School of Physiotherapy and Exercise Science

The association of body representation and nociceptive sensitivity measures with shoulder pain and disability prior to and twelve months after shoulder surgery

Gabriella Maria Bargon

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number HR178/2013 and from Sir Charles Gairdner Hospital (HREC 2013-202).

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Abstract

Background

Shoulder pain is the third most common musculoskeletal presentation in primary care settings. Many multidimensional factors have been identified for the development and persistence of shoulder pain, including patho-anatomical, lifestyle and psychosocial factors. More recently alterations in the Central Nervous System (CNS), including changes in nociceptive sensitivity and self- perception have been identified in musculoskeletal pain. These CNS factors have been shown to be implicated in the persistence, duration and level of pain. Shoulder surgery for RC disease targets the patho-anatomical features. The rates of shoulder surgery for rotator cuff (RC) disease have significantly escalated over the past decade, despite limited evidence of its efficacy. Several multidimensional preoperative prognostic factors of pain and disability outcomes after shoulder surgery for RC disease have been previously identified, yet consideration of factors related to CNS-pain processing are limited.

Aims

1. To determine the association between measures of body representation and nociceptive sensitivity, and shoulder pain and disability prior to RC surgery.
2. To assess the predictive association of these body representation and nociceptive sensitivity measures with shoulder pain and disability 12 months following RC related shoulder surgery.

Methods

A longitudinal cohort of 34 people undergoing shoulder surgery for RC disease at a tertiary hospital, were recruited. Measures of body representation (two-point discrimination, left/right judgement task and shoulder specific self-perception), nociceptive sensitivity (cold pain sensitivity and pressure pain thresholds) were obtained prior to surgery., Shoulder Pain And Disability Index (SPADI) questionnaire scores (pain and disability sub-scales considered separately) were obtained before and 12 months after surgery. Multivariable regression analysis was used to examine the association of each body representation and nociceptive sensitivity measure with i) SPADI baseline scores, adjusted for potential

confounders (Aim 1), and ii) SPADI scores 12 months after surgery, adjusted for bassline SPADI scores and potential confounders (Aim 2).

Results

Poorer two point discrimination was associated with higher levels of pain prior to surgery. Increased sensitivity to pressure (lower pressure pain threshold) was associated with higher levels of reported disability prior to surgery. No measures of body representation or nociceptive sensitivity before surgery were associated with SPADI pain and disability scores 12 months after surgery.

Conclusion

This study contributes some evidence that increased sensitivity to pressure and a poorer ability to two-point discriminate may be associated with shoulder pain and disability prior to, but not 12 months after, RC surgery. However, the sample size of this study was limited and larger studies are required to confirm the presence or absence of all associations tested in this study.

Table of Contents

List of Figures

List of Tables

Abbreviations

CNS	central nervous system
BMI	body mass index
PPT	pressure pain threshold
CPT	cold pain threshold
CPS	cold pain sensitivity
RC	rotator cuff
TPD	two-point discrimination
SPADI	shoulder pain and disability index
MRI	magnetic resonance imaging
LRJT	left/right judgement task
VAS	visual analogue scale
GP	general practitioner
CRPS	complex regional pain syndrome

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Literature Review

Introduction

Shoulder pain is associated with significant rates of disability (1). While it is estimated approximately 50% of shoulder pain resolves within 6 months (2, 3), chronic or persistent shoulder pain is estimated to be the third most common musculoskeletal presentation in primary care settings (4).

Shoulder pain is inclusive of a number of clinical conditions, which may present independently or in combination with each other. Although it is widely appreciated that all musculoskeletal presentations are associated with numerous biopsychosocial factors, diagnostic criteria continue to focus on structural labels. Diagnostic categories for shoulder pain include; subacromial impingement, Rotator cuff (RC) disease (including tears), gleno-humeral instability, frozen shoulder (adhesive capsulitis) and osteoarthritis (5). However, a lack of accepted definition and validated diagnostic criteria for these diagnostic categories further complicates terminology.

The RC comprises muscles that act as a dynamic stabiliser of the glenohumeral joint. The physiology of RC pathology is viewed as a continuum from impingement syndrome to partial and full thickness tears, beginning with repeated tendon strain and oedema, progressing to inflammation and fibrosis, and with time, partial or full thickness tears (6). The term RC disease is often interchanged with subacromial impingement or pain syndrome, subacromial bursitis, RC tendinopathy and RC tendinitis.

Assessment and management of shoulder pain has traditionally focussed on the identification and amelioration of structural problems within the shoulder, with little consideration given to other factors that might impact on pain and disability such as neurophysiological changes (7, 8), psychosocial factors and unhealthy lifestyle choices (9). As with other musculoskeletal presentations, the influence of these factors may offer some insight as to why there is a poor correlation between pain and local tissue pathology and why physical diagnostic tests that attempt to identify a specific local tissue problem demonstrate poor reliability (10) . Specifically understanding the involvement of neurophysiological changes in persistent shoulder pain may provide insight into the mechanisms underlying shoulder pain. The factors that contribute to enhanced nociceptive efficiency are complex but simply stated include the processes that modulate pain signals at

all levels of the nervous system. Persistent pain relies on an increase in excitatory or a decrease in inhibitory mechanisms (11).

The purpose of this literature review was to investigate the current understanding of the relationship of shoulder pain and disability with measures potentially indicative of neurophysiological changes in the central processing of nociceptive information, both at a local and widespread level, with a focus on shoulder pain in the context of RC disease. Measures potentially indicative of altered pain processing due to underlying neurophysiological changes are presented and their possible associations with outcomes of pain and disability before and after shoulder surgery for RC disease are evaluated, as a justification and purpose for this study. Medline (Pub med)/ EMBASE/Ovid, Web of Knowledge, Science Direct, CINAHL and Cochrane electronic data bases were searched. The following search terms were used: RC disease, shoulder pain, quantitative sensory testing, central sensitisation, RC surgery, tactile acuity, body perception disturbances, body schema, motor imagery, laterality and cortical reorganisation. Reference lists of key articles were also searched for relevant literature. Articles that combined shoulder and neck pain were not considered, as well as publications not in English.

Epidemiology

Prevalence

Shoulder pain is the third most common musculoskeletal complaint globally, following back and knee pain (12). Up to 67% of the population will experience an episode of shoulder pain in their lifetime (13). Worldwide point prevalence estimates vary greatly from 2% to 26% (3, 13). Even within the UK, these rates vary in the literature from 7% to 26% (13, 14). One month prevalence estimates have similar variability with reports ranging between 19% and 48% (13, 15). Studies of one year prevalence are mostly focussed on the Swedish population, and estimates vary between 5% and 35% (13). Higher prevalence estimates are reported within studies with less specific diagnostic criteria and larger encompassing body areas (16). Incidence rates specifically for shoulder pain over a 12 month period have been reported to be 3% (17).

The reason prevalence estimates vary so greatly across the literature may be attributed to differences in populations surveyed and differences in case definitions (16). Even when similar case definitions are used, differentiation between diagnostic categories within

shoulder pain is complicated by the poor reliability of diagnostic criteria (18). For example, when practitioners were asked to differentiate amongst six diagnostic categories, the level of disagreement was 37% in a general practice setting and 55% in an orthopaedic setting (18). For this reason, rather than defining shoulder pain further by diagnostic labels, annual incidence rates are often further defined by demographics such as age and gender. Age-specific incidence rates also vary between 0.9 to 2.5% per age bracket, peaking at middle age (13, 19). Around 1% of the population will consult a general practitioner with their shoulder pain annually (19), and 50% of these will consult more than once in the same year (20). This data highlights the fact that shoulder pain is common, peaks at middle age, contributes to health care utilisation, and in 50% of cases will require follow up consultation.

It is estimated that the presence of RC related pathology (a continuum from impingement syndrome to partial and full thickness tears RC tears) accounts for between 65 and 85% of patients presenting with shoulder pain. In a study set in general practice in the United Kingdom, with a mean age of patients of 57 years 85% were considered to be related to RC or subacromial problems based on accepted standard clinical assessments (21). Vecchio et al (1995) identified 65% of all shoulder presentations presenting to a general practice within a rheumatology clinic in the United Kingdom as RC related by patient history and clinical assessment, but with no clearly defined operational definitions. In comparison, in a study also carried out in the United Kingdom that focused on the aging population over 70 years of age, 70% were considered to have a RC tendinopathy using specific physical tests (14).

In Australia, the Bettering the Evaluation and Care of Health (BEACH) program, which is a national study of general practice activity, investigated the incidence of chronic musculoskeletal presentations within primary care. All chronic musculoskeletal presentations made up 7.3% of GP encounters, and of these shoulder symptoms (6.5%) were the third most common after back and knee complaints (12).

Burden of shoulder pain

Shoulder pain poses a significant financial burden to the health system. Considering that musculoskeletal presentations account for 7.3% of health care costs within general practice in Australia (12), and shoulder pain is the third most common musculoskeletal presentation to general practice in Australia , shoulder pain imposes considerable economic consequences (22). An Australian study of a random sample from the general population (23) found 18% of participants reporting shoulder pain or stiffness in the last week also reported significantly

lower scores on all eight domains of the SF-36 for health status and were significantly more likely to have depressive symptoms compared to those without shoulder pain. Those participants with shoulder pain also had associated high rates of medication prescription, imaging and subsequently almost 5% required specialist opinions (12).

A Swedish study conducted over a six month period estimated the mean healthcare cost per patient presenting with shoulder pain to be €326 over that period and when taking into consideration costs associated with sick leave, this value rose to close to 13 times that cost per patient per annum, indicating the substantial financial costs associated with reduced work productivity (24). The estimated societal cost of a patient awaiting shoulder surgery in Australia has been estimated to be between $16 and $57 a day, depending on their employment status (25). Considering that the rates of surgery for arthroscopic subacromial decompressions in Western Australia have increased by over 100% between 2001-2013 (26), identification of factors associated with outcomes after surgery may alleviate some of this financial burden by identifying those patients who are unlikely to benefit from surgery and can be offered less expensive, non-surgical management.

Classification of shoulder pain

Classification of shoulder pain is mostly based upon a patho-anatomical taxonomy, including labels such as bursitis, capsulitis and RC disease and tears. Identification of sub-groups within shoulder pain that consider other pain mechanisms may allow for clearer diagnosis and prognosis of outcomes of non-surgical and surgical treatment options. Unfortunately the classifications currently available present diagnostic categories that can present concurrently and employ measures with poor reliability and validity (27-29). As further outlined in subsequent sections, patients presenting with the same patho-anatomy as identified by imaging, can present with different levels of pain, disability and distress (30). Furthermore so called ‘patho-anatomy ‘ is often asymptomatic, suggesting that other factors are important for a person’s pain and disability (31). The lack of consensus on classification systems, diagnostic labels and physical diagnostic tests, and the poor correlation between radiological findings and pain levels, highlights that features beyond only patho-anatomical findings may be contributing to the pain experience. For example, levels of pain sensitivity and alterations in nociceptive processing, in addition to RC related structural changes, may be features contributing to the uniqueness of each shoulder pain presentation (32).

Factors associated with prevalence or incidence of shoulder pain

While patho-anatomical features have been broadly investigated for associations with prevalence or incidence of shoulder pain, such features do not correlate well with levels of shoulder pain and disability (33). Therefore, other factors associated with levels of shoulder pain and disability have also been considered. However, the lack of clinically meaningful diagnostic criteria for people experiencing shoulder pain makes interpretation of the literature assessing risk factors for shoulder pain difficult. Of demographic factors, female gender (23, 34), middle age (23, 35, 36), currently smoking (9, 23), obesity (23, 36, 37), and the presence of other musculoskeletal pain (34, 38) have all been identified as factors associated with the presence or development of shoulder pain. A combination of female gender and middle age is strongly associated with a higher prevalence of shoulder pain (4). Gender differences have been widely explored in relation to increased pain sensitivity and may explain why the female population have a greater risk of developing symptoms in the shoulder (39). Other factors that have been considered but have limited evidence for association with shoulder prevalence or incidence include poorer self-reported health, diabetes and lower levels of general exercise or physical activity levels (23, 37, 40, 41).

Psychosocial factors including emotional distress, depression and somatisation have been associated with shoulder pain in cross-sectional studies (21, 42) but prospective studies investigating psychosocial factors as a risk for developing shoulder pain are limited. Psychological distress and psychosomatic symptoms including faintness, nausea and tingling were identified to be significant risk factors for the onset of shoulder pain in one prospective study of 628 drivers (40). Psychological distress almost doubled the chance of reporting subsequent shoulder pain in a 12 month prospective study of newly employed workers from various diverse occupational groups (43). Yet in a community based study, depression was not predictive of development of shoulder pain over a four year time period but was found to be predictive of recurrent episodes (44). In a review of cross-sectional studies of upper extremity symptoms including shoulder pain, stress outside the work place was identified to have a significant association with upper extremity symptoms (45). Psychological distress has been previously found to be predictive of new episodes of other musculoskeletal complaints including neck and back pain (46-48).

Occupational psychosocial factors have been quite extensively explored and identified as significant risk factors for the development of shoulder pain. High job demands encompassing increased job pressure and task difficulty (37, 38, 43, 49), lower job control or

autonomy (43, 49), job strain, which is considered the interaction between job control and demand (38, 49-51), perceived lack of social support of co-workers and supervisors (43, 49, 51), lower job satisfaction (43, 49, 50), not learning new things (43), and monotonous work (43) have all been identified as significant risk factors in the occupational setting. In a review of cross-sectional studies exploring the risk factors associated with shoulder pain, again the relationship between job control and demands was highlighted as being significant as well as job dissatisfaction (52, 53). From the work psychosocial perspective specific to people with shoulder pain diagnosed as RC disease, higher autonomy and job security (36), as well as job title (54) were associated with lower risk of RC associated shoulder pain.

Workplace physical demands have also been implicated quite widely in the development and prevalence of shoulder pain. A recent review of 27 cross-sectional and longitudinal studies, including a meta-analysis, examined occupational mechanical risk factors and identified that increased physical load and repetitive overhead activities significantly increased the incidence of shoulder pain. There was low quality evidence to support that hand-arm force exertion and being exposed to vibration increased the incidence of shoulder pain (55). A previous systematic review of longitudinal studies identified strong evidence for an association with various aspects of manual handling including increased requirements of lifting, pushing, holding and carrying, increased exposure to vibration, occupations that required trunk flexion and rotation and overhead work, and development of shoulder pain (56). Individual prospective studies have presented some other risk factors within the workplace including repetitive tasks (34, 37, 38) and working in neck flexion (38). Two systematic reviews of cross-sectional studies identified similar risk factors associated with the presence of shoulder pain including vibration, repetitive tasks, prolonged and awkward positions, shoulder flexion greater than 45 degrees and overhead work, lifting more than 20kgs repetitively and force requirements of the upper limb greater than 10% of maximal voluntary contraction (52, 53). Men were more at risk when exposed to repetitive movements and vibration at baseline, compared to women, where lifting heavy loads and adopting awkward positions or postures have been found to be greater risk factors. Older age and increased body mass index have been found to be significant confounders of these mechanical risk factors (34).

When narrowing down these work-related risk factors specifically to shoulder pain diagnosed as RC disease, a higher body mass index and being over 40 years of age were associated with the diagnosis of RC disease. There was however no gender specific significance in this study. RC disease was diagnosed in a group of 733 workers if they

presented with shoulder pain in the last 12 months and had a positive reproduction of that pain on resisted shoulder abduction, internal or external rotation (36). Physically: posture, repetitive duties, arm-hand vibration (54), increased time in upper arm flexion of greater than 45 degrees and increased grip time and force in this position were identified as significant risk factors specific to pain associated with RC disease (36).

