# SENSORIMOTOR ABNORMALITIES IN CHRONIC SUBACROMIAL PAIN: THE INFLUENCE OF SEX, CONTRIBUTION OF PAIN, AND UTILITY OF USING THE CONTRALATERAL LIMB AS A CONTROL

by

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Doctor of Philosophy

Department of Human Physiology

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Title: Sensorimotor Abnormalities in Chronic Subacromial Pain: The Influence of Sex, Contribution of Pain, and Utility of Using the Contralateral Limb as a Control

Patients with subacromial pain syndrome (SPS) display a number of sensorimotor deficits including alterations in pain processing, poor proprioception, and weakness at the symptomatic limb. The primary purpose of this dissertation was to explore whether the aforementioned deficits: (1) can be quantified by using the non-involved limb as a measure of control, (2) are purely localized to the symptomatic limb or represent a more generalized deficit, (3) are influenced by the presence of subacromial pain, and (4) present similarly in male and female patients. Here, we utilized modern clinical techniques in both a patient cohort with SPS and uninjured control cohort to address these aims. The results of this dissertation are applicable towards treatment of SPS as well as scientific understanding of sex on sensorimotor behavior.

This dissertation includes unpublished coauthored material.

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This dissertation is dedicated to
My Grandma Vicky,

Your words of encouragement and genuine enthusiasm for my successes always came at the right time

Without you, I would have given up on this endeavor a long time ago

You were right Grandma -
The hardest part is getting started,
I can do anything for just another five minutes, and
The reward of a job well done, is to have it done!

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CHAPTER I

# INTRODUCTION

## Significance

Each year chronic pain affects more Americans than heart disease, diabetes, and cancer combined, making it the most cited reason for healthcare consumption (U.S. Department of Health and Human Services, 2013). Within the middle aged and working populations, shoulder pain is one of the leading sources of chronic pain, long-term disability, and psychological distress (Meislin et al., 2005). More specifically, shoulder pain ranks second or third behind back pain as the most frequent musculoskeletal complaint within the general population (Picavet and Schouten, 2003; Urwin et al., 1998). Between 7% and 26% of adults experience shoulder pain at any given time (Luime et al., 2004), producing enormous socioeconomic impacts. In 2000, the direct cost for treating shoulder pain in the United States totaled approximately $7 billion (Meislin et al., 2005), while the indirect costs associated with lost work or productivity are estimated to have exceeded this figure (Dorrestijn et al., 2011).

Shoulder pain can be particularly debilitating, with roughly 30% of persons with shoulder pain reporting limitations in activities of daily living (Picavet and Schouten, 2003). Limitations in occupational or self-care tasks arise from pain as well as difficulties producing adequate strength, performing repetitive tasks, and positioning the arm above the shoulder, near the back of the head or near the gluteal region (Hall et al., 2011; van der Windt et al., 1995). Aside from the physical burdens, patients with shoulder pain also

experience substantial psychological burdens including sleep disturbances, depression, anxiety, and lower quality of life (Bodin et al., 2014; Cho et al., 2013).

Rotator cuff tears, subacromial pain syndrome (SPS), glenohumeral osteoarthritis, glenohumeral instability, and adhesive capsulitis are all common causes of shoulder pain. Of these conditions, SPS is the predominant cause of shoulder pain, accounting for approximately half of all shoulder complaints (Dorrestijn et al., 2011; Meislin et al., 2005). SPS is known by many other names, including rotator cuff tendinopathy as well as subacromial impingement syndrome. For this dissertation, we have decided to use the term SPS, since it does not implicate any single structure or etiology in the development of the syndrome. Rather, SPS is defined as chronic pain that arises from a broad set of pathologies localized to the subacromial space.

The subacromial space, measured on radiographic images as acromiohumeral distance, is bound by the greater tuberosity of the humerus inferiorly and the coraco-acromial arch superiorly (MacDonald et al., 2000). Although the subacromial space is small, consisting of 7-14 millimeters in a healthy population (Roberts et al., 2002), it houses several crucial soft tissue structures including the subacromial bursa, the tendon of the supraspinatus (a rotator cuff muscle) and the tendon of the long head of the biceps. Trauma to any or all of the soft tissue structures found in the subacromial space can lead to SPS (Michener et al., 2003). Consequently SPS encompasses a number of pathologies including bursitis, rotator cuff or bicipital tendinopathies and partial rotator cuff tears. A large or complete tear of the rotator cuff is considered a separate disease; however rotator cuff tears are often related to SPS in that if left untreated, SPS may progress to a tear. Although not every patients with SPS will go on to develop a rotator cuff tear, the long-

term prognosis for patients with SPS is poor. Roughly 45-50% of patients with shoulder pain report persisting pain despite having seen a primary care physician in the previous six (Feleus et al., 2007; Kuijpers et al., 2004; Morrison et al., 1997), twelve (Winters et al., 1999) or twenty-four months (Cummins et al., 2009).Sex disparities exist among populations with shoulder pain in regards to treatment outcomes, with female patients experiencing a higher prevalence of repeat injuries and greater levels of disability after treatment than male patients (Razmjou et al., 2016, 2011).

Despite its prevalence, the causes of SPS are still unclear and much debated, likely owing to a heterogeneous etiology among patient populations. However, advances in research suggest that SPS arises from a complex interaction of risk factors, some of which are potentially modifiable through non-surgical means. A large body of recent research has found a relationship between specific sensory and motor abnormalities at the shoulder joint and the development or progression of SPS (Anderson and Wee, 2011; Bandholm et al., 2006; Hidalgo-Lozano et al., 2010); Consistent with many other chronic pain conditions, patients with subacromial pain have been found to have hypersensitivity (Hidalgo-Lozano et al., 2010; Paul et al., 2012), weakness (MacDermid et al., 2004; McCabe et al., 2005) and abnormal proprioception (Anderson and Wee, 2011; Machner et al., 2003) at the involved limb and these sensorimotor abnormalities may be contributing to the development or progression of SPS. To date however, little work has thoroughly examined how standard treatment influences these sensorimotor abnormalities in patients with SPS. Additionally, little work has been done to investigate whether these sensory and motor deficits arise from the commonly assumed local mechanisms, such as the nerves or muscles of the shoulder itself, or central mechanisms within the central

nervous system. This is a surprising knowledge gap given that pain is known to exert tremendous changes on the sensorimotor system at the central level in other pain conditions (Lotze and Moseley, 2007; Lund et al., 1991; Tsay et al., 2015; Woolf, 2011). As a result, it is unclear if current treatment practices are capable of rectifying the sensory and motor abnormalities found in patients with SPS, or if more targeted intervention strategies are warranted. Moreover, it is unknown if sensory and motor abnormalities present similarly in male and female patients with SPS, as females have been shown to have greater levels of sensory and motor abnormalities in other chronic pain conditions (Earle Miller et al., 2016; Speed et al., 2017; Vambheim and Flaten, 2017). Given the prevalence, burdens and poor prognosis associated with SPS, especially in the female population, these knowledge gaps represent a serious clinical problem that warrants further research, and until these knowledge gaps are adequately addressed, advancing beyond the current clinical success rate is highly unlikely.

My dissertation, *Sensorimotor Abnormalities in Chronic Subacromial Pain Syndrome: The Influence of Sex, Contribution of Pain, and Utility of Using the Contralateral Limb as a Control*, addresses the aforementioned gaps by comparing the sensorimotor abilities of patients with SPS to healthy persons without shoulder pain, both before and after standard treatment. By stratifying male and female patients into separate groups and assessing the sensorimotor abilities of male and female patients across both shoulder joints and remote lower extremities joints, my dissertation provides insight on the mechanisms contributing to sensorimotor abnormalities as well as direction for future treatment strategies. **The overarching goal of this dissertation was to investigate the**

**influence of subacromial pain and sex on sensorimotor abilities, including pain sensitivity, proprioception, and strength.**

## Innovation

For nearly one out of every two patients, treatment of SPS is inadequate and fails to fully resolve symptoms (Cummins et al., 2009). In order to improve the current clinical success rate, it is important to understand how certain risk factors, including sensory and motor abnormalities, influence the development and progression of SPS. Pain models are pivotal for establishing cause and effect relationships, and consequently a battery of pain models have been developed to better understand SPS. Similar to research on other chronic pain conditions, the pain models developed to study SPS can be divided into three distinct categories, including an acute pain-induction model, a longitudinal pain-relief model, and an acute pain-relief model. While the use of each of these three models has elucidated valuable knowledge about the relationships between subacromial pain and sensorimotor abnormalities, significant limitations are associated with each model, which substantially interfere with the extension of results beyond the model itself and into clinically relevant contexts.

The acute pain-induction model incites temporary pain, either through electrical, mechanical or chemical means, into healthy volunteers and compares a subject's pre-treatment measures to post-treatment measures (Bajaj et al., 2001). In the context of SPS research, acute pain has most frequently been induced in healthy subjects by injecting hypertonic saline into the supraspinatus muscle (Bandholm et al., 2008; Diederichsen et al., 2009), infraspinatus muscle (Madeleine et al., 2008) or subacromial space

(Diederichsen et al., 2009; Stackhouse et al., 2013). Because the acute pain-induction model relies on intra-subject comparisons that span a short time interval (minutes to hours), this model has been useful for establishing well defined cause-and-effect relationships between subacromial pain and sensorimotor abnormalities. Furthermore, the pain patterns produced by injecting hypertonic saline into the supraspinatus, infraspinatus or subacromial space are strikingly similar to the magnitude and location of pain patterns reported in patients with SPS. Despite these similarities in pain patterns, the observed effects of experimental shoulder pain on sensorimotor function differ substantially from the sensorimotor function observed in patients with SPS (Bandholm et al., 2008; Diederichsen et al., 2009; Valencia et al., 2012). Therefore even though an acute pain-induction model can reflect SPS in terms of pain patterns, it appears unable to reflect the adaptations in the central nervous system seen with chronic subacromial pain, as pain may need to be present for a longer period of time for such adaptions to occur. Substantial discrepancies have been noted between many other chronic pain conditions and their associated acute experimental pain models, which questions the validity of acute pain-induction models as a whole (Vøllestad and Mengshoel, 2005).

The longitudinal pain-reduction model is the oldest and most utilized model to assess the influence of subacromial pain on sensorimotor function. In this model, patients are assessed before and several weeks to years after receiving a treatment intervention aimed at reducing the patient's pain and disability (Dorrestijn et al., 2009; Kuhn, 2009; McClure et al., 2004). Because the longitudinal pain-reduction model relies on patient measurements before and after treatment, this model has been valuable for establishing the effectiveness of specific interventions (such as subacromial decompression surgery,

nonsteroidal anti-inflammatory drugs, rehabilitation) on long-term patient outcomes. While the longitudinal pain-reduction model has clear relevancy and clinical utility, the major limitation to this model is that it does not allow for a cause and effect relationship to be established between pain and sensorimotor function. To elaborate, many anatomical and environmental changes accompany long-term pain reduction, making it impossible to isolate the contribution of pain reduction on sensorimotor function from other variables.

The first line of treatment for patients with SPS often involves the injection of local anesthetics and corticosteroids into the subacromial space, with the anesthetics exerting an almost instantaneous reduction in pain in a large percentage of patients. In addition to its clinical utility, subacromial injections serve as an invaluable acute pain-reduction model. By assessing a patient at baseline and 15 minutes following a subacromial injection, researchers are able to have a clinically relevant model that uses patients while simultaneously controlling for extraneous variables that would occur in a longitudinal study and better isolate the influence of pain. While the use of the acute pain-reduction model has become increasingly used in research on SPS (Ben-Yishay et al., 1994; Ettinger et al., 2014, 2017; Park et al., 2008), it is not without limitations. Because patients undergo repeat testing in a short period of time, it is difficult to determine whether any changes that occur between the pre-injection and post-injection time points are due to a learning effect on the sensorimotor task or true changes in sensorimotor function. Fortunately, the use of healthy control population that also undergoes repeat testing would allow for a correction of the learning effect, better isolating the true influence of subacromial injection in patients. For this dissertation, we employed such a method. **We feel this approach was innovative because to our**

**knowledge, no previous studies have utilized the acute pain-reduction model in conjunction with a control group undergoing repeat testing to investigate the influence of subacromial pain on sensory and motor function.**

## Aims, Hypotheses, and Approach

As described earlier in the introduction, patients with subacromial pain syndrome (SPS) display a number of sensorimotor deficits including hypersensitivity to innocuous stimuli, abnormal proprioception, and weakness at the symptomatic limb. The primary purpose of this dissertation was to explore whether the aforementioned deficits: (1) can be quantified by using the non-involved limb as a measure of control, (2) are purely localized to the symptomatic limb or represent a more generalized deficit, (3) are influenced by the presence of subacromial pain, and (4) present similarly in male and female patients. These purposes were addressed via four specific aims. An overview of each specific aim as well as the corresponding hypotheses and methods are provided below.

For Aim 1 (detailed in Chapter II), a cross-sectional study incorporating young healthy participants stratified by sex was utilized. For Aim 2, Aim 3, and Aim 4, we utilized a single repeated measures study that incorporated both a patient cohort with SPS and a healthy control cohort (Chapter III). To specifically address Aim 2 (Chapter IV), Aim 3 (Chapter V), and Aim 4 (Chapter VI), subsets of data obtained from patients and controls were analyzed from the larger data set.

**<u>Aim 1</u> – To investigate whether both males and females display asymmetries at the shoulder joint within three sensorimotor modalities: pressure pain sensitivity, proprioception, and strength.**

- <u>Hypothesis 1.1</u> – Pressure pain sensitivity asymmetries would be present in a right arm dominant male population but not a right arm dominant female population.
- <u>Hypothesis 1.2</u> – Proprioception asymmetries would be present in a right arm dominant male population but not a right arm dominant female population.
- <u>Hypothesis 1.3</u> – Strength asymmetries would be present in a right arm dominant male population but not a right arm dominant female population.

**<u>Aim 2</u> – To assess peripheral sensitization (PS) and central sensitization (CS) by testing pain hypersensitivity at involved and remote locations in patients with SPS, both before and after acute pain reduction, and to explore characteristics associated with the presence of CS.**

- <u>Hypothesis 2.1</u> – Patients with SPS would demonstrate a greater sensitivity to pain at the symptomatic shoulder and remote locations (contralateral shoulder, both knees) than matched controls.
- <u>Hypothesis 2.2</u> – Upon pain reduction, patients experiencing SPS would demonstrate decreased sensitivity to pain at both shoulders and both knees relative to pre-injection values.
- <u>Hypothesis 2.3</u> – After controlling for pain duration and pain intensity, female patients would demonstrate greater sensitivity than male patients.

**<u>Aim 3</u> – To assess regional and global abnormalities to proprioceptive function by testing joint position sense at involved and remote locations in patients with SPS, both before and after acute pain reduction, and to explore characteristics associated with the presence of abnormal proprioception.**

- <u>Hypothesis 3.1</u> – Patients experiencing SPS would demonstrate worse proprioception at the symptomatic shoulder as well as remote joints (contralateral shoulder, both knees) than matched controls.
- <u>Hypothesis 3.2</u> – Upon pain reduction, patients experiencing SPS would demonstrate worse proprioception both shoulders and both knees relative to pre-injection values.
- <u>Hypothesis 3.3</u> – After controlling for pain duration and pain intensity, female patients would demonstrate greater proprioceptive errors than male patients.

**<u>Aim 4</u> – To assess regional and global weakness by testing peak isometric torque at involved and remote locations in patients with SPS, both before and after acute pain reduction, and to explore characteristics associated with weakness.**

- <u>Hypothesis 4.1</u> – Patients with SPS would demonstrate smaller peak torque values at the symptomatic shoulder and remote locations (contralateral shoulder, both knees) than matched controls.
- <u>Hypothesis 4.2</u> – Upon pain reduction, patients experiencing SPS would demonstrate greater peak torque values at both shoulders and both knees relative to pre-injection values.

- Hypothesis 4.3 – After controlling for pain duration and pain intensity, female patients would demonstrate smaller normalized peak torque than male patients.

## Acknowledgement of Co-Authored Material

This dissertation consists of unpublished co-authored material. Dr. Andrew Karduna served as a co-author for Chapters II, III, IV, V, and VI due to his contribution to editing, experimental design, advising, and project conception. In addition to Dr. Andrew Karduna, Chapters III, IV, V, and VI were also co-authored by Dr. Matthew Shapiro who assisted in recruiting patients with subacromial pain and performed the subacromial injection.

CHAPTER II

# THE INFLUENCE OF SEX ON SENSORIMOTOR ASYMMETRIES

The experiment described in this chapter was developed with Dr. Andrew Karduna who contributed substantially to this work by assisting with experimental conception, editing and advising throughout the project. I was the primary contributor to the development of the experimental design, data collection and analysis, and write up.

## Introduction

Localized hypersensitivity to pain, abnormal proprioception, and weakness have been found in persons with subacromial pain syndrome (SPS), and are thought to play a role in the progression or development of this pathology. Consequently, these sensory and motor abnormalities have become important areas of interest for clinicians and researchers (Ettinger et al., 2017; Littlewood et al., 2013). Pain sensitivity, proprioceptive function, and weakness are frequently assessed in patients with SPS by comparison with their uninjured contralateral shoulder (Coronado et al., 2011; Machner et al., 2003; McCabe et al., 2005; Potzl et al., 2004; Tyler et al., 2005). That is, deficits and subsequent treatment strategies are calculated from the assumption that prior to injury, a patient's shoulders demonstrated bilateral symmetry. The scientific assumption of this practice needs further clarification as significant asymmetries in pain sensitivity, proprioception, and strength may exist in healthy shoulders, and these asymmetries may be particularly evident in males versus females (Adamo et al., 2012). If the shoulders of

healthy males or females demonstrate asymmetries in pain sensitivity, proprioception or strength, this finding questions the validity of using a patient's uninjured shoulder as a control, particularly in research settings where a control group could be incorporated into the study design.

The lateralization of brain function has been well demonstrated, such that some functions tend to be localized to one of the two hemispheres (Hugdahl, 2011). For example, the left hemisphere has been associated with language functions, while the right hemisphere is associated with visual spatial tasks. With respect to motor control, the cerebral hemispheres demonstrate contralateral sensorimotor control, with the left arm and leg being controlled by the right hemisphere and the right arm and leg being controlled by the left hemisphere. In general, females show less cerebral lateralization than males (Wisniewski, 1998). Initial observations on sex related differences in lateralization emerged from studies on vision and hearing, which revealed that females demonstrated less lateralization in response to visual and auditory stimuli than males (Hiscock et al., 1995; Voyer, 1996). Later studies have probed sex differences in the lateralization of motor control, and showed females displayed a greater amount of bilateral activation and interhemispheric communication in response to sensorimotor stimuli (Stephen et al., 2006). It has been suggested that less lateralization and greater interhemispheric communication may arise from the larger corpus callosum present in females (Allen et al., 1991).

While neuroimaging studies have shown that males demonstrate greater lateralization in portions of the brain associated with sensorimotor control than females, few studies have been developed to assess sex differences in asymmetries during

functional sensorimotor tasks. A vast number of studies have compared pain sensitivity, proprioception, and strength between the dominant and non-dominant upper extremity, without controlling for sex. However, the literature on differences in pain sensitivity, proprioception, and strength between the dominant and non-dominant upper extremity is contradictory. Some studies have found that the dominant limb of healthy right handers displayed less pain sensitivity (Ozcan et al., 2004; P Pauli et al., 1999; Paul Pauli et al., 1999) , greater strength (Cahalan et al., 1991; Lertwanich et al., 2006; Perrin et al., 1987) and greater proprioceptive errors (Bagesteiro and Sainburg, 2002; Goble and Brown, 2008) than the non-dominant limb, while nearly just as many studies have found no difference in pain sensitivity (Kindler et al., 2011; Rolke et al., 2006; Sacramento et al., 2017), strength (Gołebiewska et al., 2008; Ivey et al., 1985; Mattiello-Rosa et al., 2008), and proprioception (King et al., 2013; Voight et al., 1996) between the limbs. Part of this discrepancy may arise from the fact that few studies have statistically or experimentally accounted for sex when assessing sensorimotor asymmetries. Many of the aforementioned studies utilized an all-male cohort of participants, while other studies were skewed towards female majority cohorts. A recent study by Adamo et al. (2012) investigated elbow proprioception while age matching men and women into separate cohorts. These authors found that asymmetries in proprioception were only present in males, and advocated for researchers to consider sex in sensorimotor control studies, especially when comparing the dominant and non-dominant upper extremities, since sex dependent asymmetries may be present in other joints as well.

In order to assess whether it is appropriate to use the non-involved limb as a measure of control for pain sensitivity, proprioception, and strength in both men and

women, additional studies exploring whether asymmetries are present in both males and females are clearly needed. Such information might not only be useful in the context SPS, but for other upper extremity disorders, such as stroke or chronic regional pain syndrome.

**The aim of this study was to investigate whether both males and females display asymmetries at the shoulder joint within three sensorimotor modalities: pressure pain sensitivity, proprioception, and strength. We hypothesized that pressure pain sensitivity (Hypothesis 1.1), proprioception (Hypothesis 1.2), and strength (Hypothesis 1.3) asymmetries would be present in a right arm dominant male population but not a right arm dominant female population..**

## Methods

### Participants

Twenty-seven uninjured female and twenty-seven uninjured male participants were included in the present study (Table 2.1). All participants were right-arm dominant and between the ages of 18-35 years. Right-arm dominance was defined as a score greater than or equal to 80 on the modified Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were: 1) current pain across the upper extremity; 2) history of surgery, traumatic injury, instability or arthritis to the shoulder, elbow or wrist; 3) current participation in a vigorous overhead activity; 4) a diagnosed chronic pain or neurological disorder; 5) current or past use of gonadal hormones opposite to biological sex; and 6) pregnancy. All participants were informed about the purpose and protocol of the project and gave their written informed consent prior to participation in the study. All experimental conditions were approved by the Institutional Review Board.

**Table 2.1.** Characteristics (means ± SDs) of male and female participants enrolled in the asymmetry study.

| | Males | Females |
|---|---|---|
| **Age** (years) | 24 ± 4 | 22 ± 4 |
| **Edinburgh Handedness Inventory** (0-100) | 96 ± 5 | 98 ± 4 |
| **Height** (cm) | 179 ± 6 | 167 ± 6* |
| **Weight** (kg) | 78 ± 13 | 66 ± 12* |
| **BMI** | 24 ± 4 | 24 ± 4 |

* Denotes a significant difference between male and female participants.

**Study Design**

The present study used a cross-sectional design with male and female participants divided into separate groups. After obtaining informed consent, participants engaged in the bilateral sensory and motor tasks in the following order: proprioception, strength, and pain sensitivity. The side selected to be tested first (dominant or non-dominant) was randomized and counter-balanced. Data collection was completed in one session.

