INVESTIGATION OF CENTRAL PAIN PROCESSING IN POST-OPERATIVE SHOULDER PAIN

By

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To my wonderful family, particularly to my understanding, supportive, proud, and patient husband, Alvaro, who has shared the many uncertainties, challenges and sacrifices for completing this process. To our wonderful kids Benjamin and Sebastian, who are the constant source of strength and happiness. I also dedicate this dissertation to my parents Gilda and Edwin who have been my role-model for hard work, persistence and dedication, and who instilled in me the inspiration to set high goals in life and the confidence to achieve them.
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<td>TS</td>
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<td>WDR</td>
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INVESTIGATION OF CENTRAL PAIN PROCESSING IN POST-OPERATIVE SHOULDER PAIN

By

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Chair: Steven Z. George
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Recent reports suggest deficits in central pain modulatory mechanisms like conditioned pain modulation (CPM) and enhanced suprathreshold heat pain response (SHPR) potentially play a role in the development of post surgical pain. However, it is still unclear whether: a) central pain modulatory mechanisms (measured by CPM and SHPR) have differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery, and b) the role of CPM and SHPR in explaining post operative clinical pain after psychological factors (pain catastrophizing and depression) are considered.

Seventy three patients with clinical shoulder pain were included in this study. Patients were examined before shoulder surgery, at 3 months, and 6 months after surgery. The primary outcome measure was pain improvement 6 months from baseline, where improvement was defined as 30% reduction in shoulder pain from baseline. 81% of our sample had an improvement in their clinical pain intensity 6 months following surgery (pain decreased 30% or more), and 19% did not improve after 6 months (pain decreased less than 30%).
Overall this study revealed that: 1) CPM, SHPR, and pain threshold did not differ at baseline in patients who improved their level of pain at 6 months from patients who did not improve, 2) Patients who improved and who did not improve their level of pain at 6 months had significant differential change of 5th pain rating of SHPR, however they did not differ on change in CPM or pain threshold, 3) The change score (baseline – 3 months) of 5th pain rating of SHPR accounted for a significant amount of variance in 6 month post surgical clinical pain intensity after psychological factors were considered, with no other QST measure contributing to the model.

Altogether, the results from the present study imply that baseline level of central pain modulation is not a risk factor for continued pain at 6 months post surgery. In contrast, the post surgical changes of 5th pain rating of SHPR was a precursor to continued postoperative pain intensity, providing evidence that changes in the central modulatory system might be a key factor in the transition to continued post operative pain.
CHAPTER 1
INTRODUCTION

In the last 10 years, there has been growing evidence reflecting that chronic post-
surgical pain is a major problem, and that chronic pain is being monitored as an
important outcome of surgery [75,94,95].

The incidence of chronic post-operative pain differs based on the type of operation
and between studies, but has been acknowledged as a common problem. Little is
known about the factors that mark the transition from “normal” acute pain after surgery
to chronic pathological pain. However, it is thought that certain groups of patients may
be at greater risk for the development of pain after surgery than others. Shnabel et al.
[125], described potential predictive factors for persistent postsurgical pain. These
predictive factors are multiple and include individual genetic factors, age and sex,
neurophysiological factors, intra operative nerve and muscle damage, postoperative
complications and acute pain in the early postoperative period. Younger patients and
females have been associated with increased risk of developing continued post surgical
pain [125]. Other studies have found that preoperative pain is a predictor for persistent
postsurgical pain [75,125]. Psychological factors, such as depression, psychological
vulnerability, and catastrophizing have also been described as predictors for persistent
postsurgical pain [66,74].

Shoulder pain represents a common musculoskeletal disorder, and has been cited
as the third most frequent musculoskeletal complaint of patients visiting a primary care
provider [156], with one year prevalence estimates ranging between 5% and 47%
[110]. Previous survey results indicate [24] that surgery contributed to pain in 22.5% of
patients seeking treatment for chronic pain, and surgery was identified as the cause of
pain for 25% of those patients with upper extremity (shoulder, arm, and hand) chronic pain.

Research suggests that different chronic pain syndromes may share similar alterations in mechanisms of central pain processing [91, 124, 133, 138], where chronic pain states are commonly associated with alterations in the central processing of noxious stimuli [126] characterized by above-average sensitivity to pain and/or below-average endogenous pain inhibitory capacity [133, 166]. Therefore, for the central processing of noxious stimuli, studies have focused on two different aspects: 1) exaggeration in temporal summation (TS) representing the facilitation of ascending pain signals, and 2) decreased conditioned pain modulation (CPM) representing deficits in diffuse noxious inhibitory control [85, 135, 138].

Peripheral injury (i.e. surgical intervention) associated with potential risk factors, may lead to an imbalance between facilitation and inhibition of pain, causing pathological consequences leading to the development of chronic pain syndromes. Recent research has focused on the assessment of experimental pain as a potential predictor for persistent postsurgical pain [125, 177], however the question of causality is still unanswered. Patients who develop post operative pain may experience higher baseline sensitization, and decreased conditioned pain modulation therefore develops into more persistent postsurgical pain. However, it could also be that these patients have normal baseline sensitization and changes in central pain modulatory mechanisms develop into persistent post surgical pain.

Since alterations in the central processing of noxious stimuli, endogenous modulation of pain, and psychological factors are involved in pain processing, it seems
reasonable to assume that they may be associated with each other and have the potential to influence the development of post-surgical chronic pain. However, it is still unclear whether a) CPM and thermal pain sensitivity (SHPR and pain threshold) differ between patients who have different outcome at 6 months, b) pain inhibitory system (CPM), and SHPR have differential changes in patients who improve from those that do not improve their level of pain at 6 months following surgery, c) pain inhibitory system (CPM), and SHPR add similar amount of variance in predicting post operative pain reports, and d) CPM and SHPR contribute additional variance to post operative clinical pain reports after consideration of relevant psychological factors (pain catastrophizing and depression).

Therefore, the primary goal of this dissertation is to test the hypotheses that: 1) central pain modulatory mechanisms (measured by CPM and SHPR) have differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery where patients who improve have decreases in SHPR and increases in CPM from preoperative to postoperative assessment compared to patients who do not improve, and 2) CPM and TS contribute additional variance to a regression model predicting post operative clinical pain after pain catastrophizing and depression are considered in the model, establishing measures of central pain processing as unique contributors to postoperative pain intensity.

The following section will review important literature that supports such hypotheses.
CHAPTER 2
LITERATURE REVIEW

Chronic Pain

The Center for Disease Control (CDC, 2000) and the International Association for the Study of Pain (IASP) define chronic pain as a condition that persists for 3 months or more. Defining when pain becomes chronic is a challenge and debatable issue. In general, it has been suggested that pain could be considered chronic if pain is unlikely to resolve or pain that lasts longer than the usual healing time (i.e., 3 to 6 months) [1].

Chronic pain is a common problem in the general population, with research indicating that between 7%–59% of the adult population suffer from chronic pain [7,23]. This broad estimate could be explained in part by variable operational definitions of pain used in different studies [23]. An international group of researchers in 10 developed countries has estimated that 37% of adults have common chronic pain conditions [149]. In the United States, this amounts to at least 116 million people in 2011. A previous large scale computer-assisted telephone survey consisting of approximately 50,000 respondents reported the prevalence, severity, treatment and impact of chronic pain in 15 European countries and Israel [11]. Results indicated that one in five (20%) adult Europeans suffered from chronic pain (pain for more than 6 months > 5 on a Numerical Rating Scale (NRS)), which is moderate (NRS = 5-7) in 2/3 of the cases and severe (NRS = 8-10) in 1/3 of the cases. In this study the overall prevalence of moderate to severe chronic pain in the general adult population was 19%.

Symptoms related to the musculoskeletal system have been indicated as the most common reason for physician visits and emergency department/outpatient hospital visits between 1994 and 1997, and have remained the most common reason ever since [15].
Musculoskeletal pain, especially joint and back pain, is the most common single type of chronic pain. Musculoskeletal pain accounts for 9.7% of all physician office visits; where estimates from year 2000 indicated that 59 million office visits resulted in a primary diagnosis related to the musculoskeletal system and connective tissue [15].

Many aspects of everyday life, working life, somatic, emotional, social well being and quality of life are affected in most people suffering with chronic pain. The problem has also been studied in a Swedish setting indicating that more than 40% of the population have problems with pain [3]. The impact on health economy is tremendous as chronic pain is estimated to be the third largest health problem in the world [82], with direct and indirect costs of treating pain estimated to be over $125 billion annually in the United States [150,151], including health care expenses, lost income and lost productivity. Pain is the primary motivator for the utilization of health care [77], where pain was the primary or secondary reason for a visit to a primary care physician in 40% of the consultations [97].

In summary, pain has significant effect on people’s daily activities, disability, and quality of life. In addition, pain is exceedingly costly in terms of direct health care costs and the indirect costs associated with disability, lost employment, and reduced income. Therefore, chronic pain is a major health care problem that affects not just individuals but populations.

**Post Operative Chronic Pain**

As previously described, chronic pain has been defined as pain that lasts longer than the usual healing time, usually 3 or 6 months [2], and is a potential adverse consequence of surgery. However, a publication by the International Association for the Study of Pain (IASP) defines persistent postsurgical pain as pain that develops after
surgical intervention and last at least 2 months [22]. Therefore, depending on the
definitions applied, data on incidence and prevalence vary significantly.

A prior review study indicated that chronic pain is common after different types of
surgery [107] (limb amputations, breast surgery, gallbladder surgery, lung surgery, and
inguinal hernia surgery), with significant variability in the incidence of chronic pain
among those surgeries (between 11.5-47%). In addition, it is estimated that half of all
patients with thoracotomy will have persistent chest wall pain 1-2 years after the surgery
[12]. A survey from pain clinics consisting of 5130 patients attending 10 outpatients
clinics in North Britain [24], indicated that 22.5% of patients implicated surgery as one of
the causes of their chronic pain. Surgery was responsible for shoulder, arm, and hand
chronic post surgical pain in 25% of patients surveyed in that study.

Despite this alarming rate of post operative chronic pain, very little is known about
the factors that mark the transition from “normal” pain after surgery to a chronic pain
state. It is thought that certain groups of patients may be at risk for the development of
pain after surgery compared to others [67]. Several preoperative risk factors have been
identified for prolonged pain after surgery, where continuous pain (greater than one
month in duration), nerve injury [67], psychologic vulnerability including pain
catastrophizing, depression, and anxiety [57,147], and repeated surgery seem to be the
most common risk factors [107].

Neuroplastic changes in the central nervous system (CNS) are additional potential
factors associated with post operative chronic pain, as these are potentially induced by
surgery or the immediate pain associated with surgical intervention [18]. Evidence
suggests that high-intensity noxious stimulation sufficient to activate C-fiber afferents,
may induce long-term pain. Specifically, peripheral injuries may lead to an imbalance between facilitation and inhibition of pain in the CNS causing pathological consequences. For example, conditions of persistent nociceptive input could lead to neuroplastic changes in the Rostral ventromedial medulla (RVM) and elsewhere provoking a sustained facilitatory or lack of inhibitory system that drives exaggerated pain [114]. In summary, epidemiological studies suggest that traumatic peripheral injuries such as surgical intervention have the potential to trigger long-lasting changes in the CNS, which may underlie the transition from acute to chronic pain [73,171,173,174].

**Shoulder Pain as a Musculoskeletal Disorder**

In terms of chronic pain, musculoskeletal disorders and complaints comprise an important public health problem due to high impact on disability, sickness absence and work disability, and health care costs [110,155]. Shoulder pain represents a common musculoskeletal disorder, experienced by the general population. The incidence of shoulder pain has been estimated at 11.2 per 1000 persons per year and is the third most frequent musculoskeletal complaint of patients visiting a primary care provider [156] after patients with lower back and neck disorders, with a one year prevalence ranging between 5% and 47% [110]. The annual incidence of consultation for a new episode of shoulder pain in Dutch general practice ranges between 12 and 25/1000/year [156]. In a community based population study [7], pain was associated with significant disability in 50% of subjects. Macfarlane et al. [93], described a similar pattern in a prospective cohort study of subjects with shoulder pain conducted in the UK. In this study, 54% of patients reported shoulder pain at follow up about 3 years later, and 90% of cases were accompanied by some disability.
From a sample of 3664, almost three-quarters (74.5%) of the Dutch population aged 25 years and over, reported musculoskeletal pain during the past 12 months\[^{110}\], 44.4% reported musculoskeletal pain lasting longer than 3 months where the second most frequently reported pain was the shoulder (after lower back). However, it is thought that patients cope with their shoulder pain without consulting a general practitioner\[^{155,156}\]. Studies revealed that in the UK, less than 40% of elderly patients with shoulder pain sought treatment\[^{14,63,80}\]. Moreover, shoulder disorders are reported to account for around 10% of all referrals to physiotherapist in the UK and the Netherlands\[^{14}\].

Shoulder pain is a common orthopedic problem that appears to have an unfavorable outcome. Only about 50% of all new episodes of shoulder pain presented in primary care show complete recovery within six months\[^{156,170}\]. However these findings should be interpreted with caution as individual studies used diverse methods to define “recovery”.