Occupation specific risk factors have also been reported. Nurses were found to have an increased risk of developing shoulder pain over a two year time period if they had: a previous episode of shoulder or neck pain, a role included primarily handling tasks (reaching, pulling and pushing) or low mood or stress at baseline (50). Professional drivers for various industries and public services were found to have an increased risk for shoulder pain over three years in a prospective study if exposed to whole body vibration, lifting loads in awkward postures for more than 45 minutes a day and above shoulder height work for more than one hour a day. Driving included earth-moving machines, forklift trucks, buses and refuse trucks. (40). Cashier or check-out workers have a 20% greater prevalence of shoulder pain than the general population (35), with the repetitive nature being considered the primary cause by the authors. Similarly, in nursing home and elderly-care workers, repetitive tasks were the only significant work-related factor identified to significantly increase the risk for the development of shoulder pain over a 12 month time period (57).

Prognosis of shoulder pain

Six studies were identified that reported on prognosis of shoulder pain in terms of symptom recovery, however comparison between them is limited due to the heterogeneity of populations studied and the outcomes used. A study following a new episode of shoulder pain in 349 patients presenting to their GP found only 23% and 49% of the participants to report a full recovery at one and 12 month follow-up respectively (58). These values are similar to those from another study of 166 patients with a new episode of shoulder pain, which reported 21% and 59% of participants to be symptom free at six and 18 month follow up respectively (59). These findings suggest that close to half of those who present with an acute episode of shoulder pain will still have persistent symptoms up to 18 months later. Winters et al (1999)(60), followed people with acute, sub-acute and chronic shoulder pain presenting to general practice. At a six month follow up, 49% had full recovery, and this increased to 59% by 12 to 18 months. These values are similar to those from the previous two studies in which only acute onset of shoulder pain was followed. In two studies investigating a mostly chronic cohort (61, 62), 36% reported full recovery at two years

follow up and at three years this rate increased to 46%. These studies indicate that a large proportion of people who develop shoulder pain will experience persistent symptoms.

Prognostic factors for shoulder pain persistence

Studies conducted in general practice, orthopaedic or physiotherapy settings have examined factors potentially prognostic of shoulder pain persistence in patients undergoing a range of non-surgical interventions. Preceding trauma and participants impression of overuse or strain have been found to be associated with favourable outcomes (58). In contrast, severe pain on initial presentation, a previous episode of shoulder pain, restricted passive abduction range, diabetes, current smoking, concomitant neck pain or other musculoskeletal pain presentations, middle age, pain on the dominant side, taking sick leave, long duration of symptoms, psychological distress, perceived lack of social support and a requirement to overuse the shoulder in daily activities were all identified as being prognostic of poor outcomes in single prospective studies (3, 9, 58, 59, 63, 64). The multidimensional nature of this range of factors suggests that factors other than patho-anatomical findings may be prognostic of outcome.

Despite a number of prognostic factors being identified individually including RC related pathology, a systematic review of prognostic factors could only find high pain levels and middle age (45-54 years) being significantly and consistently associated with poorer outcomes (2). There was moderate evidence for an association between longer duration of symptoms and higher level of disability at baseline and poorer outcomes. The authors concluded that a comparative review and consensus was difficult due to the heterogeneity in samples, design, evaluated prognostic factors and outcomes. Kuijpers et al (2004) followed up on this review with a longitudinal study, investigating prognostic factors within a cohort of 587 patients. The study concluded that longer duration of symptoms, gradual onset and high pain levels at baseline all to be consistently associated with a poor outcome (65). Furthermore this same cohort was used to identify if the prognostic factors for acute and chronic presentations differ and which has the better prognosis. Pain and disability levels at baseline were predictive of six month outcome, whereas psychosocial factors, most significantly catastrophizing and somatisation had a significant association with poor prognosis of chronic shoulder presentations (66). The most recent systematic review of prognostic factors associated with shoulder pain outcomes, corroborates the previous evidence for severe pain levels, longer duration of symptoms and adds decreased functional limitations, poor coping strategies and an accident being the cause of symptoms,

bringing into question the likely detrimental influence of compensation and liability on reported pain and disability (67).

The majority of the prognostic data comes from northern hemisphere countries. The most recently published Australasian study of 161 patients (68) identified male gender, smaller waist circumference, pain referred below the elbow, pain eased with rest, sleep disturbances, less pain with physical examination and higher physical function as measured by the SF-8 were all associated with less reported pain and disability at 12 months. Central obesity, as measured by waist circumference, has been previously associated with shoulder pain and RC disease (69). The aforementioned study by Laslett et al (2015), showed psychological factors to only be weakly associated to poor outcomes and a history of previous shoulder complaints in the opposite shoulder was the only clear predictor of poor outcome at 12 months.

Although psychosocial factors have been identified as prognostic factors for many other musculoskeletal presentations, there is less evidence for the role of psychological factors as prognostic for shoulder pain and pain-related disability outcomes (70-73). When comparing the role of psychological factors in shoulder and low back pain, psychological factors are more closely associated with poorer outcomes of persistent pain and disability in low back pain than in shoulder pain (74). Studies identifying fear avoidance behaviours offer some contradictory predictive evidence. In one study of people with shoulder pain, lower levels of fear avoidance were found to be predictive of poorer outcomes, including less change in pain, reported recovery and disability between baseline and 12 months following onset of symptoms (63). Other studies have found the opposite whereby higher levels of fear-avoidance have been associated with greater persistence of symptoms at 6 and 12 months (75, 76). The latter studies included neck and shoulder patients in their cohort which may explain some of the variability in findings. In studies of patients undergoing physiotherapy for shoulder pain, one study found expectations of a full recovery and pain self-efficacy were associated with less pain and disability at six months. On the other hand, two studies reported higher levels of distress, fear-avoidance and catastrophizing were associated with persistence of symptoms at six months (75, 77). There is growing evidence linking psychological factors including anxiety and depression to shoulder pain in general (62, 78, 79) and more specifically to RC disease (21, 42, 80-82).

One study took into consideration that prognosis may be partly associated with the stage of presentation at baseline. Participants were stratified into acute, sub-acute and chronic

groups. At six month follow up the acute group reported a 70% reduction in mean pain scores, the sub-acute, 54% and the chronic group 44 % (66). Levels of disability showed a similar trend, with the acute group reporting a 69% reduction in disability at 6 months. This suggests that although duration of symptoms has some association with length of recovery, there remains a significant number of patients who continue to have persistent symptoms independent to their stage of presentation. Identifying prognostic factors other than duration of symptoms would be helpful.

Management of RC related shoulder pain

Non-surgical management

Non-surgical management options for shoulder pain associated with RC disease include education, rest, physiotherapy, pharmacology, injection therapy, acupuncture, various electrotherapy modalities and exercise rehabilitation (83-86). Overall non-surgical management has been shown to be effective in a number of systematic reviews (87-89), with some individual studies identifying between 62-86% of patients with shoulder pain associated with RC disease reporting good outcomes (90, 91). Despite these reports, around 25-45% of patients experiencing shoulder pain will continue on to have surgical management, following failed non-surgical approaches (91-94).

The basis for surgery for shoulder pain relies on the premise that shoulder pain is a direct consequence of structural damage. Surgery for RC disease is focussed on repairing the integrity of the RC and preventing further progression of current incomplete tears. Yet, in a group of patients with isolated symptomatic full thickness supraspinatus tears, follow-up Magnetic Resonance Imaging (MRI) 42 months after initial diagnosis, showed no increase in the average tear size, and patients who declined surgery still reported high levels of satisfaction (95). This conflicts with other studies identified in a systematic review which have shown non-surgical management of full thickness, incomplete tears was associated with up to a 52% progression of tear in between 24-50% of patients in under 30 months when choosing to manage non-surgically (92). Pain at the time of the follow-up imaging was correlated to a clinically significant increase in tear size (96).

Current guidelines and recommendation offered by American academy of Orthopaedic Surgeons(97) and the University of New South Wales, Australia (98), suggest a period of non-surgical management which could include pain management, return-to-work

programmes, exercise therapy, manual therapy, acupuncture, electro-physical agents and corticosteroid injections. The evidence for many of these interventions individually is inconclusive and many are often used in conjunction with each other. The guidelines suggest a surgical consult only at the 12 week mark for symptomatic small to medium full thickness RC tears and earlier referral for larger full thickness tears, younger patients, patients presenting with significant pain and disability and where imaging and history indicates an acute tear with no evidence of chronicity.

Surgical management

Surgical interventions for shoulder pain that is presumed to be associated with RC disease include; acromioplasty, bursectomy, subacromial decompression, debridement and RC repair. Acromioplasty involves the shaving away of bone and removal of bony spurs on the underside of the acromion. Bursectomy is the removal of the subacromial bursa. Subacromial decompression may include a subacromial bursectomy and removal of coracoacromial ligament, in addition to an acromioplasty. This surgery aims to increase the subacromial space. Debridement surgery aims to remove fragments of tendon and bursa from the subacromial space. These surgical procedures may include an open, mini open or an arthroscopic approach for any of the interventions mentioned. Even with the lack of evidence to substantiate the benefit of surgical intervention over non-surgical management, rates of surgery have increased substantially. According to the Western Australian Health Department data, the number of patients undergoing surgery for RC disease has almost tripled between 2001 and 2011 (71 to 200 per 100,000)(26). Similarly the rates of RC repairs increased 141% from 1996 to 2006 in The United States. Arthroscopic repairs increased by 600% compared to a 34% increase in open approaches, illustrating a massive shift to an arthroscopic approach (99). This similar trend was also reported in Denmark and England across similar time periods (100-102). Previously there was a stronger trend towards males undergoing surgery (70%) but by 2006 the ratios were almost equal (99).

It is estimated that 250 000 RC repairs are undertaken in the United States each year costing between US$10, 000 to US$17,000 per procedure. In Western Australia in 2013 it was estimated that over AU$40 million was spent on arthroscopic RC surgery (26). Another study argued that the costs associated with surgery are worthwhile and reported that societal savings from RC repair versus non-surgical management to be around US$78 000 for patients in their thirties compared to around US$12,000 for patients in their 70's taking into consideration the level of disability associated with shoulder pain (99, 103). Taking

both these reports into consideration, finding pre-surgical factors associated with good outcomes for pain and disability would save non-surgical costs for ongoing shoulder pain and make the costs associated with surgery worthwhile.

Surgical techniques have been extensively investigated but are not the focus of this review. There is no indication from the literature that an acromioplasty offers a superior form of management to non-surgical approaches for an intact RC (104). Many RC repairs are combined with an acromioplasty, but there is not enough evidence to recommend this as normal practice (86, 105, 106). There is also inconclusive evidence for the superiority of any one particular RC repair procedure: arthroscopic, mini-open or open repair (86, 104, 106).

RC repairs may be offered to patients with partial, full thickness or massive RC tears. RC tears are considered to be massive when they are greater than 5mm or retracted back to the glenoid margin. Data from 16 studies of either arthroscopically or open RC repairs for partial thickness tears illustrate an improvement in various post-operative outcomes (pain, range of movement, function) ranging between 28.7% - 93% (107). In a study of 254 RC repairs undertaken for full thickness tears, there was a significant improvement in the American Shoulder and Elbow Score and, on average, high levels (8/10) of satisfaction (108). Although, a systematic review reported that the re-tear rates following surgery for RC repair can be up to 79% (109). The same review reported that patients experienced significant improvements in disability and pain following surgery

Despite the high levels of satisfaction and improvements in pain and disability, the re-tear rates following RC repairs are significant. A recent systematic review reported that re-tears are associated with fatty infiltrates into the tendon, larger tear size initially, advanced age and the usage of double-row repairs (110). In this review of 108 studies, the mean re-tear rate was 27% at a mean of 24 months following surgery, although some studies independent to this review have reported close to 80% re-tear rates (91, 109). The average clinical improvement in self-reported pain and disability was found to be 72% of the maximum improvement possible based on twelve different outcome scores, highlighting the fact that patient reported outcomes are good following RC repair whether the repair restored the cuff integrity or not (110).

Both surgical and non-surgical interventions show significant improvements in disability and reduction in pain, but evidence of comparative effectiveness is limited. Two systematic reviews published in 2008/9 regarding the management of subacromial impingement concluded that there was no statistical difference between non-surgical interventions,

which included physiotherapy, versus open or arthroscopic decompression for improvement of shoulder disability and pain (83, 111). A systematic review published in 2010 compared non-surgical treatment, which included physiotherapy and a number of adjuncts, with either open or mini-open RCR (105). Only one study from this review had reported a significant difference in favour of surgery for reducing pain and disability, and overall the authors of the review concluded that both interventions were effective in reducing pain and disability and the evidence too limited to make recommendations in preference of either one.

The most recent meta-analysis (112) could only identify 3 RCTs published since 2014 that matched their criteria, to assess the effectiveness of surgical RC repair compared to non-surgical approaches in reducing pain and improving range of movement and disability and quality of life. The follow-up period varied greatly between 3 months to 5 years and included 123 people treated with surgery and 129 people managed conservatively. The change in range of motion, strength, and disability was favourable towards surgery but not clinically or statistically significant. The same was seen for pain, where the change favoured surgery and although statistically significant, the 0.93 change in the visual analogue scale was not considered clinically significant (112).

In summary, guidelines for management of shoulder pain associated with RC disease recommend surgical consultation if non-surgical management is unsuccessful or if the patient presents with a large symptomatic full thickness tear considered to be the main driver of their shoulder pain (97). The rates of surgery are growing exponentially and with it the associated financial burden. There remains a lack of convincing evidence, despite increases in rates of surgery, that disability and pain outcomes are better than those for non-surgical approaches, and the rates of re-tear remain large. A clearer understanding of who might benefit most from surgical management over non-surgical management would allow selective targeting of surgery to only those likely to benefit and thus reduce the rising cost burden of surgery.

Factors associated with outcomes after RC surgery

The literature around factors associated with outcomes after RC surgery is growing. Already highlighted is the poor association between structural changes and reported pain and disability related to RC disease. This mismatch continues to be a consideration when exploring post-surgical outcomes, and has been recognised by the most recent systematic

reviews, where separate factors associated with structural (RC integrity) versus pain and disability outcomes following RC surgery have been reported on. A number of factors have been identified in individual studies to be associated with a less favourable outcome after RC surgery. The most recent systematic review of 64 studies included close to 60 000 shoulders, and could still not present conclusive high level recommendations for factors associated with superior or inferior structural, disability or self-reported outcomes following RC surgery (113). Factors associated with increased re-tear risk and poorer tendon healing after RC surgery included older age, current smoking, larger tear size, greater number of tendon involvement, fatty infiltration, and procedures that included surgery involving the acromioclavicular joint and long head of biceps tendons. Factors associated with patient reported pain and disability after RC surgery were older age, female gender, current smoking, a workers compensation claim, higher BMI, structural changes including fatty infiltration, multiple tendon pathology and larger tear size. However, the overall quality of evidence for these aforementioned factors was low to very low. Previous systematic reviews that have not separated functional and structural outcomes as clearly have identified being over the age of 55, female gender, having an active workers' compensation claim, lower bone mineral density, diabetes, being less active, limited shoulder range of movement, obesity, currently smoking and concomitant neck pain to be associated with poorer outcome following RC surgery (86, 114). Specific to the shoulder structure prior to surgery, presenting with fatty infiltration of the RC tendon, having multiple tendon involvement, concomitant biceps or acromioclavicular joint surgery and larger tear size and degree of retraction all indicate a likely poorer outcomes including pain, function and re-tear rates (86, 104, 106, 114). Convincing evidence from all the aforementioned systematic reviews for factors that are associated with disability and pain following RC surgery is limited. Even when separating factors associated with re-tear rates from those associated with pain and disability outcomes, consensus is elusive.