**Pain Sensitivity**

Pain sensitivity was tested at both shoulders utilizing a pressure pain threshold (PPT) protocol. Measures of PPT, defined as the minimum force applied that induced pain (Fischer, 1987), were obtained with the use of a hand-held pressure algometer with a one-$cm^2$ probe (Wagner Instruments). With participants in a seated position, upper extremity assessment sites were marked at the bilateral deltoid and infraspinatus muscles. The deltoid location was marked at the midpoint between the flat portion of the acromion

and deltoid insertion (Figure 2.1). The infraspinatus location was marked at the midpoint between the inferior angle of the scapula and midpoint of the scapular spine (Figure 2.1).

The researcher positioned the probe perpendicular to the assessment site and applied progressive pressure at a rate of approximately one kg/s. The participant was instructed to inform the assessor when they first perceived a sensation of pain or discomfort, at which point pressure application ceased and the PPT value was noted.

The order of testing (location and side) was blocked and randomized between participants. Four measurements were obtained for each location with a 30 second interval between measurements. The four trials were averaged to obtain one raw PPT score for the right shoulder ($\overline{X}_{PPT.Right}$) and one raw PPT score for the left shoulder($\overline{X}_{PPT.Left}$). Previous investigations have consistently shown that males have significantly larger PPT scores than females (Neziri et al., 2011). Consequently, the following normalization calculation was utilized to calculate PPT asymmetry scores:

**2.1**

$$\text{PPT Asymmetry Index (\%)} = \frac{\overline{X}_{PPT.Right} - \overline{X}_{PPT.Left}}{(\overline{X}_{PPT.Right} + \overline{X}_{PPT.Left})/2} \text{ x } 100\%$$

Using this formula, a value of 0 indicates perfect symmetry was present between the right and left sides while a positive value indicates the right limb required more pressure to induce pain sensation than the left limb.

**Proprioception**

Proprioception at both shoulders was assessed utilizing an active-active joint position sense (JPS) protocol. Measurements were obtained by affixing a 5th generation

iPod Touch to the lateral aspect of the humerus, approximately two inches above the elbow joint via an elastic band (Figure 2.2). The iPod ran on a custom developed app that emitted auditory cues and calculated joint angles with respect to gravity utilizing data from the tri-axial accelerometer and tri-axial gyroscope. The validity of the app has previously been validated in a field setting and compared to a similar protocol involving an electromagnetic tracking device(S. Edwards et al., 2016).

Each JPS trial consisted of an active positioning phase followed by an active repositioning phase. The following is an explanation of each phase of a JPS trial.

1. Baseline position – At the beginning of the trial, the participant assumed a relaxed baseline position.

2. Positioning phase – The positioning phase began with a low-pitched sound, prompting the participant to leave the baseline position. The pitch (or frequency) of the auditory tone provided the participant with feedback about the angle of their joint relative to the target. When the participant attained the target (defined as ± 3˚from the desired joint angle) the participant was directed to hold the target position and memorize its location. After holding the target for three seconds, the participant returned to the baseline position and then held the baseline position for one second.

3. Repositioning phase – Without auditory feedback from the app, the participant repositioned their joint away from baseline and into the previously memorized target. After maintaining a static position (defined as velocity less than 0.25 degrees/sec) for one second, the device recorded the participant's position.

During testing, participants were seated with their eyes closed. To minimize extraneous cues across the upper extremity, females wore sleeveless shirts or sports bras

while males wore sleeveless shirts or no shirt. Prior to data collection, participants performed several practice trials at non-test angles to become acquainted with the protocol. The number of practice trials varied by participant and was determined by the researcher based on the participant's competency with the protocol.

Assessment of the shoulder involved shoulder flexion performed in the sagittal plane while seated in a backless chair. During all testing, the participant was instructed to keep the elbow locked in extension and the thumb pointed upwards. The targets of interest for the shoulder were 70 degrees of shoulder flexion, presented three times per joint. Two distractor targets of 55 and 85 degrees were also presented. Distractor targets were utilized to ensure participants did not memorize the target of interest. The testing of sides was randomized and counterbalanced between participants.

After data collection, each trial was analyzed with custom written LabVIEW (National Instruments, Austin, TX) software. The difference between the repositioned angle and presented angle was termed *repositioning error*. If the repositioned angle involved greater excursion than the target angle this was called an overestimation and given a positive sign. The repositioning error for each of the three trials at 70 degrees was then used to calculate three raw error scores for each joint: absolute error (AE), constant error (CE) and variable error (VE).

1. Absolute Error (AE) – this was defined as the mean of the absolute repositioning errors or overall deviation error. Absolute errors represent accuracy without considering directional bias. Larger values indicate larger errors.
2. Constant Error (CE) – this was defined as the mean of repositioning errors. Constant errors represent accuracy with directional bias and were calculated as

defined by Schmidt and Lee (Schmidt and Lee, 1999). A positive value for CE indicates greater joint excursion occurred during the repositioning phase relative to the presented phase and a negative value indicates smaller joint excursion occurred during the repositioning phase relative to the presented phase.

3. Variable Error (VE) – this was defined as the population standard deviation from the mean of constant errors. Variable errors represent the ability of participants to consistently sense test positions and were calculated as defined by Schmidt and Lee (Schmidt and Lee, 1999). Larger values indicate larger variability in repositioning errors between trials.

Previous investigations have not established that males and females have different proprioceptive abilities as measures by AE, CE, or VE scores (Ángyán et al., 2007; Bjorklund et al., 2000). Consequently proprioceptive asymmetry scores were calculated for AE, CE, and VE without a normalization procedure according to the following formulas:

**2.2**

$$\text{AE Asymmetry (degrees)} = \overline{X}_{\text{AE.Right}} - \overline{X}_{\text{AE.Left}}$$

**2.3**

$$\text{CE Asymmetry (degrees)} = \overline{X}_{\text{CE.Right}} - \overline{X}_{\text{CE.Left}}$$

**2.4**

$$\text{VE Asymmetry (degrees)} = \overline{X}_{\text{VE.Right}} - \overline{X}_{\text{VE.Left}}$$

Using these conventions, a value of 0 for AE Asymmetry or VE Asymmetry indicates perfect symmetry was present between the right and left sides while a positive value indicates the right limb presented with larger errors than the left side. A value of 0 for CE

Asymmetry indicates perfect symmetry was present between the right and left sides while a positive value indicates the right limb repositioned to a more flexed angle than the right side.

**Strength**

Strength at both shoulders was assessed utilizing a maximum isomeric voluntary contractions (MVIC) protocol. Measurements were obtained from a computerized system consisting of a uniaxial load cell, amplifier, and data acquisition unit running on custom written LabVIEW (National Instruments, Austin, TX) software. Graphical representation of contraction force was visible on a monitor in real time to research personnel but not participants. Data were sampled at 1000 Hz and recorded as force. For each joint, the peak (or maximum) force produced out of the series of three trials was used for data analysis.

The testing procedure was strictly standardized, including participant positioning, contraction time, rest time between trials, number of trials per side, and verbal instruction and encouragement. Maximum isometric volunteer contractions were performed against resisted sagittal plane flexion of the upper extremity, with the shoulder in 90 degrees of flexion, the elbow in full extension and the forearm in neutral pronation/supination. Participants were in a seated position and the trunk was stabilized with straps (Figure 2.3). The load cell was mounted to a metal testing frame and positioned just proximal to the styloid process of the radius. Each joint was tested three times, with thirty seconds of rest in between each trial. The testing of sides was randomized and counterbalanced between participants. Participants were verbally encouraged by the investigator during

each muscle contraction and instructed to continue the contraction for five seconds. Feedback about performance was not given to participants.

For each joint, the peak force score (N) was converted to a peak torque score (Nm). To calculate peak torque, peak force was multiplied by the moment arm (defined as the distance between the center of the shoulder joint and the center of the load cell). The moment arm length was measured with a seamstress ruler from the center of the shoulder joint to the middle of the point of contact with the load cell. One peak torque was obtained for the right shoulder ($\overline{X}_{\text{Torque.Right}}$) and one peak torque score was obtained for the left shoulder ($\overline{X}_{\text{Torque.Left}}$). Previous investigations have consistently shown that males are significantly stronger than females (Bishop et al., 1987; Hoffman et al., 1979). Consequently, the following normalization calculation was utilized to calculate torque asymmetry scores:

**2.5**

$$\text{Torque Asymmetry Index (\% )} = \frac{\overline{X}_{\text{Torque.Right}} - \overline{X}_{\text{Torque.Left}}}{(\overline{X}_{\text{Torque.Right}} + \overline{X}_{\text{Torque.Left}})/2} \text{x } 100\%$$

Using this formula, a value of 0 indicates perfect symmetry was present between the right and left sides while a positive value indicates the right limb produced greater torque than the left side.

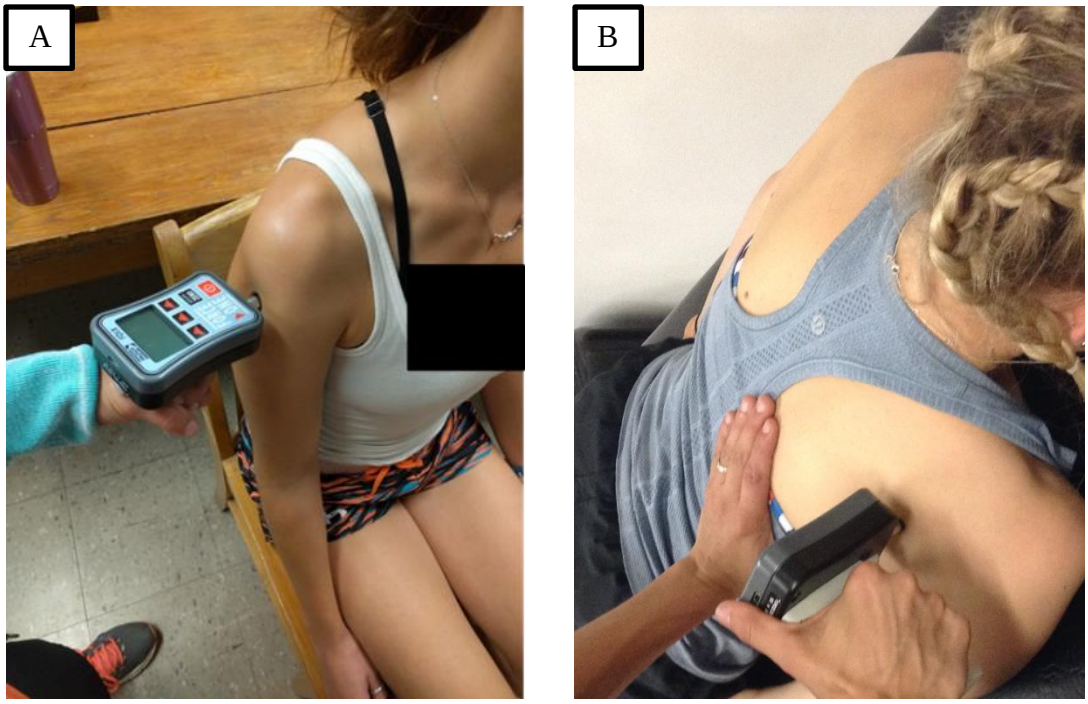


**Figure 2.1.** Experimental set-up used for pressure pain threshold (PPT) measurements during the asymmetry study. A) Deltoid location. B) Infraspinatus location.

**Statistical Analysis**

SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Values of $p < 0.05$ were regarded as statistically significant for all analysis.

**Between-Group Demographics** - To assess whether differences in demographics and anthropometrics were present between male and female participants, a series of independent t-tests were run.

**Hypothesis 1.1 – Asymmetries in pressure pain sensitivity would be present in a right-arm dominant male population but not a right-arm dominant female population.** Before addressing the hypothesis, we first tested whether males presented with significantly larger raw PPT scores than females by running an independent sample t-tests. Sex was the independent variable and average raw PPT score (expressed in kg and

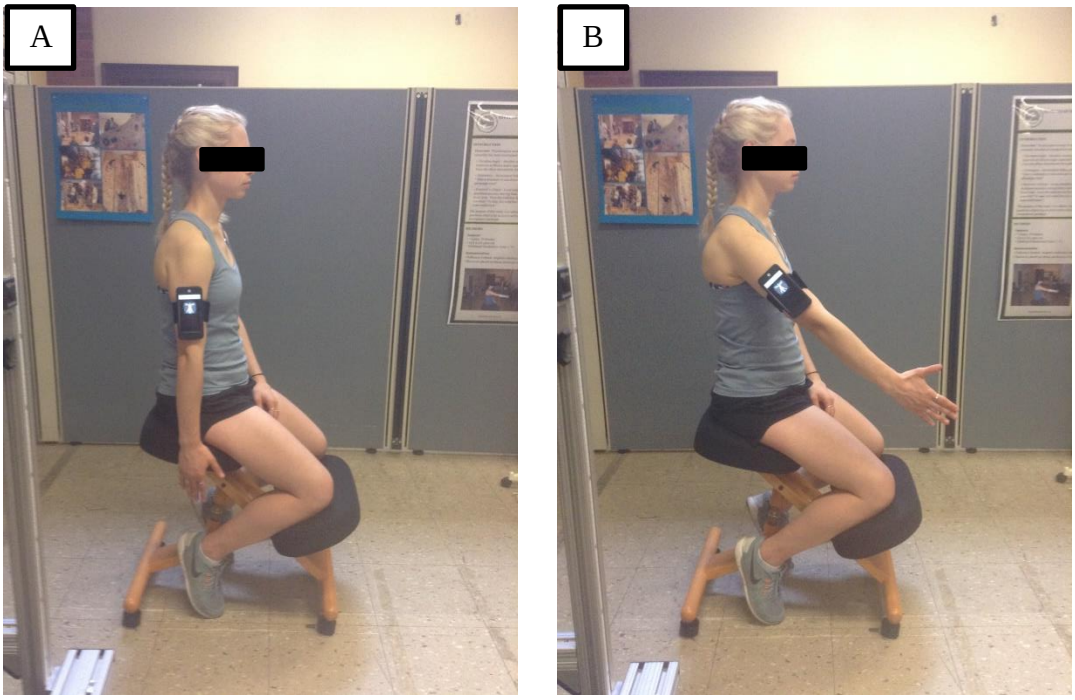


**Figure 2.2.** Experimental set-up used for proprioception measurements during the asymmetry study. A) Shoulder in rest position. B) Shoulder in reaching position.

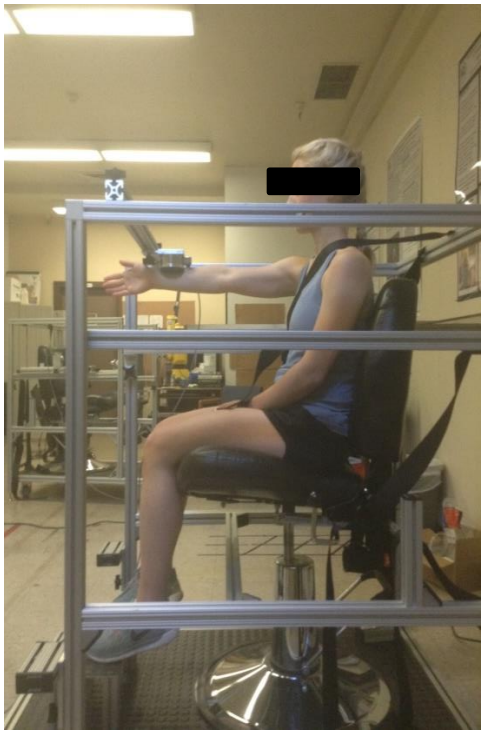

**Figure 2.3.** Experimental set-up used for peak torque (strength) measurements during the asymmetry study.

collapsed across the right and left sides) was the dependent variable. If significant differences were found between male and female participants raw PPT scores, all subsequent analyses were run with PPT Asymmetry Index scores as the dependent variable for normalization purposes.

To address our hypothesis, three one-sample t-tests were run with the following test variables against a sample value of 0: (1) PPT Asymmetry Index for males only, (2) PPT Asymmetry Index for females only, and (3) PPT Asymmetry Index for males and females pooled into one population. In addition, to determine if the magnitudes of PPT asymmetries were different between males and females, one independent-sample t-tests was run. The independent variable was sex (male, female) and the dependent variable was PPT Asymmetry Index. This entire procedure was repeated twice: once for the infraspinatus location and once for the deltoid location.

**Hypothesis 1.2 – Asymmetries in proprioception would be present in a right-arm dominant male population but not a right-arm dominant female population.** Before addressing the hypothesis, we first tested whether males and females demonstrated similar raw AE scores by running an independent sample t-test. Sex was the independent variable and average raw AE score (expressed in degrees and collapsed across the right and left sides) was the dependent variable. If no significant differences were found between male and female participants raw AE scores, all subsequent analyses were run with AE Asymmetry scores as the dependent variable, since normalization was not necessary.

To address our hypothesis, three one-sample t-tests were run with the following test variables against a sample value of 0: (1) AE Asymmetry for males only, (2) AE

Asymmetry for females only, and (3) AE Asymmetry for males and females pooled into one population. In addition, to determine if the magnitude of proprioceptive asymmetries were different between males and females, one independent-sample t-tests was run. The independent variable was sex (male, female) and the dependent variable was AE Asymmetry. This entire procedure was repeated twice more: once for CE scores and once for VE scores.

**Hypothesis 1.3 – Asymmetries in strength would be present in a right-arm dominant male population but not a right-arm dominant female population.** Before addressing the hypothesis, we first tested whether males presented with significantly larger raw torque scores than females by running an independent sample t-tests. Sex was the independent variable and average raw torque score (expressed in Nm and collapsed across the right and left sides) was the dependent variable. If significant differences were found between male and female participants raw torque scores, all subsequent analyses were run with Torque Asymmetry Index scores as the dependent variable for normalization purposes.

To address our hypothesis, three one-sample t-tests were run with the following test variables against a sample value of 0: (1) Torque Asymmetry Index for males only, (2) Torque Asymmetry Index for females only, and (3) Torque Asymmetry Index for males and females pooled into one population. In addition, to determine if the magnitude of asymmetries were different between males and females, one independent-sample t-tests was run. The independent variable was sex (male, female) and the dependent variable was Torque Asymmetry Index.

## Results

### Participant Characteristics

Independent t-tests revealed no significant differences between male and female participants in regards to age ($p=0.08$), BMI ($p=0.79$), or Edinburgh Handedness Scores ($p=0.13$). Independent t-test revealed significant differences in height ($p<0.01$) and weight ($p<0.01$), with males being taller and heavier (Table 2.1).

### Pain Sensitivity: Hypothesis 1.1

For both the infraspinatus ($p=0.001$) and deltoid ($p<0.001$) locations, males demonstrated significantly larger raw PPT scores than females. Based on this finding, subsequent analyses were run using PPT Asymmetry Index scores as the dependent variable for normalization purposes. Raw PPT score values are presented in Table 2.2.

In the male-only population, both the deltoid ($p=0.001$) and infraspinatus ($p<0.001$) demonstrated PPT Asymmetry Indexes that were significantly different than 0. Males mean PPT Asymmetry Indexes were 6-7%, indicating that the right limb experienced 6-7% more pressure compared to the left limb (Figure 2.4). In the female-only population, neither the deltoid ($p=0.15$) nor infraspinatus ($p=0.06$) demonstrated PPT Asymmetry Indexes that were significantly different from 0, despite mean values of 3-5% (Figure 2.4). When males and females were pooled into one mixed-sex population, both the deltoid ($p=0.001$) and infraspinatus ($p<0.001$) were found to have PPT Asymmetry Indexes that were significantly different from 0, with mean values of 5-6% (Figure 2.4). When males and females were compared to each other, no significant group

differences in PPT Asymmetry Indexes were found at either the deltoid (p=0.63) nor infraspinatus (p=0.28).

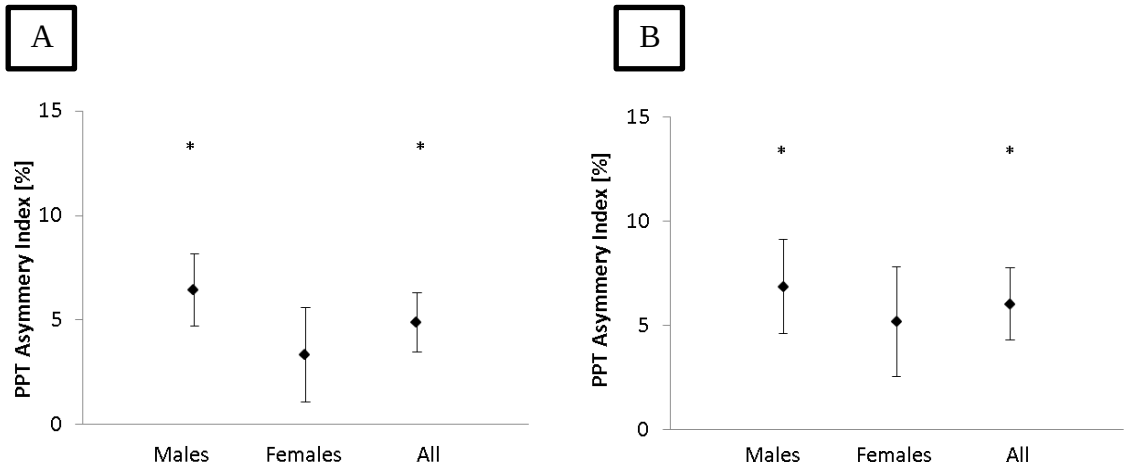


**Figure 2.4.** PPT Asymmetry Index scores (means ± SEMs) for male and female participants. A) Deltoid location. B) Infraspinatus location. *Denotes value is significantly different from 0.

**Proprioception: Hypothesis 1.2**

No significant differences were found between male and female subjects in regards to AE (p=0.18), CE (p=0.31) or VE (p=0.49) scores. Based on this finding, a normalization procedure was not needed and subsequent analyses were run using AE Asymmetry, CE Asymmetry, and VE Asymmetry scores. Raw AE, CE, and VE values are presented in Table 2.2.

In the male-only population, AE Asymmetry (p=0.03), CE Asymmetry (p=0.02), and VE Asymmetry (p=0.04) scores were significantly different than 0 (Figure 2.5). Males mean AE Asymmetry scores were 0.9 degrees, indicating that AE scores were 0.9 degrees larger at the right side compared to the left. Males mean CE Asymmetry scores were 1.2 degrees, indicating that repositioning errors at the right limb were located 1.2

degrees more flexed than left limb repositioning errors. Males mean VE Asymmetry scores were -0.6 degrees, indicating that indicating that VE scores were 0.6 degrees larger at the left side compared to the right (Figure 2.5). In the female-only population, neither AE Asymmetry ($p=0.08$), CE Asymmetry ($p=0.33$) nor VE Asymmetry ($p=0.88$) scores were significantly different than 0 (Figure 2.5). Mean AE Asymmetry, CE Asymmetry, and VE Asymmetry scores were equal to 0.4 degrees, 0.3 degrees and 0.0 degrees, respectively in the female population. When males and females were pooled into one mixed-sex population, both AE Asymmetry ($p<0.001$) and CE Asymmetry ($p=0.001$) scores were found to be significantly different than 0 while VE Asymmetry ($p=0.30$) scores were not found to be significantly different than 0 (Figure 2.5). When males and females were compared, no significant group differences in scores were found at for AE Asymmetry ($p=0.29$), CE Asymmetry ($p=0.13$) or VE Asymmetry ($p=0.15$) scores

**Strength: Hypothesis 1.3**

Males were found to have significantly larger raw torque scores than females ($p<0.001$). Based on this finding, subsequent analyses were run using the Torque Asymmetry Index as the dependent variable for normalization purposes. Raw torque score values are presented in Table 2.2.