The etiology and pathology of shoulder pain is often unclear, and the effectiveness of surgical intervention is uncertain\[^{37}\], in part because of lack of appropriate methods of assessing outcomes. The anatomical and functional structure of the shoulder seems to complicate the etiology of the problem. Some authors\[^{14,19}\] have suggested that shoulder chronic pain is due, in part, to the presence of an impingement lesion, and that when the problem has reached the point of tear (rotator cuff), the shoulder disease has progressed beyond the capability of non-operative treatment to resolve the problem. A prospective study with 349 patients with new episodes of shoulder pain\[^{156}\], indicated that the diagnosis most frequently documented was rotator cuff tendinitis with 30% of all
incident cases. This frequency may vary among studies because the lack of consensus regarding diagnostic criteria of specific shoulder disorders.

However, evidence shows that multiple potential prognostic factors could be associated with poor outcomes for patients experiencing shoulder pain. A systematic review of the literature on potential prognostic factors for shoulder disorders [81], identified with strong evidence that high pain intensity and middle age (45-54) are associated with poor outcome and higher disability. In addition, there was moderate evidence that long duration of symptoms, and high disability score at baseline predict a poorer outcome in primary care settings. In addition to the factors highlighted in the systematic review, it has also been suggested that depressive symptoms are an adverse risk factor for shoulder pain [175], and psychosocial factors are considered to contribute to the perpetuation of musculoskeletal pain, development of chronic pain, and disability [127,163].

In summary, shoulder pain represents a common musculoskeletal disorder, with an incidence estimated at 11.2 per 1000 persons per year. Moreover, the etiology and the prognosis of the effectiveness of treatment and surgical intervention may be associated with multiple potential risk factors. Therefore, increased knowledge about the prognostic value of surgical, psychosocial, biological, and patient related factors in patients with shoulder pain will help to provide patients and clinicians with adequate information regarding treatment outcome, surgery outcome, and has potential to distinguish between patients with low risk and high risk for development of chronic shoulder pain.
Central Sensitization

Prolonged or strong activity of dorsal horn neurons caused by repeated or sustained noxious stimulation may lead to increased neuronal responsiveness or central sensitization [101,136]. Central sensitization, a form of neuroplasticity, includes altered function of chemical, electrophysiological, and pharmacological systems [169]. It is characterized by hyperexcitability of dorsal horn neurons causing prolonged neuronal discharges, expansion of the receptive field, and consequently increased responses to noxious stimuli (hyperalgesia) and response to non-noxious stimuli (allodynia) [173]. These changes are related to increased excitability of spinal and supraspinal neurons [172], and may be involved in the generation of referred pain and hyperalgesia across multiple spinal segments [18]. (For details with regards to assessment and clinical relevance see temporal summation)

Evidence shows an increased sensitivity to pain, low pain threshold, and increased neuronal responsiveness occurred in a variety of chronic pain disorders [58,124,138,173]. Recent efforts have been made to investigate the clinical characteristics in a number of common musculoskeletal conditions [16,26,44-46,70] . It has been proposed that patients with chronic musculoskeletal pain should be grouped on the basis of their pathophysiological representations of pain rather than the etiology of the pathology or the anatomical location of pain [169]. Nijs et al. [105] have introduced guidelines for clinicians for the recognition of altered central pain processing in patients with musculoskeletal disorders. Embedded in the examination is the use of multiple modalities for pain sensitivity in locations local and remote to the area of the initial injury (or primary pain complaint). Individuals with unilateral conditions [44,46,70] demonstrated decreased pain thresholds bilaterally as compared to healthy controls
indicating generalized pain sensitivity. A recent report from our lab [20] investigating the differences in pain sensitivity between the involved and uninvolved extremity in patients with unilateral shoulder pain, showed that heat pain threshold does not seem to be different between sides in unilateral shoulder pain. However, side to side measurements of pain sensitivity differed when using pressure pain versus thermal pain. Since these pain assays measure different aspects of pain processing, sensitivity of deep tissue afferents versus C-fiber hyperexcitability [6,128], these findings could reflect differing pain related changes at the local and central level, and provide evidence for higher pain sensitivity in subjects with unilateral shoulder pain.

**Quantitative Sensory Testing**

Research has suggested that factors such as pain perception could also influence surgical outcomes. Quantitative sensory testing (QST) has become increasingly applied to the assessment of pain in subjects with different clinical musculoskeletal pain conditions. Furthermore, QST has been recently used in the investigation of post operative pain using different surgical models where patients can be assessed before and after surgery [60,79,167,177].

Administration of controlled noxious stimuli has been widely used for the diagnosis of sensory deficits, understanding pain perception, and to elucidate which pain pathways and mechanisms are involved under the experimental conditions. These controlled experimental peripheral stimulation given in the laboratory can generate different pain perception across healthy individuals and also across patients with similar severity of pathology [32].

Commonly used approaches are a “static view” of pain perception, which include measures of pain threshold (a static measure, could be used to determine the basal
state of the system [6]), and tolerance (a static measure which permits the investigation of suprathreshold- nociceptive processing, and reflects the results of the cerebral processing of the nociceptive data [6]). These static measures are believed to provide simple, unidimensional assessments of pain perception.

In contrast, a "dynamic view" explores potential pain modulatory mechanisms of the individuals [6], commonly assessed by temporal summation, and Conditioned Pain Modulation. As previously described, TS of suprathreshold heat pain stimuli, occurs when repetitive input over C-fibers induces enhanced responses in DH neurons. TS results in the perception of increased pain despite constant or even reduced peripheral afferent input [138] and is thus considered a perceptual manifestation of enhanced central excitability. Temporal summation can be induced in humans by the application of identical nociceptive stimuli applied to the skin with a frequency lower than 3 seconds. The progressive increase of pain sensation represents temporal summation.

CPM, described in more detail below, is a dynamic method used to engaged central pain inhibitory systems [87], and is considered a proxy measure of the amount of inhibition produced in the CNS.

A recent review [6] hypothesized that static pain psychophysics such as threshold and tolerance, may provide a limited view on the pain processing system in comparison to dynamic measures, such as TS and descending modulation of pain. In addition, measures derived from a dynamic QST approach are thought to better capture the pain modulatory ability of the central nervous system in comparison with static measures [6]. Supporting this distinction is recent work from our lab, which provides evidence for suprathreshold heat pain response as a clinically relevant dynamic QST measure for
patients with shoulder pain in comparison to static measures, even after psychological factors were considered [153].

**Temporal Summation of Suprathreshold Heat Pain Response**

Temporal summation (TS) of suprathreshold heat pain response (SHPR) results in the perception of increased pain despite constant or even reduced peripheral afferent input [138], and is thus considered a perceptual manifestation of enhanced central excitability, as opposed to a direct measure of the process. It has been demonstrated that enhanced TS of pain reflects “windup” in dorsal horn neurons [132], and involves central N-methyl-D-aspartate (NMDA) receptor mechanisms [116]. Therefore, the sensitization is thought to be a central mechanism, because the effect requires input from C nociceptors which results in the TS of pain via excessive and repetitive activation of NMDA receptors on second order neurons in the dorsal horn.

The assessment of responses to repetitive suprathreshold heat pain response (SHPR) differs from other methods of quantitative sensory testing (see below for specifics) in that responses to the repeated stimuli yield multiple possible methods of calculating pain sensitivity indices. Traditional indices derived from SHPR assessment reported in the literature include the use of mean of pain ratings [36,160], the first pain rating [131] the final pain rating [42,83,84,135], highest pain rating minus the first pain rating [35], and maximal pain rating [138]. For this dissertation study the “5th pain rating” of SHPR was used [153], which is the fifth pain rating from the fifth pulse of each trial [42,83,84,135], and is considered to represent a simple measure of suprathreshold heat pain stimuli assessment [115].
**Conditioned Pain Modulation**

Chronic pain has also been viewed as a CNS disease characterized by reduced endogenous pain inhibitory capacity [133,166]. One type of endogenous modulation of pain has been originally termed Diffuse Noxious Inhibitory Controls (DNIC) [87,117] to describe the inhibitory mechanism in animal studies. In humans, it is impossible to describe the specific mechanisms behind the process, therefore, the term “conditioned pain modulation” (CPM) was used in this dissertation [176]. CPM is typically induced by a painful stimulus applied to a remote area of the body (conditioning stimulus [176]), which induces inhibition of pain to a different painful stimulus (test- stimulus [176]). A reduction in the magnitude of the test-stimulus in response to the conditioning stimulus is considered as “conditioned pain modulation” [176] or inhibitory CPM.

The reduction in the magnitude of the test-stimulus in response to the conditioning stimulus may be influenced by nonspecific nociceptive neurons (or wide dynamic range [WDR] neurons) present in the dorsal horn of the spinal cord, and in the trigeminal brain stem [13,157]. These WDR neurons are found mainly in layer V of the dorsal horn and they respond to both high and low intensity peripheral stimuli (innocuous and noxious stimuli). WDR neurons are important convergence sites for both excitatory and inhibitory stimuli, and receives afferent fibers from more than one type of tissue (skin, organs, muscles, and joints) [157]. These specific mechanisms are not directly measured in humans; however, CPM is considered a proxy measure of the amount of inhibition produced in the CNS.

In this type of endogenous modulation of pain, the activity of pain-signaling neurons in the spinal dorsal horn and in trigeminal nuclei is attenuated in response to noxious stimuli applied to a remote area of the body. In other terms, CPM refers to the
phenomenon of one noxious stimulus inhibiting the perception of pain produced by a second noxious stimulus from a distant body site [88,89].

DNIC are not observed in anesthetized or decerebrate animals in which the spinal cord has been sectioned [161], therefore the mechanisms of DNIC is not coordinated in the spinal cord and supraspinal structures must be involved. It has been proposed that DNIC result from the physiological activation of some brain structures involved in descending inhibition. However, lesions of the mesencephalon, including the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM), including nucleus raphé magnus, did not modify DNIC [162]. In addition, animal models with complete transaction at different levels of the brainstem, show that DNIC was reduced by lesion of the subnucleus reticularis dorsalis (SRD) in the caudal medulla. In other words the SRD which is activated by nociceptive stimuli from the whole body receptive field by activity in A-delta and C fibers, may play a key role in pain processing [162].

**Clinical Considerations of SHPR and CPM**

Chronic pain has been seen as a CNS disease associated with alterations in the central processing of noxious stimuli [126]. The role that impairment of central pain modulatory mechanisms plays in the development of chronic pain has been emphasized in the literature [35,85,111,135,138,158,159], showing a less efficient “inhibitory” measure, and enhanced “excitatory” measures, and often observed together in many pain syndromes [32].

A dysfunctional pain modulation system has been seen in a variety of pain disorders such as fibromyalgia [78,85,129,137], temporomandibular disorder [96], irritable bowel syndrome [65], and chronic tension-type headache [124]. Patients from a variety of chronic pain disorders experienced increased sensitivity to pain, low pain
threshold, and enhanced TS, suggesting a central sensitization phenomenon that leads to enhanced pain perception [4]. For example, studies in patients with chronic pain after whiplash and with FM have demonstrated exaggerated pain response after sensory stimulation of healthy tissue [138,139]. In general FM patients perceived higher pain levels than healthy controls at the same intensity of thermal stimulation, and even when compared to other pain patients [72].

Interestingly, others studies relate a deficit in CPM response or a dysfunctional pain modulation system with the development of chronic pain after surgery. For example, Yarnitsky et al. [177] showed that a dynamic measure such as CPM obtained before surgery, can predict the risk for chronic post-operative (thoracotomy) pain, where patients with less effective CPM before surgery had a higher chance for development of chronic post-operative pain after surgery. Interestingly, in this study CPM were not found to be correlated with acute post-operative pain, meaning that they are two independent predictors of chronic post-operative pain. A different study [79] showed that patients with painful osteoarthritis of the hip had an impaired CPM compared with healthy controls. Interestingly, normal CPM function was seen when patients were re-assessed 9 months after surgery (total hip replacement and osteotomy) in a pain free state, meaning that probably the CPM dysfunction is maintained only during chronic pain stages. Other studies have used surgical models to determine the relationship between presurgical pain responses and acute postoperative pain [10,60,167], where in general, presurgical pain responses were significantly associated with postoperative acute pain. However, none of these studies assessed pain inhibitory system as a potential predictor of chronic postoperative pain.
We have conducted a study [154] to investigate whether central pain processing measured by CPM and SHPR was altered in 2 different musculoskeletal pain models. Our results showed that CPM did not differ between a surgical cohort and healthy controls at baseline, and surgical procedure decreased pain intensity at 3 months but did not affect CPM. In contrast SHPR differed at baseline between the surgical cohort and healthy cohort (with higher ratings for surgical cohort), and was decreased after surgery, showing values comparable with healthy controls at 3 months, providing evidence of favorable changes in CNS processing of pain.