Not all patients benefit from surgical procedures. For example, in a review of 149 RC surgery candidates only 86 (58%) reported being positive respondents at 6 months post-surgery (115). Shoulder surgery is largely directed at shoulder pathoanatomy, considered to be the trigger of nociceptive activation. There is evidence that factors other than tear integrity are associated with outcome after surgery. Re-tear rates following RC repair surgeries are high, but despite this patients often report good outcomes (110, 116). Factors beyond local tissue pathology may be contributing to pain and disability in patients with shoulder pain associated with RC disease. One explanation is that there may be different pain mechanisms

at play in patients with shoulder pain, rendering surgery less effective in those with altered perception of pain due to CNS changes, compared to those with simple local nociceptive pain and local tissue injury (117). Subsequent chapters will expand on these concepts and offer further insight into the effects of CNS processes.

Potential pain mechanisms in RC related shoulder pain

Local peripheral tissue pathology

Nociceptors are sensory receptors that respond to noxious stimuli, including thermal, chemical and mechanical changes within peripheral tissue. Nociceptors play an important role in the perception of pain from the body. Studies have identified that the tendons, joint capsule and bursae in the shoulder are richly innervated with nociceptors (117, 118). RC disease is one accepted term used to encompass pain generated by noxious input from a number of these structures, independently or in combination. In the case of local tissue injury, resultant inflammatory processes trigger the release of chemical mediators and responses that ultimately lead to the activation of these nociceptors, directly or indirectly by lowering the normal threshold at which a response would be triggered. This process is known as peripheral sensitisation and allows for local hyperalgaesia (increased pain sensitivity) and allodynia (pain due to a stimulus which does not normally provoke pain) following tissue injury (119). Peripheral sensitisation is a normal part of the body's response to injury and promotes healing and helps protect the injured part from further damage. This model of peripheral pain processing does not fully explain the mismatch between pathology and pain perception at the shoulder as it fails to explain the different reported levels of pain in patients with the same injury, why some patients present with hypersensitivity on their unaffected side or how some RC tears present asymptomatically (32).

RC tendons will respond to injury with an inflammatory phase which includes nerve in-growth and significant upregulation of the glutaminergic system (120), but the extent of glutaminergic expression does not appear to be correlated to the extent of injury or tear size (121). Glutamate is a primary neurotransmitter and potentially lowers the peripheral nerve threshold, instrumental in peripheral sensitisation (122). Increased glutaminergic expression in the dorsal horn of the spinal cord may contribute to central sensitisation. An increase in substance P has also been found in tendinopathy in general. Higher levels of substance P in the subacromial bursa have been correlated with higher shoulder pain scores and resting shoulder pain (123). In a review of painful tendinopathy, it was identified

that an upregulation of the glutamenergic system and to a lesser degree, an increase in substance P is prevalent in painful tendinopathies (120, 124).

In addition to the RC soft tissue structures, the role of the peripheral nerves in shoulder pain generation has been explored. The shoulder joint and surrounding soft tissues are innervated by the suprascapular, axillary and lateral pectoral (C5/6) nerves (117). The suprascapular nerve in particular has been implicated in shoulder pain associated with RC disease due to its supply to the supraspinatus and infraspinatus muscles. The incidence of suprascapular nerve injury identified by electromyography and nerve conduction studies in RC tears has been estimated to be up to 38% (125, 126). This nerve involvement may contribute to central sensitisation via neuropathic pain mechanisms, which is ongoing pain triggered by nerve injury (127). Conversely, suprascapular nerve involvement may also be a secondary consequence of RC disease, whereby RC tears lead to changes in function of the suprascapular nerve (128). It has been suggested that RC surgery may restore the normal course of this nerve, reducing nerve traction (125). Support for this hypothesis comes from the evidence that following RC surgery, nerve conduction studies identified partial or full recovery of the suprascapular nerve function, and that this in turn was correlated with an improvement in function and pain (125). Nerve block injections aimed at blocking nociceptive signals from the suprascapular nerve have varied outcomes (129, 130). The available evidence is limited but a meta-analysis comparing the effectiveness of suprascapular nerve blocks in 11 randomised controlled studies including 591 participants found that overall nerve blocks can be more effective in achieving pain relief than other non-surgical means of management including physiotherapy, for chronic shoulder disorders over a 12 week follow up period (131).

Diagnostic physical tests aim to reproduce symptoms generated by peripheral structures, thereby confirming a specific structural diagnosis. These tests have been shown to have poor reliability (28, 132), leading to poor inter-observer agreement of specific diagnostic classifications and labels (18). A Cochrane review of validity of these physical tests identified 170 different test combinations. Individual tests showed variable levels of sensitivity and specificity for the diagnosis of shoulder impingement and lesions of bursa, tendon and glenoid labrum. The authors concluded that there was insufficient evidence to select specific tests to be valid (combination of sensitivity and reliability) for identifying specific diagnosis such as impingement (10).

Associations between shoulder patho-anatomy and shoulder symptoms

The structural-pathology model makes better sense in acute injury where the pathology matches the extent of impairment. This model becomes more tenuous in the chronic phase and in non-traumatic presentations where tissue integrity is restored or normal, yet reported pain persists. Pain and other impairments no longer match the extent or even presence of tissue injury in chronic phases, and this is reflected in literature reporting the lack of correlation between radiological findings of pathology and symptoms.

The gold-standard tests for shoulder pathology diagnosis include MRI scan, ultrasound scan, MR arthrogram and arthroscopy (98). However, there is a very poor correlation between imaging findings and symptoms within the shoulder complex. Within a group of 208 patients reporting shoulder pain, the highest prevalence of findings on ultrasound and MR arthrogram were RC pathology (50% and 65% respectively) , subacromial bursitis (31% and 76%) and 59% for ACJ pathology with MR arthrogram alone. Despite the identification of specific pathology on imaging, less than 50% of patients had a positive anaesthetic response with injections into the proposed painful structure (30). This suggests that the pain is not being generated by these peripheral inputs.

Ultrasound studies have identified around 21% prevalence of full thickness tears in the general population, and of these up to 65% can be asymptomatic (31, 133). In a group of people who presented with unilateral shoulder pain and confirmed RC tears, 54% of them presented with RC tears on the asymptomatic side, indicating that bilateral tears are common but often not associated with pain (134). RC tears are considered part of normal age related changes, with the rate of RC tears increasing with age (31, 133-135). One in five people over the age of 50 will present with a RC tear, of which half will be asymptomatic, and one in three people over the age of 80 will present with a RC tear, of which two thirds will be asymptomatic (31, 136). These rates indicate that although the risk of developing a RC tear increases with age, so does the probability that it will be asymptomatic (31).

MRI studies have reported prevalence of asymptomatic RC tears ranging between 0% (mostly the non-dominant shoulder) to 40% on the dominant side (137, 138). As with US imaging findings discussed above, the prevalence of tears identified on MRI imaging increased with age. In a study of people with asymptomatic shoulders, 28% between the ages of 40-60 and 54% over the age of 60 were identified to have either a partial or full

thickness RC tear (135). These studies provide further support that identification of pathology alone is not sufficient to explain the pain experience when assessing RC disease.

A further consideration is the link between the success or otherwise of RC surgical repair and symptomatology following surgery. RC tear repairs are considered successful and complete when there is a continuous surface from muscle belly to insertion on the greater tuberosity of the humerus. RC repair rates are escalating, but the rate of unsuccessful repairs and substantial re-tear rates do not substantiate this exponential rise. An early review comparing clinical outcome of repaired versus non healed or re-ruptured repairs reported that around half the studies showed no statistical differences in most patient outcomes including pain, although there was some weak evidence that a successful repair led to improved strength and function (139). A more recent systematic review of surgical outcomes of RC surgery (110) estimated that in 27% of cases surgery failed to restore structural integrity of the cuff. The majority of the 77 studies included in this review reported that there was no significant difference in clinical outcome if the repair was successful compared to not, and that both intact and re-ruptured cuff repairs demonstrated improvements in pain and disability.

These findings illustrate the possibly unnecessary financial and personal burden of RC surgery considering the high percentage of surgery which fails to restore structural integrity of the RC along with the fact that despite this, many patients report improvement. This incongruence between pathology and symptoms further highlights the need to identify factors that are moderating the pain experience beyond any structural pathology that is identified.

Central pain mechanisms

Mechanisms underlying chronic pain can differ from those mechanisms driving acute trauma related painful responses. Acute pain in response to tissue injury is associated with activation of peripheral sensory receptors, whereas chronic pain may be maintained independent of peripheral input, by spinal and CNS influences. Peripheral and central sensitisation leads to a resultant state of hypersensitivity which offers protection against injury and promotes healing. However, this state does become unhelpful in time and may drive the persistence of pain and pain-related disability. In the presence of acute tissue injury, the neurophysiological changes are considered adaptive and beneficial in the healing process. The changes that occur in chronic presentations are considered mal-adaptive and instrumental in the maintenance of chronic pain. These structural and functional changes

include amplification of sensory input (11), changes in descending modulation, cortical changes in the sensory and motor cortices (140), dorsal horn changes in the spinal cord and changes in self-perception (141, 142) amongst others.

Altered nociceptive processing mechanisms

Central pain mechanisms involve processing of pain within the CNS. Many studies have mapped areas of the brain related to acute painful stimuli, and collectively labelled these the pain matrix (143). In contrast to acute pain, the following differences in CNS activation have been found in chronic conditions: increased frontal activity (indicating additional cognitive and emotional processing), decreased attention networks compared to acute pain where the protective response is required, and a difference in motivational networks (144). This lends further evidence to the notion that assessing central processing factors in addition to peripheral measures could offer some further insight into the mechanisms involved in chronic shoulder pain.

Central sensitization is an increase in the excitability of neurons within the CNS, so that normal inputs begin to produce abnormal responses and a state of hypersensitivity (11). Clinically this manifests as widespread hyperalgaesia and allodynia and is a key feature in persistent pain. In addition to this state of heightened sensitivity, there is a dampening of inhibition of neural networks resulting in even greater nociceptive sensitivity. These central changes occur in the spinal cord as well as the brain and are moderated by various descending inhibitory and facilitatory pathways (119). These descending modulatory control centres are found within the cortex, subcortex and brainstem, and project to the dorsal horn in the spinal cord (145). Evidence of central sensitisation including increased activation of the brain's pain processing centres as measured by functional neuroimaging and widespread hypersensitivity in the absence of tissue abnormality have been identified in a number of chronic pain conditions including whiplash (146, 147), RC disease (148), hand OA (149), knee OA (150), fibromyalgia(151) and chronic low back pain (152).

Evidence that central sensitisation is an important factor for consideration with regard to chronic shoulder pain is increasing. However, it is important to acknowledge that not all patients presenting with unilateral RC disease display features of central sensitisation (153, 154). Evidence of central sensitisation has been found in a subgroup of patients with unilateral RC disease in a number of studies (148, 155-157). These patients with central sensitisation represent between 65- 90% of the RC disease cohorts recruited (158).

Hyperalgaesia, an increased sensitivity to a noxious stimulus, not only locally but over the contra-lateral shoulder and remote sites (secondary hyperalgesia) was considered evidence of these central mechanisms.

Previously the majority of the research into tendon pain including the RC has been targeted at a pathology level, yet there is an increasing acknowledgement of the poor correlation between pathological changes seen within the tendon structure and pain (159). In a review of the available evidence to implicate central mechanisms as possible drivers of persistent tendon pain, hyperalgaesia to mechanical stimuli at a distal site was found in addition to local hyperalgaesia at the shoulder (RC tendons) and epicondyle (common wrist extensor tendons), indicating the likelihood of both central and peripheral pain mechanisms in patients with a diagnosis of tendon pathology at the elbow and shoulder (160). While it is understood that local tendon pathology may contribute to peripheral pain signalling, in the absence of peripheral or remote tissue abnormalities hypersensitivity to mechanical or thermal sensitivity implicates augmented pain processing at some point of the pain pathway.

Many factors well beyond the extent of tissue injury have been identified to moderate pain perception. The mesolimbic and pre-frontal brain structures which are responsible for processing fear, emotions, negative conditioning and attention, demonstrate increased activation patterns in chronic pain conditions in comparison to observations in acute pain conditions, and these in turn are correlated to duration of symptoms and chronicity (161). Psychosocial factors including cognitive (attention and pain evaluation), psychological distress (depression, anxiety, fear, anger), unhelpful behavioural responses to pain (fear avoidance, catastrophising and guarding), as well as social and cultural factors, genetics and sleep have all been identified to regulate pain experiences (162-166). These influences are thought to influence the facilitatory and inhibitory controls within the CNS.

Genetics have also been identified to play a role in the prognosis of shoulder pain. Interactions between specific genes involved in poorer endogenous pain modulation and psychological factors have been investigated for their predictive utility of pain and disability post-surgery for RC related shoulder pain (165, 167, 168). Six interactions between pain modulatory genes and psychological factors including fear and pain catastrophizing were identified to predict pain and disability after surgery for RC related shoulder pain. Previously psychological influences (including fear avoidance, catastrophising and general psychological stress) have been identified as being associated with poorer outcomes in chronic shoulder pain independently from genetic factors (65, 74).

The poor correlation between shoulder pain and local pathology may implicate the CNS as an important moderator in the development and maintenance of chronic shoulder pain. These central changes, which allow for an alteration in sensory transmission, are thought to also lead to resultant neurophysiological changes in the spinal cord and brain, specifically the cortex. Therefore, assessment of neurophysiological pain processing can be considered important in the consideration of mechanism for chronic shoulder pain.

Clinical assessment of altered nociceptive processing

Quantitative sensory testing (QST) is defined as an investigation of the functional state of the somatosensory system by means of application of calibrated stimuli and assessment of subjective perceptual thresholds (169). QST is a means of assessment of the underlying mechanisms and pathways that may contribute to the development and maintenance of persistent pain. This method of sensory testing evaluates the integrity of neural functioning from the peripheral afferent via spinal tracts to the brain and gives a quantifiable measure of sensitivity to mechanical, electrical and thermal stimuli. QST offers a clinical means of assessing the neuro-physical mechanisms that are found in sensory augmentation as well as assessing the CNS capacity to facilitate or inhibit this sensory input (170).

Localised increased pain sensitivity is considered an indication of peripheral sensitisation, whereas increased nociceptive sensitivity on the contra-lateral unaffected side or at a remote region is considered a combination of enhanced facilitation and altered descending inhibitory controls (11). An association between an increase in pain sensitivity and altered brain function have been identified using Functional Magnetic Resonance Imaging (fMRI) providing further evidence of altered brain activation in response to an increase in pain sensitivity to QST stimuli (145). In addition to identifying the presence of pain sensitivity, QST measures have also been used to develop somatosensory profiles (171, 172), assess the descending pain control function of the CNS (170), to explore differences between symptomatic presentations and asymptomatic controls, identify impairments in sensory function, and to predict outcome of certain interventions (170). Many thermal, mechanical, chemical and electrical QST modalities exist whereby detection, thresholds and tolerances can be measured. QST outcomes have been identified to be predictive of outcome in individuals with whiplash (173), epicondylalgia (174), post-thoracotomy (175), knee and hip osteoarthritis (176-178).