In the male-only population, the shoulders demonstrated a Torque Asymmetry Index that was not significantly different from 0 ($p=0.69$). Males mean Torque Asymmetry Index was 1%, indicating that torque values produced on the right side were 1% larger than the left side (Figure 2.6). In the female-only population, the shoulders demonstrated a Torque Asymmetry Index that was significantly different than zero ($p=0.03$), with a mean of 5% (Figure 2.6). When males and females were pooled into one

mixed-sex population, the shoulders were found not to have a Torque Asymmetry Index significantly different from 0 (p=0.06), despite a mean of 3% (Figure 2.6). When males and females were compared to each other, no significant group differences in Torque Asymmetry Indexes were found (p=0.17).

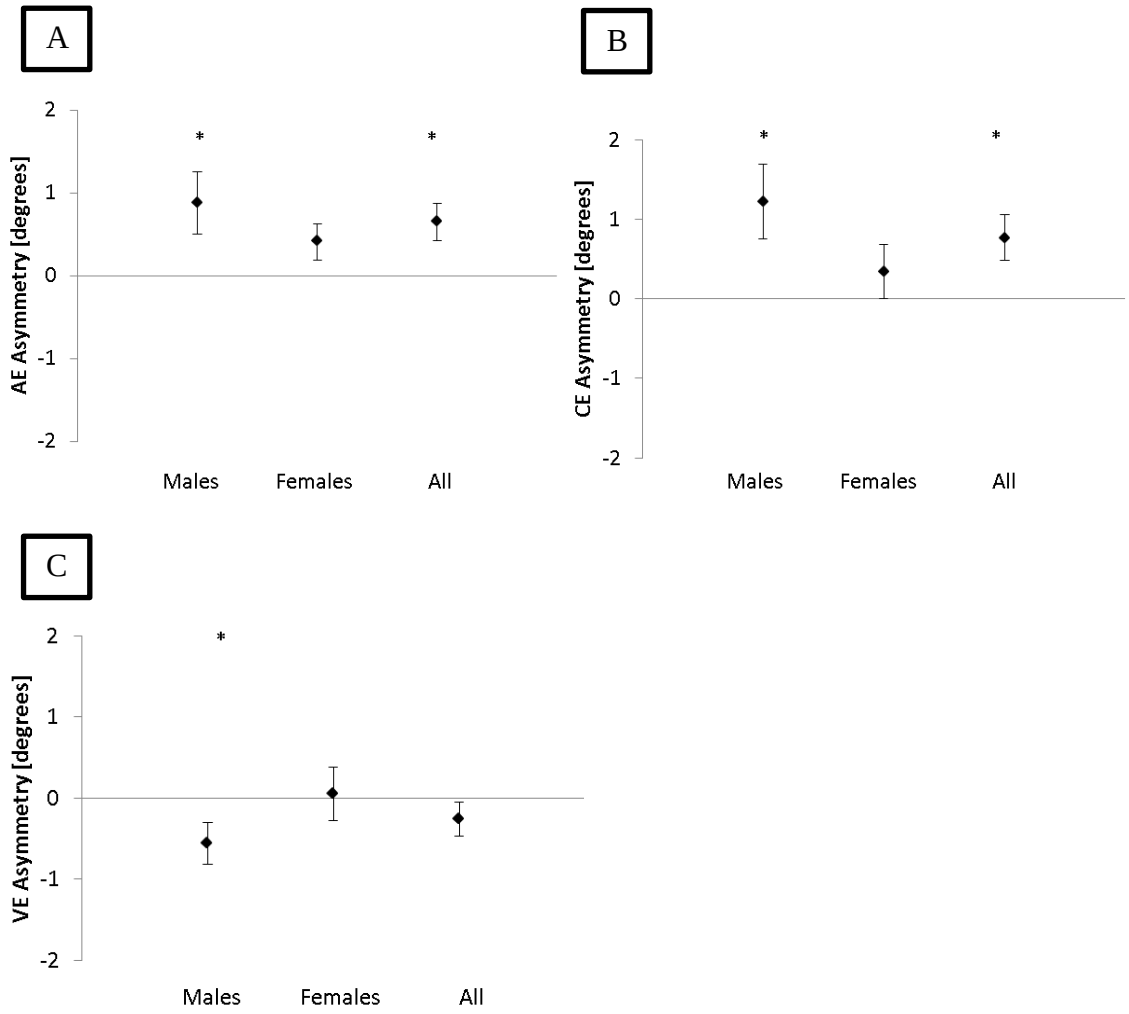


**Figure 2.5.** Proprioception Asymmetry scores (means ± SEMs) for male and female participants. A) Absolute errors. B) Constant errors. C) Variable errors. *Denotes value is significantly different from 0.

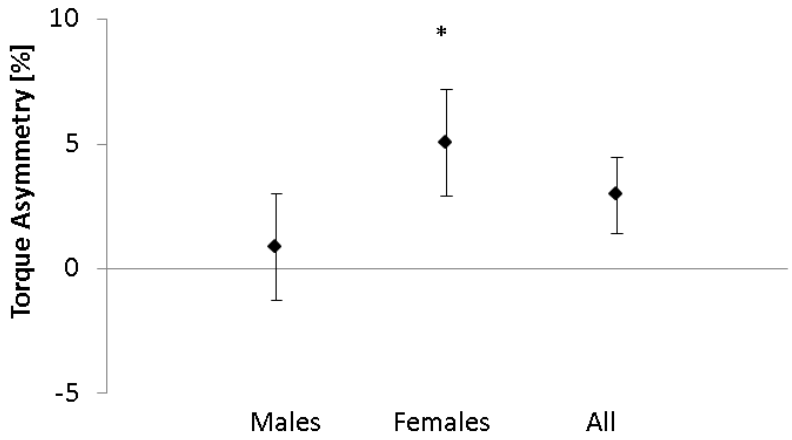


**Figure 2.6.** Torque Asymmetry Index scores (means ± SEMs) for male and female participants. Positive values indicate larger torque was exerted by the right versus left side. *Denotes value is significantly different from 0.

**Table 2.2.** Raw (means ± SDs) pressure pain threshold (PPT), proprioception, and peak torque (strength) scores for male and female participants enrolled in the asymmetry study.

| | **Males** | | **Females** | |
|---|---|---|---|---|
| | Dominant | Non-dominant | Dominant | Non-dominant |
| **PPT** | | | | |
| Deltoid (kg) | 3.6 ± 1.4 | 3.4 ± 1.4 | 2.4 ± 0.9 | 2.2 ± 0.8 |
| Infraspinatus (kg) | 3.9 ± 1.9 | 3.6 ± 1.7 | 2.5 ± 0.9 | 2.4 ± 0.9 |
| **Proprioception** | | | | |
| AE (degrees) | 4.1 ± 2.8 | 3.2 ± 2.7 | 3.0 ± 1.8 | 2.7 ± 1.8 |
| CE (degrees) | 3.6 ± 3.5 | 2.4 ± 3.5 | 2.4 ± 2.7 | 2.0 ± 2.4 |
| VE (degrees) | 1.8 ± 1.0 | 2.4 ± 1.2 | 1.9 ± 1.1 | 1.9 ± 1.4 |
| **Strength** | | | | |
| Shoulder Flexion (Nm) | 56.3 ± 12.2 | 29.6 ± 7.3 | 56.0 ± 13.4 | 27.9 ± 6.0 |

## Discussion

The aims of the present study were to investigate whether both males and females display asymmetries at the shoulder joint within three sensorimotor modalities, including pressure pain sensitivity, proprioception, and strength. We hypothesized that asymmetries in pressure pain sensitivity, proprioception, and strength would be present in a right-arm dominant male population but not a right-arm dominant female population. The results corresponding to each sensorimotor modality are discussed below.

Our hypothesis that asymmetries in proprioception would be present in a right-arm dominant male population but not a right-arm dominant female population was supported. Males demonstrated proprioception asymmetry scores that were significantly different from 0 within all three metrics of proprioception, AE, CE, and VE. Specifically, the non-dominant limb of male participants demonstrated better repositioning accuracy than the dominant limb by ~0.9 degrees, due to a smaller overshooting bias and more variable pattern at the non-dominant limb. These results fit well with previous literature which is currently split as to whether the non-dominant limb has a proprioceptive advantage (Bagesteiro and Sainburg, 2002; Goble and Brown, 2008) or no asymmetries are present (King et al., 2013; Voight et al., 1996). Specifically, a recent systematic review article by our lab investigated the effects of arm dominance on shoulder proprioception (Conner et al., 2017). Six of the articles meeting inclusion criteria had results showing a non-dominant limb advantage while another twenty articles found no evidence for asymmetries. Based on the results of the review, there is likely an underlying effect of arm dominance that is small and is being obscured by confounding variables. Since a sex effect was not investigated in many other studies looking at

proprioceptive asymmetries, and the present study found a significant non-dominant limb advantage for males only, it is possible that the conflicting results from earlier studies could have reflected the proportion of male/female participants (Adamo et al., 2012).

Similar to our results on proprioception, our hypothesis that asymmetries in pressure pain sensitivity would be present in a right-arm dominant male population but not a right-arm dominant female population was also supported. Across both shoulder locations (deltoid and infraspinatus), males demonstrated PPT asymmetry scores that were significantly different from 0, with 6-7% greater pressure being tolerated by the dominant versus non-dominant limb. In contrast, females PPT asymmetry scores at both shoulder locations were not significantly different from 0, despite 3-5% greater pressure being tolerated by the dominant versus non-dominant limb. Like our results on proprioception, these results fit well with previous literature which is currently split as to whether the non-dominant limb has greater sensitivity to pain than the dominant limb sensitivity (Ozcan et al., 2004; P Pauli et al., 1999; Paul Pauli et al., 1999) or no asymmetries are present (Kindler et al., 2011; Rolke et al., 2006; Sacramento et al., 2017). To our knowledge, no systematic reviews have been conducted to detail the number of studies that have looked at the effect of arm dominance on pain sensitivity. Since a sex effect was not investigated in many other studies looking at PPT asymmetries, and the present study found a significant non-dominant limb advantage for males only, it is possible that the conflicting results from earlier studies could have reflected the proportion of male/female participants. The small sample size of some previous studies could also contribute to the lack of a dominance effect.

Our last hypothesis that asymmetries in strength would be present in a right-arm dominant male population but not a right-arm dominant female population was not supported. While both males and females exerted greater peak torque across the right versus left shoulder, these asymmetries only reached significance in the female (mean 5%) but not male population (mean 1%). Previous literature is currently split as to whether the dominant limb is stronger than the non-dominant limb (Cahalan et al., 1991; Lertwanich et al., 2006; Perrin et al., 1987) or no asymmetries are present (Gołebiewska et al., 2008; Ivey et al., 1985; Mattiello-Rosa et al., 2008). To our knowledge, no systematic reviews have been conducted to detail the number of studies that have looked at the effect of arm dominance on strength. Much of the discrepancy in previous literature may have to do with the varied protocols and populations (athletes versus non-athletes) that have been used to assess strength. However since a sex effect was not investigated in many other studies looking at strength asymmetries, and the present study found a significant dominant limb advantage for females only, it is possible that the conflicting results from earlier studies could have reflected the proportion of male/female participants. The small sample size of some previous studies could also contribute to the lack of a dominance effect.

It is interesting to note that in both of our sensory measures, proprioception and pressure pain threshold, it was the non-dominant limb of males that demonstrated a heightened sense of touch and position. The dynamic dominance hypothesis of handedness is gaining increasing acceptance as an explanation for upper extremity asymmetries and may explain the non-dominant limb advantage noted in our proprioception and pressure pain measures (Sainburg, 2002). The dynamic dominance

hypothesis states that the dominant limb/non-dominant hemisphere specializes in performing dynamic movements while the non-dominant limb/dominant hemisphere specializing in holding static postures. Such roles for the upper extremities are evident in many activities of daily living where the dominant arm manipulates an object in the visual field while the non-dominant limb stabilizes it without the aid of vision. A heightened sense of arm position and sensitivity to pain in the non-dominant limb as noted in the present study seems advantageous for protecting the non-dominant limb from harm in the absence of vision.

Although it is difficult to determine the origin of larger sensory asymmetries in males versus females, some insight may be provided by a combination of structural and physiological differences associated with sex. Specifically, females demonstrate less lateralization as imaging studies have shown greater interhemispheric interactions and bilateral activation patterns in females versus males (Rabinowicz et al., 2002; Wisniewski, 1998). Functionally, females also demonstrate less lateralization during visual or auditory tasks (Hiscock et al., 1995). That strength asymmetries were more pronounced in females as opposed to males was a surprising finding. The degree to which repeated use or a genetically inheritable trait contributes to asymmetries is more difficult to ascertain with strength.

By finding significant asymmetries between the dominant and non-dominant limb among healthy controls in three sensorimotor modalities, our results suggest that using a patient's uninjured contralateral shoulder to quantify sensorimotor deficits may be inappropriate, especially in research settings where a control group could be incorporated into the analysis. Depending upon the side (dominant versus non-dominant) that is

injured, sensorimotor deficits could be artificially inflated or masked by solely relying on values obtained from the injured limb. Since the development of normative asymmetry indexes is beyond the scope of the present study, the use of a control population may be preferable when assessing sensorimotor modalities in clinical populations in research settings. Moreover, since the present study found sensorimotor asymmetries to be sex dependent, it is also important to sex match controls to clinical populations.

There are several limitations to the present study. The first limitation concerns the fact that shoulder sensorimotor tasks were performed in limited positions. For example, proprioception was only assessed with a flexion task; however it is possible that different motions such as abduction, external/external rotation, etc. could yield different results. Similarly, strength was only assessed at 90 degrees of flexion, and other positions and motions could also yield different results. Another limitation is that only a young population (18-35 years) was evaluated in this study, therefore our results cannot be reliably extended to older populations. It is possible that as persons age, sensorimotor asymmetries present differently. The use of two populations (young and older) could have helped account for this. Also, there is likely a difference in asymmetries between right and left-arm dominant persons.

## Conclusions

The present study found that asymmetries in three sensorimotor modalities, pressure pain threshold, proprioception, and strength, did not present uniformly in male and female participants at the shoulder joint. Specifically, male participants exhibited significant asymmetries in the two sensory modalities, pressure pain threshold and

proprioception, while females did not. Males' sensory asymmetries tended to favor greater sensitivity in the non-dominant limb. In contrast, female participants exhibited significant asymmetries in the motor modality, strength, while males did not. Females' motor asymmetries favored greater strength in the dominant versus non-dominant limb. Taken together, these findings suggest sex may be an important variable of consideration when comparing the dominant to non-dominant limb or healthy to injured limb. Moreover, it may be inappropriate to use the healthy limb as a measure of control researcher studies looking at populations with shoulder injuries.

## Bridge

In the present study (Chapter II), for shoulders of a young uninjured population, asymmetries in pain sensitivity, proprioception, and strength were found to be present and sex dependent. These finding suggest that when assessing sensorimotor modalities in populations with shoulder injuries, the healthy limb may be an inadequate reference as a control. Consequently, as we designed our next study, as outlined in Chapter III, we built on the findings of the present study by including a control group that was tightly matched for arm dominance, sex, and age to serve as a reference when evaluating sensorimotor deficits in patients with chronic shoulder pain.

CHAPTER III

STUDY DESIGN AND RESULTS COMMON TO AIM 2, AIM 3, and AIM 4

The experiment described in this chapter was developed with Dr. Andrew Karduna who contributed substantially to this work by assisting with experimental conception, editing and advising throughout the project. Dr. Matthew Shapiro further contributed to the study by assisting in recruiting patients with subacromial pain and performing the subacromial injection. I was the primary contributor to the development of the experimental design, data collection and analysis, and write up.

## General Procedures

To address Aim 2 (Chapter IV), Aim 3 (Chapter V), and Aim 4 (VI), which all center on a patient population with chronic subacromial pain, we developed one large study which is detailed in this chapter. The methods and results shared in the present chapter are common to Aim 2, Aim 3, and Aim 4. Then in the next three chapters (Chapters IV – VI), we analyzed specific subsets of the data that pertained to each aim.

The present study used a repeated-measures design with two participant groups: (1) patients with subacromial pain syndrome and (2) uninjured controls. Both patient and control participants were tested at two time points. For patient participants, the two time points included immediately prior to and fifteen minutes after receiving a subacromial

injection. For control participants, the two time points were separated by a fifteen minute rest period (Figure 3.1).

Self-reported measures, including information about health history, demographics and Disability of the Arm, Shoulder and Hand (DASH) scores were obtained once prior to session 2. Instrumented measures including Visual Analog Scale (VAS), pain sensitivity, proprioception, and strength testing were obtained twice, once prior and once after the injection/rest period. For Aim 2, we looked at the data pertaining to pain sensitivity in Chapter IV. For Aim 3, we looked at the data pertaining to proprioception in Chapter V. Finally, for Aim 4, we looked at the data pertaining to strength in Chapter VI (Figure 3.1).

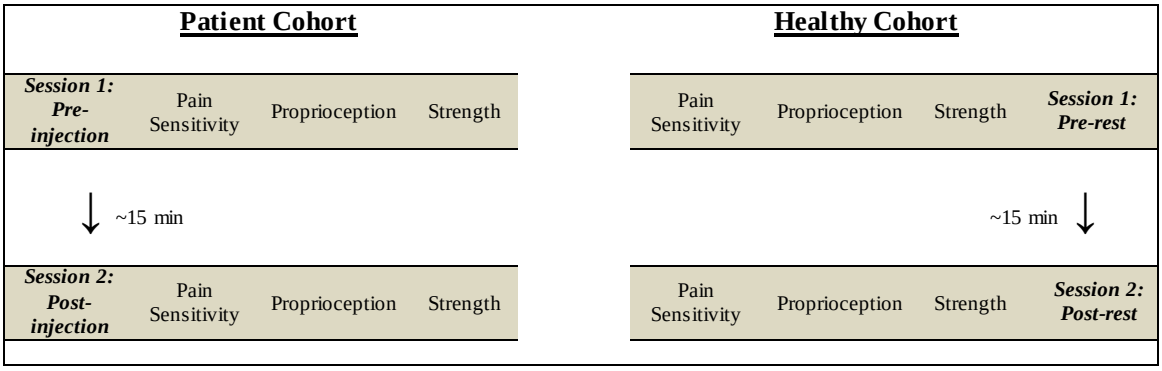


**Figure 3.1.** Study design for Aim 2, Aim 3, and Aim 4

All data collection was completed on one day. Written and verbal instructions of testing procedures were provided, and written consent was obtained from each participant prior to testing. The experimental protocol was approved the Institutional Review Board at the University of Oregon.

## Methods

### Patient Participants

A total of twenty patients (ten males and ten females) presenting to Slocum Center for Orthopedics and Sports Medicine for unilateral subacromial pain syndrome (SPS) were included in the present study (Table 3.2 and Table 3.3). Prior to recruitment, patients met with a single treating orthopedist and were diagnosed with stage II impingement, also known as subacromial pain syndrome. Moreover, each patient participant had elected to receive a subacromial anesthetic injection as part of their standard of care treatment prior to the recruitment process. Subacromial injections for patient participants were administered by the same physician, MS, utilizing a 23 gauge needle and an anterolateral approach. The subacromial injection consisted of both an anesthetic (6 cc 0.5% Marcaine with Epinephrine) and corticosteroid agent (1 cc DepoMedrol). Following the injection, patient participants were given a 15 minute adjustment period during which time they were asked to move their arm to help disperse the agents within the subacromial bursa.

To be diagnosed with stage II impingement, patients must have demonstrated a positive sign to the treating physician on at least three of the following five manual tests prior to receiving the injection: Hawkins-Kennedy, Neer, painful arc, empty can (Jobe), and painful external rotation resistance. After receiving the injection, the manual tests were repeated. In order to be diagnosed with stage II impingement, a patient had to demonstrate a positive injection sign, meaning their pain was significantly reduced during the manual tests in the post-injection testing relative to the pre-injection testing.

Exclusion criteria for patients included: a positive Spurling test, shoulder dislocation within the past three months, reproduction of shoulder pain with active or passive cervical range or motion, signs of a rotator cuff tear on manual tests (drop-arm test, lag signs, gross external rotation weakness) or imaging (fMRI or ultrasound were only available for some patients). Every patient had recent images (radiography or fMRI) to confirm the absence of moderate or severe glenohumeral arthritis. The healthy contralateral limb was also screened with manual tests to rule out bilateral impingement. Additional inclusion and exclusion criteria, as determined from the attending orthopedist's physical exam and the patient's self-reported history questionnaire, are provided in Table 3.1.

**Control Participants**

A total of twenty uninjured control participants (ten males and ten females) were recruited from the surrounding community via posted flyers and general advertisements. Each control participant was matched to a specific patient participant for age (±five years), sex, arm dominance and leg dominance (Table 3.2). Inclusion and exclusion criteria for control participants are provided in Table 3.1.

**Self-Reported Measures**

**Health History & Demographics -** Information regarding age, sex, arm dominance, leg dominance and health history were obtained from each participant. Arm and leg dominance were determined by asking participants to indicate which limb (left, right) they would use to hold a pen and kick a ball, respectively. Anthropometric

measurements (height, weight, limb length, limb circumference) were taken by research personnel.

