to consider a longer post surgical follow up period. In addition, future research on central pain processing will determine whether patients with elevated post surgical pain after surgery have the same central pain processing response as patients without pain after surgery. This assessment would potentially provide evidence to support the presence of abnormal neuroplastic changes over time due to the development of chronic pain stage. Another limitation is that CPM and SHPR were the only QST measures reported in this study, future studies should include additional measures, such as pressure pain threshold, heat pain threshold and tolerance to have a more comprehensive QST assessment. In addition to that, the trials of SHPR (using different temperatures) were provided in a consecutive order waiting 60 seconds in between. However, there is still potential for an order effect. Future studies should consider a random order between temperatures.

Previous analysis from our group did not find an effect for taking pain medication on QST measures⁹, however, since there is a potential for influence on central pain processing, future studies should account for this confounding factor. Lastly, EIMP is an appropriate model to study acute pain mechanisms as it has a longer duration of pain in comparison to other experimental pain models, providing a good link to clinical pain conditions. However, this experimental model uses a controlled mechanism of injury which resolves on its own and is thus not totally comparable with clinical pain.

Despite these limitations, the current study represents a novel contribution to the literature by exploring changes in pain processing in 2 different musculoskeletal shoulder pain models. Our results provide evidence of altered central pain processing for the cohort with clinical shoulder pain. Longitudinal studies involving quantitative sensory testing are rare and this study demonstrated that conditioned pain modulation was not affected by induced shoulder pain in the healthy cohort, or by the decreased pain in the clinical cohort. These findings support the idea that CPM would change only with longer lasting pain, and that diminished CPM may be associated with longer experienced pain, and is not a precursor of chronic pain.

The present study further supports the potential utility of SHPR in a clinical population³³. Elevated SHPR at baseline resolved following shoulder surgery, potentially indicating that this measure is sensitive to immediate changes in central pain processing. However, future longitudinal studies need to investigate the implications of having central pain dysregulation before shoulder surgery and the development of chronic post operative pain.

Perspective

Longitudinal studies involving quantitative sensory testing are rare. In exploring 2 musculoskeletal shoulder pain models (exercise-induced muscle pain and surgical pain), conditioned pain modulation was unchanged from pre to post assessment in both models. Suprathreshold heat pain response decreased after shoulder surgery and was comparable

to healthy controls, suggesting this measure may be sensitive to decreases in clinical pain intensity.

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Figure 1.
Schematic representation of research design and group comparison

Figure 2. Baseline difference between cohorts on the absolute difference of CPM (a), percent change of CPM (b), 5th pain rating at 50°C (c), and pre-CPM and post-CPM (d). Their respective standard deviation are shown for a, and c.

Table 1

Demographic characteristics for the age and sex matched groups.

	Healthy Cohort N=56	Clinical Cohort N=58	
<i>Subject's characteristics</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>P-Value</i>
Age	28.71 (8.44)	32.34 (11.55)	>0.05
Gender			>0.05
- Male	40 (71.4%)	41 (70.7%)	
- Female	16 (28.6%)	17 (29.3%)	
Dominant Side			>0.05
- Right	54 (96.4%)	54 (89.7%)	
- Left	2 (3.6%)	6 (10.3%)	
Ethnicity			>0.05
- Hispanic or Latino	7 (12.5%)	5 (8.6%)	
- Non Hispanic or Latino	48 (85.7%)	50 (86.2%)	
- Unknown or not reported	1 (1.8%)	3 (5.2%)	
Race			>0.05
- Asian	4 (7.1%)	1 (1.7%)	
- Native Hawaiian or Other	1 (1.8%)	0	
- Pacific Islander			
- Black or African American			
- White	2 (3.6%)	1 (1.7%)	
- More Than One Race			
- Unknown or Not Reported	44 (78.6%)	51 (87.9%)	
	3 (5.4%)	2 (3.4%)	
	1 (1.8%)	3 (5.2%)	
BPI			
- Baseline	0.43 (0.73)	3.01 (1.94)	
- post 48 hours	2.22 (1.64)	-----	
- Rating >0 after 48 hours	53	-----	
- post 96 hours	(94.6%) 1.00	1.33 (0.18)	
- 3 month after surgery	(1.03)	-----	

Table 2

Experimental pain assessment for healthy cohort and clinical cohort.

<i>Experimental pain assessment</i>	Healthy Cohort N=56	Clinical Cohort N=58	<i>P-Value</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	
5 th pulse at 48°C baseline	20.35 (23.06)	27.79 (22.18)	>0.05
post 48 hours	20.76 (24.28)	-----	
post 96 hours	19.24 (22.92)	-----	
3 month after surgery	-----	19.72 (18.68)	
5 th pulse at 50°C baseline	24.98 (25.41)	36.65(24.16)	<0.05
post 48 hours	27.13 (27.74)	-----	
post 96 hours	25.75 (26.67)	-----	
3 month after surgery	-----	27.95 (22.98)	
Pre CPM baseline	19.78 (20.38)	29.90 (22.19)	<0.05
post 48 hours	18.59 (18.72)	-----	
post 96 hours	18.97 (20.78)	-----	
3 month after surgery	-----	20.90 (12.91)	
Post CPM baseline	9.98 (12.95)	20.71 (19.32)	<0.05
post 48 hours	9.83 (12.74)	-----	
post 96 hours	9.86 (12.85)	-----	
3 month after surgery	-----	14.27 (12.77)	
Absolute difference CPM baseline	9.8 (12.43)	9.27 (12.13)	>0.05
post 48 hours	8.76 (10.24)	-----	
post 96 hours	9.11 (13.06)	-----	
3 month after surgery	-----	6.70 (8.72)	
Percent change CPM baseline *	54.12%	17.08%	<0.05
post 48 hours	35.51%	-----	
post 96 hours	49.91%	-----	
3 month after surgery	-----	35.67%	

* Reported means are based on calculation of individual percent changes.