The German Research Network on Neuropathic Pain (DFNS) has proposed a standardised protocol for QST testing in humans, yet the majority of the literature presented in this review did not utilise this protocol set or sequence of QST measures (179). The reasoning behind the recommendation for standardised sequencing of testing lies in the fact that different static and dynamic measures of QST measure different neuro-physical mechanisms within CNS and peripheral processing domains and there appears to be a low correlation between these mechanisms (180).Static measures assess nociceptive sensitivity to various stimuli whereas dynamic measures assess the CNS's ability to modulate pain, either facilitatory or inhibitory. It is argued that inclusion of more dynamic methods of QST to assess the inhibitory and facilitatory effects of the CNS processes is more useful (181). Conditioned Pain Modulation (CPM) is used as a means of assessing diffuse noxious inhibitory controls and overall descending inhibition. Temporal Summation (TS) on the other hand assesses the CNS facilitatory pathways and effects. A study conducting cluster analysis of 13 various QST measures independent of confounders was inconclusive in terms of identifying patterns of association between various QST modalities or particular patterns of pain response (182). The challenge with QST measures is that they remain a subjective evaluation and open to moderation by a number of biological and psychological factors. Reference values for all QST measures are consistently dependent on age, gender and test site (183).

1.3.2.1.1 *Pressure Pain Thresholds (PPT)*

PPT is the most commonly used QST measure of static pain threshold, and is a means of assessing sensitivity of the Aδ and C afferents (184). These myelinated and unmyelinated afferents form the pain conducting fibres of nociceptors. A decrease in the mechanical pressure threshold at the site of a pain problem is considered a sign of local sensitivity, which may still be attributed to ongoing inflammation locally and peripheral sensitisation. Sensitisation or lowered thresholds at remote sites are considered a feature of central sensitisation or decreased inhibitory control and under control of the CNS. Lowered thresholds in the absence of tissue injury or abnormality have been associated with cortical changes measured by functional MRI (145).

The majority of patients with musculoskeletal pain will present with sensitivity (reduced pressure thresholds) at the site of pain. Generalised PPT hypersensitivity in remote areas with no evidence of tissue abnormalities, considered indicative of altered CNS processing, have been previously reported in people with chronic whiplash (147), low back pain (152, 185) hip (186) and knee osteoarthritis (187).

Lower PPTs at local and remote sites, considered indicative of increased nociceptive sensitivity have also been reported in numerous studies of RC disease (8, 153-157, 188-190). Evidence to support a role for central sensitisation in people with shoulder pain attributed to RC disease has been found by a number of research groups by identification of lower PPT at sites remote to the painful shoulder (8, 155-157). Conversely there are also studies refuting the presence of central sensitisation in RC disease due to the absence of widespread sensitivity. In some studies, PPT values taken over sites remote to the painful shoulder have failed to identify PPT values indicating heightened sensitivity (153, 154, 188).

Demographic and other biological factors found to be associated with lower PPT include female gender (174, 191-193), waist to hip ratio (191), pain catastrophizing (192), psychological distress (191, 192), poorer sleep quality and higher pain levels (192). Gender differences appear to reduce with increased age (183). In a large scale study of normative data collection for QST values, non-noxious QST measures of thresholds to detection of thermal and mechanical stimuli were unrelated to age, but pain thresholds including PPT were significantly increased with increasing age (183, 192).

1.3.2.1.2 *Cold Pain Sensitivity (CPS)*

Decreased Cold Pain Thresholds (CPT) at local and remote sites have been identified in patients presenting with elbow lateral epicondylalgia (194), whiplash associated disorder (195, 196), chronic low back pain (197), fibromyalgia (198), hip osteoarthritis (186) and knee osteoarthritis (199). CPT measures have also been identified to be predictive of poorer outcome in whiplash associated disorders (196, 200), lateral epicondylalgia (174) and post gynaecological surgery (201). Decreased CPT has been associated with female sex (174, 191), psychological distress in terms of depression, anxiety, pain catastrophizing (191, 192) and poor sleep quality (192).

To date, investigations of CPT independently or taking into consideration the influence of psychological distress in people with shoulder pain is limited. Only one study had used CPT measures on a group of patients awaiting shoulder surgery, but their focus was to identify the association between psychological factors (fear and pain catastrophizing) and CPT and pain, not to identify the associations between CPT and pain and disability. Fear of pain was found to be associated with increased sensitivity to cold in this group of patients awaiting shoulder surgery (202).

Thermography is an expensive means of testing CPT and requires regular calibration to ensure reliability of the equipment. For these reasons, investigation into clinically applicable alternatives to be used in the broader clinical setting is required. A clinical means of estimating nociceptive sensitivity to cold has been developed whereby an ice block is held in contact with the skin in order to assess Cold Pain Sensitivity (CPS). The validity of this test compared to laboratory based CPT equipment has been established (192, 203).

The association between nociceptive processing measures and musculoskeletal pain and disability

The association between QST laboratory based assessments (including PPT and CPT) and patient reported pain and disability in musculoskeletal pain conditions is still under investigation. In a meta-analysis of studies of people with spinal pain, there was a poor correlation between various QST stimuli findings (including PPT, CPT and heat pain thresholds), and patient reported pain and disability. Threshold QST measures were only able to explain 2% of the variance in patient reported pain and disability (204), irrespective of the type of pain stimulus. Studies assessing QST measures in cohorts with RC disease that have associated those measures to patient reported pain and disability are limited to one study. This study reported higher PPT measures over the affected shoulder and remotely over the anterior aspect of the tibia, indicative of less nociceptive sensitivity, were associated with better functional performance and less self-reported disability (205).

Overall, studies of QST in RC disease suggest pain processing is heterogeneous (153, 156, 157), with some people displaying signs of peripheral sensitisation (local hypersensitivity), some with central sensitisation (global sensitivity) and others a combination. It has been hypothesised that this pattern of variable sensitivity may account for why some patients do not respond to non-surgical or surgical therapies focussing on peripheral injury mechanisms, yet others do (157).

People with a predominant element of central sensitisation for their shoulder pain may not respond to surgery which targets peripheral pathology, with the potential for persistence of pain post-surgery in this group (8). Therefore the use of PPT/CPT as indicators of central sensitisation may assist in the decision for surgery. However, there remains limited evidence to substantiate or refute the association of PPT/CPT at the time of shoulder surgery with pain and disability levels after surgery.

The association between nociceptive processing measures and outcomes after musculoskeletal surgery

QST measures (as indicators of altered CNS processing) prior to surgery have been investigated for their predictive utility in terms of outcomes following surgery (8, 176, 206), with PPT being the most commonly utilised measure. Tissue hypersensitivity as measured by PPT (locally and widespread), conditioned pain modulation using heat and pressure stimuli, temporal summation using von Frey mechanical stimulation and pain thresholds to electrical stimuli has been detected pre-operatively in knee (176, 181, 207, 208), hip (177, 178, 186), thoracic spine (175) and back (209) pain patients awaiting surgery. Many of these studies have identified that the hypersensitivity of structures normalised following surgery, indicating there may be a peripheral drive of augmented CNS processing, though placebo controlled surgery trials would be needed to fully explore this idea. In selected studies on hip and knee arthroplasties, authors have suggested that once post-operative pain had settled, the CNS related signalling and local hypersensitivity normalised (178, 186, 207). Other studies have shown that despite an overall reduction in tissue sensitivity, there remains a subgroup of surgical patients where various measures of altered CNS processing including conditioned pain modulation, PPT and pain thresholds to electrical stimuli have been found to be predictive of poorer outcome following thoracotomy (175), knee (176, 181, 207, 208) and hip (177) arthroplasty surgery. Various QST protocols have been proposed to assess widespread sensitivity and augmented pain signalling, including static, Conditioned pain modulation and temporal summation sensory measures, but there is insufficient data to substantiate a bias towards one. In patients about to undergo knee and hip surgery, PPT has been identified to be significantly lowered compared to controls, indicative of increased sensitivity, and levels have been shown to normalise following surgery, and to be predictive of pain and disability following surgery (177, 181). In a cohort of patients undergoing knee arthroplasty, PPT measures over the knee and at the remote site (forearm) were significantly lower, which was considered indicative of widespread sensitisation, and lower PPT at the remote site was predictive of poorer outcomes of pain and disability at one year following surgery (176). This same group investigated the predictive utility of PPT in patients awaiting hip and knee arthroplasties and found a combination of reduced PPT indicative of widespread hyperalgaesia and more advanced OA on x-ray to be predictive of better outcome in hip arthroplasty, compared to reduced PPT scores with less severe OA on x-ray which predicted a poorer outcome in knee arthroplasty (177). This indicated the potential presence of a subgroup of patients for whom knee pain

was moderated to a greater extent by the CNS than by peripheral pathology, and for whom poorer pain and disability outcomes after knee arthroplasty were observed. The contradictory findings suggest that widespread hypersensitivity in the absence of significant pathology is associated with poorer outcomes only after knee arthroplasty, and suggests that various measures of nociceptive sensitivity and their association with post-surgical outcomes may be joint specific.

The association between nociceptive processing measures and outcomes after shoulder surgery

There remains limited evidence to substantiate or refute the association of QST measures before shoulder surgery with outcome after surgery. The presence of punctate sharpness sensitivity in patients awaiting RC surgery was significantly associated with higher pain levels and lower disability outcomes three months after surgery (148). Dynamic thermal pain sensitivity tests (conditioned pain modulation) in a sample of people with mixed diagnosis undergoing shoulder surgery was not associated with outcomes of pain and disability three or six months following surgery (190).

Altered body representation mechanisms

The *body schema* is a theoretical construct outlining how the dynamic sensory-motor representation of the body guides movement/interaction with the environment (210). Inputs from tactile, motor, vestibular, proprioceptive, visual and auditory systems are integrated with brain grounded maps of the body to shape the body schema. The best known of these brain grounded maps is the representation of the body surface in the primary somatosensory cortex (the sensory homunculus), but there are others, including the motor cortex and insular cortex (211). The accuracy of these cortical representations relies on cortical inhibition making neural inputs more precise. A combination of peripheral and central sensitisation and cortical disinhibition can lead to changes within the cortex (212) and potential disruption of the body schema.

Increasing evidence is emerging on the cortical changes that occur in the somatosensory cortex following periods of pain. These changes have been identified by neuroimaging including identification of blood flow changes on MRI images and magnetoencephalography which maps brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain. Changes have been identified in individuals with complex regional pain syndrome (CRPS) (213, 214) , low back pain (140), limb amputation (215),

trigeminal neuralgia (216), carpal tunnel syndrome (217), herpes simplex virus (218) and patella femoral joint pain (219). Cortical changes that have been identified include either an expansion or shrinkage of the cortical representation of the painful area, invasion of neighbouring body representations (in the case of amputation), or increased somatosensory activity/response and altered microstructure and blood flow (140, 216, 220) . The extent of cortical changes have been associated with pain intensity in CRPS (214, 221), and a normalisation of the primary somatosensory cortex has been observed to accompany a significant reduction in pain (222) {Gustin, 2012 #15}.

Changes in the motor cortex seem to mirror these changes identified in the somatosensory cortex. These motor cortex changes include a shift in map position and site specific map volume changes (223). These changes have been identified in chronic pain conditions such as phantom limb pain (215), CRPS (224), knee osteoarthritis (225), fibromyalgia (226) and low back pain (227). The magnitude of these changes is also correlated to the level of pain experienced and chronicity (218, 220, 228). This “blurring” of brain grounded motor and sensory maps may result in increased and inaccurate pain area identification, greater potential for spatial summation of noxious inputs, decreased tactile precision and reduced motor precision (229).

CNS related changes within the motor cortex of people with shoulder pain linked to RC disease may be an important consideration for the reason why a large proportion of patients don’t respond well to non-surgical or surgical interventions aimed at local tissue pathology. Body representation is a complex concept and encompasses many different ways of representing the body, two of the most commonly discussed are body schema and body image. Body schema is based on the integration of sensory and motor information with a stored body model, It is a less conscious, constantly varying body representation that gives us accurate awareness of where we are in space (postural schema) and the ability to localise where on the body surface we have been stimulated (superficial schema). Body image is a more conscious and enduring representation which is similarly contributed to by sensory-motor inputs and the integrity of brain grounded maps, but further to this relies on higher level integration of social, emotional and contextual factors. Chronic pain has been shown to lead to disruptions to body image, particularly perceptual body image, or the way the body feels to the owner. Together these changes in body schema and body image may manifest in the inability to accurately mentally rotate a painful body part, inaccurate body spatial reference frames, poor body-size perception, a distorted feeling of body ownership, inability to accurately localise tactile stimuli , reduction in tactile acuity and poor proprioception (230,

231). These subjective feelings of foreignness and poor self-perception have been identified in up to 84% of CRPS patients, with almost half of them experiencing both cognitive (feelings of foreignness) and motor components (additional attention needed to make voluntary movements) of this perceptual dysfunction (232, 233). Amputees experiencing phantom limb pain report co-existing perceptions that their missing limbs feel swollen, heavy, immobile or floating (230, 234). More recently these self-perceptual impairments were assessed amongst low back pain sufferers, with similar findings (141). Slower or less accurate mental manipulation of movements of an injured body part has been shown to be present in chronic pain presentations including CRPS (235), low back pain (229), OA (236), and shoulder pain (237). People with CRPS have also been shown to be less accurate than pain free people when determining their body midline (238) or position their hand in specifically directed positions using a clock face reference (239). Distorted body size also features in conjunction with the other self-perceptual distortions, with people with CRPS overestimating the size of their hands (240). All these changes appear to be related to duration of symptoms, but not pain severity (241). Deficits in tactile acuity have been identified in people with CRPS (242), phantom limb (243, 244), brachial plexus avulsion (244), low back pain (245) and shoulder pain (237). Interventions that potentially target body representation with specific sensory and motor retraining have been effective in normalising these cortical changes and have been shown to significantly reduce pain levels in CRPS and phantom limb pain (244).

Very little evidence is available to explain or identify cortical changes that occur with shoulder pain. Accurate body representation relies on transmitted information of proprioceptive state. Proprioception in turn is considered imperative for accurate movements. Disruptions to the internal representations may affect the model of the body utilised for precise movement (246). There is limited evidence available regarding proprioceptive deficits in RC disease. People with RC tendinopathy have been found to have poor active and passive joint position sense (247, 248), but these have been shown to be significantly restored following subacromial decompression surgery (248, 249).These studies offer some limited evidence that changes in body representation may be present prior to shoulder surgery in people with chronic shoulder pain, and may change following surgery.

Clinical assessment of altered body representation

It has been established that persistent pain is associated with changes in body representation. This might be due to conscious issues related to beliefs and attitudes about the body, degradation of sensory and motor information streams or disruption of brain

grounded maps of the body, or all three mechanisms acting together (212). Many different measures are used as a means of assessing body representation, most of which are not direct but rather measures of particular constructs believed to contribute to different types of body representation. These include tactile acuity, stimulus localisation, proprioceptive acuity and laterality judgements. Some other measures such as spatial referencing, body size estimation and self-reported body perception (231) are likely to be more direct measures of body representation, as they ask direct questions about body perception. Clinical studies have shown that pain perception can be manipulated by disrupting body perceptual representation (250-252). Additionally, management strategies that aim to restore normal body representation have been shown to reduce pain perception and normalise cortical changes in CRPS, phantom limb pain and chronic low back pain (253-255).