**Table 3.1.** Inclusion and exclusion criteria for patients with subacromial pain syndrome and controls.

| **Inclusion Criteria** | | |
|---|---|---|
| | **Patients** | **Controls** |
| Age 18-65 y/o | ✓ | ✓ |
| Diagnosed with unilateral subacromial impingement, in absence of a suspected rotator cuff tear | ✓ | |
| Pain present for longer than one month | ✓ | |
| Received a subacromial injection with a positive injection sign | ✓ | |
| **Exclusion Criteria** | | |
| | **Patients** | **Controls** |
| Cervical range of motion restrictions or injury | ✓ | ✓ |
| Cervical pain or pathology | ✓ | ✓ |
| At the <u>bilateral</u> shoulders:<br>- Moderate or severe glenohumeral osteoarthritis<br>- Humeral head fractures<br>- Glenohumeral arthroplasty<br>- Rotator cuff tears or repairs<br>- Joint laxity<br>- Pain at rest (*non-involved shoulder for patients; bilateral shoulders for controls*) | ✓ | ✓ |
| At the <u>bilateral</u> knees:<br>- Tibiofemoral osteoarthritis<br>- Total knee replacement<br>- ACL tears or reconstruction<br>- Pain at rest | ✓ | ✓ |
| Neurological or chronic pain disorders | ✓ | ✓ |
| Pregnancy | ✓ | ✓ |

**Disability of the Arm, Shoulder and Hand (DASH) Questionnaire** - The DASH questionnaire was administered to patients and controls prior to the injection/rest period. The DASH is a self-assessment questionnaire made up of 30 questions to measure

physical function and symptoms affecting the upper extremities. The questionnaire is scored from 0-100, with higher scores indicating greater disability (Hudak et al., 1996). The DASH has been shown to provide valid outcome measures (Gummesson et al., 2003) and is frequently employed in studies assessing patients with SPS (Camargo et al., 2015, 2009; Ribeiro et al., 2016).

**Instrumented Measures**

**Measurement of Pain Intensity -** Pain intensity was measured by utilizing a series of visual analog scales (VAS) scales that asked the participants to indicate the highest pain intensity they experienced during a series of three maximum isomeric voluntary contractions (MVICs). The results were scored from 0-10 centimeters (0 cm = no pain, 10 cm = worst pain imaginable) in increments of one millimeter. Participants completed the VAS for the involved shoulder (IS), contralateral shoulder (CS), ipsilateral knee (IK) and contralateral (CK) at two time points: pre-injection and post-injection. Maximum isometric voluntary contractions at the shoulder joint were performed against resisted flexion, with participants in a seated position with the shoulder at ninety degrees of flexion. Maximum voluntary isometric contractions at the knee joint were performed against resisted extension, with participants in a seated position with the hip and knee joints flexed to ninety degrees. All MVICs were five seconds in duration with an interval of 30 second rest period between trials. Participants were blinded to their previous scores.

**Pain Sensitivity** - Pain sensitivity was tested at both upper extremities and both lower extremities utilizing a pain pressure threshold (PPT) protocol. Further details

about the PPT protocol can be found in Chapter IV, as pain sensitivity data was used to address Aim 2.

**Proprioception** - Proprioception at both shoulders and both knees was assessed utilizing a joint position sense (JPS) protocol. Further details about the JPS protocol can be found in Chapter V, as proprioception data was used to address Aim 3.

**Strength** - Strength at both shoulders and both knees was assessed using a maximum voluntary isometric contraction (MVIC) protocol. Further details about the MVIC protocol can be found in Chapter VI, as strength data was used to address Aim 4.

**Statistical Analysis**

**Pain Reduction** - To determine whether patients with SPS experienced a significant reduction in shoulder pain after the injection, dependent t-tests were run on patient data only. The independent variable was time: pre-injection and post-injection. The dependent variable was VAS score at the involved shoulder.

**Patient vs. Control Demographics** - To assess whether differences in demographics, anthropometrics, DASH, and VAS scores were present between patients with SPS and controls, a series of independent t-tests were run.

**Male Patient vs. Female Patient Demographics** - To assess whether differences in demographics, anthropometrics, DASH, and VAS scores were present between female and male patients with SPS, a series of independent t-tests were run. To determine

whether patients experienced a significant reduction in shoulder pain after the injection, dependent t-tests were run comparing pre-injection VAS scores to post-injection VAS scores across the involved shoulder.

## Results

An important requirement for this study was the successful reduction of shoulder pain in patients with SPS following a subacromial injection. Thus while twenty-one patients with SPS were recruited into the study, one patient was removed from the analysis owing to a lack of pain reduction as reported on post-injection versus pre-injection VAS scores. The data presented are from the remaining twenty patients with SPS and the twenty controls that were matched to each patient. SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Values of $p < 0.05$ were regarded as statistically significant for all analysis.

### Pain Reduction

The subacromial injection resulted in a marked reduction in pain for patients with SPS ($p<0.001$) resulting in a mean 54% reduction in pain scores (Table 3.3).

### Patient vs. Control Characteristics

No significant differences were found between patient and control participants with respect to age, BMI, height or weight (all $p>0.05$). Significant differences were found between the two groups with respect to DASH scores, pre-injection VAS scores across the involved shoulder, and post-injection VAS scores across the involved shoulder (all $p<0.001$) (Table 3.2).

**Table 3.2.** Characteristics (means ± SDs) of patients with subacromial pain syndrome and controls.

| | Patients | Controls |
|---|---|---|
| **Sex** (males/females) | 10 / 10 | 10 / 10 |
| **Age** (years) | 51 ± 10 | 52 ± 10 |
| **Height** (cm) | 169 ± 10 | 171 ± 10 |
| **Weight** (kg) | 86 ± 18 | 80 ± 17 |
| **BMI** | 30 ± 5 | 27 ± 4 |
| **Dominant Arm** (Right/Left) | 16 / 4 | 16 / 4 |
| **Dominant Leg** (Right/Left) | 16 / 4 | 16 / 4 |
| **Injured Shoulder** (Dominant/Non-dominant) | 6 / 14 | --- |
| **DASH** | 38.6 ±16.8 | 2.6 ±3.6* |
| **Pre-injection VAS** (0-10) | 6.5 ± 2.6 | 0.0 ±0.1* |
| **Post-injection VAS** (0-10) | 2.9 ± 1.4 | 0.0 ±0.1* |

* Denotes a significant difference between patients with SPS and controls.

**Male Patient vs. Female Patient Characteristics**

No significant differences were found between male and female patients with respect to age, BMI, DASH scores, pre-injection VAS scores across the involved shoulder, and post-injection VAS scores across the involved shoulder (all $p>0.05$). Significant differences were found between the two groups with respect to height and weight (both $p<0.001$) (Table 3.3).

**Table 3.3.** Characteristics (means ± SDs) of male and female patients with subacromial pain syndrome.

| | **Males** | **Females** |
|---|---|---|
| **Number** | 10 | 10 |
| **Age** (years) | 52 ± 8 | 51 ± 11 |
| **Height** (cm) | 176 ± 10 | 163 ± 7$^{+}$ |
| **Weight** (kg) | 97 ± 16 | 76 ± 15$^{+}$ |
| **BMI** | 31 ± 5 | 29 ± 4 |
| **Dominant Arm** (Right/Left) | 9 / 1 | 7 / 3 |
| **Dominant Leg** (Right/Left) | 9 / 1 | 7 / 3 |
| **Injured Shoulder** (Dominant/Non-dominant) | 2 / 8 | 4 / 6 |
| **DASH** | 36.8 ± 22.9 | 40.3 ± 7.5 |
| **Pre-injection VAS** (0-10) | 7.0 ± 2.2 | 6.0 ± 2.9 |
| **Post-injection VAS** (0-10) | 3.4 ± 1.6 | 2.6 ± 0.8 |

+ Denotes a significant difference between male and female patients with SPS.

## Bridge

In this chapter we described the participants and general methods utilized for Aim 2 (Chapter IV), Aim 3 (Chapter V), and Aim 4 (Chapter VI) and ran statistical analyses on various demographic, disability, and pain variables. We found that patients with SPS had similar demographics to controls. This finding helped establish the validity of using data from control participants enrolled in this study as a baseline to compare the sensorimotor abilities of patients with SPS in the next chapter as well as upcoming chapters. We also found that male patients with SPS were similar in demographics as well as disability and pain scores to female patients with SPS. This finding helped

establish the validity of comparing the sensorimotor abilities of male and female patients in the next chapter as well as upcoming chapters. Finally, we found that patients with SPS experienced a significant reduction in pain following the subacromial injection. This finding helped establish the validity of using the injection intervention as an acute-pain reduction model and comparing the pre-injection sensorimotor abilities of patients with SPS to their post-injection values in the next chapter as well as upcoming chapters. In the next chapter, Chapter IV, we specifically looked at the sensorimotor modality of pain sensitivity, and its associations with sex and pain.

CHAPTER IV

# PAIN HYPERSENSITIVITY IN SUBACROMIAL PAIN SYNDROME

The experiment described in this chapter was developed with Dr. Andrew Karduna who contributed substantially to this work by assisting with experimental conception, editing and advising throughout the project. Dr. Matthew Shapiro further contributed to the study by assisting in recruiting patients with subacromial pain and performing the subacromial injection. I was the primary contributor to the development of the experimental design, data collection and analysis, and write up.

## Introduction

Following peripheral injury and inflammation, the nervous system utilizes a process called sensitization to change the response characteristics of neurons and protect the body from further damage. Sensitization is characterized by amplified neural responses to peripherally applied stimuli, ultimately resulting in pain hypersensitivity. Mechanisms responsible for this phenomena include, but are not limited to, reduced membrane thresholds, altered gene expressions and expanded receptor fields (Costigan et al., 2009; Koltzenburg et al., 1994; Woolf, 1983).

In the early stages of injury and inflammation, sensitization is thought to largely be confined to primary afferent neurons within the injured area, a phenomenon referred to as peripheral sensitization (PS). Peripheral sensitization serves an essential role for healing, because it triggers salient warning sensations that lead to avoidance behaviors

and protect the injured area from further harm. However, in the presence of prolonged or intense pain, sensitization can transition from a helpful response to a harmful one. Specifically, prolonged or intense pain can initiate sensitization processes in nociceptive pathways across multiple levels of the central nervous system (CNS) in locations remote from the site of injury, a phenomenon termed central sensitization (CS). Since CS involves changes to neurons in the CNS, perceived pain intensity may be decoupled from the degree of tissue pathology (Costigan et al., 2009). Central sensitization has been observed in many chronic pain conditions (Bajaj et al., 2001; Herren-Gerber et al., 2004; Lluch et al., 2014; Petersen-Felix and Curatolo, 2002; Svendsen et al., 2004; Svensson et al., 2001), and is receiving increasing attention as a potential mechanism for the development and maintenance of chronic pain.

Invasive procedures limit the direct measurement of sensitization in human patients, however quantitative sensory testing (QST) has allowed researchers and clinicians to obtain indirect measurements (Curatolo et al., 2006). Quantitative sensory testing can be assessed with several different modalities, with the most common involving the application of a temporary stimulus to the periphery and assessing the resulting pain response. Hypersensitive pain responses include sensations of pain at stimulus intensities that do not generally evoke pain in healthy participants or more intense pain sensations at standardized stimulus intensities. Using these methods, PS is detected whenever pain hypersensitivity is observed after the sensory stimulation of the injured area. Since peripheral mechanisms cannot account for hypersensitivity at healthy tissues that are remote to the site of injury, CS is detected whenever pain hypersensitivity is observed after stimulation of healthy areas.

Quantitative sensory testing has demonstrated that when compared to controls, patients with subacromial pain syndrome (SPS) are hypersensitive to a variety of experimentally applied stimuli, including heat, cold, prick and pressure (Alburquerque-Sendín et al., 2013; Coronado et al., 2014; Gwilym et al., 2011; Hidalgo-Lozano et al., 2010; Kindler et al., 2011; Paul et al., 2012). Specifically, hypersensitivity has consistently been observed across the symptomatic shoulder (Alburquerque-Sendín et al., 2013; Gwilym et al., 2011; Hidalgo-Lozano et al., 2010; Paul et al., 2012), providing compelling evidence for the presence of PS. Remote locations, including the asymptomatic shoulder (Alburquerque-Sendín et al., 2013; Paul et al., 2012; Ribeiro et al., 2016) and lower extremities (Alburquerque-Sendín et al., 2013; Hidalgo-Lozano et al., 2010; Paul et al., 2012; Ribeiro et al., 2016) have shown inconsistent hypersensitivity, suggesting that CS may be present in subsets of the population (Sanchis et al., 2015). In light of this, additional information is needed about the relationship between CS and subacromial pain, as well as the individual characteristics associated with the development of CS, as the SPS population is likely to demonstrate heterogeneity. Female populations with pathologies of the rotator cuff suffer from higher levels of disability and pain compared to male populations, both prior to and after receiving treatment (Razmjou et al., 2011). It is possible that CS is more prevalent in female patients with SPS, contributing to the sex related differences in disability and pain. To our knowledge, no previous studies have assessed whether the development of CS is dependent upon sex in a population with SPS. This knowledge gap is surprising given the fact that females are known to more susceptible to the development of CS than males in other chronic pain conditions (Jensen and Petersen, 2006).

The presence of CS may hold particular promise for developing novel interventions aimed at treating SPS. Specifically, the presence of CS suggests that rather than solely being a product of peripheral tissue damage, the pain associated with SPS may have a central contribution. If patients with SPS display similar characteristics to animal models exhibiting CS (Latremoliere and Woolf, 2009), only a small degree of noxious input (mild tissue injury) is needed to maintain the sensitized state of neurons.

It is currently unknown whether PS or CS persist after the reduction of subacromial pain. To our knowledge, only one investigation has assessed hypersensitivity in patients with SPS pre and post-treatment (Camargo et al., 2015). In that study, after a physical therapy regime, patients with SPS demonstrated reduced hypersensitivity (a higher pain tolerance) at the involved shoulder and contralateral shoulder, but not the lower extremity post-treatment. Given the lack of a healthy control group, these results are difficult to interpret. Another study has used pre-treatment data on CS to predict post-treatment functional outcomes (Gwilym et al., 2011), however CS itself was not assessed post-treatment. In that study, patients who presented with greater levels of CS prior to treatment reported greater pain intensity post-treatment. This finding is not surprising given that several studies have shown a patient's current pain intensity is highly correlated to CS level (Hidalgo-Lozano et al., 2010; Kindler et al., 2011). Central sensitization may not necessarily be a static condition, as long as peripheral pain is removed. A modulation of CS is associated with the acute removal of pain in other chronic conditions (Herren-Gerber et al., 2004), suggesting that CS is dynamic and responsive to the influence of peripheral nociceptors. However if CS persists in a

population of patients with SPS after pain reduction, clinical interventions may need to look beyond treatment for the local shoulder and also focus on central pain management.

**The primary aim of the present study was to assess PS and CS by testing pain hypersensitivity at involved and remote locations in patients with SPS, both before and after acute pain reduction. The secondary aim of the present study was to explore characteristics associated with the presence of CS. We hypothesized that patients with SPS would demonstrate a greater sensitivity to pain at the symptomatic shoulder and remote locations (contralateral shoulder, both knees) than matched controls (Hypothesis 2.1). We further hypothesized that upon pain reduction, patients experiencing SPS would demonstrate decreased sensitivity to pain at both shoulders and both knees relative to pre-injection values (Hypothesis 2.2). Finally, we hypothesized that after controlling for pain duration and pain intensity, female patients would demonstrate greater sensitivity than male patients (Hypothesis 2.3).**

## Methods

### General Methods and Participants

For Aim 2, Aim 3, and Aim 4, a single repeated measures study incorporating both a patient cohort with SPS and control cohort was utilized. The methods and participants for this large study have previously been described in Chapter III. In the

present Chapter (IV), to specifically address Aim 2, pain sensitivity measurements from this larger dataset were evaluated and are expanded upon below.

**Pain Sensitivity**

Pain sensitivity was tested at both upper extremities and both lower extremities utilizing a pressure pain threshold (PPT) protocol. Measures of PPT, defined as the minimum force applied which induces pain, were obtained by utilizing a hand-held pressure algometer with a one-$cm^2$ probe (Wagner Instruments). With participants in a seated position, upper extremity assessment sites were marked at the bilateral deltoid muscles, at the midpoint between the flat portion of the acromion and deltoid insertion (Figure 4.1). With participants in standing position, lower extremity assessment sites were marked at the bilateral vastus lateralis muscle, approximately five inches superior from the lateral edge of the patella (Figure 4.1). The researcher positioned the probe perpendicular to the assessment site and applied progressive pressure at a rate of approximately one kg/s. The participant was instructed to inform the assessor when they first perceived a sensation of pain or discomfort, at which point pressure application ceased and the PPT value was noted. Four measurements were obtained for each location with a 30 second interval between measurements. The order of testing (location and side) was blocked and randomized between participants.

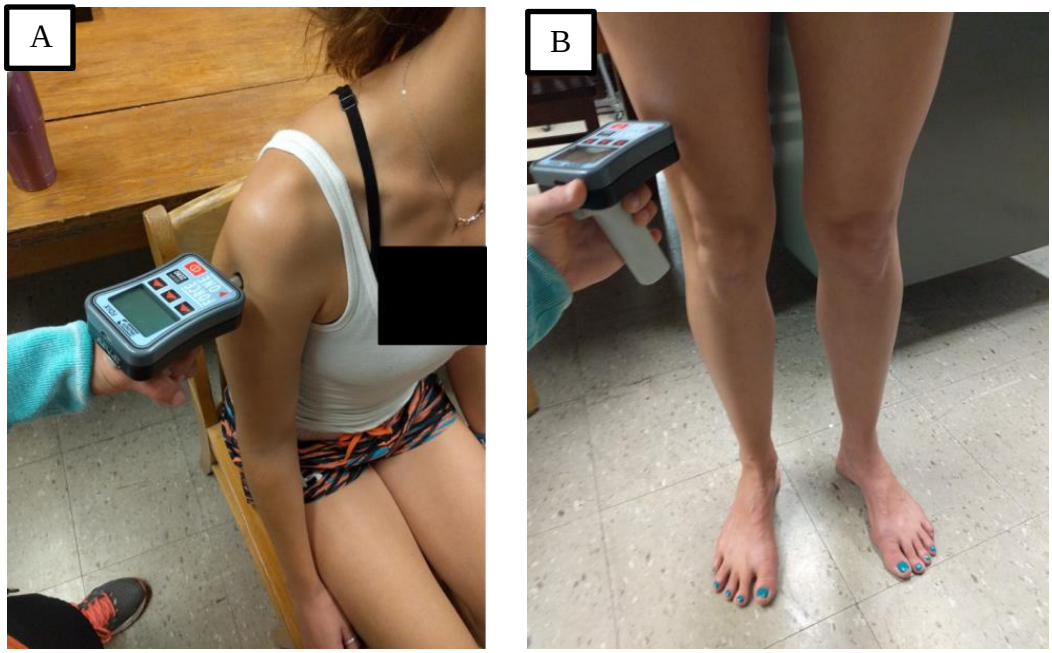


**Figure 4.1.** Experimental set-up used for pressure pain threshold (PPT) measurements during the subacromial pain study. A) Deltoid location. B) Vastus lateralis location.

**Data Analysis**

Pre-injection PPT scores were calculated for each joint by taking the mean of the four assessments. Larger values indicate greater pressure was required to induce pain sensation. To assess the influence of the subacromial injection, the change in PPT scores was calculated for each joint by subtracting mean pre-injection PPT scores from mean post-injection PPT scores. A positive value indicates greater pressure was required to induce pain sensation during the post-injection condition relative to the pre-injection condition.

For the secondary analysis exploring the influence of sex, we created standardized z-scores for each of the four joints: involved shoulder, contralateral

shoulder, ipsilateral knee, and contralateral knee. Standardized z-scores were computed for each female patient using the equation below:

**4.1**

$$\text{Standarized Female Z} - \text{Score: } \frac{X_{i.F} - \overline{\overline{X}}_{Controls.F}}{\sigma_{\overline{X}.F}}$$

$\overline{X}_{Controls.F}$ is the mean PPT for the female control participants, $\sigma_{\overline{X}.F}$ is the standard deviation of PPT scores for the female control participants, and $\overline{X}_{i.F}$ is the PPT score for an individual female patient participant. Likewise, standardized z-scores were computed for each male patient using the equation below:

**4.2**

$$\text{Standarized Male Z} - \text{Score: } \frac{X_{i.M} - \overline{X}_{Controls.M}}{\sigma_{\overline{X}.M}}$$

$\overline{X}_{Controls.M}$ is the mean PPT for the male control participants, $\sigma_{\overline{X}.M}$ is the standard deviation of PPT scores for the male control participants, and $\overline{X}_{i.M}$ is the PPT score for an individual male patient participant.

**Statistical Analysis**

SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Values of $p < 0.05$ were regarded as statistically significant for all analysis. Following conventional ANOVA logic, interaction effects were evaluated before proceeding to main effects.

**Hypothesis 2.1– Patients with SPS would demonstrate a greater sensitivity to pain at the symptomatic shoulder and remote locations (contralateral shoulder, both**

**knees) than matched controls.** To determine if there were differences in sensitivity between patient and control participants prior to treatment, a single two-way mixed model ANOVA was used. The dependent variable was PPT score. The between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). An *a priori* interaction contrast was also run for PPT scores to assess whether the differences between PPT scores for patient and control participants were different between the involved shoulder and remote joints. The *a priori* interaction contrast was coded as a group {1, -1} by joint {3, -1, -1, -1} interaction. To provide additional confirmation on the presence of hypersensitivity at the involved shoulder, an *a priori* paired t-test was run comparing patient's involved shoulder to patient's non-involved shoulder.

**Hypothesis 2.2 – Upon pain reduction, patients experiencing SPS would demonstrate decreased sensitivity to pain at both shoulders and both knees relative to pre-injection values.** To determine if a pain reducing treatment influenced sensitivity a single two-way mixed model ANOVA was used. The dependent variable was change in PPT scores after treatment. The between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). An *a priori* interaction contrast was also run for change in PPT scores to assess whether the differences between PPT scores for patient and control participants were different between the involved shoulder and remote joints. The *a priori* interaction contrast was coded as a group {1, -1} by joint {3, -1, -1, -1} interaction.

**Hypothesis 2.3 – After controlling for pain duration and pain intensity, female patients would demonstrate greater sensitivity than male patients.** For this secondary analysis, we ran a total of four hierarchical multiple regression models, one for each joint (involved shoulder, non-involved shoulder, ipsilateral knee, contralateral knee) on patient data only. Standardized z-scores for PPT values were the dependent variable. Pain duration, pain intensity and sex were the independent variables. Sex was represented by dummy coded variables (0 = male, 1 = female). Pain duration and pain intensity were added to the model first, while sex was added to the model later to see if it increased the predictive power.

## Results

### Pre-injection Sensitivity: Hypothesis 2.1

The *a priori* interaction comparison was significant ($p<0.01$), revealing that differences in patients and controls PPT scores were location dependent (involved joint versus remote joints). Based on this finding, pairwise comparisons were conducted. PPT scores at the involved shoulder were significantly smaller ($p=0.02$) in the patient (M=2.9 kg) versus control population (M=4.1 kg), with a mean difference of 1.2 kg (Figure 4.2). Across all three remote joints, patient participants demonstrated smaller PPT scores than controls, with mean between group differences of 0.5 kg (Figure 4.2). However these between-group differences were not significant, neither when the remote joints were pooled into one composite score ($p=0.38$) nor when individual joints were analyzed including the contralateral shoulder ($p=0.29$), ipsilateral knee ($p=0.43$), and contralateral

knee (p=0.49). Additionally, the *a priori* paired t-test revealed that PPT scores were significantly smaller ($p<0.01$) at patients' involved (M=2.9 kg) versus contralateral shoulder (M=3.4 kg), with a mean side-to-side difference of 0.5 kg (Figure 4.2).