In summary, evidence suggests that altered central processing of noxious stimuli might be relevant in the pathogenesis of pain disorders [78,85,118,124]. The evidence showed above highlights altered pain inhibition as a potential factor in chronic pain pathophysiology. However, as the majority of the studies are cross-sectional, it is impossible to elucidate whether SHPR and/or CPM have predictive ability in chronic post-operative pain, or if impaired SHPR and/or CPM are related with continued post operative pain. In addition, while there is extensive literature linking enhanced “excitatory” measures and less efficient “inhibitory” measure to the development and maintenance of chronic pain [5,18,131], it is still difficult to determine whether these neuroplastic changes precede the clinical pain outcome. The current study addresses this issue and potentially provides evidence to support the presence of abnormal neuroplastic changes over time as a precursor of continue post operative pain.

**Psychological Factors and Chronic Pain**

Evidence suggests that psychological factors are important determinants of how a painful stimulus is experienced and modulated [135,146]. Abundant evidence indicates that psychological factors influence the perception of pain and exert significant influence
on the development and maintenance of chronic pain conditions [53,92,164]. Moreover, psychological factors modulate pain sensitivity [121], but few investigations have considered the combined influences of psychological factors and experimental pain sensitivity on clinical pain intensity.

Depression is the most common psychosocial factor linked to chronic pain [120]. The prevalence of depression among chronic pain patients varies from 30-54% [9]. In primary care settings it has been estimated that 27% of patients with musculoskeletal pain conditions also have complaints consistent with major depressive symptoms [8]. Interestingly, George et al. [48], have shown that depressive symptoms have potential to adversely influence pain intensity ratings and functional status reports across multiple musculoskeletal pain categories. In addition, De Souza et al. [27], have shown that within fibromyalgia patients, a more pronounced deficit in pain inhibition and increased clinical pain, was found in those patients with depressive symptoms.

In addition to depression, several other pain-related characteristics are proposed to interfere with pain sensitivity.

Catastrophizing is defined as an exaggerated "mental set" that affects the perception of an actual or anticipated painful experience [146], where the three main characteristics are rumination, helplessness, and magnification [140]. Research found that pain catastrophizing was significantly positively associated with increased pain and physical and psychosocial dysfunction in a variety of chronic pain patients [55,59,68,103,109,144]. Recent research suggests that pain catastrophizing was found to be positively associated with pain perception in healthy subjects [146] and chronic pain conditions [106,141,145]. Others revealed that pain catastrophizing, depression,
and anxiety [57,147] influence the development of post operative pain. A study [53] investigated whether psychological variables and a specific genotype influenced pain ratings for a cohort of patients receiving operative treatment of shoulder pain. Interestingly, pain catastrophizing was a unique contributor to clinical pain ratings, and the interaction between pain catastrophizing and COMT diplotype influence pain ratings in that population. Pain catastrophizing has been positively related to experimental pain reports [30,34,36,123,142] and delayed onset muscle soreness [143].

In addition, fear of pain is suggested to play an important role in the development of chronic pain conditions [164]. High levels of pain-related fear are reported among patients diagnosed with chronic pain [21,100]. Moreover, previous authors also demonstrated that pain related fear and avoidance was associated with disability in patients with chronic low back pain [21,51,92,165], with chronic musculoskeletal pain [28,164], fibromyalgia [25,152], and with significantly higher pain intensity, disability, and functional impairment [21,98,99,152].

Interestingly, pain-related fear is also associated with pain sensitivity in healthy subjects in experimental pain models such as cold pressor task, heat pain, and ischemic pain [49,54,122,123]. In addition, fear of pain had a consistent influence on outcome measures after experimentally induced shoulder pain using delayed onset muscle soreness protocol [50]. Recent work from our group [153] suggested that subjects with elevated suprathreshold heat pain response, pain catastrophizing, and depression scores had higher clinical pain intensity ratings in pre and post operative assessments. Furthermore, results showed that psychological factors alone contributed a significant additional 17% of the variance in clinical pain intensity [153]. Since our
previous findings have shown that pain catastrophizing and depression are potentially the most relevant psychological factors in predicting post operative clinical pain intensity in a population with similar characteristics [153], we a priori selected for the current dissertation study the same relevant psychological factors to explore the contribution of them in post operative clinical pain intensity in a longer follow up period (6 months).

Collectively, these results suggest that identifying psychological risk factors is potentially important in predicting post-surgical outcome or in determining who will be more sensitive to painful stimuli, as research has indicated that psychological processes can influence treatment and surgical outcome [38]. Specifically, by assessing baseline psychological factors prior to surgical procedures, health care professionals may be able to determine who will be more likely to have enhance post operative pain and develop appropriate treatments plans.

**Theoretical Models on Chronic Post Operative Pain**

Chronic post operative pain states have been viewed as complex, multidimensional developmental process where certain groups of patients may be more at risk for pain development after surgery than others [67]. However, the specific mechanisms that underlie the transition from “normal” pain after surgery to a chronic or continued pain state are still unknown.

It has been proposed that patients with chronic musculoskeletal pain should be grouped on the basis of their pathophysiological representations of pain rather than the etiology of the pathology or the anatomical location of pain [169]. Therefore, the interactions among alldynia, hyperalgesia, abnormal temporal summation, lack of descending pain inhibition and psychological distress within the same model, could
become an important tool for identification of patients at risk of development of chronic post-surgical pain, regardless of the anatomical site.

**Psychological Distress Model**

The fear-avoidance model (FAM) of musculoskeletal pain is an important model to explain the development of musculoskeletal pain problems [163], which refers to the avoidance of movements or activities based on fear. The model explains why some individuals with acute musculoskeletal pain recover, while others develop chronic pain. According to this model there are two pain responses: *confrontation* or the adaptive response, and *avoidance* or the non-adaptive response. The model postulates that the potential precursors of pain-related fear and consequent disability are negative appraisals about pain and pain catastrophizing, which were found to be positively associated with pain sensitivity in healthy subjects [146] and chronic pain conditions [106,141,145]. The fear-related avoidance behavior is translated to avoidance of physical activity causing a circle and a multisystem impact (musculoskeletal, cardiovascular) enhancing the pain problem [164]. Therefore, patients with inadequate coping styles and catastrophic beliefs may develop an irrational fear of movement. Subsequent to pain and inactivity, reactivity of the sympathetic system, muscle reactivity and depression would enhance the painful experience [163]. Specifically, if pain following injury or surgery leads to catastrophic thinking about a sensation, the catastrophizing continues to intensify, fear and activity avoidance of all potentially painful experiences may develop [164].

**Idiopathic Pain Disorders Model**

The development of idiopathic pain disorders (often characterized by pain and motor dysfunction, autonomic imbalance, and neuroendocrine system and sleep
abnormalities) has been recently hypothesized to result from two intermediate phenotypes, psychological distress and pain amplification [29]. In this model, an individual’s genetic vulnerability and environmental events interact to influence the state of pain amplification (enhanced pain sensitivity), and psychological distress.

To specifically define the mechanisms that contribute to a state of pain amplification is not easy at this stage, but research findings suggests that this construct could be explained by the interaction of enhanced pain perception to a noxious stimulus, central sensitization phenomena, aberrant pain modulatory systems, and psychological distress.

The FAM [163] emphasizes the effect of psychological factors in the development of chronic pain and disability. A recent randomized trial [56] showed that a reduction of pain intensity was associated with reduction in fear-avoidance beliefs and pain catastrophizing, showing that a reduction in these psychological factors remains an appropriate treatment target because of their association with pain intensity. The idiopathic pain disorders model [29] proposed the interaction between pain amplification, psychological distress, genetic factors and the environment. It has been suggested that in patients seeking operative treatment of their shoulder pain, the interaction between pain catastrophizing and COMT diplotype influences pain severity [53], providing support for a biopsychosocial model, such as the idiopathic disorders model.

Even though these models were not developed for predicting post-surgical pain, and most of the work exploring pain related fear has focused on patients with non-specific diagnoses or injury [90], these models could be still applicable in post operative
chronic pain. In this case, the pain may no longer be explained by the injury (or surgical procedure), and fear can become dysfunctional [90]. Moreover, research literature supports that chronic post-operative pain states have been associated with psychological factors [112,113], endogenous pain modulation [35,61,65,85,129,177] and pain summation [130,133].

Along with the idea of having multiple factors that interact in the development of chronic pain, a panel of experts representing varying health care agencies, industry, and pain researchers formed IMMPACT [31] (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials), to determine which domains should be included in the standard assessment of pain outcomes, confirming the interaction between physical and emotional states. Therefore, the interaction between enhanced pain perception, central sensitization phenomenon and aberrant pain modulatory systems, with pain catastrophizing and depression could provide better understanding of continued post operative pain.
CHAPTER 3
RESEARCH HYPOTHESES

The primary goal of this dissertation was to test the following hypotheses:

Hypothesis 1

Central pain modulatory mechanisms (measured by CPM and SHPR) have differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery, where patients who improve have decreases in SHPR and increases in CPM from preoperative to postoperative assessment compared to patients who do not improve.

Our hypothesis 1 was tested by addressing two integrated specific aims:

Specific Aim 1-a

To determine if the pain inhibitory system (CPM), pain sensitivity (SHPR and pain threshold), and psychological factors differ at baseline among patients who do not improve after 6 months (decrease of less than 30% in shoulder pain from surgery), and who improve after 6 months (decrease of at least 30% in shoulder pain from surgery).

Support of specific aim 1-a. We have conducted a study [154] to investigate whether central pain processing measured by CPM and Suprathreshold heat pain response (SHPR) was altered in 2 different musculoskeletal pain models. The goals of the 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 used for these analyses. The healthy cohort was examined before inducing EIMP, 48 and 96 hours later. The clinical cohort was examined before shoulder surgery and 3
months later. CPM was assessed using temporal summation of heat pain as an experimental stimulus, and cold water bath as a conditioning stimulus.

At baseline, 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 pain intensity but did not change CPM or SHPR. Finally, shoulder surgical procedure decreased pain intensity at 3 months but did not affect CPM. In contrast SHPR was decreased and showed values comparable with healthy controls at 3 months, supporting the presence of neuroplastic changes on pain modulation system as a potential precursor of pain development.

In the current study, our suggested aim attempted to further investigate whether baseline modulatory capacity (baseline CPM and pain sensitivity) differs among patients who do not improve after 6 months compared to those who do improve after 6 months from surgery.

**Specific Aim 1-b**

To determine whether 3 months changes in pain inhibitory system (CPM), and pain sensitivity (SHPR and pain threshold) measures are related with clinical pain status at 6 months post-surgery (not improved vs. improved).

**Support of specific aim 1-b.** Studies imply that chronic pain is associated with changes in central nervous system (CNS) processing of pain-related information [124,133,135,137,138]. However, the majority of studies in this area are cross-sectional comparisons of patient and control groups and such study designs cannot distinguish the temporal direction of changes in pain processing, because CNS pain processing involves dynamic mechanisms that changes over time with long lasting pain.
Our preliminary data mentioned above revealed no effect of acute pain induced by DOMS on pain processing. Data also shows that patients with shoulder surgical procedure showed decreased pain intensity at 3 months but did not exhibit changes in CPM. In contrast SHPR was decreased and showed values comparable with healthy controls at 3 months, providing evidence of favorable changes in CNS processing of pain.

Our suggested aim attempted to further investigate whether these changes in pain modulation systems (CPM and SHPR) are a precursor to clinical pain status at 6 months after surgery (improvement vs not improvement). This approach will advance previous work in this area due to its longitudinal nature and is fundamental to investigate whether a) changes in pain modulation were precursors of continued pain, b) pain modulation deficiencies were associated with the duration of pain, and c) to support the presence of neuroplastic changes in pain modulation as a potential precursor of chronic pain development.

**Hypothesis 2**

CPM and SHPR contribute additional variance to a regression model predicting post operative clinical pain after pain catastrophizing and depression are considered. This hypothesis will establish measures of central pain processing as unique contributors to postoperative pain intensity.

Our hypothesis 2 was tested by addressing two integrated specific aims:
Specific Aim 2-a

To determine which dynamic QST measure (CPM, SHPR) might be the most clinically relevant measure in predicting 6 months post operative clinical shoulder pain.

Support of specific aim 2-a. QST has become commonly used for the assessment of pain in subjects with clinical conditions. However, there is no consensus about which type of QST is the best predictor of clinical pain responses.

We have conducted a prior study [107] to determine a) which QST measure is most strongly associated with clinical pain intensity, and b) if the identified QST measure continued to predict clinical pain intensity in a model including relevant psychological factors. Fifty-nine patients seeking treatment for shoulder pain underwent experimental pain assessment involving heat and pressure stimuli. The patients also completed validated questionnaires for pain intensity, pain catastrophizing, anxiety, and depression. In our preliminary data we found that the 5th pain rating of SHPR contributed an additional 10% variance in clinical pain intensity. This was a significant addition to the multivariate model and, no other QST measure contributed additional variance. The 5th pain rating remained a significant contributor to clinical pain intensity when psychological factors were included in the model. Furthermore, subjects with elevated 5th pain rating, pain catastrophizing, and depression scores had higher clinical pain intensity ratings in pre and post operative assessments [107].