1.3.2.6.1 *Self- reported body self-perception*

Altered body perception includes both cognitive and motor components, whereby the patient may report that their body part feels dead or foreign to them (cognitive) or that their body part feels like a dead weight and is difficult to move without a great deal of focus of attention (motor). These changes in self-perception have previously been phrased cognitive neglect, which is distinct from hemispatial neglect seen after a brain injury such as stroke (232). These neglect-like symptoms have been further explored within the CRPS population. The motor component of impaired body perception in people with CRPS included delayed initiation of movement, decreased speed of movement and smaller amplitudes of movement (256). From a sensory perspective, patients described their affected limb to be disconnected, a poor awareness of limb position, a distorted mental image, and a discrepancy between what is felt and the appearance of the painful part (233, 256). These observations directed the formulation of the Neurobehavioural Questionnaire, a 5 item questionnaire to measure symptoms of cognitive and motor neglect. Galer and Jensen utilised this tool to identify that 84% of 224 people with CRPS indicated at least one symptom of either motor or cognitive neglect (232). When compared to a control group with chronic limb pain of other origins, both groups reported experiencing elements of neglect, but the CRPS group were identified as having significantly more severe symptoms, and a greater number of people with CRPS reported both motor and cognitive elements of neglect indicating altered body perception (257). Recently the role of body perception in chronic low back pain has been explored (141). A modified version of the neglect questionnaire used by Galer and Jenson was used to identify that altered body perception

is also prevalent in people with chronic low back pain, with over 10% of the 251 low back patients included in the study reported perceptual deficits “occasionally” to “always”. Neglect-like symptoms have also been identified in 36% of people three weeks following total knee arthroplasty, which reduced to 18% at the six week mark (258). No studies have investigated this construct with people experiencing shoulder pain.

1.3.2.6.2 *Left / Right Judgment Tasks (LRJT)*

Motor imagery is a mental process by which an individual rehearses or simulates a given action, and can be either implicit or explicit. The left / right judgement task is an implicit motor imagery task thought to reflect the integrity of the postural schema. The task involves viewing an image of a limb or body part in various positions and judging whether it is left or right. The task requires a mental rotation of the limb or body part in order to match it to the image. Both reaction time and accuracy are measures of left/ right judgement task performance, both of which are influenced by the degree of imagined movement required to align oneself with an image, constraints to actual (rather than imagined) movement, and the presence of pain, female gender, older age and handedness (235, 259).

Left/right judgement tasks have been evaluated extensively in pain populations (235, 236, 260-263). There is evidence that impaired performance on left/right judgement tasks is present in CRPS, osteoarthritis of the knee and people experiencing chronic back pain (229, 235, 236, 260-263). All these studies have identified that left/right judgement task performance deficits in participants with pain are specific to the affected body part.

To date, the study of left/right judgement task performance with regard to the shoulder have been limited to pain free samples. In a large scale internet-based study on people without shoulder pain, gender and dominance was not significantly associated with either reaction time or accuracy. Older age was associated with slower reaction time but not accuracy, indicating older participants take longer to recognise the images. There was no reaction time/accuracy trade off though, as those participants who were quicker were also more accurate (Breckenridge 2017). To date, left/right judgement task performance has not been reported for people experiencing shoulder pain.

1.3.2.6.3 *Two Point Discrimination (TPD)*

TPD is the ability to discern that two nearby objects touching the skin are truly two distinct points, not one. TPD is dependent on the concentration of sensory receptors in an area, the

size of the receptive fields of these receptors and the fidelity of the representation of that body area in primary somatosensory cortex. TPD has been shown to change very rapidly with pain (264, 265), and it is thought that these changes represent disruption of cortical contribution to the task (264).

People with chronic pain have been identified as having poorer ability to discriminate two-points than people without pain (229, 266, 267), with the difference related to both pain intensity and degree of cortical reorganisation. In people with CRPS, a reduction in TPD ability has been significantly related to the extent of cortical reorganisation and pain intensity (268, 269).

In people with CRPS and osteoarthritis of the knees TPD impairment has been demonstrated to occur locally at the site of the pain and be significantly different to the same site on the unaffected side, (266, 267). Specific changes in cortical representation identified by fMRI have been linked to the corresponding skin regions where this tactile impairment occurs (266).

TPD measures in both normative populations and populations with pain have been shown to have large variability, with wide standard deviations (150, 270-272). Variability in both protocols and individual factors are considered reasons for this, but have not been confirmed. Duration of symptoms does not appear to be related to reduced levels of TPD, but increased BMI, reduced waist-hip ratios and older age do (273, 274). It is hypothesised that obese people have a distorted body image, as experimental studies have identified that obese people have a distortion in estimating body part size and overestimate distances during tactile discrimination tasks (275). Gender appears to be inconsistently related to TPD. In studies of people both with and without knee pain, females demonstrated better tactile acuity than males regardless of pain status (150, 273) whereas gender has not been associated with TPD in studies of people with low back pain (150) or global and upper limb assessments in pain-free people (270, 276).

Normative TPD data has been collected for the shoulder, and the association of TPD at the shoulder with other measures of body representation has been explored. In a study of 30 people without shoulder pain (237) TPD data was obtained from anterior, middle and posterior deltoid of the dominant and non-dominant shoulder. There was no significant difference in TPD acuity in different locations on the same shoulder, but the dominant shoulder had significantly lower tactile acuity compared to the non-dominant side. This differed from normative data in the knee where there were no side to side differences but

location differences between medial and lateral aspects of the same knee (273). Although dominant sides have been shown to have greater cortical somatosensory representation due to increased use (277, 278) the pattern of levels of acuity of TPD does not reflect this.

TPD may offer some insight into the accuracy of the superficial schema and deficits in the ability to accurately dissociate two points may give insight into the extent of changes in body representation. Identification of these in turn may offer some guidance to include strategies that have been shown to normalise aspects of body representation in the management of shoulder pain.

Summary

A substantial proportion of people show improvements after RC surgery, with reports of up to 93% of people undergoing surgery reporting improvements in pain and disability following surgery (107) and high levels of satisfaction overall (108). However, there does remain a group of patients (up to 42%) who continue to have persistent pain following RC surgery (115). Surgical rates for RC related shoulder pain in Western Australia are escalating and with them the associated costs (26). The ability to identify patients who may fail to improve after surgical interventions directed at peripheral pathology may assist clinical decision making. Many factors associated with outcome following various surgical procedures for shoulder pain have been identified and include personal and surgical related factors, yet the ones identified still do not explain a significant proportion of the outcomes following surgery (114). The emerging knowledge of the role of alterations in nociceptive processing mechanisms and body representation in chronic pain suggest these factors are potentially associated with pain and pain-related disability outcomes following shoulder surgery (206, 279). Tissue sensitivity, left/right judgment tasks, TPD and body perceptual deficits have all been proposed as indicators of changes in central pain processing. Left/right judgment tasks, TPD and body perception are all measures hypothesized to related to the body schema or body representation within the CNS, whereas tissue sensitivity could be considered as conceptually distinct and an indicator of augmented signalling resulting in heightened sensitivity within the CNS. Identification of these potential alterations in CNS processing prior to surgery may indicate the patient is a potential risk for poor outcomes following RC surgery.

Aims and Significance

Shoulder pain is common and surgical approaches to address shoulder pain and disability associated with RC pathology are escalating. Many prognostic factors have been identified to be associated with pain and disability following RC related surgeries but there is no consensus as to which are most important. CNS processing is proposed as a likely factor to be taken into consideration and this study assesses its association with pain and disability following RC related surgery. Findings of this study may help to identify those patients who may not benefit from surgical interventions.

This study proposed two aims:

1. To determine the association between measures of body representation and nociceptive sensitivity, and shoulder pain and disability prior to RC surgery
2. To assess the predictive association of these body representation and nociceptive sensitivity measures and pain and disability following RC related shoulder surgery

Study 1

Introduction

Chronic or persistent shoulder pain is estimated to be the third most common musculoskeletal presentation in primary care settings (4, 12). Rotator Cuff (RC) disease can account for up to 85% of these cases (21). It poses a significant financial burden (12) and is associated with significant rates of disability (59). The RC comprises a group of four muscles that act together as a dynamic stabiliser of the glenohumeral joint. Defining exactly what is meant by RC disease is problematic as degenerative changes within this muscle complex are considered a normal part of aging and the extent of identifiable pathology is poorly correlated with patient reported pain and disability (31, 280). Furthermore, approximately 50% of cases of acute shoulder pain continue to persist for longer than 6 months (2, 281), beyond the period of normal soft tissue healing. This suggests factors unrelated to peripheral pathology may be implicated in promoting the persistence of pain in RC related shoulder pain.

More recently CNS related factors have been suggested as a likely contributor to the persistence of shoulder pain and pain related disability for some individuals. Chronic pain can result in changes within the CNS (220), including changes in body representation and alterations in nociceptive sensitivity (11). Central sensitisation is an amplification of nociceptive functioning leading to a state of generalised pain hypersensitivity (11) and recent systematic reviews concluded that there is some consensus that central sensitisation presents in people with RC related pain (32, 158). Although not widely investigated in people with shoulder pain, changes in body representation have been identified in other musculoskeletal pain problems (231). These include changes in brain grounded maps of the affected body part, disruption of the sensorimotor representation of the body responsible for guiding action (referred to as the body schema), as well as changes to the consciously felt body or body image (220, 269). Treatment strategies that try to normalise CNS functioning have been shown to have a significant impact on patient's reported pain and disability in some chronic pain disorders (212, 228, 282). Finally, the potential confounding role that some factors may play in the association between CNS changes and patient reported pain and disability warrants consideration. These include gender, age, duration of symptoms, psychological distress and weight related factors.

There is currently some evidence to substantiate the presence of central sensitisation and subsequent nociceptive sensitivity within people with RC related shoulder pain, but to our knowledge there is little evidence to implicate altered body representations and their association with shoulder pain and disability.

Aim

To determine the cross-sectional association between measures of body representation and nociceptive sensitivity and self-reported shoulder pain and disability adjusting for potential confounders in a cohort of individuals with RC related shoulder pain.

Research Methods

Design

A cross-sectional study of people undergoing RC surgery was conducted at a tertiary hospital in Perth Western Australia. Ethical approval from both Curtin University (HR 178/2013) and Sir Charles Gairdner Hospital (HREC 2013-202) was granted, and all participants provided informed consent. The present cross-sectional study makes use of baseline data collected as part of a longitudinal cohort study investigating body representation and nociceptive sensitivity measures as predictors of outcome after shoulder surgery.

Participants

Thirty-four participants were consecutively recruited from people waitlisted for RC surgery between June 2014 and June 2015. These participants were sourced from the waitlists of three surgeons who were currently operating at Sir Charles Gairdner Hospital (SCGH), a public hospital in Nedlands, Western Australia. Participants were considered for inclusion if they were scheduled for subacromial decompression (SAD) and/or RC repair (RCR), via arthroscopy, mini-open or open approach, were over the age of 18 and lived in the Perth metropolitan area. People were excluded if they presented with glenohumeral joint osteoarthritis as the primary pathology, concomitant systemic disease such as Type 1 diabetes, rheumatoid arthritis, malignancies or local cancer, previous neck surgery or RC surgery on the same shoulder, inability to understand English or inability to attend 3 and 12-month follow up reviews (e.g. due to rural residence). Figure 0.1 outlines the flow of participant recruitment.

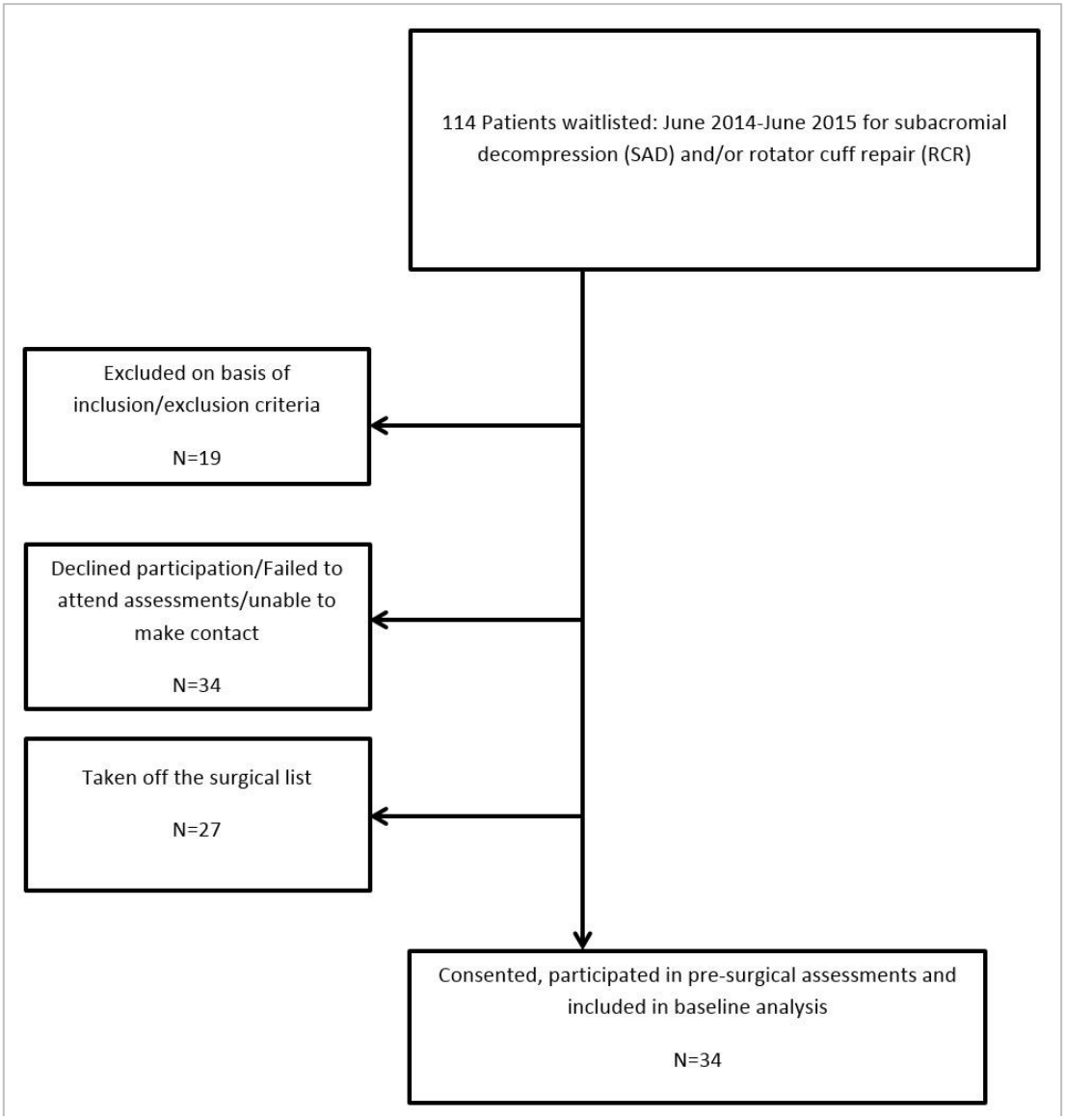

Figure 0.1 Study 1: Flowchart of participant

Procedure

Baseline data were collected at the preoperative assessment, where eligible patients were presented with detailed information regarding the project and requested to sign a consent form. All consenting participants next provided basic demographic data and had their height, weight and waist circumference measured. General medical details, medication use and basic clinical information were obtained for each participant. Participants then completed questionnaires assessing shoulder related disability, emotional state and self-reported body perception followed by physical testing to assess superficial schema (TPD), postural schema (LJT) and nociceptive sensitivity (PPT and CPT). Testing was carried out in the same order and by the same investigator for each participant.