**Post-injection vs. Pre-injection Sensitivity: Hypothesis 2.2**

For the change in PPT scores after treatment, the *a priori* interaction comparison was significant ($p<0.05$), revealing that differences between change scores in the patients and controls populations were location dependent (involved joint versus remote joints). Based on this finding, pairwise comparisons were conducted. Change scores at the involved shoulder were on average 0.3 kg greater in the patient population, however this between-group difference did not reach statistical significance (p=0.18) (Figure 4.3). Across the three remote joints, patient and control participants demonstrated similar change scores (mean between-group difference = 0.1 kg). Pairwise comparisons confirmed that between-group differences were not significant neither when the remote joints were pooled into one composite score (p=0.68) nor when individual remote joints were analyzed including the contralateral shoulder (p=0.22), ipsilateral knee (p=0.69), and contralateral knee (p=0.96).

**Within-Group Differences: Hypothesis 2.3**

For each of the four joints (involved shoulder, contralateral shoulder, ipsilateral knee, contralateral knee), the associated regression model incorporating only pain duration and pain intensity was non-significant (all $p>0.05$), however the addition of sex to the model significantly improved the prediction of standardized z-scores (all $p<0.01$). Therefore for each of the four joints, a simpler model incorporating only the main effects

of sex (Male = 0, Female = 1) was examined to determine how sex predicted z-scores (Table 4.1). For each joint, sex alone predicted over 44% of the variance in z-scores ($R^2$ range: 0.44 to 0.59, all $p<0.01$), and for all four joints, females patients' z-scores were predicted to be significantly smaller than males (*B* range: -1.26 to -1.81, all $p<0.01$). Moreover, follow-up one sample t-tests revealed z-scores for males were not significantly different from zero at the involved shoulder ($p=0.55$), non-involved shoulder ($p=0.59$), ipsilateral knee ($p=0.21$), or contralateral knee ($p=0.27$) (Figure 4.4). Follow-up one sample t-tests revealed z-scores for females were significantly different from zero at the involved shoulder ($p<0.001$), non-involved shoulder ($p<0.001$), ipsilateral knee ($p<0.01$) and contralateral knee ($p<0.01$) (Figure 4.4).

## Discussion

The aims of the present study were three-fold. First, we examined whether patients with SPS would exhibit characteristics of peripheral and central sensitization by looking at sensitivity across the involved shoulder as well as remote joints. Second, we assessed the effects of pain reduction (via an anesthetic injection) on sensitivity at the involved shoulder as well as remote joints. Lastly, we explored characteristics associated with the presence of PS and CS such as pain duration, pain intensity, and sex. Each of our hypotheses and corresponding results are discussed below.

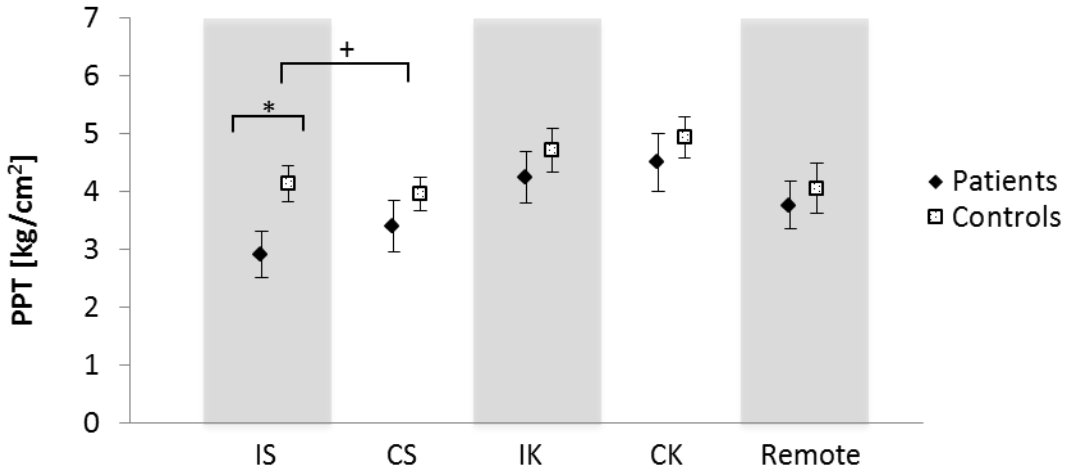


**Figure 4.2.** Pre-injection pressure pain threshold (PPT) scores (means ± SEMs) for patients with SPS and controls. Analyzed joints include the involved shoulder (IS), contralateral shoulder (CS), ipsilateral knee (IK), contralateral knee (CK), and average of the CS, IK, and CK joints (Remote). * Denotes a significant between-group difference. + Denotes a significant within-group difference.

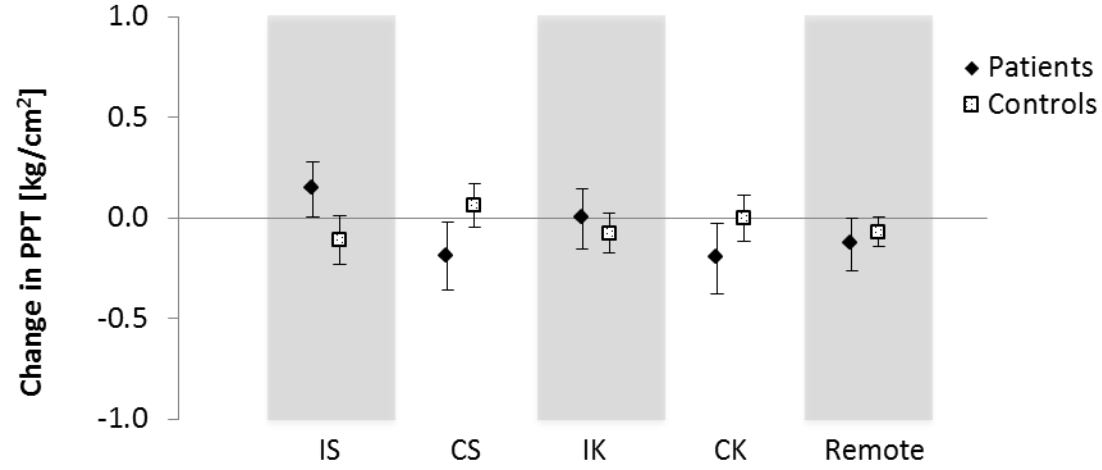


**Figure 4.3.** Change in pressure pain threshold (PPT) scores (means ± SEMs) for patients with SPS and controls following the injection/rest period. Analyzed joints include the involved shoulder (IS), contralateral shoulder (CS), ipsilateral knee (IK), contralateral knee (CK), and average of the CS, IK, and CK joints (Remote).

**Table 4.1.** Regression results for standardized pain pressure threshold (PPT) z-scores for male and female patients. *B* is the unstandardized beta, and represents the slope of the line between the independent and dependent variables. *SE B* is the standard error for the unstandardized beta.

| | Involved Shoulder | | Contralateral Shoulder | | Ipsilateral Knee | | Contralateral Knee | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** |
| 1st Model | | | | | | | | |
| Pain Duration (months) | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.01 | 0.01 |
| Pain Intensity (VAS 1-10) | 0.00 | 0.11 | 0.13 | 0.12 | 0.11 | 0.08 | 0.15 | 0.11 |
| $R^2$ | 0.01 | | 0.06 | | 0.11 | | 0.15 | |
| 2nd Model | | | | | | | | |
| Pain Duration (months) | -0.01 | 0.01 | -0.01 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 |
| Pain Intensity (VAS 1-10) | -0.08 | 0.07 | 0.05 | 0.09 | 0.06 | 0.07 | 0.09 | 0.09 |
| Sex (0 = male; 1 = female) | -2.02** | 0.37 | -1.83* | 0.49 | -1.22* | 0.34 | -1.55* | 0.71 |
| $\Delta R^2$ | 0.66** | | 0.44* | | 0.39* | | 0.33* | |
| 3rd Model | | | | | | | | |
| Constant | -0.19 | 0.25 | 0.24 | 0.33 | 0.24 | 0.22 | 0.30 | 0.32 |
| Sex (0 = male; 1 = female) | -1.81** | 0.36 | -1.75* | 0.46 | -1.26* | 0.32 | -1.70* | 0.45 |
| $R^2$ | 0.59** | | 0.44* | | 0.47* | | 0.44* | |

*Denotes significance at $p < 0.01$. ** Denotes significance at $p < 0.00$

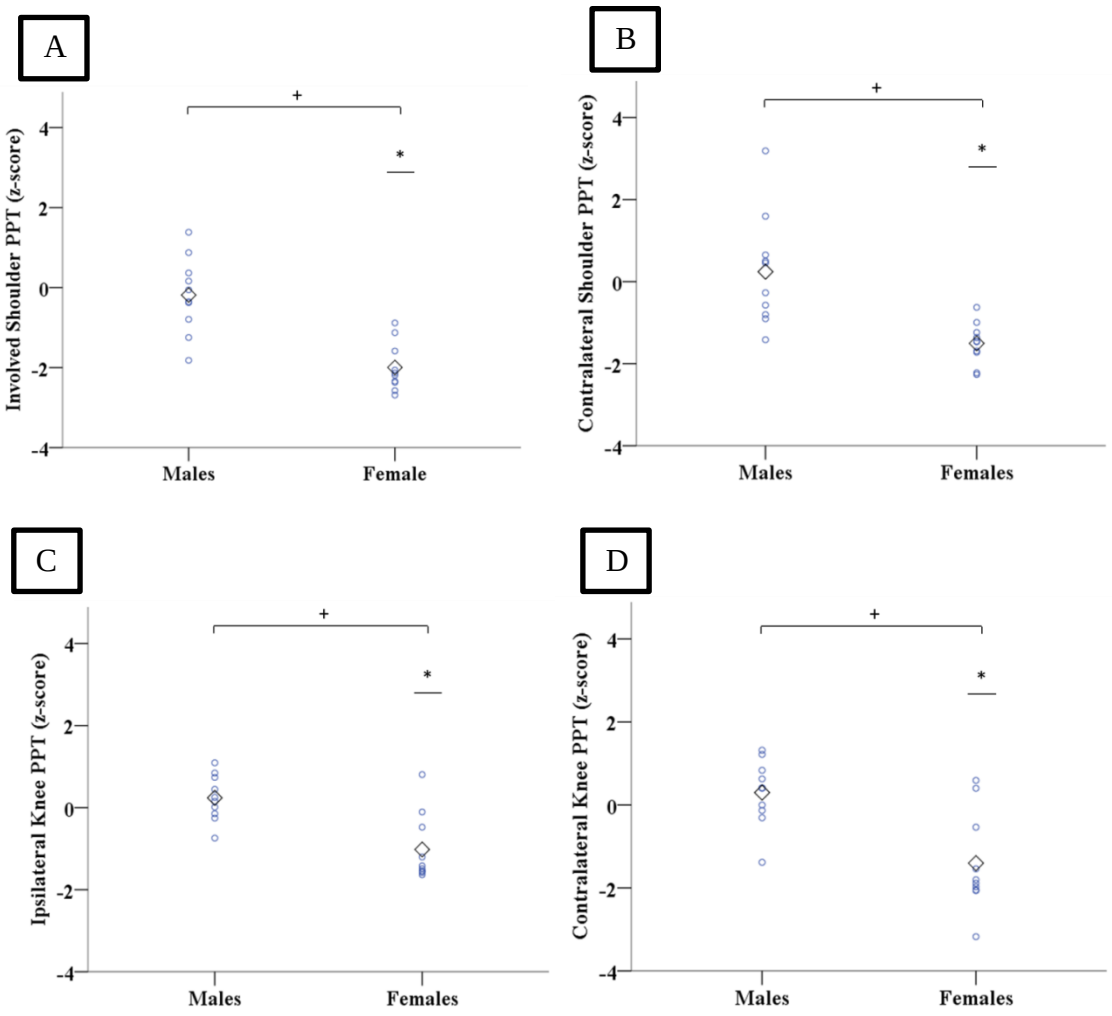


**Figure 4.4.** Pain pressure threshold (PPT) z-scores for male and female patients. A) Involved shoulder. B) Contralateral shoulder. C) Ipsilateral knee. D) Contralateral knee. Circles represent individual scores while diamonds represent group means. + Denotes a significant difference between male and female patients. * Denotes a significant difference from a one-sample test value of 0.

Our first hypothesis that patients with SPS would demonstrate greater hypersensitivity than controls at the symptomatic shoulder as well as remote joints (contralateral shoulder, bilateral knees) was not supported. Our results found that patients had significantly lower PPT values at the involved shoulder only (Figure 4.1) in

comparison to controls, with the mean between-group differences being 1.22 kg. While lower PPT scores were observed at remote joints, these differences did not reach significance. Patients involved shoulder was also found to have significantly lower PPT values compared to the contralateral shoulder, with the mean side-to-side difference being 0.48 kg.

Two previous studies have also found smaller PPTs on the order of 0.9-1.0 kg when the involved deltoid of patients was compared to controls. In contrast to the present study, these studies also demonstrated significantly smaller PPTs across the contralateral deltoid and lower extremities (Alburquerque-Sendín et al., 2013; Paul et al., 2012). Collectively, the present study paired with the findings of the previous studies suggest that persons with SPS have PS while only subsets of the population have CS. Consequently, it may be overly simplistic to classify SPS as having neuropathic tendencies. Instead, a greater emphasis on identifying the characteristics that put individuals most at risk for developing CS may be needed, including the influence of pain intensity, pain duration, and sex. Our results on the relationship between sex and sensitization are discussed later.

Our second hypothesis that pain reduction (via an anesthetic injection) would result in decreased sensitivity across the involved shoulder and remote joints of patients with SPS relative to pre-injection data was not supported. No changes to sensitivity were observed following the injection (Figure 4.3). To our knowledge, only one previous study has assessed the influence of a pain reducing treatment on PPT scores in a population with SPS. In contrast to the present study, Camargo et al. found that both the symptomatic and contralateral shoulders demonstrated greater PPTs in the post-treatment

session compared to the pre-treatment session (2015), providing evidence that both PS and CS were reversed after the reduction of pain. The discrepancies between the present study and Camargo et al. may arise from differences in the length of time pain was reduced in patients as well as the mode of intervention. The present study assessed patients only 15 minutes after pain reduction induced via an anesthetic injection while Camargo et al. studied patients after four weeks of physical therapy intervention.

Our third hypothesis that after controlling for pain duration and pain intensity, female patients would demonstrate greater sensitivity than males was supported. Our results revealed significantly greater z-scores in female compared to male patients at both the involved and remote joints, suggesting that the development of PS and CS in the SPS population may be sex specific. Moreover, when z-scores were compared to a sample test value of 0, neither the involved shoulder nor any of the remote joints of males were differently different than 0, while all joints of female patients were significantly smaller than 0. This suggests that female patients with SPS may be more predisposed to the development sensitization, which could be a contributing factor to the higher incidence of subacromial pain and poor outcomes in females. Interestingly, pain intensity and pain duration did not demonstrate a significant correlation with z-scores, suggesting that greater sensitization was not present in those with greater pain intensity or prolonged pain.

There are several limitations to the present study. The first limitation concerns the fact that only one quantitative sensory test (PPT) was utilized in this study as a proxy to assess the presence of peripheral and central sensitization. It is possible that other quantitative sensory tests such as heat or cold tolerance would yield different conclusions

about the association between subacromial pain and sensitization. Also, there may be a difference between the acute and prolonged reduction of pain, therefore future studies are needed to look at the long-term effects of pain reduction on sensitization.

## Conclusions

The present study found that as a whole, patients with SPS demonstrated hypersensitivity to pressure pain across the involved shoulder, providing evidence for PS, while remote joints demonstrated hypersensitivity that did not reach statistical significance. However, when patients with SPS were separated by sex, females demonstrated both PS and CS. Taken together, these findings suggest PS is associated with SPS while substantial heterogeneity likely exists with respect to CS, and one factor contributing to this heterogeneity may be sex. Moreover, pain reduction (through an anesthetic injection) had no influence on sensitivity in the short-term. Further studies are required to investigate which characteristics are associated with the development of PS versus CS as well as the influence of long-term pain reduction on peripheral and central sensitization.

## Bridge

In the present chapter, patients with SPS were found to present heterogeneously in regards to the presence of PS and CS, with greater sensitization in females in the present study. This finding may help explain why females are reported to develop SPS disproportionally to males and have worse outcomes after treatment. No changes to sensitization were found after the injection intervention. While female with SPS had

greater sensitivity than their males, and treatment did not normalize sensitivity scores, it is still unclear how sex or treatment are related to other sensorimotor abilities. The next chapter, Chapter V, investigates the sensorimotor modality proprioception and the influence of sex and pain reduction on proprioceptive function.

CHAPTER V

# PROPRIOCEPTIVE ABNORMALITIES IN SUBACROMIAL PAIN SYNDROME

The experiment described in this chapter was developed with Dr. Andrew Karduna who contributed substantially to this work by assisting with experimental conception, editing and advising throughout the project. Dr. Matthew Shapiro further contributed to the study by assisting in recruiting patients with subacromial pain and performing the subacromial injection. I was the primary contributor to the development of the experimental design, data collection and analysis, and write up.

## Introduction

Proprioception is the ability to sense limb movement and position(Riemann and Lephart, 2002). Healthy proprioception is necessary to achieve optimal motor control and experimental or pathological disturbances to proprioception result in detrimental changes to coordinated agonist/antagonist activation as well as movement patterns (Ghez and Sainburg, 1995; Messier et al., 2003; Park et al., 1999). Poor proprioception has been documented at the symptomatic shoulder of patients with subacromial pain syndrome SPS (Anderson and Wee, 2011; Bandholm et al., 2006; Machner et al., 2003; Maenhout et al., 2012; Morl et al., 2011). Consequently, poor proprioception may be contributing to the abnormal motor patterns associated with SPS, which may in turn contribute to the development or progression of the disease.

Although an association between poor proprioception and SPS has been established with limited evidence (Fyhr et al., 2015), including evidence for a worse sense of joint position (Anderson and Wee, 2011; Morl et al., 2011), a higher threshold to detection of passive motion (Machner et al., 2003), and a decreased ability to produce steady force or estimate force (Bandholm et al., 2006; Maenhout et al., 2012), the mechanisms of this link are not well established. It has been suggested that changes to proprioception in SPS are the result of dysfunction to mechanoreceptors surrounding the symptomatic shoulder (Fyhr et al., 2015), as trauma and muscle atrophy could decrease the overall number of mechanoreceptors while pain could alter fusimotor activity (Thunberg et al., 2002). If mechanoreceptor dysfunction is indeed to blame, poor proprioception is a local effect of SPS and should be confined to the symptomatic shoulder. Alternatively, it is possible that poor proprioception in SPS arises from global mechanisms that are distinct from mechanoreceptor dysfunction. General mechanisms could include: i) interference in the transmission of afferent information within the spinal cord secondary to pain, ii) interference in the interpretation or integration of afferent information at supraspinal centers secondary to pain, or iii) global proprioceptive deficits that pre-existed the development of SPS and predisposed the patient to injury.

The extent to which global mechanisms contribute to poor proprioception in patients with SPS can be evaluated by measuring proprioception across the symptomatic shoulder, asymptomatic shoulder and remote joints. If deficits are present at the asymptomatic shoulder and a remote joint, a general mechanism of poor proprioception would be implicated since local mechanoreceptor dysfunction would be insufficient to explain deficits extending beyond the symptomatic shoulder. Interestingly, a number of

studies looking at upper and lower extremity musculoskeletal injuries have shown proprioceptive deficits across both the involved and non-involved limb (V Baker et al., 2002; Bank et al., 2013b; Koralewicz and Engh, 2000; Roberts et al., 2000), despite the presence of a unilateral injury. One study has even found that after reconstructive surgery for unilateral glenohumeral instability, proprioception across both shoulders significantly improved compared to baseline (Potzl et al., 2004), while another study has found that upper extremity proprioceptive impairments accompany knee osteoarthritis and lower extremity deficits in proprioception (Lund et al., 2008). These findings imply general mechanisms are contributing to proprioceptive deficits, in at least some unilateral musculoskeletal conditions.

Unfortunately few studies have compared the non-involved shoulder or remote joints of patients with SPS to healthy participants. Hence, it remains unconfirmed whether general mechanisms contribute to the proprioceptive deficits in this population. While a few studies have attempted to statistically compare the non-involved shoulder of patients with SPS to controls, these studies were underpowered (Anderson and Wee, 2011; Haik et al., 2013). Furthermore, to our knowledge, only one study has assessed proprioception at a joint other than the shoulder in patients with SPS. Compared to healthy controls, a previous study in our lab found poorer joint position sense at the symptomatic shoulder and ipsilateral elbow of patients with SPS than uninjured controls (Ettinger et al., 2017). Due to the presence of bi-articular muscles crossing the shoulder and adjacent elbow joint as well as the shared innervation between these joints, we were unable to deduce whether local or generalized mechanisms contributed to the deficits at the elbow joint. In light of this, there is a need to clarify whether proprioceptive deficits

are a local or global presentation in SPS and whether pain helps or hinders proprioception. It would also be helpful to investigate the individual characteristics associated with the development of abnormal proprioception, as the SPS population may demonstrate heterogeneity. Female populations with pathologies of the rotator cuff suffer from higher levels of disability and pain compared to male populations both prior to and after receiving treatment (Razmjou et al., 2011). It is possible that proprioceptive deficits are more prevalent in female patients with SPS, contributing to the sex related differences in disability and pain. To our knowledge, no previous studies have assessed whether proprioceptive abnormalities are dependent upon sex in a population with SPS despite the fact that other sensory abnormalities, including hypersensitive pain processing is more enhanced in females than males with chronic pain (Jensen and Petersen, 2006).

**The primary aim of the present study was to assess regional and global abnormalities to proprioceptive function by testing joint position sense at involved and remote locations in patients with SPS, both before and after acute pain reduction. The secondary aim of the present study was to explore characteristics associated with the presence of abnormal proprioception. We hypothesized that patients experiencing SPS would demonstrate worse proprioception at the symptomatic shoulder as well as remote joints (contralateral shoulder, both knees) than matched controls (Hypothesis 3.1). We further hypothesized that upon pain reduction, patients experiencing SPS would demonstrate worse proprioception both shoulders and both knees relative to pre-injection values (Hypothesis 3.2). We also hypothesized that after controlling for pain duration and pain intensity, female**

**patients would demonstrate greater proprioceptive errors than male patients (Hypothesis 3.3).**

## Methods

### General Methods and Participants

For Aim 2, Aim 3, and Aim 4, a single repeated measures study incorporating both a patient cohort with SPS and control cohort was utilized. The methods and participants for this large study have previously been described in Chapter III. In the present Chapter (V), to specifically address Aim 3, proprioception measurements from this larger dataset were evaluated and are expanded upon below.