Because our preliminary study only considered SHPR as a dynamic measure, our suggested aim attempted to further investigate which dynamic QST measure (using additional dynamic measure such as CPM) might be the most clinically relevant measure in predicting 6 months post operative pain.
Specific Aim 2-b

To determine if the strongest dynamic measure (CPM or SHPR) determined in Specific Aim 2-a, contributes additional variance to baseline and post operative clinical shoulder pain after relevant psychological factors (PCS, PHQ-9) are considered into the model.

Support of specific aim 2-b. Our preliminary data suggested that subjects with elevated 5th pain rating of SHPR, pain catastrophizing, and depression scores had higher clinical pain intensity ratings in pre and post operative assessments [153]. In addition, after accounting for age, sex and 5th pain rating of TS, the psychological factors contributed an additional 17% of the variance in clinical pain intensity with a significant addition to the model.

The proposed specific aim, attempted to further investigate in an independent sample of patients if dynamic measures and psychological factors are unique predictors of pain outcomes after the inclusion of a different dynamic measure (CPM) that was not considered in our previous analysis. Specifically, the aim investigated if the strongest dynamic measure (from Specific Aim #2a) still contributes to the model in predicting post operative clinical shoulder pain, after controlling for psychological factors.

Relevance of Specific Aims

Understanding pain inhibitory systems and pain summation is important because they may reflect the function of central modulatory systems, which have been implicated in development of chronic pain syndromes. If our hypotheses are confirmed it would add further evidence to support that a) pain descending inhibitory mechanisms and excitatory pain summation change over time and are precursors to continued postoperative pain intensity, b) are clinically relevant phenomena based on association
with clinical pain intensity reports, and c) are independent of psychological factors (an already established risk factor for development of chronic pain) in explaining post operative clinical pain intensity outcomes. In addition, if these hypotheses are confirmed it will provide additional evidence that the central modulatory system might be a potential target to prevent and treat chronic pain.

The novelty of this dissertation is that it specifically differentiates between different indirect measures of pain descending inhibitory mechanisms (CPM) and excitatory pain summation (SHPR) as potential measures that change over time producing deficiencies in pain modulation mechanisms as a precursor of continued post-operative pain. Moreover the investigation of QST factors and psychological factors within the same sample of patients with shoulder pain make this study a potentially novel contribution to the literature. Additionally, we have chosen a novel model of post-operative pain, as patients can be assessed before surgery (acute and subacute pain) and tracked for pain outcomes following a surgical procedure, taking into consideration the majority of the problems that arise when investigating chronic post operative pain.
CHAPTER 4
METHODS

Research Design

This prospective study involves patients that underwent shoulder surgery (arthroscopic) where the majority of the procedures were limited to the glenohumeral joint and included rotator cuff repair, adhesive capsulitis, acromioplasty, and labral repair (Table 4-1 for specifics). Patients underwent baseline assessments, which included psychological questionnaires, and psychophysical approaches to measure individual sensitivity and endogenous pain modulation. Patients were re-assessed at 3-month, and 6-month follow up time points (Figure 4-1). All assessments were performed by evaluators who were blinded to psychological measure data. Baseline assessment of patients was performed 24 to 48 hours before patient’s shoulder surgery.

Participants

This prospective design includes data from consecutive subjects seeking operative treatment of shoulder pain, who were recruited from University of Florida’s Orthopedics Sports Medicine Institute (OSMI). All participants provided informed consent before participating in this study.

Inclusion Criteria

The inclusion criteria for being a participant in the surgical cohort were: (a) between 18 and 85 years of age, (b) complaints of pain limited to anterior, lateral, or posterior shoulder, (c) documented or suspected rotator cuff tendinopathy (evidence from clinical examination or imaging studies) including small (<1 cm), medium (1-3 cm), and large (3-5 cm) tears, (d) documented or suspected adhesive capsulitis (evidence from clinical examination or imaging studies), (e) documented or suspected SLAP
(Superior Labrum from Anterior to Posterior) lesion (evidence from clinical examination or imaging studies), and (f) scheduled for arthroscopic surgery.

**Exclusion Criteria**

The exclusion criteria were: (a) current complaints of pain greater than the past 3 months involving neck, elbow, hand, low back, hip, knee, or ankle, (b) massive or complete rotator cuff tear (>5 cm), (c) documented shoulder OA or RA, (d) prior shoulder surgery within the past year or currently complaining of pain from prior shoulder surgery, (e) current shoulder fracture, tumor, or infection, (f) previously diagnosed chronic pain disorder (including, but not limited to IBS, fibromyalgia, TMD CLBP, etc), (g) current psychiatric management, and (h) current gastrointestinal or renal illness [153].

**Measures**

**Demographic and Historical Information**

Study participants completed a standard intake information form. Demographic data collected at initial evaluation include gender, age, employment status, litigation status, marital status, educational level, and health history. Historical data include the type of onset of symptoms, the length of time of the symptoms, the number of previous episodes of musculoskeletal pain, and previous treatments for pain.

**Clinical Shoulder Pain Intensity**

Clinical shoulder pain intensity was assessed with the Brief Pain Inventory (BPI) [17] (Appendix A), which includes a numerical rating scale (NRS) for pain intensity. Subjects rated their pain intensity over three conditions, the present pain intensity, the worst pain intensity over the past 24 hours, and the best pain intensity over the past 24 hours. These 3 ratings were summed and divided by 3 for use in data analyses [69].
Experimental Pain

Suprathreshold heat pain response

Suprathreshold heat pain response (SHPR) was tested at the thenar eminence of the surgical and non-surgical sides (side of shoulder surgery and opposite side of shoulder surgery) with a thermode of 27 mm surface area by a Contact Heat Evoked Potential Stimulator (CHEPS) (Medoc Advanced Medical Systems, Ramat Yishai, Israel). This apparatus is composed of an HP-thermode that provides extremely fast heating rates of up to 70°C/s and cooling rates of up to 40°C/s.

The CHEPS was programmed to deliver 5 consecutive heat pulses that rapidly rise from an adapting temperature to a peak temperature of 46, 48 or 50°C (depending on the test) 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 [33,47].

Peripheral thermal input occurring at 0.33 Hz or less induced pain summation in human beings, where input at 0.20 Hz or greater did not induced pain summation [116]. Subjects verbally rated the intensity of each thermal pulse on a numerical rating scale from 0 = “no pain” to 100 = “the worst pain imaginable” [47]. Additionally, subjects were asked to rate the magnitude of the delayed pain intensity following each heat pulse.

The procedure was performed three times in a consecutive order, the first one using 46°C, the second using 48°C, and the third one using 50°C as a thermal stimulus, to determine the patient’s moderate level of pain to be used in a following assessment (for specifics see CPM assessment below).

This study used the “5th pain rating” which was the fifth pain rating from the fifth pulse of each trial [42,83,84,135], which is considered to represent a simple measure of SHPR assessment [115]. In addition, we wanted to include it as a potentially clinically
relevant measure of pain sensitivity since our previous study suggested that the 5th pain rating of a SHPR train accounted for a significant proportion of variance in shoulder pain intensity [153].

**Heat pain threshold and tolerance**

Subjects received a continuously ascending heat stimulus on their involved and uninvolved arms. The stimulus started at 35°C and increased at a rate of 0.5°C/second. Subjects were asked to press a button and then rate their pain with a 0 (no pain) -100 (worst pain imaginable) NRS at the first sensation of pain. Two different trials were performed, and the average of the two temperatures was calculated as the heat pain threshold. In a separate trial subjects were asked to indicate when the heat became so painful that they wished it to stop. Two separate tolerance trials were performed and the average temperature was recorded as heat pain tolerance.

**Conditioned pain modulation (CPM)**

*Test stimulus (SHPR):* SHPR was tested at the thenar eminence of the uninvolved hand, using CHEPS (described above). Sequences of 5 consecutive heat pulses with 2.5 s and with interpulse intervals of 2.5 s were delivered [33,47]. The temperature used for the test stimulus (SHPR) was determined from the previous SHPR assessment, and was 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” [47]. Additionally, subjects were asked to rate the magnitude of the delayed pain intensity following each heat-tap. Subjects were also asked to provide ratings of heat sensations 15 s and 30 s
after the last heat stimulus (aftersensation) [134]. We selected SHPR as the test stimulus because evidence suggests that CPM effects are largest for C-fiber mediated pain [64,117]

*Conditioning stimulus (Cold-pressor pain):* Subjects were instructed to immerse their surgical side hand 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.

**Conditioned pain modulation procedure**

After baseline experimental pain assessment participants underwent the CPM assessment with the application of the test stimulus (described above) on the non-surgical side. After 30s from the last heat stimulus, subjects were instructed to immerse their surgical side hand 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 hands 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. The protocol was created with consecutive stimuli (test stimulus, then conditioning stimulus, hand removed from water, and then test stimulus) (Figure 4-2)

**Psychological Factors**

As previously described, our preliminary study has shown that pain catastrophizing and depression are potentially the most relevant psychological factors in predicting post operative clinical pain intensity in a population with similar characteristics [153]. Therefore for our current study we selected the same relevant psychological factors to
explore the contribution of them in post operative clinical pain intensity in a longer follow up period (6 months).

**Depression**

Self-report of depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9)[103] (Appendix B). The PHQ-9 is a 9-item self-reported questionnaire designed to evaluate the presence of depressive symptoms during the prior 2 weeks. As a severity measure, scores can range from 0 (absence of depressive symptoms) to 27 (severe depressive symptoms). Each of the 9 items, asking for each of the DSM-IV diagnostic criteria, can be scored from 0 (not at all) to 3 (nearly every day). As a diagnostic measure, major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least “more than half the days” (a score of 2) in the past 2 weeks, and one of the symptoms is depressed mood or anhedonia.

Studies support its validity, feasibility, and its capacity to detect changes of depressive symptoms over time[62].

**Pain catastrophizing**

Pain catastrophizing was measured by the Pain Catastrophizing Scale (PCS) [140] (Appendix C). The PCS has 13 descriptions of pain experience assessing catastrophic cognitions, for example: “I feel I can´t go on”, “There´s nothing I can do to reduce the intensity of the pain”. Subjects were asked to indicate whether they agreed with these statements by using a 5-point rating scale (0, “not at all” to 4, “all the time”) to rate the frequency of these cognitions. A PCS sum score was calculated for all items (range, 0 – 52), with a high score indicating a high level of pain catastrophizing.
Overall Procedure

Figure 4-2 showed a schematic representation of each testing session. Study participants completed a standard intake information form after signing the informed consent. Demographic data collection was followed by completion of validated questionnaires (Pain Catastrophizing, PHQ-9, and Brief Pain Inventory).

Patients underwent the experimental pain assessment, which consisted of the assessment of SHPR (at 3 different temperatures), heat threshold, and heat tolerance. The experimental pain assessment was performed in both hands. Finally patients underwent CPM assessment (described above).

Influence of Attentional Distraction

The conditioning stimulus in the induction of CPM is a potential source of distraction. Studies have shown that the inhibitory effects on the perceived pain after the application of non-painful stimuli as a conditioning stimulus could be explained by the influence of attentional distraction [86,108,148]. Furthermore, when the conditioning stimulus is similar in quality to the test-stimulus, the attentional distraction from pain occurs more easily [119].

In order to account for attentional distraction in this study, we used different stimuli for test (heat) and conditioning (cold water) stimuli. In addition, patients were instructed to pay attention to the specific stimulus (test-stimulus or conditioning stimulus) to rate their pain intensity. In addition, the protocol was created with consecutive stimuli (conditioning first, then removed, followed by test stimulus) instead of stimuli in parallel to decrease distraction. We did not ask the patient to rate their level of attention to each stimulus, therefore there is no data associated with the amount of attention or distraction that subjects have.
Primary Measure of Interest

Reports in the literature revealed that a high percentage of patients having shoulder surgery (rotator cuff repair) remain with pain. However, the specific prevalence of chronic pain after shoulder surgery may vary among studies because the lack of consensus regarding the definition of chronic pain.

The primary analysis of this dissertation attempted to determine whether conditioned pain modulation (CPM), and pain sensitivity (SHPR and pain threshold), change differentially over time from baseline to 3 months after surgery in patients who improve, and who do not improve their level of pain 6 months after the shoulder surgery. We selected this time because 6 months would be the most appropriate amount of time to determine prediction of continued pain after surgery [2].

Patients were classified according to their BPI scores for postoperative pain intensity (6 months after surgery) into two groups “improved” and “not improved”. Improvement was defined as a decrease of at least 30% in shoulder pain from baseline to 6 months after surgery. Patients who did not improve had a decrease of less than 30% in shoulder pain, and patients who improved had a decrease of at least 30% in shoulder pain from baseline to 6 months after surgery.

We have selected 30% reduction in shoulder pain from baseline, because literature suggests that 30% reduction is associated with individuals reporting notable improvement on the patient global impression of change [40,41]. In addition, it has been suggested that in studies with baseline pain variability, the clinical relevance should be defined in terms of percent change [41].
Sample Size Estimate

Based on previous data [52], we hypothesize that for a repeated measure ANOVA, the minimum sample size for 0.80 power, alpha level 0.05, and an effect size of 0.31 is 84 to detect clinically meaningful change from pre to post operation.