Measures

Shoulder Pain and Disability

Shoulder specific pain and disability was evaluated using the self-administered Shoulder Pain and Disability Index (SPADI)(283), which has been shown to have good reliability and responsiveness (284, 285). The SPADI consists of 13 items, five pain-related and eight disability-related, each with an 11 point Likert scale, referenced to symptoms over the last week. For each subscale, the mean of non-missing items was imputed for those cases missing two or less items. A sum for each subscale was calculated and converted to a percentage ranging from 0-100, with higher values indicating higher levels of pain and disability.

Nociceptive sensitivity and body representation

2.2.3.1.1 *Nociceptive sensitivity*

Measures of Pressure Pain Threshold (PPT) and Cold Pain Sensitivity (CPS) were taken at two sites; locally at the shoulder over the mid-deltoid, 2cm proximal to the insertion site, of the shoulder scheduled for surgery and distally over the lower leg at the mid muscle belly of the opposite tibialis anterior, with participants laying supine with their hands resting on their abdomen. Thirty seconds between repeated measures was allowed to minimise summation effects. A mean of the three values for each site was calculated for both PPT and CPS. PPT measures at the shoulder then leg were completed initially, followed by the CPS measures at the same sites and in the same order. There was approximately a one minute break between the four sets of measures (CPS- shoulder and leg and PPT- shoulder and leg) to allow for documentation.

PPT was assessed using a digital algometer (Somedic, Hörnby, Sweden) with a $1cm^2$ probe. To familiarise the participant with the process a demonstration was first performed on the opposite hand. Testing involved applying a gradually increasing force perpendicular to the skin surface. The amount of pressure measured in KPa at which the participant first reports a sensation of pain is considered the threshold. Participants were instructed to indicate this threshold by pressing a button, at which point the procedure was immediately terminated and the value recorded, with the participant blinded to the pressure recordings. Pressure algometry has been found to be a reliable measure of PPT (286).

Cold Pain Sensitivity (CPS) was assessed by application of two ice blocks (32mm x 40mm), in a plastic bag, for a 10-second period. At the end of 10-seconds participants were asked to rate the maximum level of discomfort experienced on an 11–point numerical rating scale where 0 indicated a cold sensation but no discomfort and 10 indicated the worst pain imaginable. Assessment of CPS using ice blocks is a simple, inexpensive measure of cold hyperalgesia that has been previously validated against the use of a thermode (203). A numerical rating of greater than 5 has been strongly associated with cold hyperalgesia when compared with thermode testing of cold pain thresholds (CPT). Participants were instructed to let the examiner know if they were experiencing 10/10 pain prior to the completion of the 10 seconds, and in that case the test period was ceased and a maximum score of 10 was recorded.

2.2.3.1.2 *Self-reported body perception*

Self-reported shoulder specific body perception was assessed with the modified Neurobehavioural Questionnaire, which identifies the extent of shoulder specific neglect or perceptual disruption. The original questionnaire developed by Galer and Jenson (1999) included 5 questions designed to identify neglect-like features in patients presenting with CRPS. Statements 1 (“If I don’t focus my attention on my painful limb it would lie still, like dead weight”) and statement 3 (“I need to focus all of my attention on my painful limb to make it move the way I want it to”) identify motor neglect. Statement 2 (“My painful limb feels as though it is not part of the rest of my body”) and statement 5 (“My painful limb feels dead to me”) identify cognitive neglect. Statement 4 (“My painful limb sometimes moves involuntarily, without my control”) identifies the perception of involuntary movements (232). The Galer and Jenson version used a dichotomous scale requiring a ‘true/false’ response. Frettloh et al (2006), modified the Galer and Jenson version by including a 6-point Likert scale (1=never to 6= always) (257). The questionnaire used in this present study had a slight modification on the Frettloh et al (2006) version, where the 6-point Likert scale rated from 0= never to 5=always. Participants were instructed to indicate the degree to which their shoulder felt that way when they were experiencing pain, with 0 indicating “never” and 5 “always”. The questionnaire thus ranges from 0 to 25 points, with a higher score indicating a higher degree of shoulder specific perceptual disruption. (Appendix D, page 137)

2.2.3.1.3 *Left/Right Judgement Task*

Participants used the Recognise Application ™ (noigroup, Adelaide, Australia) to perform the left/right judgement tasks. Patients were seated with legs uncrossed and both feet placed flat on the floor. An iPad was centred on the participant's midline on a table of appropriate height, allowing for the forearms to rest evenly on the surface. Shoulder images were randomly displayed for 10 seconds in different positions and varying degrees of rotation. The participants were required to judge as quickly and accurately as possible as to whether the image they were currently viewing was left or right, and to press the corresponding button on the iPad. Previously validated *Recognise* software, (229), was used to determine accuracy (% correct) and speed of recognition (ms) of the judgement task. A trial run of 40 images was undertaken initially and these data discarded. Participants then completed two test runs of 40 images each with a 30 second break between each run. The average accuracy and speed scores from the two test runs were used for analysis.

2.2.3.1.4 *Two point discrimination (TPD)*

TPD threshold was assessed using a set of digital sliding callipers over the middle deltoid muscle of the affected shoulder, parallel to its muscle belly. TPD assessment involved applying pressure to the skin using the callipers and questioning the participant as to whether it felt as if the skin contact was being made by one point or whether they were able to differentiate two separate points of contact. A familiarisation trial was performed on the opposite forearm with the patient in sitting. One ascending and one descending trial was performed, with the participant observing the process. The participant reported either one or two points at each time calliper contact was made.

Following this participants were positioned supine with their hands resting on their abdomen and the callipers were centred on the middle deltoid muscle belly for assessment. The amount of pressure applied was until the first signs of skin blanching. Three taps at each spacing were applied approximately half a second apart and the participant was simultaneously asked to indicate if they felt two separate points or only one. Ascending trials commenced from 0mm and the separation distance was incrementally increased by approximately 5mm until the patient was able to discriminate two individual stimuli. If the patient was unsure, the stimulus was repeated. Descending trials commenced with a separation distance 30mm above the ascending threshold and the distance was decreased by 5mm increments until the participant felt only one point. Three ascending and three

descending trials were used, giving six measures in mm. These six values were then averaged for analysis purposes, with smaller numbers indicating better tactile acuity. This TPD methodology has been shown to be reliable (272).

Potential confounders

Variables considered as potential confounders of the association between body representation measures and SPADI scores, or nociceptive sensitivity measures and SPADI scores were assessed. These were gender(174, 191-193, 235), age (183,192,259), Body Mass Index (BMI) (273,274), waist circumference(191), duration of symptoms (273) and symptoms of depression, anxiety and stress (191-192). BMI was calculated by dividing the participants weight in kilograms (measured by scales) by their height in meters squared (measured using a stadiometer). Waist circumference is considered a measure of central rather than whole body adiposity and was measured using a tape measure and rounded to the nearest cm. Duration of symptoms was assessed by the following question: “How long have you had shoulder symptoms prior to surgery?” with the response categories “less than one month”, “1-3 months”, “3-6 months”, “6-12 months”, “12-24 months” and “longer than 2 years”.

The Depression Anxiety Stress Scale (DASS) is a 42 item self-report questionnaire designed to measure the negative emotional states of depression, anxiety and stress (287). The DASS has been identified to be a reliable and valid instrument (287, 288) and clinically applicable (289). Each of these 3 subscales contains 14 items. The participant is required to respond to 42 statements regarding how they felt over the past week, using a 4-point Likert scale. The scale ranges from 0 indicating that the statement “did not apply”, to 3 indicating that it “applied very much or most of the time”. The mean of non-missing items was imputed for each subscale for those cases missing two or less items. A total sum score was calculated ranging from 0-126 with higher scores reflecting more negative emotional state.

Statistical Analysis

Preliminary inspection of the data was conducted to assess normality of distributions. PPT at the shoulder site, left/ right judgement task reaction time and TPD were log-transformed to normalise skew. CPS and self-reported body perception were assessed using nonparametric correlation procedures due to the floor and ceiling effects respectively, rendering them unamenable to log transformations, and these variables were transformed

to binary indicator variables indicating a score of 0 versus >0 for linear regression models described below. For left/ right judgement task where reaction times and accuracy were tested for both the operated and non-operated sides, a repeated measures t-test verified an absence of significant differences between sides, therefore the mean of both sides was used for further analysis.

Descriptive statistics were reported as means and standard deviations for continuous measures, medians and IQR for non-normally distributed variables and as frequencies for categorical variables. To assess potential confounding associations between independent and dependent variables (body representation measures, nociceptive sensitivity measures and SPADI scores), and gender, age, BMI, waist circumference, duration of symptoms and emotional status, Pearson's, Spearman's and point biserial correlation coefficients were used for continuous, ordinal and categorical data respectively.

The individual subscales (SPADI pain and SPADI disability) were considered separately as dependent variables, as body representation and nociceptive sensitivity measures have been shown to be differentially associated with pain and disability (33). A series of univariable linear regressions were used to assess the association between each body representation and nociceptive sensitivity measure as independent variables and SPADI pain or disability scores as the dependent variable. Following on from this, multivariable regression analysis was used to examine the association of each body representation and nociceptive sensitivity measure with SPADI scores adjusted for those variables considered as potential confounders of the measured association by virtue of their association with both the independent and dependent variable at $p<0.10$. Results are presented as standardised and unstandardised regression coefficients with associated 95% confidence intervals, and R^2 values are included for all associations where the p-value for regression coefficients was <0.05. All data were analysed using the IBM SPSS statistical package, version 22 (SPSS Inc, Chicago, IL).

An *a priori* power calculation estimated a sample of 100 participants would be required to give 83% power to detect R^2 contribution of 7% for a single sensitivity or perceptual measure in multivariable regression models.

Results

The waitlist for RC surgery included 114 patients over the study period. Of these, 19 patients didn't meet inclusion criteria, 34 patients declined participation and 27 were

removed from the waitlist prior to consenting to participate in the study. The remaining 34 patients were recruited and consented to participate in the study. Baseline data is summarised in Table 0.1. There was a slightly higher percentage of males (58.8%) in the study sample. Participants had a mean (± standard deviation) age of 61.1 ± 13.6 years, a mean BMI of 29.8 ±7.1 and a mean waist circumference of 104.1 ± 17.2 centimetres. Of the 34 participants, 15 (44.1%) had experienced more than 2 years of symptoms, and only 5 participants (14.7%) reported less than a 6 month history of shoulder pain.

The median of the DASS total was 5.5 (1.0- 25.3), overall indicating very low (sub-clinical) levels of anxiety and depression. SPADI pain score was 61.7% (14-100) and SPADI disability score 49.9% (0-91.3).

The median value of the neurobehavioural questionnaire was 0 with 16 of 30 participants (53.3%) scoring 0 and 14 (46.7%) participants scoring above 0, indicating some degree of perceptual disruption.

Left/right judgement tasks showed a median reaction time of 1.8seconds and an accuracy of 87.8%. The median for TPD threshold was 50.7mm. The median value for PPT at the shoulder was 457.7KPa and the mean value at the ankle was 795.6Kpa.

CPS at both the shoulder and leg had a median of 0 indicating floor effects for cold thresholds. Seventeen of 34 participants (50%) scored a value of 0 for CPS at the shoulder and 17 of 34 scored a value above 0, indicating some degree of pain or discomfort with the ice application. At the leg 24 of 34 participants (70.6%) scored a value of 0, while 10 (24.4%) participants scored a value above 0. The number of missing values for each variable in baseline data is indicated in Table 0.1. A previous study into whiplash associated disorder found no VAS value perfectly discriminated the presence of cold hyperalagesia but a value>5 gave a positive likelihood of 8.44 (203). Since this study only presented with 6 (shoulder CPS) and 4 (ankle CPS) participants respectively with VAS values over 5, zero was used as the cut off to indicate CPS.

Table 0.2 displays the correlations between variables considered as potential confounders and dependent and independent variables. Gender was associated with both shoulder SPADI pain scores and leg PPT at $p<=0.10$. Waist circumference was associated with both SPADI pain and disability scores and shoulder PPT and CPS at $p<0.10$. These variables were considered as potential confounders of the associations of interest in subsequent multivariable models.

Table 0.3 displays the results of the series of linear regression models for SPADI pain and disability. Models with PPT and CPS as independent variables were performed unadjusted and adjusted for confounders identified as described above. An association was considered significant when P<=.05. There was no association, either adjusted or unadjusted, between SPADI pain and body representation or sensitivity variables other than two point discrimination (coeff=15.9, 95%CI=0.2, 31.6, p= .048). Poorer levels of tactile acuity were associated with higher shoulder pain scores, with 13.7% of the variability in the SPADI pain score being attributed to TPD scores. There was evidence of an association between SPADI disability and PPT at the shoulder in both an unadjusted model and after adjustment for waist circumference (adjusted coeff= -12.5, 95% CI -24.4, -.6, p=.040), with the data indicating that people who are more sensitive to pressure reported higher levels of disability. PPT at the shoulder alone only explained 18.0% variability in the SPADI disability scores and the model including adjustment for waist circumference explained 20.9%. SPADI disability scores were not associated with any other body representation or sensitivity measures.