### Proprioception

Proprioception at the involved shoulder (IS), contralateral (shoulder), ipsilateral knee (IK) and contralateral knee (CK) was assessed utilizing an active-active joint position sense (JPS) protocol. Measurements were obtained by affixing a 5th generation iPod Touch to participants. For the shoulder joints, the iPod was attached to the lateral aspect of the humerus, approximately two inches above the elbow joint via an elastic band (Figure 5.1). For the knee joints, the iPod was attached to the lateral aspect of shank, approximately two inches above the ankle via an elastic band (Figure 5.1).

The iPod ran on a custom developed app that emitted auditory cues and calculated joint angles with respect to gravity utilizing data from the tri-axial accelerometer and tri-axial gyroscope. The validity of the app has previously been validated in a field setting and compared to a similar protocol involving an electromagnetic tracking device(S.

Edwards et al., 2016). Each JPS trial consisted of an active positioning phase followed by an active repositioning phase. Following is an explanation of each phase of a JPS trial.

1. Baseline position – At the beginning of the trial, the participant assumed a relaxed baseline position.

2. Positioning phase – The positioning phase began with a low-pitched sound, prompting the participant to leave the baseline position. The pitch (or frequency) of the auditory tone provided the participant with feedback about the angle of their joint relative to the target. When the participant attained the target (defined as ± 3˚from the desired joint angle) the participant was directed to hold the target position and memorize its location. After holding the target for three seconds, the participant returned to the baseline position and held the baseline position for one second.

3. Repositioning phase – Without auditory feedback from the app, the participant repositioned their joint away from baseline and into the previously memorized target. After maintaining a static position (defined as velocity less than 0.25 degrees/sec) for one second, the device recorded the participant's position.

During testing, participants were seated with their eyes closed. To minimize extraneous cues across the lower extremity, both male and female participants wore shorts and removed their shoes. Likewise, to minimize extraneous cues across the upper extremity, females wore sleeveless shirts or sports bras while males wore sleeveless shirts or no shirt. Prior to data collection, participants performed several practice trials at non-test angles to become acquainted with the protocol. The number of practice trials varied by participant and was determined by the researcher based on the participant's competency with the protocol.

Assessment of the shoulder joints involved shoulder flexion performed in the sagittal plane while seated in a backless chair. During all testing, the participant was instructed to keep the elbow locked in extension and the thumb pointed upwards. Four targets were presented in a random order at the shoulder, once each at: 75, 80, 85, and 90 degrees. Assessment of the knee joints involved knee extension performed seated with the hip flexed to 90 degrees. During all testing, the participant was instructed to keep the ankle locked at 90 degrees. Four targets were presented at the knee, once each at: 40, 45, 50, and 55 degrees. The testing of joints and sides was randomized and counterbalanced between participants.

**Data Analysis**

After data collection, each trial was analyzed with custom written LabVIEW (National Instruments, Austin, TX) software. The difference between the repositioned angle and presented angle was termed *repositioning error*. If the repositioned angle involved greater excursion than the target angle this was called an overestimation and given a positive sign.

Two dependent variables were calculated for the pre-injection JPS assessments at each of the four joints:

1. Constant Error (CE) – this was defined as the mean repositioning error. Constant errors represent accuracy with directional bias and were calculated as proposed by Schmidt and Lee (Schmidt and Lee, 1999). A positive value for CE indicates greater joint excursion occurred during the repositioning phase relative to the

presented phase and a negative value indicates smaller joint excursion occurred during the repositioning phase relative to the presented phase.

2. Variable Error (VE) – this was defined as the population standard deviation from the mean of constant errors. Variable errors represent the ability of participants to consistently sense test positions and were calculated as proposed by Schmidt and Lee (Schmidt and Lee, 1999). Larger values indicate larger variability in repositioning errors between trials.

Two dependent variables were calculated for the influence of injection on JPS at each of the four joints:

1. Change in Constant Error (ΔCE) – this was defined as the mean difference between the post-injection and pre-injection constant error scores. A positive sign indicates greater joint excursion occurred in the post-injection condition relative to the pre-injection condition.
2. Change in Variable Error (ΔVE) – this was defined as the mean difference between the post-injection and pre-injection variable error scores. A positive sign indicates greater variability occurred in the post-condition condition relative to the pre-injection condition.

For the secondary analysis exploring the influence of sex, we created standardized z-scores for each of the four joints: involved shoulder, contralateral shoulder, ipsilateral knee, and contralateral knee. Standardized z-scores were computed for each patient using the equation below:

**5.1**

$$\text{Standarized Z} - \text{Score: } \frac{X_i - \overline{X}_{\text{Controls}}}{\sigma_{\overline{X}}}$$

$\overline{X}_{\text{Controls}}$ is the mean CE or VE for the control participants, $\sigma_{\overline{X}}$ is the standard deviation of CE or VE scores for the control participants, and $X_i$ is the CE or VE score for an individual patient participant.

**Statistical Analysis**

SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Values of $p < 0.05$ were regarded as statistically significant for all analysis. Following conventional ANOVA logic, interaction effects were evaluated before proceeding to main effects.

**Hypothesis 3.1 – Patients experiencing SPS would demonstrate worse proprioception at the symptomatic shoulder as well as remote joints (contralateral shoulder, both knees) than matched controls.** To determine if there were differences in JPS scores between patient and control participants prior to treatment, a total of two two-way mixed-effects ANOVAs were used. The two dependent variables were constant error and variable error scores prior to treatment. For both ANOVAs, the between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). Two *a priori* interaction contrasts were also run for constant and variable errors to assess whether the differences between JPS scores for patient and control participants were different

between the involved shoulder and remote joints. The *a priori* interaction contrasts were coded as a group {1, -1} by joint {3, -1, -1, -1} interaction.

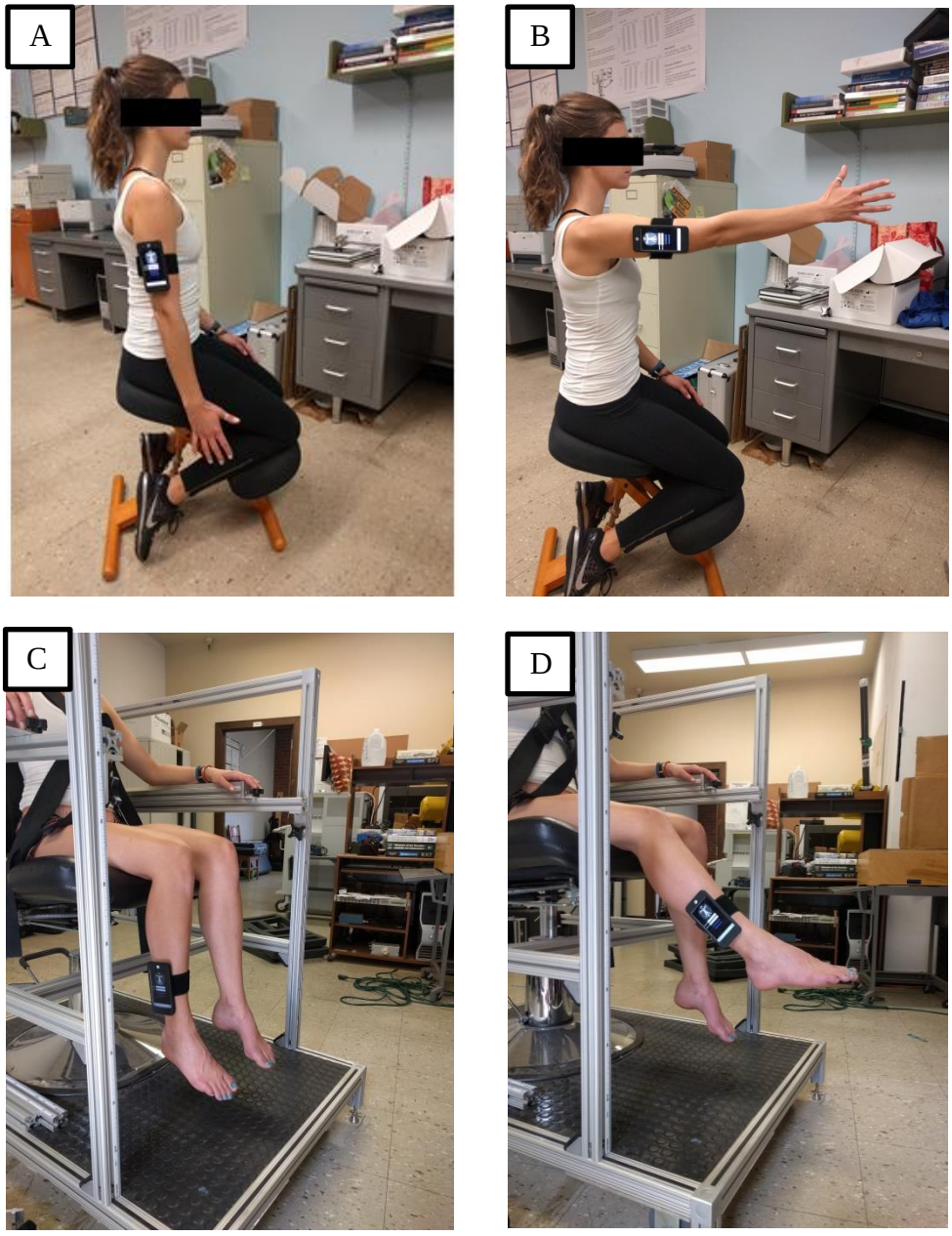


**Figure 5.1.** Experimental set-up used for proprioception measurements during the subacromial pain study. A) Shoulder in rest position. B) Shoulder in reaching position. C) Knee in rest position. D) Knee in reaching position.

**Hypothesis 3.2 – Upon pain reduction, patients experiencing SPS would demonstrate worse proprioception both shoulders and both knees relative to pre-injection values.** To determine if a pain reducing treatment influenced JPS a total of two two-way mixed model ANOVA were used. The two dependent variables were change in constant error and change in variable error scores after treatment. For both ANOVAs, the between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). Two *a priori* interaction contrasts were also run for change in constant and change in variable errors to assess whether the differences between JPS scores for patient and control participants were different between the involved shoulder and remote joints. The *a priori* interaction contrasts were coded as a group {1, -1} by joint {3, -1, -1, -1} interaction.

**Hypothesis 3.3 – After controlling for pain duration and pain intensity, female patients would demonstrate greater proprioceptive errors than male patients.** For this secondary analysis, we ran a total of four hierarchical multiple regression models, one for each joint (involved shoulder, non-involved shoulder, ipsilateral knee, contralateral knee) on patient data only. Standardized z-scores were the dependent variable. Pain duration, pain intensity and sex were the independent variables. Sex was represented by dummy coded variables (Males = 0, Females = 1). Pain duration and pain intensity were added to the model first, while sex was added to the model later to see if it increased the predictive power.

## Results

### Pre-injection Proprioception: Hypothesis 3.1

For constant errors, the *a priori* interaction comparison was non-significant ($p=0.35$), revealing that differences between patient and control populations did not depend upon location (involved shoulder versus remote joints). We next looked at the ANOVA interaction, where the group*joint interaction ($p=0.64$) was also found to be non-significant. Finally, following conventional ANOVA logic, we looked at the main effects. The main effect of joint ($p=0.70$) was non-significant while the main effect of group was significant ($p<0.05$). Across all four joints, both patient and control participants demonstrated a repositioning bias in favor of an overshoot (Figure 5.2). This overshoot was significantly smaller in patients (M=2.0 degrees) versus controls (M=3.4 degrees) however, as group was found to be a significant main effect ($p<0.05$).

For variable errors, the *a priori* interaction comparison was non-significant ($p=0.57$). Following this finding, we looked at the ANOVA group*joint interaction which was also non-significant ($p=0.24$). The main effects of joint ($p=0.76$) and group ($p=0.68$) were also found to be non-significant for variable error (Figure 5.2).

### Post-injection vs. Pre-injection Proprioception: Hypothesis 3.2

For the change in constant errors after treatment, the *a priori* interaction comparison was non-significant ($p=0.75$), revealing that differences between patient and control populations did not depend upon location (involved shoulder versus remote joints). We next looked at the ANOVA interaction, where the group*joint interaction ($p=0.59$) was also found to be non-significant. Finally, following conventional ANOVA

logic, we looked at the main effects. The main effect of joint (p=0.91) was non-significant. Across all four joints, patient participants demonstrated greater overshoots of the target after the injection (M=0.7 degrees), while no changes were observed for controls (M=0.0 degrees) (Figure 5.3). This between-group difference did not reach significance however, as the main effect of group was non-significant (p=0.19).

For the change in variable errors after treatment, the *a priori* interaction comparison was non-significant (p=0.79). Following this finding, we looked at the ANOVA group*joint interaction which was also non-significant (p=0.64). The main effects of joint (p=0.62) and group (p=0.80) were also found to be non-significant for change in variable error (Figure 5.3).

**Within-Group Differences: Hypothesis 3.3**

For both standardized constant error z-scores as well as standardized variable error scores at all four joints (involved shoulder, contralateral shoulder, ipsilateral knee, contralateral knee), the associated regression models incorporating only pain duration and pain intensity were all non-significant (all p>0.05). Moreover, the addition of sex to the models did not significantly improve the prediction of standardized z-scores (all p>0.05) (Table 5.1 and Table 5.2). None of the Beta coefficients associated with the predictors were significant (all p>0.05).

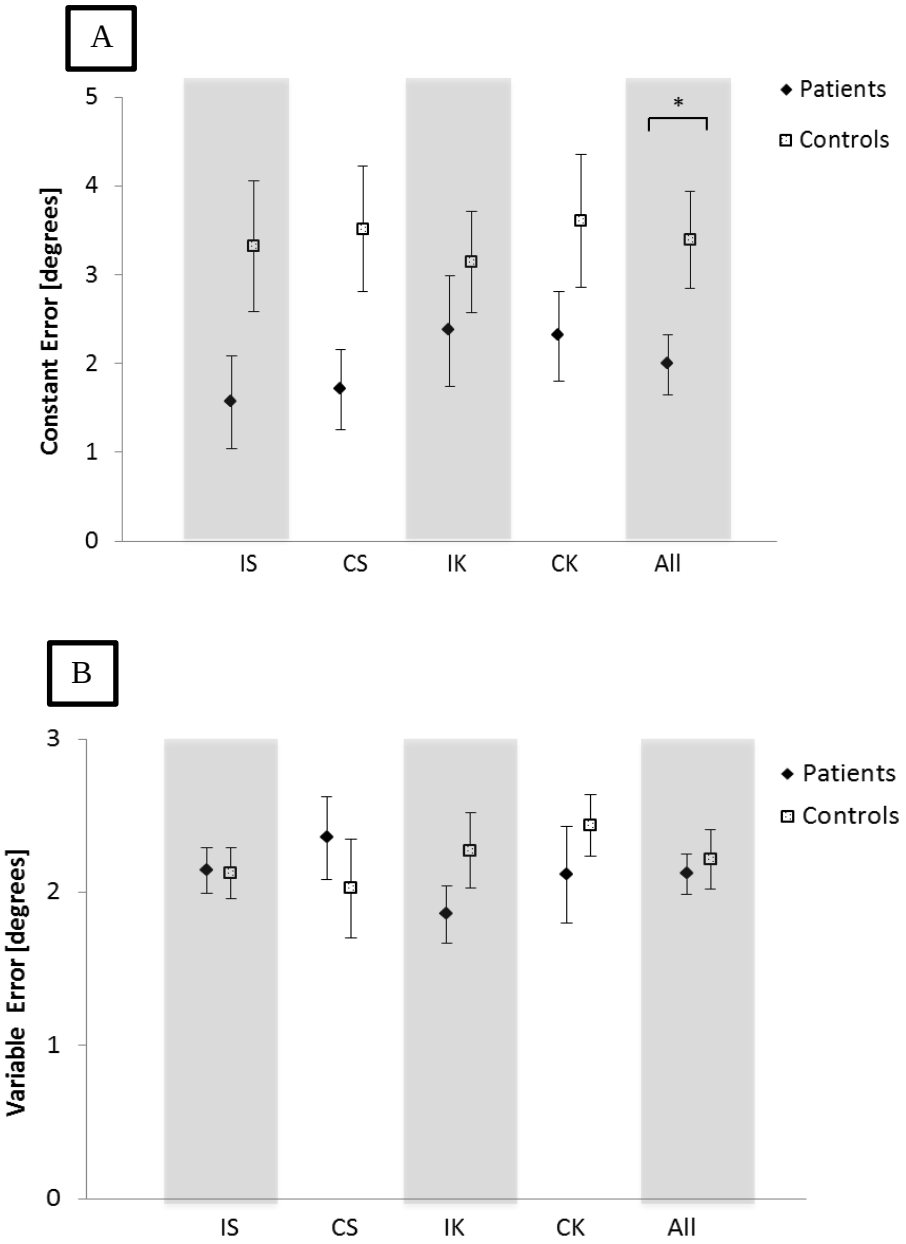


**Figure 5.2.** Pre-injection proprioception scores (means ± SEMs) for patients with SPS and controls. A) Constant error scores. B) Variable error scores. * Denotes a significant between-group difference.

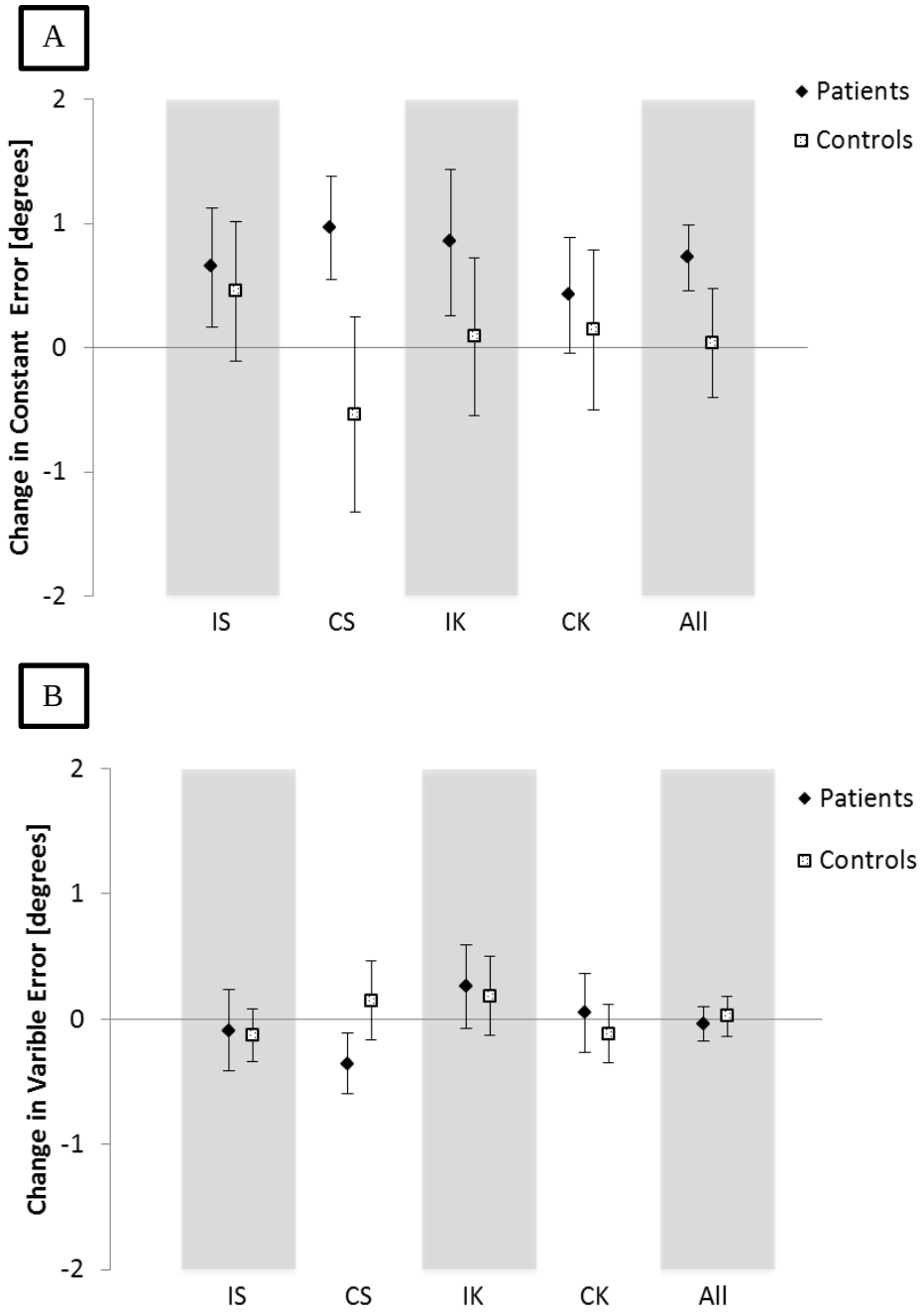


**Figure 5.3.** Change in proprioception scores (means ± SEMs) for patients with SPS and controls following the injection/rest period. A) Constant error scores. B) Variable error scores.

**Table 5.1.** Regression results for standardized constant error z-scores for male and female patients. *B* is the unstandardized beta, and represents the slope of the line between the independent and dependent variables. *SE B* is the standard error for the unstandardized beta.

| | Involved Shoulder | | Contralateral Shoulder | | Ipsilateral Knee | | Contralateral Knee | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** |
| 1st Model | | | | | | | | |
| Pain Duration (months) | 0.03 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 |
| Pain Intensity (VAS 1-10) | 0.11 | 0.06 | 0.12 | 0.05 | 0.10 | 0.06 | -0.04 | 0.08 |
| $R^2$ | 0.17 | | 0.28 | | 0.11 | | 0.01 | |
| 2nd Model | | | | | | | | |
| Pain Duration (months) | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 |
| Pain Intensity (VAS 1-10) | 0.00 | 0.06 | 0.11 | 0.05 | 0.10 | 0.06 | -0.02 | 0.09 |
| Sex (0 = male; 1 = female) | -0.23 | 0.33 | -0.14 | 0.28 | -0.18 | 0.31 | 0.43 | 0.45 |
| $\Delta R^2$ | 0.02 | | 0.01 | | 0.02 | | 0.05 | |

**Table 5.2.** Regression results for standardized variable error z-scores for male and female patients. *B* is the unstandardized beta, and represents the slope of the line between the independent and dependent variables. *SE B* is the standard error for the unstandardized beta.

| | Involved Shoulder | | Contralateral Shoulder | | Ipsilateral Knee | | Contralateral Knee | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** |
| 1st Model | | | | | | | | |
| Pain Duration (months) | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | -0.01 | 0.01 |
| Pain Intensity (VAS 1-10) | -0.04 | 0.08 | -0.11 | 0.07 | -0.03 | 0.07 | -0.24 | 0.13 |
| $R^2$ | 0.01 | | 0.13 | | 0.02 | | 0.21 | |
| 2nd Model | | | | | | | | |
| Pain Duration (months) | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | -0.01 | 0.01 |
| Pain Intensity (VAS 1-10) | -0.02 | 0.09 | -0.12 | 0.08 | -0.05 | 0.07 | -0.26 | 0.14 |
| Sex (0 = male; 1 = female) | 0.43 | 0.45 | -0.17 | 0.40 | -0.61 | 0.35 | -0.49 | 0.71 |
| $\Delta R^2$ | 0.05 | | 0.01 | | 0.16 | | 0.02 | |

## Discussion

The aims of the present study were three-fold. First, we examined whether proprioceptive impairments were present at a local (involved shoulder only) or global level (remote joints) in a population with SPS. Second, we assessed the effects of pain reduction (via an anesthetic injection) on proprioceptive measures at local and global levels in a population with SPS. Lastly, we explored characteristics associated with the presence of abnormal proprioception such as pain duration, pain intensity, and sex. Each of our hypotheses and corresponding results are discussed below.