In a repeated measures design, several hypotheses can be tested and each hypothesis has a different impact on the sample size needed for adequate power. In Specific Aim 1, separated repeated measures ANOVAs were used to determine a differential effect of group and time (improved vs. not improved over time). For practical reasons sample size estimates were based on change over time using the statistical software G*Power version 3.1.3 [43].

Statistical Analysis

Data analysis was conducted over a series of steps using SPSS, Version 18.0. Significance levels were set a priori at p<0.05 for all comparison. Descriptive statistics (mean, standard deviation) were calculated for all variables. The distributions of variables were tested for normality by visual examination and with Kolmogorov-Smirnoff test before used in analysis. For analysis purposes measurements from both arms were averaged into one score, because paired t-test shows nonsignificant differences (p > 0.05) between measures in the right side versus left side.

For analysis purposes on CPM, we followed recent recommendations [176] on presenting results and calculation of CPM 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 as follows:
\[(\text{post CPM} - \text{pre CPM}) / \text{pre CPM} \] \times 100

Pearson correlations were calculated between clinical shoulder pain intensity, experimental pain measurement (absolute difference of CPM, percent change of CPM, and 5\textsuperscript{th} pain rating), and psychological factors at baseline and 6 months after surgery.

**Specific Aim 1-a: Baseline Differences among Groups**

ANOVA models were used to determine baseline differences on 5\textsuperscript{th} pain rating, absolute difference of CPM, percent change of CPM, and the magnitude of pain threshold between groups (patients who improve and patients who do not improve their level of pain at 6 months). We used ANOVA models because we wanted to be consistent with the model used in exploring baseline difference before and after controlling for baseline level of clinical pain. In addition, repeated measures ANOVA were used to assess baseline effect of pain inhibition (pre CPM, and post CPM) between groups, and to determine baseline differences on pain summation (TS) among groups.

**Specific Aim 1-b: Changes of Measurements over Time**

Repeated measures ANOVA was used to assess the effect of time (baseline, and 3 months after surgery) on the absolute difference of CPM, the percent change of CPM, 5\textsuperscript{th} pain rating, and pain threshold by condition (improved vs. not improved). For this analysis the between groups factor was condition (improved vs. not improved), and the within subjects factor was time (baseline, and 3 months after surgery). Simple contrasts were used in case the interaction terms were significant to determine differences on CPM, 5\textsuperscript{th} pain rating, or pain threshold between groups.
Specific Aim 2-a: Clinically Relevant QST Measures in Explaining Baseline and 6 Months Clinical Pain Intensity

Multiple regression models were conducted to assess which QST measure accounted for significant amount of variance in clinical pain intensity. These models determined whether baseline, 6 months, and raw change score (baseline-3 months) of QST measures accounted for significant variance in clinical pain intensity at baseline and 6 months. Regression models included age, sex, and shoulder pain duration in the first step to control for these potentially confounding factors, and QST measures (5th pain rating of SHPR, CPM, percent change of CPM, and pain threshold) in the second step of the regression model in a stepwise manner. Stepwise regression was used to create a parsimonious model consisting of QST measures with the strongest association with clinical pain intensity. Variance inflation factor (VIF) was reported for the model to investigate potential multicollinearity among independent variables.

Specific Aim 2-b: Contribution of Psychological Factors in Explaining Baseline and 6 Months Clinical Pain Intensity

Separate hierarchical regression models were conducted to determine the contribution of baseline psychological measures in explaining baseline clinical pain intensity and in predicting 6 months clinical pain intensity. In addition a different hierarchical regression model was built to determine the contribution of 6 months psychological measures to 6 months clinical pain intensity. Age, sex, and shoulder pain duration were considered in the first step to control for these potentially confounding factors, and psychological variables (PCS, PHQ-9) were entered in the second step in a hierarchical manner. In addition, a different regression model was built to determine the contribution of the clinically relevant QST (determined in previous analysis) in explaining 6 months clinical pain intensity, after psychological factors were considered. Age, sex,
shoulder pain duration, and psychological factors were considered in the first step to control for these potentially confounding factors, and the appropriate QST measure from previous analysis was entered in the second step. VIF was reported for the final model to investigate potential multicollinearity among the independent variables.

In addition, we used repeated measures ANOVA to explore the effect of time (baseline, and 3 months after surgery) on psychological factors by condition (improved vs. not improved). For this analysis the between groups factor was condition (improved vs. not improved), and the within factor was time.
Figure 4-1. Schematic representation of research design and group comparison

Figure 4-2. Schematic representation of each testing session
CHAPTER 5
RESULTS

Subjects

Although the study estimated a sample size of 84 to detect clinically meaningful interactions, results were obtained from 73 subjects seeking operative treatment of shoulder pain. At the time of the analysis this ongoing study had 78 patients with 6 months follow up completed. From those, 3 patients did not have information on their baseline BPI, and 2 patients had missing information on BPI at 6 months. Therefore cases with only baseline and 6 months completed data on BPI were included in this analysis, resulting in a total sample size of 73 subjects. No difference between included and excluded patients was noted in any of the variables (p>0.05).

Descriptive statistics for the demographic, clinical pain and medical history are summarized in Table 5-1. Experimental pain assessment and psychological characteristics from the sample at baseline, 3 months, and 6 months post surgery are summarized in Table 5-2. All continuous dependent variables were found to approximate a normal distribution by visual examination and were appropriate for our planned ANOVA’s and multiple regression analyses.

Because the 5th pain rating at 48°C and the 5th pain rating at 50°C were highly correlated at baseline and at 6 months (r’s between 0.90 and 0.97 ), only the 5th pain rating at 50°C was used in subsequent analyses.

Figure 5-1 shows the distribution of pain intensity difference (baseline pain – 6 months pain), and the distribution of the percentage of change in pain intensity [(6 months pain- baseline pain) / baseline pain] * 100. As we previously described, we have selected pain improvement 6 months after surgery as our primary outcome
measure. We selected 30% reduction in shoulder pain from baseline, because literature suggests that it is associated with individuals reporting notable improvement on the patient global impression of change, and is generally equivalent to a raw reduction (raw pain difference) of two points on average [40,41].

Using this definition our data showed that 81% of our sample had an improvement on their clinical pain intensity 6 months after surgery, and 19% did not improved after 6 months. No difference was noted for the demographic and medical history between the two groups (p>0.05).

Pearson correlations among clinical shoulder pain intensity, experimental pain measurement, and psychological factors at baseline and 6 months after surgery are summarized in Table 5-3. Overall, baseline clinical pain intensity had significant positive association with baseline 5th pain rating (r = 0.23, p<0.05), and baseline PCS (r = 0.25, p<0.05). Clinical pain intensity at 6 months had a significant positive association with 6 months PCS (r = 0.39, p<0.01). Baseline 5th pain rating had a significant positive association with 6 months CPM (r = 0.27, p<0.05), and negative association with baseline pain threshold (r = -0.47, p<0.01). While 6 months 5th pain rating had a negative association with pain threshold at baseline (r = -0.33, p<0.01), and 6 months (r = -0.37, p<0.01).

**Hypothesis 1**

Hypothesis 1 stated that central pain modulatory mechanisms have differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery. Our hypothesis was tested by addressing two integrated specific aims.
Specific Aim 1-a: Baseline Differences among Groups

Simple ANOVAs showed no significant differences in the absolute difference of CPM [F(1,68) = 0.06; p=0.81; d= 0.08], in the percent change of CPM [F(1,67) = 0.024; p=0.88], in the 5th pain rating at 50°C [F(1,70) = 3.65; p=0.06; d= 0.65], or in pain threshold [F(1,69) = 1.918; p=0.17; d= 0.43] between groups (improved vs. not improved). These results did not change after controlling for baseline pain intensity.

In a follow up analysis of these results, repeated measures ANOVA was used to assess baseline group differences (within session) in pain inhibition (pre CPM, and post CPM). The interaction term CPM*group was not significant [F(1,68) = 0.06; p=0.81]; however, there was a significant inhibitory effect within groups [F(1,68) = 18.15; p<0.001], showing that conditioning stimulus produced a significant inhibitory effect in both groups (Figure 5-2).

In addition, repeated measures ANOVA was used to assess baseline group differences in pain summation (five repetitive pulses). The interaction term SHPR*group was not significant [F(1.39,97.54) = 0.45; p=0.77], showing that the SHPR due to repetitive heat stimulus did not differ among groups (Figure 5-3). The main effect of summation was not significant.

Exploratory analysis showed no significant baseline differences in PCS [F(1,71) = 0.76; p=0.39; d= 0.26], or in PHQ-9 [F(1,71) = 2.27; p=0.14; d= 0.51] between groups (improved vs. not improved), even after controlling for baseline pain intensity.

Specific Aim 1-b: Changes of Measurements over Time

To assess whether central pain modulatory mechanisms had differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery, repeated measures ANOVA was conducted. Table 5-4
shows all predictors variables over time with the significances and the magnitudes of the interactions. Changes in absolute difference on CPM \[F(1,65) = 0.74; p=0.39; d=1.42\], and percent change of CPM \[F(1, 63) = 0.001; p=0.98\] over time (pre surgical stage and 3 months after surgery) had no significant effect on condition 6 months after surgery (improved vs. not improved) (Figures 5-4 and 5-5). The interaction term \(\text{time}^*\text{condition}\) was also non significant for pain threshold \[F(1,67) = 1.12; p=0.74; d=0.32\] (Figure 5-6).

However, the interaction term \(\text{time}^*\text{condition}\) for the 5th pain rating at 50°C was significant \[F(1,68) = 4.92; p=0.03; d= 0.35\], meaning that the change of 5th pain rating over time (pre surgical stage and 3 months after the surgery) differed based on 6 months pain intensity improvement. (Figure 5-7). After decomposing the interaction term, results showed that the improved pain intensity group significantly decreased their mean of the 5th pain rating at 3 months post surgery (baseline mean= 38.54 (25.29); 3 months mean= 31.30 (26.61); \(p= 0.02\)). The not improved group increased their mean of the 5th pain rating at 3 months but not in a significant manner (baseline mean= 25.46 (16.44); 3 months mean= 33.75 (23.58); \(p= 0.20\)).

In a follow up analysis of these results, we wanted to explore whether sex interfered with the effect of condition over time, since sex differences in experimental pain sensitivity have been well documented and recent work from our group showed that females with shoulder pain displayed enhanced sensitivity to experimental pain [76].

Repeated measures ANOVA was used to assess the interaction term between time, condition, and gender. The three-way interaction terms were not significant for
each of our independent variables (CPM, percent change of CPM, 5th pain rating at 50°C), indicating that gender did not modify our main findings over time.

Considering that these results showed no baseline differences between groups, and show evidence of changes in central pain modulatory mechanisms only for one of our measures (SHPR), Hypothesis 1 was partially supported.

**Hypothesis 2**

Hypothesis 2 stated that CPM and SHPR contribute additional variance to a regression model predicting post operative clinical pain after pain catastrophizing and depression are considered. Our hypothesis was tested by addressing two integrated specific aims.

**Specific Aim 2-a: Clinically Relevant QST Measures in Explaining Baseline and 6 Months Clinical Pain Intensity**

Hierarchical regression analyses were conducted to determine the contribution of baseline, 6 months, and 3 months change score of QST measures to baseline and 6 months clinical shoulder pain intensity. Age, sex, and pain duration accounted for 15% of the total variance in baseline clinical shoulder pain intensity where only age, and sex were significant predictors. There was no significant contribution from QST measures (5th pain rating, CPM, percent change of CPM, pain threshold). The regression models predicting 6 months pain intensity with baseline and concurrent factors did not have significant baseline QST predictors.

However 3 months change score of QST explained an additional 10% of the variance for 6 months clinical pain intensity ($p=0.03$), where change score of the 5th pain rating ($\beta=-0.34$, $p=0.01$) was the unique significant predictor (Table 5-5). These results did not change after accounting for baseline clinical pain, indicating that 3
months change score of the 5th pain rating was still the unique significant predictor of 6 months clinical pain intensity even after controlling for baseline clinical pain.

VIFs indicated minimal multicollinearity concerns among the independent variables.

**Specific Aim 2-b: Contribution of Psychological Factors in Explaining Baseline and 6 Months Clinical Pain Intensity**

After accounting for age, and sex, and pain duration, the baseline psychological factors (PCS, PHQ-9) contributed an additional 7% of the variance in baseline clinical pain intensity with a significant addition to the model ($R^2=0.22$, $p=0.002$) (Table 5-6). In this model, PCS was the unique psychological factor that contributed significant variance to baseline clinical pain intensity ($\beta=0.26$, $p=0.02$). In predicting 6 months clinical pain intensity, the model with baseline psychological factors was not significant ($p>0.05$) (Table 5-7). However, 6 months psychological factors explained an additional 20% of the variance for 6 months clinical pain intensity, where PCS ($\beta=0.46$, $p<0.001$) was the unique significant predictor (Table 5-8).