Table 0.1 Participants demographic and clinical information (N=34)

Characteristic	Mean (SD), Median (p25, p75) or N (%)	Min-Max
Demographics		
Gender n males (%)	20 (58.8%)	
Age years	61.1 (13.6)	21-79
Body mass index	29.8 (7.1)	19.8- 47.0
Waist circumference(cm)	104.1 (17.2)	75- 134
Duration of symptoms* n (%)		
0-3M	2 (5.9%)	
>3-6M	3 (8.8%)	
>6-12M	5 (14.7%)	
>12-24M	6 (17.6%)	
>24M	15 (44.1%)	
Psychological distress (DASS total)[#]	5.5 (1, 25.3)	
Clinical Measures		
SPADI[ǂ]		
Pain score	61.7 (20.4)	14.0- 100
Disability score	49.9 (22.1)	0- 91.3
Neurobehavioral Q[Δ] (0-25)	0.0 (0, 3.3)	
LJT		
Reaction (Sec)	1.8 (1.6, 2.3)	78.8- 98.8
Accuracy (%)	87.8 (7.3)	
TPD (mm)	50.7 (37.7, 67.8)	
PPT (KPascals)		
Shoulder	457.7 (263.0, 717.8)	196.7-1399.4
Leg	795.6 (339.9)	
CPS (VAS 0-10)		
Shoulder	(0.0, 2.3)	
Leg	0.0 (0.0, 0.0)	

Abbreviations: SD, standard deviation; IQR, interquartile range; N, number; SPADI, Shoulder Pain and Disability Index; JLT, laterality judgement task; TPD, two-point discrimination; PPT, pressure pain threshold; CPS, Cold Pain Sensitivity; DASS, Depression Anxiety Stress Scale.
*Data missing 3 cases; [ǂ] Data missing 5 cases; [Δ] Data missing 4 cases; [#] Data missing 8 cases

Table 0.2 Demographics, duration of symptoms and psychological distress in relation to body representation, nociceptive sensitivity and SPADI scores

	SPADI Pain	SPADI Disability	Neglect	Laterality Reaction (ln)	Laterality Accuracy	TPD (ln)	PPT Shoulder (ln)	PPT Leg	CPS Shoulder	CPS Leg
Gender	**-.310[c]**	-.106*[c]	-.269[c]	**.009[c]**	-.042[c]	-.193[c]	**-.293[c]**	**-.578[c]**	.150[c]	.081[c]
	p =.100	p =.578	p=.151	**p =.960**	p =.815	p=.282	**p=.092**	**P<.000**	p=.397	p=.648
Age	.128[a]	.182[a]	.202[b]	**.572**	-.175[a]	**.412[a]**	-.132[a]	**-.355[a]**	-.110[b]	.087[b]
	p=.508	p=.335	p=.284	**P<.000**	p=.322	**p=.017**	p=.456	**p=.039**	p=.535	p=.624
Body mass index	**.346[a]**	.193[a]	.022[b]	.160[a]	.035[a]	.126[a]	**-.383[a]**	**-.291[a]**	-.205[b]	.175[b]
	p=.066	p=.308	p=.908	p=.367	p=.849	p=.486	**p=.025**	**p=.095**	p=.245	p=.322
Waist circumference	**.411[a]**	**.370[a]**	.121[b]	.258[a]	-.057[a]	.279[a]	**-.332[a]**	-.169[a]	**-.293[b]**	.059[b]
	p=.027	**p=.044**	p=.525	p=.140	p=.747	p=.116	**p=.055**	p=.338	**p=.093**	p=.739
Duration of symptoms	-.085[b]	-.122[b]	-.039[b]	**-.414[b]**	.123[b]	.020[b]	-.024[b]	.261[b]	.122[b]	.066[b]
	p=.662	p=.519	p=.837	**p=.020**	p=.510	p=.915	p=.897	p=.156	p=.512	p=.725
DASS total	.071[b]	.005[b]	**.351[b]**	-.033[b]	.195[b]	.119[b]	-.059[b]	.117[b]	-.266[b]	-.109[b]
	p=.731	p=.979	**p=.079**	p=.874	p=.339	p=.562	p=.775	p=.570	p=.190	p=.597

[a]Pearson's correlation coefficient; [b]Spearman's correlation coefficient ; [c]Point-biserial correlation coefficient

Abbreviations: SPADI, Shoulder Pain and Disability Index; JLT, laterality judgement task; TPD, two-point discrimination; PPT, pressure pain threshold; CPS, Cold Pain Sensitivity; DASS, Depression Anxiety Stress Scale.

Table 0.3 Associations between body representation and nociceptive sensitivity variables and SPADI pain and disability adjusted for potential confounding variables

		SPADI pain			SPADI Disability		
		Regression Coefficient (95%CI)	**P-value**	**Standardised coefficient**	**Regression Coefficient (95%CI)**	**P-value**	**Standardised coefficient**
PPT Shoulder (ln)	Unadjusted	-7.8 (-19.4–3.8)	.177	-.26	**-15.2(-26.6– -3.7)**	**.011**	**-.46**[d]
	Adjusted[a]	-3.7(-15.6–8.2)	.525	-.12	**-12.5 (-24.4– -0.5)**	**.040**	**-.38**[e]
PPT Leg[f]	Unadjusted	-0.0 (-3.0 –2.0)	.847	-.04	-1.0 (-4.0 – 1.0)	.361	-.17
	Adjusted[b]	-2.6 (-5.4 – 0.2)	.067	-.45			
CPS Shoulder[g]	Unadjusted	2.2 (-13.6-18.0)	.778	.05	0.6 (-16.2-17.4)	.939	.01
	Adjusted[a]	11.5(-4.1-27.2)	.142	.29	10.2 (-7.3-27.7)	.243	.23
CPS Leg[g]	Unadjusted	-0.6 (-20.1-18.9)	.950	-.01	-3.7 (-23.5 – 16.2)	.707	-.07
Neurobehavioural Q[h]	Unadjusted	4.7 (-11.3-20.8)	.552	.12	2.5 (-14.9-19.8)	.773	.06
Laterality Reaction (ln)	Unadjusted	10.5 (-14.6 –35.6)	.399	.16	12.8(-14.1– 39.7)	.337	.18
Laterality Accuracy	Unadjusted	-0.2 (-1.7– 1.3)	.779	-.06	-1.09 (-2.7 – .5)	.167	-.26
TPD (ln)	Unadjusted	**15.9 (0.2– 31.6)**	**.048**	**.37**[c]	11.2 (-6.6 – 28.9)	.290	.24

adjusted for [a]waist circumference, [b]gender; [c] R^2=.137; [d] R^2= .180; [e] R^2= .209

[f]Regression Coefficient represents expected increase in SPADI score for 100Pa

[g]Regression Coefficient represents difference in SPADI score between those with CPT=0 versus CPT>0

[h]Regression Coefficient represents difference in SPADI score between those with Neglect=0 versus Neglect>0

Abbreviations: SPADI, Shoulder Pain and Disability Index; TPD, two-point discrimination; PPT, pressure pain threshold; CPS, Cold Pain Sensitivity.

Discussion

The purpose of this study was to investigate the cross-sectional associations between measures indicative of altered CNS processing and pain and disability in a group of people awaiting shoulder surgery. Overall, only a few associations were observed between measures of pain and disability and measures indicative of altered CNS processing. These included an association between disability and PPT at the shoulder and an association between pain and TPD. No associations were observed between any of the other measures of nociceptive sensitivity or body representation and pain and disability.

This study was powered to require a sample of 100 participants, which would give 83% power to detect R^2 contribution of a single sensitivity or perceptual measure of 7% in multivariable regression models. The smaller than anticipated sample size of 34 combined with the large number of associations tested has meant that this study is limited to only detect strong 'true' associations and is also more subject to chance findings or type 1 errors.

Association between measures of nociceptive sensitivity before surgery and SPADI scores before surgery

The pain and disability scores in this study were similar to other studies investigating pain and disability in people with RC related shoulder pain (21, 280). The association between various measures indicative of altered CNS processing (including nociceptive sensitivity) and self- reported pain and disability within the literature is variable. A meta-analysis of the association of various QST measures with pain and disability in people with spinal pain identified that various pain threshold measures showed little relationship to self-reported pain and disability, accounting for only around 2% of the variance in pain or disability scores (204). PPT at the shoulder site in this current study accounted for 18% variability in disability, but was not associated with pain. Coronado et al (2014) (157) identified variable patterns of sensitivity when measuring PPT over the affected shoulder, unaffected shoulder and masseter muscles, in a cohort of participants with unilateral shoulder pain, but similarly found no association between PPT and clinical pain intensity. Previous studies investigating whiplash associated disorders have also reported no association between PPT locally and remote to the cervical spine and reported pain (290). Within the literature pertaining to RC related shoulder pain however, decreased PPT at the painful shoulder has been associated with higher average clinical pain levels (153, 154), spontaneous pain intensity (155) as well

as disability scores (154, 205). All the studies that found this association between PPT and pain investigated PPT measures over a number of shoulder muscles. One reason for the lack of any identified association between PPT and shoulder pain in the current study may be the use of only a standardised area over the middle deltoid which may not have been representative of their symptomatic area of pain. Conversely, a number of papers have also reported finding no association between PPT (locally and remotely) and reported pain in RC related shoulder pain (157, 205, 291). A few likely explanations exist for why the data not only in this study but others is inconclusive: the choice and validity of QST measures as a marker of central sensitisation is poorly understood (11), the lack of confirmation within this cohort of central sensitisation influences and the fact that pain is defined as an unpleasant sensory and emotional experience and therefore may not be a direct reflection of nociceptive sensitivity. Finally the most significant limiting factor that needs to be acknowledged was the small sample size, which meant the study was underpowered to detect meaningful associations. Coronado et al (2014) found that people with unilateral shoulder pain were variable with regard to their pain sensitisation states, with no clear pattern as to whether a state of peripheral sensitisation (local hypersensitivity) or central sensitisation (widespread hypersensitivity) dominated, indicating further research is required to distinguish between the two.

The neurophysiological mechanisms of CPS and PPT assessments are not fully understood and may explain the discrepancy in findings in terms of associations between these measures and self-reported shoulder pain and disability. Hyperalgaesia locally is considered an indication of peripheral sensitisation driven by local pathology and associated inflammatory processes. Changes in CNS processing may still impact on local sensitivity and this is more likely true of CPS, which is dependent on input from cutaneous receptors, than PPT, which is dependent on input from deep structures more likely to be influenced by local tissue inflammation. RC pathology presents subcutaneously and often requires deeper palpation of tissues to illicit a pain response, as is found in PPT. CPS testing assesses nociceptive sensitivity of the cutaneous nociceptors and can present augmented pain responses independent to triggering a nociceptive response from the deep tissues (11). The mismatch between local clinical pain sensitivity and reported pain in this study illustrates the fact that other factors including the CNS, psychological status and sociocultural factors may be implicated. More widespread sensitivity of uninjured tissues remote to the painful area is considered more indicative of altered CNS processing (11). Pain being primarily driven by peripheral inputs from the RC complex, rather than by significant CNS amplification may

explain why local measures of PPT were associated with disability in this study, particularly as local CPS showed no relationship with pain and disability, and both PPT and CPS over the leg site were not related to either pain or disability. Reported pain is not only an indication of nociceptive sensitivity but can be moderated by many biopsychosocial influences, and the lack of direct association between PPT measures and reported pain of participants further highlights this aspect. This study did not specifically investigate the presence of central sensitisation as no pain free control group was included for comparison. We can therefor only make comment on the fact that those participants who were more sensitive to pressure reported higher levels of disability. We have no evidence to support the fact that in comparison to normal pain free controls that our cohort was particularly sensitised and have either peripheral or central pain augmentation. Most of the participants included in this study may not have presented with altered nociceptive processing, a possibility supported by the very low pain scores seen with the CPS testing both locally and remotely. In support of this idea, evidence to refute widespread sensitisation in unilateral shoulder pain has been reported by previous studies (153, 154, 188).

In this current study, CPS measures showed little association with patient reported pain and disability either independently or when adjusted for waist circumference. These findings were consistent at both the shoulder and remotely over the lower leg. It is important however to highlight skewed distributions of CPS measures for both the shoulder and leg, meaning that only a small group of people had quite high measures of CPS, and the sample size may have been inadequate to detect significant associations. The presence of local and generalised cold hyperalgesia has been identified in a number of pain populations including lateral epicondylalgia (174, 292), low back pain (197), knee and hip osteoarthritis (186, 293), and chronic whiplash-associated disorder (294). CPT measures in those studies have been defined by specific cut-off scores and Z-score analysis, giving values indicating nociceptive hypersensitivity to cold stimuli. To date there is no definitive means of quantifying cold hyperalgaesia. These studies showing nociceptive hypersensitivity to cold stimuli were also associated with higher levels of pain and disability. Cold hyperalgaesia is considered an important prognostic factor in whiplash associated disorder (294, 295) and lateral epicondylalgia (292). Cold sensitivity has not previously been investigated at the shoulder and may not be associated with RC related shoulder pain sensitisation pattern, but this would need to be explored in a larger population sample. The neurophysiological mechanisms underpinning cold sensitivity are not fully understood and a standardised protocol to define its presence is still lacking.

Association between measures of body representation before surgery and SPADI scores before surgery

Levels of self-reported body perception disruption specific to the shoulder in this study were very low, with over 60% of the participants indicating zero degree of neglect for each item. CRPS patients have been found to have significantly higher reported levels of neglect (257). Similar to CRPS patients (257) the participants experiencing RC pain in this study scored the highest for item two where perceptual disruption is described as the "need to focus attention in order to make it move". Although 38.5% of the participants in this study indicated a degree of agreement with this statement, only three participants reported feeling this disruption always or most of the time. There has been little investigation into cognitive neglect associated with chronic RC disease. Finding difficulty in moving a limb may not be an indicator of perceptual changes but rather a consequence of peripheral pathology in RC disease. In this study both explicit and implicit measures of body representation, namely self- reported shoulder specific body image and left/right judgement task performance, were unrelated to reported pain or disability. The majority of participants scored no to low levels of perceptual cognitive and motor deficits, which may explain why no association to reported pain and disability could be identified. Investigation of altered body representation in patients presenting with shoulder pain are still limited. To our knowledge no previous studies have reported on alterations in self-reported body perception specific to the shoulder. Previous studies have identified body perceptual deficits similar to neglect in CRPS (257, 296) and low back pain (141) . Two of these studies showed an association between perceptual disruptions and pain in CRPS and low back pain(141, 296), however perceptual disruptions were only associated with disability in low back pain (141) and not in CRPS (257).

Left/right judgement tasks are considered a measure of postural schema. Two studies have assessed left/right judgement tasks of the shoulder in pain-free populations (237, 297), but this is the first study we are aware of that has assessed this domain in patients presenting with RC related shoulder pain. Participants in this study showed similar reaction times to pain-free shoulder populations (1.8 vs 1.7 seconds) but slightly lower levels of accuracy (88% vs 94%). Previous studies assessing the association between the presence of low back pain and left/right judgement tasks also found reaction time to be unaffected by the presence or absence of back pain, when comparing participants with current back pain to pain free participants both with and without a history of back pain. The participants experiencing a current episode of low back pain did however have lower accuracy scores

than the group of participants who had a history of back pain but were symptom free at the time of the testing (142, 298). The same was found for a group of participants diagnosed with knee OA, where reaction times were similar compared to pain free controls, but accuracy of the knee OA group was compromised (236). Both the reaction times and accuracy measures in this study were not significantly different for the affected and unaffected sides, unlike in people with knee OA (236) where accuracy measures but not reaction times were influenced by the presenting side of pain and CRPS patients where both reaction time and accuracy of the affected limb were poorer (235, 242). Reaction times are thought to be reflective of the time it would take to mentally position the body part, select the correct side and confirm this choice (299) whereas accuracy is thought to be a measure of disruption of cortical proprioceptive maps needed for motor processes (142). Slower left/right judgement task reaction times have been linked to reported pain in previous studies of CRPS (235, 260, 300), but were not associated with pain in a study of low back pain(298). A relationship between accuracy of left/right judgement tasks and disability has been reported in cervical pain (301) and between accuracy and reported pain in low back pain (298). This current study failed to find a relationship between either accuracy or reaction time of the left/right judgement tasks and pain and disability. Bowering et al (2014), similarly failed to associate reaction time with reported low back pain, but did find an association with accuracy and pain. The results of this study offer some preliminary data to consider that people with RC related shoulder pain may not all have altered proprioceptive maps considering the lack of difference in left/right judgement tasks accuracy and reaction times between affected and unaffected side measures and the lack of association between left/right judgement tasks and reported pain and disability.

TPD was positively associated with pain in our study, indicating that the higher the TPD values i.e. the poorer the participants' tactile acuity, the higher their reported pain scores. A previous systematic review identified studies of CRPS cohorts investigating TPD acuity to have also found a positive correlation between larger TPD values and higher reported average pain in two studies and current pain intensity in another study. This review found no association between these variables within low back pain, non-specific chronic pain and arthritic pain (302). The current study aligns with the findings within the CRPS cohorts where TPD acuity and reported pain are associated, but the lack of consensus across all musculoskeletal presentations may indicate that an association between TPD and pain in all chronic musculoskeletal presentations may be condition or location specific. Although this study showed an association between TPD and pain, this study also showed high levels

of variability between participants. To identify if the findings of this study are consistent with other shoulder pain cohorts larger studies may be required with clearer defined methods of TPD assessment.