Our first hypothesis that patients with SPS would demonstrate worse proprioception at the symptomatic shoulder as well as remote joints (contralateral shoulder, bilateral knees) than matched controls was not supported. In contrast, our results showed that patients had significantly better repositioning accuracy (as measured by constant errors) across all four tested joints (Table 5.1) than controls. The superior accuracy of the patient group could not be explained by changes in the variability of repositioning, as the consistency of errors between the four trials (as measured by variable error) was not significantly different between patients and controls.

Previous studies utilizing JPS protocols similar to ours have found a strong tendency for healthy populations to overshoot presented targets, with reported errors for shoulder flexion(Ettinger et al., 2017; King et al., 2013; S. Edwards et al., 2016) and knee extension (Vanessa Baker et al., 2002; Stillman et al., 1998) being on the order of 2°- 5° and 0.5°- 4°, respectively. An overshoot bias, similar to those reported above, was found at the bilateral shoulders and knees (Table 5.2) of patient and control participants enrolled in the present study. Across all joints, the overshoot bias was ~1.4° smaller in patients

compared to controls, resulting in better accuracy in the patient population. The tendency for patients with shoulder pain to undershoot the target relative to controls is in agreement with a previous JPS study by Anderson et al. (Anderson and Wee, 2011) conducted in the scapular plane. In the Anderson et al. study, patients with Chronic Rotator Cuff Pathology (which encompasses both SPS and glenohumeral instability) had a propensity to underestimate targets across not only the involved shoulder but the non-involved shoulder as well, while controls tended to overestimate targets. In contrast to the present study, these relative undershoots resulted in worse proprioceptive acuity in the patient population. Using a force reproduction tasks, Maenhout et al.(2012) also found differences in the involved and non-involved shoulders of patients with SPS compared to controls. Specifically, patients overestimated the force target across both shoulders by ~6% while controls underestimated the force target by ~6%. This resulted in no proprioceptive advantage for either group. Collectively, the present study paired with the findings of Anderson et al. and Maenhout et al. suggest that persons with SPS have altered proprioception across both shoulders; however these alterations may lead to improved, impaired or equivalent magnitudes of errors relative to controls depending upon the task. Consequently, it may be overly simplistic to quantify proprioceptive acuity based on the magnitude of errors alone, and classify alterations as a proprioceptive 'advantage' or 'deficit.' Instead, a greater emphasis on investigating the specific sensory, motor, or integration mechanisms underlying the proprioceptive alterations in a population with SPS are required.

Earlier studies have generally proposed that local sensory and motor factors, including differences in the number and sensitivity of mechanoreceptors or abnormal

recruitment of scapulothoracic muscles patterns play a role in the altered proprioceptive ability of patients with SPS. These concepts imply that proprioceptive alterations should be limited to the symptomatic shoulder and potentially the contralateral asymptomatic shoulder. However the fact that we found alterations across not only both shoulders but both knees argues against a local relationship. Our results indicate that patients with SPS have more global alterations in proprioception that cannot be entirely explained by mechanisms localized to the shoulder joints. To our knowledge, only one other study has assessed proprioception at a joint other than the shoulder in patients with SPS. Consistent with our results, a previous study in our lab (Ettinger et al., 2017) found proprioceptive alterations at the ipsilateral elbow during a joint positioning task. A possible explanation for the presence of proprioceptive alterations at remote joints is that these alterations preceded and precipitated the development of SPS. Although it was beyond the scope of the present cross-sectional study to investigate this theory, our results following the anesthetic injection suggest that pain may be a contributing factor and alterations are secondary to the development of SPS.

Our second hypothesis that pain reduction (via an anesthetic injection) would result in worse proprioception at the symptomatic shoulder and remote joints relative to pre-injection values was partially supported. Following the injection, all tested joints demonstrated a trend for greater overshoots and diminished proprioceptive accuracy (as measured by constant errors) on the order of ~0.7° compared to pre-treatment (Table 5.2). Consequently, patient constant error scores became more similar to controls errors scores after the injection; however patients still demonstrated smaller errors. No changes in the

consistency of repositioning (as measured by variable errors) were found following the injection.

To our knowledge, only one previous study has assessed the influence of an anesthetic injection on proprioception in a population with SPS. Similar to the present study, an earlier study performed by our lab (Ettinger et al., 2017) found that the symptomatic shoulder demonstrated greater overshoots and diminished proprioceptive accuracy on the order of ~1.8° in the post-injection session compared to the pre-injection session. Unlike the present study, these changes reached statistical significance. Moreover, patients were found to have significantly larger errors than controls in the post-injection session but not pre-injection session. The discrepancies between the present study and our earlier study (Ettinger et al., 2017) may arise from differences in pain reduction between the patient populations. The present study found a pain reduction of ~54% while the earlier study found a reduction of ~72% following treatment. If pain is indeed contributing to proprioceptive alterations, it seems logical that greater reductions in pain could account for the more robust changes demonstrated by the earlier study.

In our earlier study (Ettinger et al., 2017), we suggested that a reduction in sensory information likely contributed to the increase in proprioceptive errors post-injection. Specifically, patients with SPS may use pain, a very salient sensory signal, to help gauge the position of their arm and thus alleviation of pain reduces proprioceptive inputs. Against this argument however, is the fact that patients in the present study were found to have larger errors across remote joints as well as the involved shoulder after the injection, implicating more global factors.

Several factors could explain the global changes to proprioception that occurred between the pre-injection and post-injection sessions. First, the changes could be related to changes in cognitive attention. Joint positioning tasks demand a high degree of concentration (Lund et al., 2008) and lower levels of concentration may actually improve proprioception. Ghai et al.(Ghai et al., 2016) found smaller proprioceptive errors across the knee joint when participants performed a secondary cognitive task simultaneously versus no cognitive task. These findings agree with the Reinvestment Theory, which proposes that automatic movement patterns can be disrupted and impaired if the performer tries to exert to much conscious control over the movements (Masters and Maxwell, 2008). Pain is known to disrupt attentional performance in both healthy adults exposed to acute pain and patients with chronic pain (Eccleston and Crombez, 1999; Kucyi and Davis, 2015; Moore et al., 2012). This implies that patients in the present study likely had larger attentional disruptions prior to treatment when pain was high versus after the pain reducing injection, thus providing a proprioceptive advantage for the pre-injection session.

Another explanation for the global changes to proprioception after treatment could be related to a central pain inhibition across the motor system. Numerous studies have shown that muscles adapt to pain by reducing movement velocity, range of motion, muscle forces, and agonist activity (Graven-Nielsen et al., 2002, 1997; Lund et al., 1991). The Pain Adaption Model explains such behaviors as a protective adaption aimed at protecting the body from further harm (Lund et al., 1991). While the Pain Adaptation Model has primarily been investigated in relation to alterations at the symptomatic joint, increasing evidence suggests that pain can induce motor alterations at the contralateral or

remote joints. If patients had reduced movement velocities or greater agonist inhibition in the pre-injection condition, pain inhibition could explain the relative underestimation of targets in the pre-injection versus post-injection condition. The pre-injection bias is also likely to reduce torques across the joint, which again points at a protective mechanism that limits muscle strains.

Our third hypothesis that after controlling for pain duration and pain intensity, female patients would demonstrate greater proprioceptive errors than male patients was not supported. Our results did not reveal significant z-score differences between male and female patients, suggesting that the proprioceptive abnormalities noted in the SPS population were not sex specific. Therefore our results do not support the notion that sex specific differences in proprioceptive impairments contribute to the higher rates of subacromial pain and failed treatment noted in female versus male patients. Interestingly, pain intensity and pain duration did not demonstrate a significant correlation with z-scores, suggesting that greater proprioception abnormalities were not present in those with greater pain intensity or prolonged pain.

There are several limitations to the present study. The first limitation concerns the fact that only one of the sub-modalities of proprioception (joint position sense) was evaluated in this study. It is possible that other modalities such as kinesthesia and force steadiness would yield different conclusions about the influence of pain on global proprioceptive abilities. While a repeated model design for both our control and patient participants accounted for any learning bias or fatigue, we cannot conclusively establish a causal role for pain reduction and proprioceptive changes. It is possible that the changes observed between testing sessions were the result of the mechanical effects or anxiety of

the injection. The use of a placebo treatment condition for our patients or exposure to an anesthetic injection for controls could have helped account for this. Also, there may be a difference between the acute and prolonged reduction of pain, therefore future studies are needed to look at the long-term effects of pain reduction on proprioception.

## Conclusions

The present study found that patients with SPS demonstrate altered proprioception across not only the involved shoulder but remote joints as well, including the contralateral shoulder and bilateral knees. Specifically, patients with SPS when compared to controls were found to utilize a repositioning bias with smaller overshoots across each of the tested joints. Moreover, pain reduction (through an anesthetic injection) resulted in larger repositioning errors as compared to pre-treatment values, across all tested joints. Female patients did not exhibit greater proprioceptive abnormalities than male patients. Taken together, these findings suggest proprioception is altered at a global rather than local level in persons with SPS and that pain may play a role in initiating a central protective mechanism. Further studies are required to investigate whether sensory, motor or integration centers are responsible for the differences in JPS noted between patients and controls as well as the influence of long-term pain reduction.

## Bridge

In the present chapter, we found that proprioception was abnormal at both the involved and remote joints of persons with subacromial pain syndrome, but these

abnormalities did not appear to be sex dependent. Moreover, the reduction of pain coincided with changes in proprioceptive function that were more similar to the proprioceptive function of uninjured controls than the pre-injection testing session. Since proprioception is an important component for motor control, it is possible that motor abnormalities may also present at the involved and remote joints, and may be influenced by the reduction of pain. The next chapter, Chapter VI investigated strength, a motor modality, and the influence of sex and pain reduction on weakness across the involved shoulder and remote joints.

CHAPTER VI

# WEAKNESS IN SUBACROMIAL PAIN SYNDROME

The experiment described in this chapter was developed with Dr. Andrew Karduna who contributed substantially to this work by assisting with experimental conception, editing and advising throughout the project. Dr. Matthew Shapiro further contributed to the study by assisting in recruiting patients with subacromial pain and performing the subacromial injection. I was the primary contributor to the development of the experimental design, data collection and analysis, and write up.

## Introduction

Weakness frequently accompanies chronic and acute pain (Bank et al., 2013a; Graven-Nielsen et al., 2002; Lund et al., 1991). While multiple hypotheses have emerged regarding the precise neurophysiological pathways contributing to this weakness (Hodges and Tucker, 2011; Lund et al., 1991), it is generally accepted that weakness is induced to protect damaged muscles from further injury. To elaborate, pain appears to override motor commands, inhibiting motor unit recruitment and force generation in an effort to protect the injured structures from further damage (Tucker et al., 2009). In the case of subacromial pain syndrome (SPS), significant weakness in abduction and external rotation has been consistently demonstrated at the symptomatic shoulder (Leroux et al., 1994; MacDermid et al., 2004; McCabe et al., 2005; Tyler et al., 2005). This weakness is interpreted as inhibition of the supraspinatus and infraspinatus, as the supraspinatus is

accepted to contribute to abduction and external rotation while the infraspinatus external rotation (Escamilla et al., 2009; Webb et al., 2014). An inhibition of the supraspinatus and infraspinatus is consistent with current pain models, as the nociceptive stimulus associated with SPS is accepted to arise from near or even within these muscles (Ben-Yishay et al., 1994; Park et al., 2008; Soifer et al., 1996), and thus inhibition of these muscles could be interpreted as a protective mechanism. While rotator cuff weakness may offer protection to these muscles in the acute phases of subacromial pain, the prolonged weakness associated with SPS may lead to further disease progression.

In healthy individuals, the humeral head remains relatively fixed on the glenoid during reaching tasks (Deutsch et al., 1996; Yamaguchi et al., 2000), allowing the greater tuberosity of the humerus to freely pass underneath the acromion. In contrast, the humeral head has been observed to migrate superiorly on the glenoid in much of the SPS population (Deutsch et al., 1996), especially at higher elevation angles. Since the subacromial space is relatively small, even a subtle narrowing of acromiohumeral distance is a potential mechanisms for substantial compression of soft tissue structures and subsequent pain for at least a subset of patients (Karduna et al., 2005).

One factor that likely contributes to a narrowing of acromiohumeral distance in the SPS population is weakness or an insufficient contribution from the rotator cuff. Due to the mobility of the glenohumeral joint and its limited bony congruence, the dynamic action of the rotator cuff muscles plays a crucial role in providing stability to the joint (Apreleva et al., 2000). Among other actions, the rotator cuff muscles preserve the size of the subacromial space by limiting superior translation of the humeral head (Yanagawa et al., 2008), especially during elevation tasks. When lifting the arm, the deltoid muscle

serves as the prime mover of the glenohumeral joint. However, contraction of the deltoid muscle also produces shear forces which serve to superiorly displace the humeral head (Yanagawa et al., 2008). To offset the superior displacement invoked by the deltoid, compressive and inferior shear forces are generated by contraction of the rotator cuff muscles (Halder et al., 2001). Subsequently, a proper balance of rotator cuff and deltoid forces results in limited movement of the humeral head. In contrast, weakness of the rotator cuff muscles results in an increase in superior translation of the humeral head (Chen et al., 1999; Keener et al., 2009; San Juan et al., 2013) and a narrowing of the subacromial space.

Patients with SPS have been shown to have a high incidence of both rotator cuff weakness as well as a reduction in subacromial space (Burkhart, 1995; Deutsch et al., 1996). While these observations do not define whether a cause and effect relationship exists between rotator cuff weakness and superior translations of the humeral head, this relationship can be examined with experimental models. Experimental fatigue (Chen et al., 1999) and suprascapular nerve blocks (San Juan et al., 2013) have been shown to result in superior translations of the humeral head that were not present prior to the experimentally induced rotator cuff weakness. On the other hand, there is ample evidence that some patients with SPS possessed congenital narrowing of the subacromial space prior to developing rotator cuff weakness or pain, due to bony anatomy (Balke et al., 2014, 2013). Nonetheless, regardless of whether narrowing of the subacromial space preceded or ensued from the onset of SPS and rotator cuff weakness, the prevention of further subacromial space narrowing is thought to be crucial to prevent disease

progression. Consequently, to maintain subacromial space, it may be necessary for patients to regain rotator cuff strength.

Due to consistent observations of rotator cuff weakness in SPS and the potential effects of this weakness on the size of the subacromial space, it is important to understand the mechanisms underlying rotator cuff weakness. Like other pain conditions, nociceptive pathways may be playing a role in the weakness observed in SPS. Healthy participants exposed to experimental subacromial pain demonstrate a substantial loss of strength relative to their strength pre-pain induction (Stackhouse et al., 2013). Patients with large rotator cuff tears, a condition which is thought to be a continuum of SPS, demonstrate large increases in shoulder strength minutes after experiencing pain reduction from a subacromial injection (Itoi et al., 1997; Kirschenbaum et al., 1993). Given these findings, the weakness observed in patients with SPS may be directly modulated by pain. In light of this, additional information is needed about the relationship between weakness and subacromial pain as well as the individual characteristics associated with the development of weakness as the SPS population is likely to demonstrate heterogeneity. Female populations with pathologies of the rotator cuff suffer from higher levels of disability and pain compared to male populations both prior to and after receiving treatment (Razmjou et al., 2011). It is possible that shoulder weakness is more prevalent in female patients with SPS, contributing to the sex related differences in disability and pain. To our knowledge, no previous studies have assessed whether the development of weakness is dependent upon sex in a population with SPS. This knowledge gap is surprising given the poorer outcomes noted in female patients.

When assessing strength deficits, clinicians and research alike often compare the symptomatic side of patients experiencing subacromial pain to the non-symptomatic side (McCabe et al., 2005; Tyler et al., 2005). This technique assumes that pain does not modulate strength at the healthy side, which may be an erroneous assumption. While a number of investigations have obtained strength measurements from the asymptomatic shoulder of persons with SPS (Camargo et al., 2008; Leroux et al., 1994; MacDermid et al., 2004; Mattiello-Rosa et al., 2008; Tyler et al., 2005), few of these investigations have statistically compared the non-involved shoulder of patients to healthy controls (Camargo et al., 2008; Leroux et al., 1994; Mattiello-Rosa et al., 2008). Of the studies that have made this comparison, two have found strength deficits at the non-involved shoulder (Camargo et al., 2008; Mattiello-Rosa et al., 2008) and one has found no deficits (Leroux et al., 1994). Additional studies are needed to confirm whether rotator cuff weakness presents bilaterally in patients with SPS. Furthermore, given the cross-sectional nature of these previous studies, it cannot be determined whether pain was related to the deficits at the non-involved limb. However, acute pain has been shown to cause bilateral changes in motor unit recruitment (Schomburg et al., 2015)and cortical activation (Xiao et al., 2015) in animal models. If pain is leading to bilateral weakness in the SPS population, it would be inappropriate to use the non-involved limb as a control. In addition to the motor disturbances noted at the non-involved arm including altered kinematic patterns (Hebert et al., 2002) and longer times to perform occupational tasks or produce peak torque (Camargo et al., 2008; Madeleine et al., 1999), persons with SPS also display larger COP displacement while performing occupational tasks (Madeleine et al., 1999), suggesting that motor control abnormalities may extend beyond the bilateral shoulders.

**The primary aim of this study was to assess regional and global weakness by testing peak isometric torque at involved and remote locations in patients with SPS, both before and after acute pain reduction. The secondary aim of the present study was to explore characteristics associated with weakness. We hypothesized that patients with SPS would demonstrate smaller peak torque values at the symptomatic shoulder and remote locations (contralateral shoulder, both knees) than matched controls (Hypothesis 4.1). We further hypothesized that upon pain reduction, patients experiencing SPS would demonstrate greater peak torque values at both shoulders and both knees relative to pre-injection values (Hypothesis 4.2). We also hypothesized that after controlling for pain duration and pain intensity, female patients would demonstrate smaller normalized peak torque than male patients (Hypothesis 4.3).**

## Methods

### General Methods and Participants

For Aim 2, Aim 3, and Aim 4, a single repeated measures study incorporating both a patient cohort with SPS and control cohort was utilized. The methods and participants for this large study have previously been described in Chapter III. In the present Chapter (VI), to specifically address Aim 4, strength measurements from this larger dataset were evaluated and are expanded upon below.

**Strength**

Strength at the involved shoulder (IS), contralateral (shoulder), ipsilateral knee (IK) and contralateral knee (CK) was assessed utilizing a maximum isomeric voluntary contractions MVIC protocol to calculate peak torque. Measurements were obtained from a computerized system consisting of a uniaxial load cell, amplifier, and data acquisition unit running on custom written LabVIEW (National Instruments, Austin, TX) software. Graphical representation of contraction force was visible on a monitor in real time to research personnel but not participants. Data were sampled at 1000 Hz and recorded as force. For each joint, the peak (or maximum) force produced out of the series of three trials was used for data analysis.

The testing procedure was strictly standardized, including participant positioning, contraction time, rest time between trials, number of trials per side, and verbal instruction and encouragement. The MVICs at the shoulder joint were performed against resisted sagittal plane flexion of the upper extremity, with the shoulder in 90 degrees of flexion, the elbow in full extension and the forearm in neutral pronation/supination. Participants were in a seated position and the trunk was stabilized with straps (Figure 6.1). The load cell was mounted to a metal testing frame and positioned just distal to the medial and lateral epicondyles of the humerus. The MVICs at the knee joint were performed against resisted sagittal plane extension, with the hip and knee joints flexed to ninety degrees and ankle joint in a neutral position (Figure 6.1). Participants were in a seated position and the trunk and thighs were stabilized with straps (Figure 6.1). The load cell was mounted to a metal testing frame and positioned four inches proximal to the medial and lateral malleoli of the ankle.

Each joint was tested three times, with thirty seconds of rest in between each trial. The testing of sides was randomized and counterbalanced between participants. Participants were verbally encouraged by the investigator during each muscle contraction and instructed to continue the contraction for five seconds. Feedback about performance was not given to participants.

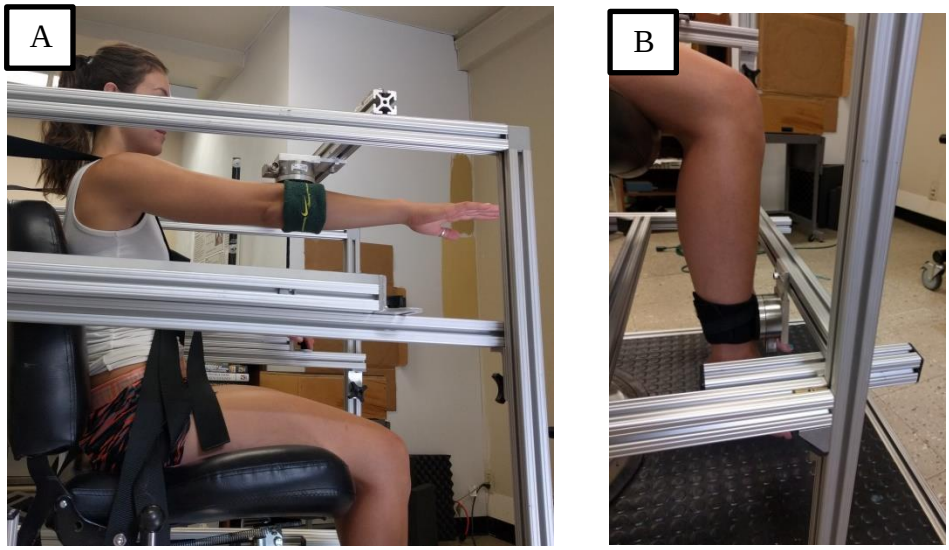


**Figure 6.1.** Experimental set-up used for peak torque (strength) measurements during the subacromial pain study. A) Shoulder flexion. B) Knee extension.