In addition, a different regression model was built to determine the contribution of the 3 months change score of 5th pain rating in explaining 6 months clinical pain intensity, after psychological factors were considered. After accounting for age, sex, pain duration, and baseline psychological factors (PCS, PHQ-9), the 3 months change score of 5th pain rating 12% of the variance in 6 months clinical pain intensity with a significant addition to the model ($R^2=0.23$, $p=0.01$) (Table 5-9). In this model, the 5th pain rating was the unique factor that contributed significant variance to 6 months clinical pain intensity ($\beta=-0.37$, $p=0.002$). When the 3 months change score of 5th pain rating was entered into the model PCS was no longer a significant contributor. The
same trend of results was obtained when accounting for psychological factors at 3 months, and after accounting for baseline clinical pain.

In addition, we explored changes of psychological factors over time (pre surgical stage and 3 months after surgery) on condition (improved vs. not improved). Results showed that changes of PCS [F(1, 71) = 0.93; p=0.34; d= 0.06], and PHQ-9 [F(1, 69) = 0.05; p=0.83; d=0.53] had no significant effect on condition at 6 months after surgery. VIF showed minimal multicollinearity concerns among the independent variables in all regression models.

Our results show that pain catastrophizing was a strong contributor to concurrent pain reports at baseline and 6 months post operative. However, after accounting for age, sex, pain duration, and psychological factors, the measure of central pain processing (change score of 5th pain rating) contributed an additional 12% of the variance in post operative clinical pain intensity with a significant addition to the model, and where pain catastrophizing was no longer significant. This result establishes measures of central pain processing as unique contributors to postoperative pain intensity; therefore Hypothesis 2 was completely supported.
Figure 5-1. Frequencies on: A) Clinical pain difference (change score of BPI), B) Percentage of change on clinical pain intensity (percentage of change of BPI)
Figure 5-2. Baseline group differences in pain inhibition

Figure 5-3. Baseline group differences in pain summation
Figure 5-4. Change on absolute difference on CPM over time between groups

Figure 5-5. Change on percent change of CPM over time between groups
Figure 5-6. Change on pain threshold over time between groups

Figure 5-7. Change on 5th pain rating over time between groups
**Table 5-1.** Demographic characteristics and summary of medical history for the sample

<table>
<thead>
<tr>
<th>Subject's characteristics</th>
<th>Improved Group N=59</th>
<th>Not improved Group N=14</th>
<th>P-Value* Δ score BPI Mean (SD)</th>
<th>P-Value** Δ score BPI Mean (SD)</th>
<th>r with Δ score BPI (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.07 (19.24)</td>
<td>48 (17.86)</td>
<td>0.61</td>
<td>0.12 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.91</td>
<td>0.02</td>
<td>-0.28† (0.02)</td>
</tr>
<tr>
<td>- Male</td>
<td>43 (72.9%)</td>
<td>10 (71.4%)</td>
<td>1.82 (1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>16 (27.1%)</td>
<td>4 (28.6%)</td>
<td>3.23 (2.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant Side</td>
<td></td>
<td></td>
<td>0.81</td>
<td>0.55</td>
<td>-0.07 (0.55)</td>
</tr>
<tr>
<td>- Right</td>
<td>52 (88.1%)</td>
<td>12 (85.7%)</td>
<td>2.27 (2.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Left</td>
<td>7 (11.9%)</td>
<td>2 (14.3)</td>
<td>1.78 (2.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.73</td>
<td>0.32</td>
<td>-0.05 (0.65)</td>
</tr>
<tr>
<td>- Hispanic or Latino</td>
<td>5 (8.5%)</td>
<td>0</td>
<td>3.13 (2.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Non Hispanic or Latino</td>
<td>51 (86.4%)</td>
<td>14 (100%)</td>
<td>2.11 (2.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unknown or not reported</td>
<td>3 (5.1%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.83</td>
<td>-0.03 (0.83)</td>
</tr>
<tr>
<td>- Asian</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Native Hawaiian or Other Pacific Islander American</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Black or African American</td>
<td>3 (5.1%)</td>
<td>1 (7.1%)</td>
<td>3.17 (2.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>50 (84.7%)</td>
<td>12 (85.7%)</td>
<td>2.13 (2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- More Than One Race</td>
<td>4 (6.8%)</td>
<td>1 (7.1%)</td>
<td>2.20 (3.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unknown or Not Reported</td>
<td>2 (3.4%)</td>
<td>0</td>
<td>2.67 (2.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Side</td>
<td></td>
<td></td>
<td>0.85</td>
<td>0.77</td>
<td>0.04 (0.77)</td>
</tr>
<tr>
<td>- Right</td>
<td>32 (54.2%)</td>
<td>8 (57.1%)</td>
<td>2.13 (2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Left</td>
<td>27 (45.8%)</td>
<td>6 (42.9%)</td>
<td>2.28 (2.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPI</td>
<td></td>
<td></td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Baseline</td>
<td>3.61 (2.28)</td>
<td>2.48 (1.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 3 months after surgery</td>
<td>1.54 (1.56)</td>
<td>2.29 (2.03)</td>
<td>0.13</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>- 6 months after surgery</td>
<td>0.80 (0.90)</td>
<td>2.81 (2.12)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain duration (weeks)</td>
<td>71.17 (86.69)</td>
<td>100.36 (129.82)</td>
<td>0.31</td>
<td></td>
<td>-0.04 (0.76)</td>
</tr>
<tr>
<td>Previous rehabilitation</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.15</td>
<td>-0.18 (0.15)</td>
</tr>
<tr>
<td>- Yes</td>
<td>31 (52.5%)</td>
<td>4 (28.6%)</td>
<td>2.61 (2.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>23 (39%)</td>
<td>10 (71.4%)</td>
<td>1.81 (2.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>5 (8.5%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder pathology (Acromioplasty)</td>
<td>28 (47.5%)</td>
<td>6 (42.9%)</td>
<td>0.76</td>
<td></td>
<td>0.05 (0.68)</td>
</tr>
<tr>
<td>Shoulder pathology (Bursae resection)</td>
<td>20 (33.9%)</td>
<td>2 (14.3%)</td>
<td>0.16</td>
<td></td>
<td>0.20 (0.09)</td>
</tr>
<tr>
<td>Shoulder pathology (Labrum repair)</td>
<td>28 (47.5%)</td>
<td>5 (35.7%)</td>
<td>0.43</td>
<td></td>
<td>-0.11 (0.34)</td>
</tr>
<tr>
<td>Shoulder pathology (Other)</td>
<td>49 (83.1%)</td>
<td>10 (71.4%)</td>
<td>0.33</td>
<td></td>
<td>0.06 (0.64)</td>
</tr>
</tbody>
</table>

* P-Value: Significance of between groups comparison (t-test)
** P-Value: Significance between subgroups of subject’s characteristics (t-test or ANOVA)
† Correlation is significant at the 0.05 level.
Table 5-2. Experimental pain assessment and psychological characteristics for the sample.

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Improved Group N=59</th>
<th>Not improved Group N=14</th>
<th>P-Value</th>
<th>Cohen’s d</th>
<th>r with Δ score BPI (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; pulse 50°C baseline</td>
<td>38.54 (25.29)</td>
<td>24.93 (16.78)</td>
<td>0.06</td>
<td>0.65</td>
<td>0.30* (0.01)</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; pulse 50°C at 3 months</td>
<td>31.11 (26.42)</td>
<td>33.75 (23.58)</td>
<td>0.75</td>
<td>0.11</td>
<td>0.08 (0.52)</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; pulse 50°C at 6 months</td>
<td>25.53 (21.65)</td>
<td>25.23 (21.64)</td>
<td>0.96</td>
<td>0.01</td>
<td>0.10 (0.42)</td>
</tr>
<tr>
<td>Pre CPM baseline</td>
<td>32.17 (25.70)</td>
<td>23.57 (22.66)</td>
<td>0.26</td>
<td>0.36</td>
<td>0.25* (0.03)</td>
</tr>
<tr>
<td>Pre CPM at 3 months</td>
<td>24.97 (17.91)</td>
<td>20.37 (14.31)</td>
<td>0.41</td>
<td>0.29</td>
<td>0.24* (0.04)</td>
</tr>
<tr>
<td>Pre CPM at 6 months</td>
<td>20.74 (15.28)</td>
<td>25.68 (18.46)</td>
<td>0.32</td>
<td>0.29</td>
<td>0.01 (0.91)</td>
</tr>
<tr>
<td>Post CPM baseline</td>
<td>24.65 (24.84)</td>
<td>15.29 (18.17)</td>
<td>0.21</td>
<td>0.44</td>
<td>0.29* (0.02)</td>
</tr>
<tr>
<td>Post CPM at 3 months</td>
<td>18.65 (17.06)</td>
<td>16.78 (19.15)</td>
<td>0.74</td>
<td>0.10</td>
<td>0.19 (0.13)</td>
</tr>
<tr>
<td>Post CPM at 6 months</td>
<td>14.56 (13.31)</td>
<td>15.86 (11.35)</td>
<td>0.75</td>
<td>0.11</td>
<td>0.13 (0.31)</td>
</tr>
<tr>
<td>Absolute difference CPM baseline</td>
<td>7.50 (12.76)</td>
<td>8.40 (8.68)</td>
<td>0.81</td>
<td>0.08</td>
<td>-0.04 (0.74)</td>
</tr>
<tr>
<td>Absolute difference CPM 3 months</td>
<td>6.53 (9.25)</td>
<td>3.58 (10.59)</td>
<td>0.33</td>
<td>0.30</td>
<td>0.12 (0.33)</td>
</tr>
<tr>
<td>Absolute difference CPM 6 months</td>
<td>5.97 (7.82)</td>
<td>9.81 (10.79)</td>
<td>0.15</td>
<td>0.41</td>
<td>-0.18 (0.15)</td>
</tr>
<tr>
<td>Percent change CPM baseline</td>
<td>22.72%</td>
<td>24.89%</td>
<td>0.88</td>
<td>-----</td>
<td>0.01 (0.96)</td>
</tr>
<tr>
<td>Percent change CPM at 3 months</td>
<td>31.15%</td>
<td>32.03%</td>
<td>0.94</td>
<td>-----</td>
<td>-0.12 (0.35)</td>
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<tr>
<td>Percent change CPM at 6 months</td>
<td>31.24%</td>
<td>29.37%</td>
<td>0.85</td>
<td>-----</td>
<td>-0.19 (0.13)</td>
</tr>
<tr>
<td>Pain threshold baseline</td>
<td>43.86 (2.28)</td>
<td>44.78 (2.00)</td>
<td>0.17</td>
<td>0.43</td>
<td>-0.09 (0.47)</td>
</tr>
<tr>
<td>Pain threshold 3 months</td>
<td>44.30 (2.39)</td>
<td>45.11 (2.58)</td>
<td>0.29</td>
<td>0.33</td>
<td>-0.09 (0.44)</td>
</tr>
<tr>
<td>Pain threshold 6 months</td>
<td>44.58 (2.32)</td>
<td>45.23 (1.87)</td>
<td>0.35</td>
<td>0.31</td>
<td>-0.09 (0.48)</td>
</tr>
<tr>
<td>PCS baseline</td>
<td>9.86 (6.97)</td>
<td>8.07 (6.72)</td>
<td>0.39</td>
<td>0.26</td>
<td>0.13 (0.26)</td>
</tr>
<tr>
<td>PCS 3 months</td>
<td>8.42 (7.99)</td>
<td>9.21 (9.39)</td>
<td>0.75</td>
<td>0.09</td>
<td>0.04 (0.73)</td>
</tr>
<tr>
<td>PCS 6 months</td>
<td>5.74 (5.42)</td>
<td>10.00 (7.85)</td>
<td>0.02</td>
<td>0.64</td>
<td>-0.23 (0.06)</td>
</tr>
<tr>
<td>PHQ-9 baseline</td>
<td>2.81 (3.98)</td>
<td>4.50 (2.62)</td>
<td>0.14</td>
<td>0.51</td>
<td>-0.21 (0.08)</td>
</tr>
<tr>
<td>PHQ-9 3 months</td>
<td>2.65 (3.31)</td>
<td>4.50 (3.50)</td>
<td>0.07</td>
<td>0.54</td>
<td>-0.22 (0.07)</td>
</tr>
<tr>
<td>PHQ-9 6 months</td>
<td>2.52 (3.51)</td>
<td>5.29 (3.69)</td>
<td>0.01</td>
<td>0.77</td>
<td>-0.33** (0.01)</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level.
*Correlation is significant at the 0.05 level.
Table 5-3. Correlations among clinical shoulder pain intensity, experimental pain measurement, and psychological factors at baseline and 6 months after surgery