**Data Analysis**

For each joint, the pre-injection peak force score (N) was converted to a peak torque score (Nm). To calculate peak torque, peak force was multiplied by the moment arm (defined as the distance between the center of the shoulder joint and the center of the load cell). The moment arm was measured with a seamstress ruler from the center of the joint (shoulder or knee) to the middle of the point of contact with the load cell. Larger

peak torque values indicate greater strength was exerted against the load cell. To assess the influence of the subacromial injection, the change in peak torque scores was calculated for each joint by subtracting peak pre-injection torque scores from peak post-injection torque scores. A positive value indicates greater torque (strength) was applied during the post-injection condition relative to the pre-injection condition.

For the secondary analysis exploring the influence of sex, we created standardized z-scores for each of the four joints: involved shoulder, contralateral shoulder, ipsilateral knee, and contralateral knee. Standardized z-scores were computed for each female patient using the equation below:

**6.1**

$$\text{Standarized Female Z} - \text{Score: } \frac{\overline{X}_{\text{i.F}} - \overline{X}_{\text{Controls.F}}}{\sigma_{\overline{X}.F}}$$

$\overline{X}_{\text{Controls.F}}$ is the mean peak torque for the female control participants, $\sigma_{\overline{X}.F}$ is the standard deviation of peak torque scores for the female control participants, and $\overline{X}_{\text{i.F}}$ is the Peak Torque score for an individual female patient participant. Likewise, standardized z-scores were computed for each male patient using the equation below.

**6.2**

$$\text{Standarized Male Z} - \text{Score: } \frac{\overline{X}_{\text{i.M}} - \overline{X}_{\text{Controls.M}}}{\sigma_{\overline{X}.M}}$$

$\overline{X}_{\text{Controls.M}}$ is the mean peak torque for the male control participants, $\sigma_{\overline{X}.M}$ is the standard deviation of peak torque scores for the male control participants, and $\overline{X}_{\text{i.M}}$ is the peak torque score for an individual male patient participant.

**Statistical Analysis**

SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Values of $p < 0.05$ were regarded as statistically significant for all analysis. Following conventional ANOVA logic, interaction effects were evaluated before proceeding to main effects.

**Hypothesis 4.1– Patients with SPS would demonstrate smaller peak torque values at the symptomatic shoulder and remote locations (contralateral shoulder, both knees) than matched controls.** To determine if there were strength differences between patient and control participants prior to treatment, a single two-way mixed model ANOVA was used. The dependent variable was peak torque. The between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). An *a priori* interaction contrast was also run for peak torque scores to assess whether the differences between torque scores for patient and control participants were different between the involved shoulder and remote joints. The *a priori* interaction contrast was coded as a group {1, -1} by joint {3, -1, -1, -1} interaction. To provide additional confirmation on the presence of weakness at the involved shoulder, an *a priori* paired t-test was run comparing patient's involved shoulder to patient's non-involved shoulder.

**Hypothesis 4.2 – Upon pain reduction, patients experiencing SPS would demonstrate greater peak torque values at both shoulders and both knees relative to pre-injection values.** To determine if a pain reducing treatment influenced strength a

single two-way mixed model ANOVA was used. The dependent variable was change in peak torque after treatment. The between-subject effect was group and the within-subject effect was joint. Group had two levels: (a) patient and (b) control. Joint had four levels: (a) involved shoulder (IS), (b) contralateral shoulder (CS), (c) ipsilateral knee (IK), and (d) contralateral knee (CK). An *a priori* interaction contrast was also run for change in peak torque to assess whether the differences between torque for patient and control participants were different between the involved shoulder and remote joints. The *a priori* interaction contrast was coded as a group {1, -1} by joint {3, -1, -1, -1} interaction.

**Hypothesis 4.3 – After controlling for pain duration and pain intensity, female patients would demonstrate smaller normalized peak torque than male patients.** For this secondary analysis, we ran a total of four hierarchical multiple regression models, one for each joint (involved shoulder, non-involved shoulder, ipsilateral knee, contralateral knee) on patient data only. Standardized z-scores for torque were the dependent variable. Pain duration, pain intensity and sex were the independent variables. Sex was represented by dummy coded variables. Pain duration and pain intensity were added to the model first, while sex was added to the model later to see if it increased the predictive power.

## Results

### Pre-injection Peak Torque: Hypothesis 4.1

The *a priori* interaction comparison was significant ($p<0.01$), revealing that differences between patients and controls peak torques were location dependent (involved

joint versus remote joints). Based on this finding, pairwise comparisons were conducted. Peak torques at the involved shoulder were significantly smaller ($p=0.04$) in the patient population ($M= 34.9$ Nm) versus the control population ($M=48.5$ Nm), by a mean of 13.6 Nm (Figure 6.2). There were no significant differences between groups at the remote joints, neither when the remote joints were pooled into one composite score ($p=0.92$) nor when individual joints were analyzed including the contralateral shoulder ($p=0.68$), ipsilateral knee ($p=0.75$), and contralateral knee ($p=0.79$). Additionally, the *a priori* paired t-test revealed that peak torques were significantly smaller ($p<0.001$) at patients' involved ($M=34.9$ Nm) versus contralateral ($M=48.7$ Nm) shoulder, with a mean side-to-side difference of 13.8 Nm (Figure 6.2).

**Post-injection vs. Pre-injection Peak Torque: Hypothesis 4.2**

For the change in peak torque after treatment, the *a priori* interaction comparison was non-significant ($p=0.46$), revealing that differences between patient and control populations did not depend upon location (involved shoulder versus remote joints). We next looked at the ANOVA interaction, where the group*joint interaction ($p=0.69$) was also found to be non-significant. Finally, following conventional ANOVA logic, we looked at the main effects. Neither was the main effect of joint ($p=0.76$) nor group ($p=0.76$) significant (Figure 6.3).

**Within-Group Differences: Hypothesis 4.3**

For the involved shoulder, the associated regression model incorporating only pain duration and pain intensity was non-significant ($p=0.31$), however the addition of

sex to the model significantly improved the prediction of standardized z-scores (p=0.03). Therefore a simpler model incorporating only the main effects of sex (Male = 0, Female = 1) was examined to determine how sex predicted z-scores at the involved shoulder (Table 6.1). Sex alone predicted 27% of the variance in z-scores (p=0.02), and females patients z-scores were predicted to be significantly smaller than males (*B*= -1.49, p=0.02). Moreover, a follow-up one sample t-test revealed z-scores for males were not significantly different from zero at the involved shoulder (z-score=-0.69, p=0.10) while z-scores for females were significantly smaller than zero (z-score=-2.18, p<0.001) (Figure 6.4).

For each of the three remote joints (contralateral shoulder, ipsilateral knee, contralateral knee), the associated regression models incorporating only pain duration and pain intensity were non-significant (all p>0.05). Neither did the addition of sex to the models significantly improve the prediction of standardized z-scores (all p>0.05). To increase power, simpler models incorporating only the main effects of sex were examined to determine how sex predicted z-scores at each remote joint (Table 6.1). The simpler models were also found to be non-significant (all p>0.05) (Table 6.1).

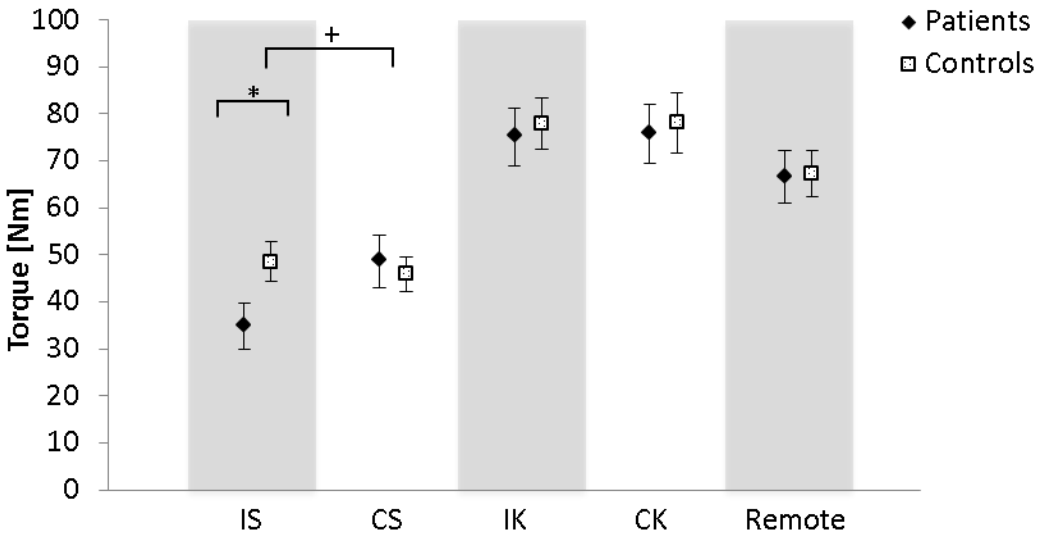


**Figure 6.2.** Pre-injection peak torque (strength) scores (means ± SEMs) for patients with SPS and controls. Analyzed joints include the involved shoulder (IS), contralateral shoulder (CS), ipsilateral knee (IK), contralateral knee (CK), and average of the CS, IK, and CK joints (Remote). * Denotes a significant between-group difference. + Denotes a significant within-group difference.

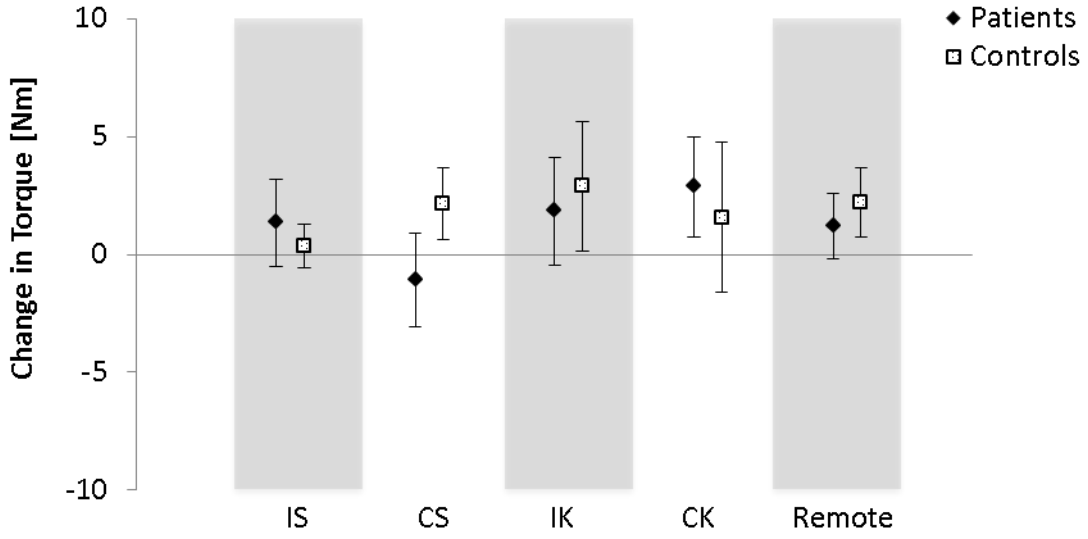


**Figure 6.3.** Change in peak torque (strength) scores (means ± SEMs) for patients with SPS and controls following the injection/rest period. Analyzed joints include the involved shoulder (IS), contralateral shoulder (CS), ipsilateral knee (IK), contralateral knee (CK), and average of the CS, IK, and CK joints (Remote).

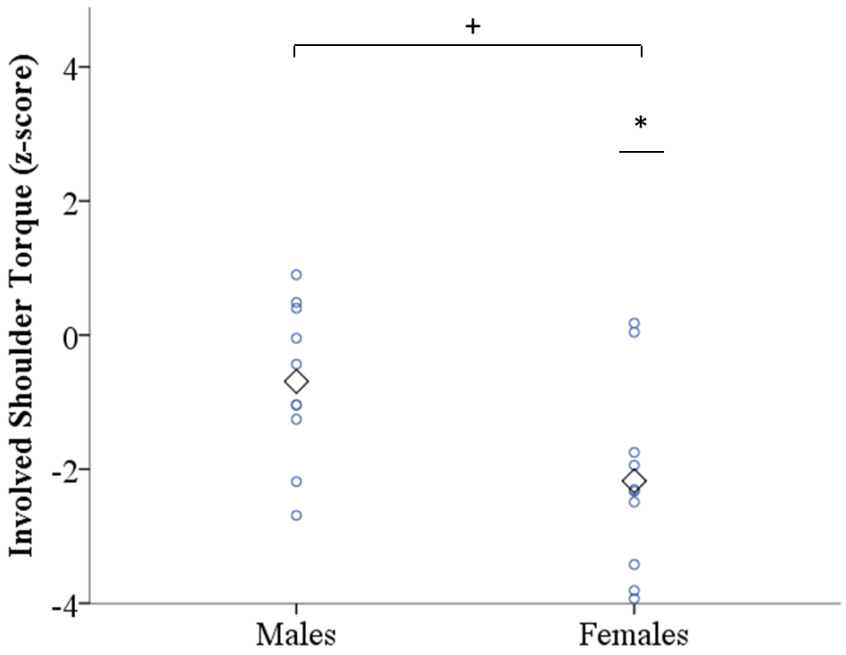


**Figure 6.4.** Peak torque z-scores for male and female patients at the involved shoulder. Circles represent individual scores while diamonds represent group averages. + Denotes a significant difference between male and female patients. * Denotes a significant difference from a one-sample test value of 0.

## Discussion

The aims of the present study were three-fold. First, we examined whether patients with SPS would smaller peak torque values than controls across the involved shoulder as well as remote joints. Second, we assessed the effects of pain reduction (via an anesthetic injection) on peak torque at involved shoulder as well as remote joints. Lastly, we explored characteristics associated with weakness such as pain duration, pain intensity, and sex. Each of our hypotheses and corresponding results are discussed below.

**Table 6.1.** Regression results for standardized peak torque (strength) z-scores for male and female patients. *B* is the unstandardized beta, and represents the slope of the line between the independent and dependent variables. *SE B* is the standard error for the unstandardized beta.

| | Involved Shoulder | | Contralateral Shoulder | | Ipsilateral Knee | | Contralateral Knee | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** | ***B*** | ***SE B*** |
| 1st Model | | | | | | | | |
| Pain Duration (months) | 0.01 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 |
| Pain Intensity (VAS 0-10) | -0.06 | 0.13 | 0.14 | 0.14 | -0.08 | 0.08 | -0.06 | 0.08 |
| $R^2$ | 0.13 | | 0.05 | | 0.15 | | 0.13 | |
| 2nd Model | | | | | | | | |
| Pain Duration (months) | 0.01 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 |
| Pain Intensity (VAS 0-10) | -0.12 | 0.12 | 0.09 | 0.14 | -0.11 | 0.08 | -0.10 | 0.07 |
| Sex (0 = male; 1 = female) | -1.45* | 0.61 | -1.22 | 0.76 | -0.77 | 0.39 | -0.77 | 0.38 |
| $\Delta R^2$ | 0.23* | | 0.15 | | 0.16 | | 0.18 | |
| 3rd Model | | | | | | | | |
| Constant | -0.69 | 0.41 | 0.61 | 0.46 | 0.18 | 0.27 | 0.13 | 0.26 |
| Sex (0 = male; 1 = female) | -1.49* | 0.58 | -1.22 | 0.65 | -0.75 | 0.39 | -0.75 | 0.36 |
| $R^2$ | 0.27* | | 0.16 | | 0.17 | | 0.19 | |

* Denotes significance at $p < 0.05$

Our first hypothesis that patients with SPS would demonstrate smaller peak torque compared to controls at the symptomatic shoulder as well as remote joints (contralateral shoulder, bilateral knees) was partially supported. Our results found that patients had significantly smaller peak torque values at the involved shoulder only (Figure 6.1). Controls produced 48.5 Nm of torque at the involved shoulder while patients produced 34.9 Nm, resulting in between-group differences of 13.6 Nm or 28% less torque in the patient group. This finding suggests patients with SPS in the present study had substantial weakness. Similarly, patients involved shoulder was also found to have significantly lower peak torques compared to the contralateral shoulder, with the mean side-to-side difference being 13.8 Nm or 28% less torque at the involved shoulder.

Previous strength testing of populations with SPS have utilized a variety of test positions including external rotation, internal rotation, abduction, and elevation motions among others, as well as a variety of protocols, including isometric and isokinetic, making it difficult to directly compared the results of the present study to previous studies in terms of magnitudes of weakness. Nonetheless our results are consistent with a large body of literature demonstrating weakness at the involved shoulder of patients with SPS in a variety of positions and during a variety of protocols (Camargo et al., 2008; Leroux et al., 1994; MacDermid et al., 2004; McCabe et al., 2005; Tyler et al., 2005; Warner et al., 1990). Moreover, our results also suggest that the weakness patient with SPS experience is significant as a value of 15% is commonly accepted as clinically relevant.

Limited studies have found emerging evidence for motor abnormalities across the noninvolved shoulder of persons with SPS including changes in time to peak torque or acceleration (Camargo et al., 2010; Mattiello-Rosa et al., 2008). Moreover, while a large

number of studies assess strength across the non-involved shoulder, few have statistically compared this shoulder to a control population. To our knowledge, only one study has found peak torque deficits in the non-involved shoulder (Camargo et al., 2008). The present study found no evidence for weakness at the non-involved shoulder. Collectively, these findings make it difficult to determine whether strength deficits are present bilaterally in a population with SPS. Nonetheless, given that patients with SPS are likely to utilize their non-involved arm more than they did prior to injury, it is likely that some motor adaptations have occurred.

Our second hypothesis that pain reduction (via an anesthetic injection) would result in increased strength across the involved shoulder and remote joints of patients with SPS was not supported. No changes to peak torque were observed across any joints following the injection (Figure 6.3). In the long-term, patients with SPS have been shown to experience strength gains across the involved shoulder after a variety of interventions that successfully reduced their pain (McClure et al., 2004; Viswanath et al., 2013; Yu et al., 2006), however it is unclear whether strength gains are possible after the acute reduction in pain. Similar to the present study, Park et al. failed to find isometric strength gains across the involved shoulder in a population of 153 patients with SPS thirty minutes after a subacromial injection (Park et al., 2008). Interestingly, Park et al. also tested a population with rotator cuff tears, finding that strength gains did occur (Park et al., 2008). A number of other studies have shown acute strength gains after a pain relieving injection in populations with rotator cuff tears or mixed rotator cuff tear and SPS populations (Ben-Yishay et al., 1994; Itoi et al., 1997; Kirschenbaum et al., 1993). Collectively our results paired with previous studies suggest that patients with SPS may not have the same motor

responses to acute pain removal as patients with rotator cuff tears, despite the fact that SPS and rotator cuff tears are viewed as a continuum of diseases. Unlike patients with rotator cuff tears, in order for patients with SPS to regain strength, additional time or interventions may be needed in addition to a subacromial injection. The lack of changes to strength could also be due to the position that we used. A flexion task such as the one we used required contributions from both the supraspinatus and deltoid. However it is possible that a different motion that required more torque generation to come from the impaired rotator cuff muscles, such as external rotation, could show greater inhibition and changes.

Our third hypothesis that after controlling for pain duration and pain intensity, female patients would demonstrate greater weakness than male patients was supported. Our results revealed significantly greater z-scores at the involved shoulder in female compared to male patients, indicating that female patients experienced greater weakness than male patients. Interestingly, pain intensity and pain duration did not demonstrated a significant correlation with z-scores, suggesting that greater strength deficits were not present in those with greater pain intensity pain or prolonged pain. To our knowledge, no previous studies have evaluated whether sex differences contribute differentially to motor responses in SPS. Similar to our study however, Higgins et al. found that females with rotator cuff tears exhibited greater normalized strength deficits than males(Earle Miller et al., 2016). The association between weakness and the female sex may hold promise future research on shoulder pain as female patients generally report greater physical limitations than male patients both before and after treatment.

There are several limitations to the present study. The first limitation concerns the fact that only one position was utilized in this study to assess strength. It is possible that other positions such as external rotation would yield different conclusions about the influence of pain on rotator cuff strength. Also, there may be a difference between the acute and prolonged reduction of pain, therefore future studies are needed to look at the long-term effects of pain reduction on strength.

## Conclusions

The present study found that patients with SPS demonstrate weakness, as measured by smaller peak torques, across the involved shoulder while remote joints appear to demonstrate normal strength. Female patients were shown to exhibit greater levels of weakness than male patients at the involved shoulder. Moreover, pain reduction (through an anesthetic injection) had no influence on strength in the short-term. Further studies are required to investigate which characteristics are associated with the development of weakness as well as the influence of sex on motor responses to treatment.

# CHAPTER VII

# CONCLUSIONS

Patients with subacromial pain syndrome (SPS) display a number of sensorimotor deficits including alterations in pain processing, poor proprioception, and weakness at the symptomatic limb. The primary purpose of this dissertation was to explore whether the aforementioned deficits: (1) can be quantified by using the non-involved limb as a measure of control, (2) are purely localized to the symptomatic limb or represent a more generalized deficit, (3) are influenced by the presence of subacromial pain, and (4) present similarly in male and female patients. Here, we utilized modern clinical techniques in both a patient cohort with SPS and uninjured control cohort to address these aims. The results of this dissertation are applicable towards treatment of SPS as well as scientific understanding of sex on sensorimotor behavior.

Clinicians and researchers frequently determine whether an individual patients or patient population have alterations in sensorimotor function by utilizing the contralateral limb as a control. Our results have shown that asymmetries exist between the dominant and non-dominant shoulders in regards to pressure pain threshold, proprioception, and strength. Moreover, the asymmetries associated with each of these sensorimotor modalities were each found to be sex dependent. The implications of our results raise concerns about the utility of using the contralateral limb as a control, and instead give weight to the use of a control group that is tightly matched for sex and arm dominance,

especially in research settings. In the long-term, it may be advantageous to develop a correction factor for clinical use.

This dissertation also found that sensorimotor abnormalities may not be limited to the involved shoulder of persons with subacromial pain syndrome. Specifically, we found evidence for heightened sensitivity to pressure pain threshold and improved proprioception across remote limbs as well as the involved limb, while weakness appeared to be localized to the involved shoulder. These results suggest that, at least in some subsets of the population, subacromial pain syndrome may have some neuropathic involvement. Consequently, some patients may require interventions that extend beyond treating the local shoulder joint.

Much to our surprise, no statistically significant changes occurred after the reduction of pain in any of our measured sensorimotor modalities. The absence of significant sensorimotor changes after acute pain reduction makes it difficult to determine the extent to pain is contributing to the sensorimotor abnormalities found in this study. Nonetheless, we feel the use of an anesthetic injection model that acutely reduces pain, may be an advantageous for other chronic pain conditions affecting the joints, such as knee osteoarthritis.

In two of our three sensorimotor measures, abnormalities were sex dependent, with females demonstrating greater abnormalities than males. This finding should be explored further as this may help explain why females have higher incidents of subacromial pain and failed treatment.

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