<table>
<thead>
<tr>
<th></th>
<th>BPI B</th>
<th>BPI 6m</th>
<th>Cfiber50 B</th>
<th>Cfiber50 6m</th>
<th>CPM B</th>
<th>CPM 6m</th>
<th>%change CPM B</th>
<th>%change CPM 6m</th>
<th>PCS B</th>
<th>PCS 6m</th>
<th>PHQ B</th>
<th>PHQ 6m</th>
<th>Threshold B</th>
<th>Threshold 6m</th>
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</thead>
<tbody>
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<td>BPI B</td>
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<td>.331</td>
<td>.234</td>
<td>-.129</td>
<td>-.177</td>
<td>-.132</td>
<td>-.227</td>
<td>.248</td>
<td>.053</td>
<td>-.088</td>
<td>-.193</td>
<td>-.037</td>
<td>-.050</td>
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<td>.009</td>
<td>-.137</td>
<td>.046</td>
<td>-.220</td>
<td>-.045</td>
<td>.151</td>
<td>.385</td>
<td>.158</td>
<td>.177</td>
<td>.099</td>
<td>.068</td>
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<tr>
<td>Cfiber50 B</td>
<td>1</td>
<td>.581**</td>
<td>.129</td>
<td>.274</td>
<td>-.062</td>
<td>.042</td>
<td>.051</td>
<td>-.139</td>
<td>.176</td>
<td>-.147</td>
<td>-.465*</td>
<td>-.154</td>
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<td>Cfiber50 6m</td>
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<td>-.025</td>
<td>.230</td>
<td>-.092</td>
<td>-.203</td>
<td>-.221</td>
<td>-.143</td>
<td>.092</td>
<td>-.072</td>
<td>-.330*</td>
<td>-.366*</td>
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<td>.594**</td>
<td>.348</td>
<td>.049</td>
<td>-.165</td>
<td>-.065</td>
<td>-.105</td>
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<td>.015</td>
<td>.300*</td>
<td>.084</td>
<td>.065</td>
<td>.006</td>
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<td>%change CPM B</td>
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<td>.158</td>
<td>-.005</td>
<td>-.199</td>
<td>-.046</td>
<td>.000</td>
<td>.069</td>
<td>.167</td>
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<td>%change CPM 6m</td>
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<td>-.197</td>
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<td>.102</td>
<td>.253</td>
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</tr>
<tr>
<td>PCS B</td>
<td>1</td>
<td>.334*</td>
<td>.385*</td>
<td>.236</td>
<td>-.117</td>
<td>-.067</td>
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<td>PCS 6m</td>
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<td>.269</td>
<td>.343**</td>
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<td>-.026</td>
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<tr>
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<td>-.009</td>
<td>.004</td>
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</table>

B=Baseline; 6m=6 months after surgery
**. Correlation is significant at the 0.01 level.
*. Correlation is significant at the 0.05 level.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Comparison at 6 months</th>
<th>Baseline Mean (SD)</th>
<th>3 months Mean (SD)</th>
<th>Within group change Mean (SD)</th>
<th>P-Value interaction</th>
<th>Cohen’s d Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th pulse 50°</td>
<td>Improved</td>
<td>38.54 (25.29)</td>
<td>31.11 (26.42)</td>
<td>6.30 (21.97)</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>24.93 (16.78)</td>
<td>33.75 (23.58)</td>
<td>-8.29 (22.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute difference CPM</td>
<td>Improved</td>
<td>7.50 (12.76)</td>
<td>6.53 (9.25)</td>
<td>0.03 (12.20)</td>
<td>0.39</td>
<td>1.42</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>8.40 (8.68)</td>
<td>3.58 (10.59)</td>
<td>5.07 (11.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change CPM</td>
<td>Improved</td>
<td>22.72%</td>
<td>31.15%</td>
<td>-----</td>
<td>0.98</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>24.89%</td>
<td>32.03%</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain threshold</td>
<td>Improved</td>
<td>43.86 (2.28)</td>
<td>44.30 (2.39)</td>
<td>-0.31 (1.91)</td>
<td>0.736</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>44.78 (2.00)</td>
<td>45.11 (2.58)</td>
<td>-0.27 (2.33)</td>
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<td></td>
</tr>
<tr>
<td>PCS</td>
<td>Improved</td>
<td>9.86 (6.97)</td>
<td>8.42 (7.99)</td>
<td>1.67 (9.73)</td>
<td>0.33</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>8.07 (6.72)</td>
<td>9.21 (9.39)</td>
<td>0 (4.29)</td>
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<td></td>
</tr>
<tr>
<td>PHQ-9</td>
<td>Improved</td>
<td>2.81 (3.98)</td>
<td>2.65 (3.31)</td>
<td>0.26 (3.49)</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Not Improved</td>
<td>4.50 (2.62)</td>
<td>4.50 (3.50)</td>
<td>0.25 (2.01)</td>
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</tbody>
</table>

*Interaction effect size was calculated using the within group mean change and SD. The difference between “improved” and “not improved” groups was calculated and divided by the averaged SD of the within group change.
Table 5-5. Explaining 6 months post operative clinical pain with change score of QST

<table>
<thead>
<tr>
<th>Variable</th>
<th>R²</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Model</strong></td>
<td>0.06</td>
<td>0.01</td>
<td>0.01</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.13</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.34</td>
<td>0.39</td>
<td>-0.11</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Pain duration</td>
<td>0.002</td>
<td>0.002</td>
<td>0.13</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td><strong>2nd Model</strong></td>
<td>0.16</td>
<td>0.03</td>
<td>0.13</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.002</td>
<td>0.002</td>
<td>0.13</td>
<td>0.28</td>
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</tr>
<tr>
<td><strong>5th pain rating</strong></td>
<td></td>
<td></td>
<td></td>
<td>-0.34</td>
<td>0.01</td>
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</tbody>
</table>

Table 5-6. Explaining baseline clinical pain intensity with psychological predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>R²</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Model</strong></td>
<td>0.15</td>
<td>0.03</td>
<td>0.01</td>
<td>0.21</td>
<td>0.06</td>
</tr>
<tr>
<td>Age</td>
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<td>0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
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<td>-0.33</td>
<td>0.004</td>
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<td>Pain duration</td>
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<td>0.003</td>
<td>0.07</td>
<td>0.51</td>
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<tr>
<td><strong>2nd Model</strong></td>
<td>0.22</td>
<td>0.03</td>
<td>0.54</td>
<td>-0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>Constant</td>
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<tr>
<td>Age</td>
<td>0.03</td>
<td>0.01</td>
<td>0.09</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-1.36</td>
<td>0.54</td>
<td>0.26</td>
<td>0.02</td>
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</tr>
<tr>
<td>PCS baseline</td>
<td>0.09</td>
<td>0.04</td>
<td>0.26</td>
<td>0.02</td>
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</table>
Table 5-7. Explaining 6 months post operative clinical pain intensity (baseline psychological predictors)

<table>
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<th>B</th>
<th>SE</th>
<th>β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.01</td>
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<td>0.11</td>
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<td>-0.17</td>
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<td>0.002</td>
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Table 5-8. Explaining 6 months post operative clinical pain intensity (6 months predictors)

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<th>B</th>
<th>SE</th>
<th>β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
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<td>0.01</td>
<td>0.20</td>
<td>0.10</td>
</tr>
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<td>-0.56</td>
<td>0.37</td>
<td>-0.17</td>
<td>0.14</td>
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<tr>
<td>Pain duration</td>
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<td>0.002</td>
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<td>0.27</td>
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<td>-0.13</td>
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<td>0.002</td>
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Table 5-9. Explaining 6 months post operative clinical pain intensity with change score of 5th pain rating

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<th>Variable</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Model</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>0.19</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.32</td>
<td>0.38</td>
</tr>
<tr>
<td>Pain duration</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline PCS</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline PHQ</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; pain rating</td>
<td>-0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>
The purpose of this dissertation was to investigate the relationship between central pain modulatory mechanisms, psychological factors, and surgical outcome. Specifically we hypothesized that central pain modulatory mechanisms would have differential changes in patients who improve from those that do not improve their level of pain intensity 6 months after shoulder surgery. This hypothesis was partially supported, as suprathreshold heat pain response (SHPR) had differential changes over time, where the improved group significantly decreased at 3 months in comparison with the not improved group which remained stable. However conditioned pain modulation (CPM) and pain threshold did not differ between patients with different 6 months post surgical outcome at baseline or with 3 months change scores. Our secondary hypothesis was that CPM and SHPR would contribute additional variance to a regression model predicting post operative clinical pain after pain catastrophizing and depression are considered. Investigation of this hypothesis established measures of central pain processing as contributors to postoperative pain, in comparison to previously identified psychological factors of relevance. Our results revealed that the change score of SHPR is independent of baseline or 3 months psychological factors and makes a unique contribution to post operative 6 months pain intensity scores. However, we should consider that the small sample size may decrease the power for detecting true differences; therefore future study in a larger cohort of patients seeking shoulder surgery is necessary to validate these results.

The present study offers several advances to prior studies. First, these are novel data because few longitudinal studies have investigated changes in central pain
modulatory mechanisms that may occur after surgery. Second, the present study specifically differentiated between descending inhibitory mechanisms and excitatory pain summation as potential measures that are a precursor of continued post operative pain. Third, patients included in this study underwent shoulder surgery; therefore this study extends the pain literature investigating continued post operative pain to a broader range of surgical procedures than typically reported. Fourth, the exploration of the clinical relevance of dynamic QST, in comparison to psychological factors in predicting 6 months post operative shoulder pain intensity, made this study a novel contribution to the literature as past studies typically incorporate either QST or psychological measures.

We first investigated if baseline modulatory capacity (baseline CPM and pain sensitivity) differed among patients who do not improve their level of pain after 6 months compared to those who improved their level of pain after 6 months. Our results revealed that there were no significant baseline differences in modulatory capacity between those that improved pain 6 months post-operatively and those that did not. The alteration of central processing of noxious stimuli [126] characterized by above-average sensitivity to pain (increased excitability of nociceptive neurons) and/or below-average endogenous pain inhibitory capacity (decreased inhibition) [133,166], are thought to be a result of continuous nociceptor input [173]. Even though we did not measure directly nociceptor responsiveness, we used CPM and SHPR as both of these are accepted proxy or indirect measures of central pain processing [6].
In a previous study [154] the 5th pain rating of SHPR and the percent change of CPM were elevated for patients with shoulder pain compared to healthy controls (Figures 6-1 and 6-2), however the absolute difference of CPM did not differ.

Considering the current results in that context, we believed that pre-operatively patients had indication of central pain dysregulation, as evidenced by their elevated response to thermal stimulus. Our results showed no baseline differences on the 5th pain rating or percent change of CPM for patients who improved and who do not improved their level of pain after 6 months from surgery, even after controlling for baseline pain intensity, and pain duration (Figures 6-1 and 6-2). Therefore, there was no indication of baseline differences on level of central sensitization for the measures used in this study. These results imply that elevated sensitization (to thermal stimuli) is expected prior to surgery, but that further determination of risk at baseline by QST is not likely in this patient population. This finding could be explained by the strong activity of dorsal horn neurons caused by the constant noxious stimulation that patients have before surgery (similar baseline pain intensity between groups), which may lead to a similar increased neuronal responsiveness or central sensitization [101,136]. 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 [78,79,85,138,168]. We controlled for pain duration in this study as previous studies suggest a negative association between chronicity and post surgical pain intensity, where the longer the pain duration, the more likely they are to have poor surgical outcome [75,125]. These current findings also extend the literature by suggesting that preoperative pain duration is not necessarily a contributor to post
surgical outcome (since patients from both groups have similar preoperative pain duration and different post surgical outcome) and might be associated with different factors to predict post surgical outcome.

Measures of central pain modulatory mechanisms might measure different components of central pain processing. CPM represents a reduction in the magnitude of one stimulus in response to a second stimulus site [88,89], therefore it is an indication of endogenous pain inhibition or “inhibitory” measure. On the other hand, SHPR results in the perception of increased pain despite constant or even reduced peripheral afferent input [132,138], therefore, it is considered a perceptual manifestation of enhanced central excitability or a “facilitatory” measure. Therefore, these measures are considered two independent constructs which might influence the risk for chronic pain by their balance. For example, the combination of high pain sensitivity (higher “facilitatory” measure) and low endogenous pain inhibition (lower “inhibitory” measure) may confer the greatest risk for clinical pain [32,35,60]. However, in order to improve the predictive capability, future studies are needed to investigate the interaction between different QST measures.

Yarnitsky et al. [177] explored the predictive ability of CPM, indicating the potential for CPM to predict the development of chronic post operative pain. In addition, Kosek et al. [79] 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 treated. The present study shows no differences at baseline or differential changes on CPM or pain threshold between patients who improved and who do not improved their level of pain at 6 month from surgery, adding more information to
this relatively small literature. In addition, a deficit of endogenous pain inhibitory systems has been suggested to contribute to some chronic pain conditions predominantly to fibromyalgia [72,78,79,85,111,135]. However, CPM was not found to be deficient in other conditions such as low back pain[72], rheumatoid arthritis[91], vestibulodynia [71], or Parkinson disease [104]. Wijk and Veldhuijzed [157] proposed a hypothesis to explain differences in CPM saying that CPM would be deficient in “medically unexplained pain syndromes”. Combined results of CPM from our previous [154] and present study revealed that there were no differences on CPM between surgical cohort and healthy controls, no baseline differences, and no differential changes on CPM between patients with different post surgical outcome in this clinical sample. These findings provided additional support to Wijk and Veldheijzed's hypothesis. Furthermore, these findings suggested that inhibitory measures remained stable over time and it may not be sensitive as excitatory measures to immediate changes in clinical pain severity among patients with shoulder pain.

Multiple studies imply that chronic pain is associated with changes in central nervous system (CNS) processing of pain-related information [124,133,135,137,138], however the question of causality remains unanswered due to the nature of research designs. Even though a prospective study without a control group does not specifically elucidate the question of causality, our design answered the temporal aspect of important clinical questions. Our previous study [154] showed that patients with shoulder surgery decreased pain intensity at 3 months but a decrease did not occur with CPM. In contrast, SHPR decreased after 3 months showing values comparable with healthy controls at that point. This overall “normalization” of SHPR 3 months after
shoulder surgery provided evidence of favorable changes in CNS processing of pain, at least when thermal stimuli were applied. The current study extends our previous results by reporting differential changes on modulatory capacity between patients who improved and who did not improve their level of pain 6 months after surgery. Results revealed that changes on CPM over time (baseline-3 months post surgery) did not differ between groups. Interestingly and supporting our previous findings, SHPR had differential changes between groups, where the improved group significantly decreased over time in comparison with the not improved group which remained stable (Figure 5-4). The fact that the SHPR decreased between baseline assessment and 3 months after surgery in the improved group, indicates that changes in CNS processing of pain 3 months after surgery were a precursor of 6 months post surgical outcome. In addition, our current data extent previous findings by showing that only the group experiencing changes in CNS processing of pain was likely to have 6 months improvements in pain intensity. This change in SHPR, followed the same pattern as those described for CPM by Kosek et al. [79], where normal CPM function was seen when patients were re-assessed 6 months after surgery in a pain free stage. However we must consider that these two measures of central pain modulatory mechanisms might measure different components of central pain processing. Our findings further suggest that the SHPR as an excitatory measure could be more sensitive to immediate changes in clinical pain severity among patients with shoulder pain when compared to CPM. In addition, our findings substantiate that these two measures of central pain processing might be independent constructs, but further research is necessary to validate this statement.
Prior experimental studies have found elevations on measures assessing pain sensitivity and have stated that experimental pain sensitivity is one of the strongest predictors of surgical outcomes [79,177]. However, these authors did not explore the possibility that such changes may occur only in some patients. Our results added to this finding by showing that 3 months post surgical change on 5th pain rating was the best predictor of post surgical outcome at 6 months (Table 5-9)[153]. This implies that the 5th pain rating of SHPR appears to be a dynamic function that may be more sensitive to central neuroplasticity and a potential treatment target for this patient population. This is particularly important finding given that it held true even after controlling for variables that prior studies have shown to be related to post surgical pain such as preoperative pain duration, age, and sex.

Elevations in pain sensitivity are common among patients with long pain duration, however the present study shows no baseline differences on level of sensitization between patients with different 6 moth post surgical outcome. This could indicate that the baseline level of sensitization (measured by SHPR and CPM) may not identify patients at risk for continued pain at 6 months post surgery. In addition, the finding that the change in pain sensitivity is a stronger factor than baseline sensitivity in predicting post surgical pain is an important finding with high clinical implications. Central neuroplasticity as a potential treatment target might imply that changes of the 5th pain rating as an excitatory measure represent an intermediary step in the link between intervention (surgery) and desired outcome, and a potential key factor in the transition to either decrease of pain or symptom persistence 6 months after surgery. Therefore monitoring post surgical changes of an excitatory measure are likely to play a greater
role with early identification of patients at risk for poor post surgical outcome, as compared with inhibitory measures. However, future studies are needed to investigate potential treatment implications.

Psychological characteristics have been extensively examined in relation to pain perception and clinical outcomes, and have become an accepted factor in the development of chronic pain [51,92,164]. In addition to being important determinants of pain sensitivity, psychological characteristics also seem to play a fundamental role on how a painful stimulus is modulated [121,142,157]. The exploration of QST measures and the role of psychological factors [36,53,54,121] in healthy subjects or in cross-sectional studies of patients with chronic pain conditions has been widely investigated. However, there is limited evidence from longitudinal studies or from patients with shoulder and other upper extremity pain conditions. This raises the question of whether dynamic QST, contributes additional significant variance to clinical shoulder pain after psychological factors are considered.

Our results showed that, as expected from previous analyses, none of the QST measures utilized in this study had a significant predictive ability in 6 months post operative clinical shoulder pain. However, the change score of the 5th pain rating of SHPR was a predictor of 6 months post operative pain. In addition, pain catastrophizing accounted for a significant proportion of concurrent variance at baseline and 6 months after surgery. Interestingly, the hierarchical model explaining 6 months post operative pain with baseline psychological factors and the change score of 5th pain rating (Table 5-9), shows that the change score of our SHPR was the strongest predictor while baseline pain catastrophizing was not significant. These findings suggest that
psychophysical assessment specifically of excitatory pain sensitivity measures and measures of psychological distress are not redundant and they measure different pain constructs from psychological distress, supporting previous findings [54,153]. Future experimental pain studies might benefit from the inclusion of multiple pain measures (such as pain catastrophizing and 5th pain rating of SHPR), confirming that pain is multidimensional in nature and involves sensory discriminative and affective components [102]. However based on our results, it seems that a change on experimental pain measure (5th pain rating of SHPR) has higher predictive ability of postoperative pain intensity than pain catastrophizing. In exploring the associations among psychological factors and clinical pain intensity, our results as expected revealed that pain catastrophizing had a strong concurrent association with clinical pain at baseline and 6 months.

Some limitations of this study will need to be addressed by future research. First, 30% reduction in clinical pain intensity from baseline to 6 months was used as a cut-off to determine patient’s level of pain improvement. This decision was made based on previous studies using various outcome measures which have established that 30% change in pain intensity is consistently associated with individuals reporting notable improvement [39,41]. However our cut-off is focused solely on pain and not associated with patient’s self report of improvement (such as patient global impression of change) or function (from self-report of physical performance). Future studies looking at psychophysical measurements over time based on pain outcome should include additional measures of upper extremity disability and patient’s perception of post surgical improvement to establish a cut-off with higher clinical relevance. In addition, it
is also important to consider that by using change score measures (baseline -3 months) we are using a time frame closer to the outcome (in comparison to baseline score), however this time frame still has predictive ability of 6 months outcome and important clinical relevance. Second, CPM, SHPR, and heat pain threshold were the only QST measures reported in this study, future studies should include additional measures, such as pressure pain threshold, heat pain tolerance to have a more comprehensive QST assessment. Also, this study lacked a comparison group; therefore it is impossible to establish cause and effect of the relationship. Last, even though literature suggests that the incidence of chronic post operative shoulder pain is high [12], we believe that a surgical model with higher incidence of post operative chronic pain might be a better model to study changes on central pain processing associated with development of continued post operative pain. This surgical model would provide a more balance design with a better power to establish differences on central pain processing response between patients with elevated post operative pain and patients without pain after surgery. Even though the study had enough power to detect changes in pain intensity after 3 months post surgery, future study is necessary to validate these results in a larger cohort of patients seeking shoulder surgery. A larger cohort may increase effect sizes and may detect clear changes between groups at 6 months post surgery.

In summary, the present study suggests that there was no baseline difference in the level of central sensitization between patients who improve their level of pain at 6 months from surgery and who do not improve. Considering that not all patients with sensitization develop continued post surgical pain, this finding implies that baseline level of central sensitization was not a risk factor for continued pain at 6 months post surgery.
Therefore these measures may not be very useful in developing screening tools for identifying those at risk of poor surgical outcomes. In contrast, this study suggests that the 5th pain rating of SHPR differentially changed over time, where the improved group significantly decreased over time, and was a precursor to continued postoperative pain intensity. In addition, the change in 5th pain rating of SHPR is the strongest and clinically relevant experimental pain measure, and was independent of pain catastrophizing in explaining post operative pain intensity ratings. These findings suggest that patients having shoulder surgery might benefit with monitoring of pain catastrophizing and 5th pain rating of SHPR at baseline and 3 months post surgery to better predict 6 months post surgical outcome. This finding also provides evidence that excitatory changes in the central modulatory system might be a unique factor in the transition to continued post operative pain and a potential treatment target to monitor during postoperative period to distinguish between those that are likely to develop chronic pain syndromes and those that are not.
Figure 6-1. Comparison of baseline 5th pain rating between current study (patients who improved vs. who do not improve), and previous study (healthy subjects vs. patients having shoulder surgery) [154].

Figure 6-2. Comparison of baseline percent change of CPM between current study (patients who improved vs. who do not improve), and previous study (healthy subjects vs. patients having shoulder surgery) [154].
CHAPTER 7
CONCLUSIONS

This prospective study investigated whether central pain modulatory mechanisms have differential changes in individuals having different pain outcome 6 months after shoulder surgery, and the role of CPM and SHPR in explaining post operative clinical pain after psychological factors were considered. Results revealed that there were no baseline differences on level of sensitization between patients who improved and patients who do not improved their level of pain at 6 months; however there might be baseline signs of central sensitization in all patients evidenced by an increased 5th pain rating of SHPR. This study also demonstrated that patients from both groups had significant differential changes in an excitatory pain sensitivity measure; however, they did not differ on pain descending inhibitory mechanisms or basal state of the system (pain threshold). In addition, the change in 5th pain rating of SHPR was the strongest and clinically relevant experimental pain measure, and was independent of pain catastrophizing in explaining post surgical clinical pain intensity. In summary the results imply that baseline level of sensitization was not a risk factor for continued pain at 6 months post surgery. In contrast, the 5th pain rating of SHPR changed over time and this change was a significant precursor to continued postoperative pain intensity at 6 months, providing evidence that the central modulatory system might be a unique factor in the transition to continued post operative pain.
APPENDIX A
BRIEF PAIN INVENTORY (BPI)

1. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

2. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.
   0  1  2  3  4  5  6  7  8  9  10
   No Pain
   Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.
   0  1  2  3  4  5  6  7  8  9  10
   No Pain
   Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain on the average.
   0  1  2  3  4  5  6  7  8  9  10
   No Pain
   Pain as bad as you can imagine

5. Please rate your pain by circling the one number that tells how much pain you have right now.
   0  1  2  3  4  5  6  7  8  9  10
   No Pain
   Pain as bad as you can imagine
6. If you had to spend the rest of your life with the symptoms you have right now, how would you feel about it?

1. Very dissatisfied
2. Somewhat dissatisfied
3. Neutral
4. Somewhat satisfied
5. Very satisfied
APPENDIX B
PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: ___________________________ DATE: ___________________________

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use “✓” to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several Days</th>
<th>Most of the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(add columns: __________ + __________ + __________ = TOTAL: ___)

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card.)

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>

PHQ-9 is adapted from PRIME MD TODAY, developed by Dr. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr. Spitzer at rls@columbia.edu. Use of the PHQ-9 may only be made in accordance with the Terms of Use available at http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

ZT274388
PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.
2. If there are at least 4 ✔️s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.
3. Consider Major Depressive Disorder
   —If there are at least 5 ✔️s in the blue highlighted section (one of which corresponds to Question #1 or #2)
   Consider Other Depressive Disorder
   —If there are 2 to 4 ✔️s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✔️s by column. For every ✔️: Several days = 1   More than half the days = 2   Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients’ files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION
for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9
For every ✔️: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>None</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>
APPENDIX C
PAIN CATASTROPHIZING SCALE (PCS)

ψ

PCS

Client No.: _______ Age: _____ Sex: M( ) F( ) Date: __________

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

When I’m in pain ...

1. I worry all the time about whether the pain will end.
2. I feel I can’t go on.
3. It’s terrible and I think it’s never going to get any better.
4. It’s awful and I feel that it overwhelms me.
5. I feel I can’t stand it anymore.
6. I become afraid that the pain will get worse.
7. I keep thinking of other painful events.
8. I anxiously want the pain to go away.
9. I can’t seem to keep it out of my mind.
10. I keep thinking about how much it hurts.
11. I keep thinking about how badly I want the pain to stop.
12. There’s nothing I can do to reduce the intensity of the pain.
13. I wonder whether something serious may happen.

...Total
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Carolina Valencia graduated from Universidad Catolica de Valparaiso Chile with a bachelor of science in kinesiology and a professional degree in physical therapy. Briefly after becoming a Physical Therapist, Carolina was asked to be part of the faculty in the same University (Universidad Catolica de Valparaiso, Chile). She also was recruited as a Physical Therapist in the University Student Health Center (from the same University), where she was responsible for senior students during their clinical practice.

Carolina worked for 5 years as a clinician in musculoskeletal disorders. As a result of academic involvement, she came to be one of the first Physical Therapist in Chile working in the area of Physical Rehabilitation in hospitalized patients with psychiatric dysfunctions. Carolina became part of a multidisciplinary team working in the social reinsertion of patients with schizophrenia.

Carolina also tried to find an explanation from a musculoskeletal point of view to maxillofacial pain. She studied with Dr. Mariano Rocabado who helped her to understand the complexity of craniomandibular and craniovertebral dysfunctions. After working for more than 3 years implementing different techniques, exercise programs, and trying to restore the proper positioning in patients having craniomandibular dysfunction (pre and post surgery), she realized that the pathology, or the type of injury was not enough to predict a final outcome.

In 2006, Carolina moved to University of Florida at Gainesville to pursue her PhD in Rehabilitation Science and gain expertise in musculoskeletal pain. She graduated in December 2011.