Associations between SPADI pain and disability scores before surgery and potential confounding factors

This study found that higher levels of self-reported pain and disability were significantly associated with larger waist circumference measures, but not with other potential confounding variables (duration of symptoms, psychological distress, age or gender). Increased BMI and measures of central obesity have been reported to be associated with higher levels of self-reported pain and disability in people experiencing shoulder pain, as measured by the SPADI, ASES (American Shoulder and Elbow Surgeon) and SST (simple shoulder test) (78, 80, 303). This present study also observed higher levels of BMI with higher levels of reported pain, but this association was not statistically significant, most likely due to the limited power of the study. A previous study also found higher BMI and waist circumference measures to be the only demographic variables associated with higher SPADI scores (78). Weight related factors have been previously linked to RC related shoulder pain. Obesity has been found to be a significant risk factor in the presence and severity of RC tears (304, 305). Waist circumference and hip-to-waist ratios have been related to an increase in prevalence of RC disease (69) and higher BMI has been associated with higher levels of reported pain and disability (78). Of all the weight related factors considered, the strongest association for shoulder pain found was waist circumference and hip-waist ratios, which are both measures of central obesity (69). Increased weight related factors have been linked with an increase in pro-inflammatory cytokines (interleukein-1, Interleuken-6 and TNFα) (124), which in turn have been associated with nociceptive hypersensitivity (117). It is hypothesised that central obesity is related to impaired glucose metabolism, resulting in an accumulation of by-products of proteins or lipids that become glycated as a result of exposure to increased sugar levels and accumulate in tendons (306). These by-products form dysfunctional crosslinks within the collagen fibres of tendons leading to alteration in tendon structure, and can also trigger a number of pro-inflammatory pathways and perpetuate a cycle of inflammation (307).

In this study the majority of participants (44%) had experienced their pain for greater than 24 months, but did not have significantly higher levels of reported pain and disability than those who had a shorter duration of symptoms. There is conflicting evidence concerning

the relationship between duration of symptoms and self-reported pain and disability. The duration of a person's symptoms has been shown to be positively correlated with disability and self-reported greatest pain (154), but not with the SPADI (280), ASES (American Shoulder and Elbow Surgeon) (33), WORC (Western Ontario Rotator Cuff) (33), pain on presentation (308), and a combination of various shoulder status outcomes (309) in previous research. RC disease is considered a continuum and part of normal aging processes, with a 50% likelihood of developing a RC tear when over the age of 60 (135). Up to 65% of RC tears can be asymptomatic (31), making an exact date of onset of symptoms often difficult to determine with degenerative RC pathology. Additionally, all the participants included in this study were recruited from a public hospital surgical waitlist and therefore this study may be biased to more chronic presentations.

The sample in this study had low levels of psychological distress in general compared to reports in other studies (78, 80, 280), and there was no association between these values and either patient reported pain or disability. Only between 15-30% of the participants in this study scored outside of what is considered normal values for the individual depression, anxiety and stress scales. The fact that this particular sample did not show an even distribution of psychological distress, as well as the small sample size, would make finding any associations difficult and unreliable. There is however growing evidence linking psychological factors including anxiety and depression to shoulder pain in general (78, 79) and more specifically to people with RC related shoulder pain (21, 42, 80-82). Similar to this study, a previous investigation into the role of CNS processes in elbow tendon pathology, found low levels of anxiety and depression in participants with tendon pathology which were comparable to asymptomatic controls (174). Coombes et al (2015) did not find a link between mental health and self-reported pain and disability in chronic elbow tendinopathy. Despite the fact that some studies have identified that pathology at the site of musculoskeletal pain is not well correlated to self-reported pain and disability (31, 310, 311), the results of this study do not support psychological distress as a likely explanation for pain and disability levels. This is in contrast to a recent study that identified the importance of psychological factors in comparison to actual tissue pathology in RC related shoulder pain, reporting that these psychological factors have a greater association with pain and disability in comparison to RC tear size (80).

The incidence of both symptomatic and asymptomatic tears increases with age (31). Despite these figures, there was no evidence in this study to support a relationship between increasing age and an increase in self-reported pain and disability. Similar to our

study, previous studies investigating the association of age with pain and disability have found no association (33, 312). These studies, similar to the current one, included participants with a mean age around 60 years. In contrast, Curry et al (2015), identified in a cross-sectional study of patients with diagnosed RC tears that self-reported pain and disability was significantly associated with age. Patients younger than 60 years reported having significantly more pain and greater disability than patients over 60 years of age. The authors hypothesised that this finding may be related to the difference in physical demands of younger patients. A gradual decline in physical demands and physical capacity and lower expectations of shoulder capacity may be reflected in less pain and disability being reported in some older groups but this is not consistent. The lack of findings of an association between age and pain and disability in our study and other studies may reflect the fact that age is not a direct indicator of disability and activity of the shoulder and perhaps the level of physical requirements or shoulder activity would show a clearer association with pain and disability in the shoulder.

It has become widely accepted that females have greater persistent pain prevalence than males (39), report pain more frequently (313) and have higher levels of medication intake to manage their pain (39, 314). In this study, females had higher levels of pain than the males, although this was not a statistically significant difference. A previous study on 59 participants awaiting surgery for shoulder pain, identified that age and gender accounted for 12.7% of variability in clinical pain intensity (315). Our small sample size is the most likely reason for the lack of significance, as female gender has been previously associated with higher SPADI pain and disability scores in RC related shoulder pain (280, 312, 316).

Associations between potential confounding factors and measures indicative of CNS processing

Confounders and nociceptive sensitivity measures

Our final consideration was to assess associations between potential confounders: age, gender, duration of symptoms, waist circumference, BMI and psychological distress and measures indicative of CNS processes. PPT was associated with BMI and gender but not with any other variables, whilst CPS was not significantly associated with any considered variables in our study. Females experiencing shoulder pain have previously been found to have lower thresholds to pressure pain compared to males (153, 189, 193). Our study partially corroborates this, finding females had a trend towards lower thresholds to

pressure pain compared to males at the painful shoulder site (p=.092) and significantly so over the lower leg (p=.002). Female gender has been also associated with lower thresholds to pressure pain in pain free participants (183, 191), whiplash associated disorder (317) and low back pain (318). BMI was significantly associated with PPT at the leg in this study indicating that a higher BMI was associated with lower tolerance to mechanical pressure. Lowered thresholds have been found to be associated with obesity in pain free populations (319, 320). The relationship between PPT measures specifically at the shoulder and BMI in people with shoulder pain has not previously been investigated. It would make sense if both PPT over the shoulder and remotely over the leg were associated with decreased pressure pain thresholds due to increased local inflammatory cytokines found in the subcutaneous tissues of people with larger BMI values. Consistent with the evidence the observed correlations in the current study indicate a similar strength and direction of association between PPT at the shoulder and BMI and PPT at the leg with BMI although low power may have limited detection of statistically significant results.

PPT and psychological distress were unrelated in our sample. Previous studies investigating shoulder pain have assessed psychological domains and found a correlation between fear avoidance (157), pain catastrophizing (157, 188) and fear of pain (157) with lower PPT measures. As previously mentioned, the current sample showed very low levels of psychological distress, and combined with the low power of the study likely explains the lack of any detected association. Additionally there was no evidence within this study of an association between age and PPT scores at the shoulder. A recent systematic review and meta-analysis has identified pain thresholds increase with age for most physical stimuli, likely explained by a decline in somatosensory function with age, yet the relationship for pressure pain thresholds and age remains unclear (321). The explanation offered for this finding was that other measures of pain thresholds selectively assess superficial nociceptors, whereas assessments of pressure would assess superficial and deep tissue nociceptors, which may be differently affected by age. PPT at the leg was significantly associated with age, indicating that older patients were more sensitive to pressure pain. This finding has been previously found in older healthy pain free male participants (322). The association between age and perception of experimental pain is not fully understood.

Finally, no association was found between measures of nociceptive sensitivity and duration of symptoms in the current study. Coronado et al 2014 (157), investigated the presence of widespread sensitivity (thermal and mechanical) in RC related shoulder pain and found a positive association between the presence of general nociceptive hypersensitivity and

duration of symptoms, but did not report on its association with reported pain levels or disability. The aforementioned study used pain free controls as a comparison group and were able to identify those participants who in comparison to the controls were sensitised. Unlike the current study, no control was used and a larger sample may be required to investigate this association.

Although CPS was not associated with any variables assessed as potential confounders in our study, previous studies have identified female gender, younger age and poorer mental health to be associated with decreased CPT indicating greater sensitivity in pain free populations (183, 191) and female gender, pain catastrophizing, poor sleep quality, higher levels of depression and anxiety has been associated with decreased CPT in neck pain patients (192). George and colleagues (315) identified that age and gender accounted for 7.3% of variability in CPT scores in a study of 59 participants seeking operative procedures for shoulder pain. Studies using cold thermal thresholds in RC related shoulder pain cohorts to assess nociceptive functioning are limited making comparative observations difficult. Unlike the available evidence, this study made use of CPS, making a comparison even more challenging. Only six participants presented with CPS scores >5 over the affected shoulder, indicating hypersensitivity to cold. These numbers don't allow for identifying any associations between CPS scores with gender and age.

Confounders and measures of body representation

Age and duration of symptoms were the only variables associated with measures of body representation in this study. TPD was positively related to age, indicating that older patients had a greater tactile threshold. Age has been previously identified as a correlate of TPD in some pain free populations (274, 323-325). Conversely a number of studies have shown age to have no association between TPD and age in the knee (273) and shoulder (276). Most of the studies included in a systematic review and meta-analysis of various musculoskeletal conditions including low back pain, CRPS and rheumatoid and osteoarthritis failed to use age-matched controls to fully explore this association between age and TPD, and therefore no conclusive data is available (302). These age related changes have been identified to not be related to age related changes in skin compliance but rather changes in the nervous system (326, 327). Additionally these age related changes in TPD have been linked with age-related cortical re-organisation and changes in CNS controlled inhibition (327).

In this study, an increase in left/right judgement task reaction time for identifying an image was also associated with increased age. There was however no association between age and left/right judgement task accuracy. Similarly Breckenridge et al (2017) also found age was related to increased reaction time but not decreased accuracy, finding that older participants were slower to identify the images of the shoulder in pain free participants. Reaction time is considered a process of deciding on side, mentally positioning the appropriate body and confirming this, each of these processes may slow with aging. Age has been linked to increased reaction times in patients with neck pain (259) and in pain free individuals (328). Similar to our study previous studies, including two studies with over 1000 participants, have found no association between age and accuracy (236, 259, 298, 328). Arguably the current study is not adequately powered to detect an association, but these referenced studies have had adequate power and provide stronger evidence of a lack of association between age and left/right judgement task accuracy.

This study identified an association between increasing left/right judgement task reaction time and increasing duration of symptoms, similar to the findings in a CRPS cohort (242). Duration of symptoms has been previously linked to the extent of cortical reorganisation in a population with chronic low back pain (269) and in people with an amputation (215). Since left/right judgement tasks are considered a means of assessing postural schema and are reliant on accurate proprioceptive and cortical maps, the extent of reorganisation defined by duration of symptoms may offer an explanation for increased reactions times with participants presenting with longer duration of symptoms. Surprisingly, a previous study of cervical and whiplash related pain identified an opposite association with duration of symptoms, whereby the more chronic the presentation the faster the reaction time, without any sacrifice in accuracy (261). These results were considered evidence that perceptual learning occurs as an adaptation in more chronic presentations.

Similar to our findings, previous studies have not identified a relationship between duration of symptoms and TPD in knee OA (267), low back pain (329), rheumatoid arthritis (330) or CRPS (221). As previously mentioned, the overall levels of self-reported body perception disruption were very low in the current study, and may offer a reason for the observed lack of association. Unlike the present study however, duration of symptoms have been associated with increased reports of disrupted body perception when self-reported questionnaires on body representation have been used (250, 296). There is evidence available that the extent of cortical reorganisation is linked to duration of symptoms and may explain this finding (220). Our final confounders taken into consideration were gender

and weight related factors. This study found no associations between gender and TPD or left/right judgement tasks. Previous studies assessing gender differences in TPD acuity have had mixed findings, with significant differences found in some (150, 273) and not in others (270, 274, 331). Previous studies of left/right judgement tasks have concurred with this current study and also found no association with gender (298, 332) and dominance (298, 332). This current study also found little association between either BMI or waist circumference and TPD, but unlike our study, there is evidence for the association between TPD and BMI/ waist circumference measures in back (274) and knee (273) regions. TPD studies offer very variable and inconsistent results, mostly attributed to variable testing protocols (333). Weight related factors affect skin sensitivity and detection thresholds and standardised methodology especially with regards to the extent of pressure used may play an important role in ensuring comparability of future studies. .

Strength and Limitations

To our knowledge this is the first study investigating the relationship of both altered body representation and nociceptive sensitivity in one cohort, and their relationship with self-reported pain and disability in people with RC related shoulder pain. Several limitations from this study should be acknowledged. No clear conclusion could be made from the findings of this study due to the small sample size of 34. Initial power calculations estimated a sample of 100 participants would be required to give sufficient power to detect an R^2 increment of 0.07 attributable to a single sensitivity or perceptual measure in multivariable regression models. Only 114 patients were waitlisted and 27 of those were subsequently removed from the waitlist. Of the remaining likely participants, only 34 consented to take part or matched the inclusion criteria. These low numbers meant the study was underpowered to detect meaningful associations and the small sample size also limited the number of variables that multivariable models could be adjusted for. As normative data are lacking, measures of nociceptive sensitivity and measures of body representations in a matched control sample without pain in this study would have enabled clearer observations regarding widespread pain sensitivity and disruptions in body representation in unilateral shoulder pain. Additionally the neurobehavioural neglect questionnaire was developed for distal arm pain from CRPS and may not have been ideal for proximal arm pain as is evidenced by the large number of zero scores. Finally the results of this study are limited to patients presenting with shoulder pain awaiting RC surgery within a public health service.

Implications for future research

This study offers some limited data to contribute to the growing body of literature in shoulder pain implicating altered CNS processing as a contributing factor associated with persistent pain and disability experienced by people with RC related shoulder pain. Recommendations for future studies would include the use of a larger sample and the inclusion of a control group. The aim of this study was not to identify the presence of central sensitisation, but rather whether any measures indicative of altered CNS processing including nociceptive sensitivity and changes in body representation are associated with shoulder pain and disability in people with RC disease. Greater participant numbers would be required to identify if there is a specific sub-group within RC related shoulder pain cohorts that present with CNS related factors as their main driver of persistent pain and disability. Only a small number of participants presented with heightened pain responses to cold and pressure or poorer tactile acuity and left/ right judgements indicative of disruption of body representation. For more meaningful analysis a larger sample would be required to identify what associations truly exist in shoulder pain.

Clinical implications

Shoulder pain is a very prevalent musculoskeletal complaint. This study offers some consideration of the fact that body representation (TPD) and nociceptive sensitivity (PPT) are related to self-reported shoulder pain and disability in people with RC related shoulder pain. These changes implicate central and peripheral nervous system changes that are not yet fully understood. Taking these findings into consideration, assessing nociceptive hypersensitivity as measured by PPT and altered body representation as measured by TPD may be helpful. A subgroup of patients presenting with shoulder pain diagnosed as RC disease may not respond well to management strategies that only focus on local tissue pathology. These patients may also not benefit from surgical processes which are patho-anatomically based and aim to rectify the RC dysfunction as is evidenced by the number of patients who present with ongoing pain following surgery or those who have re-tears but report significant improvements and good outcomes. The use of some simple bedside tools to obtain measures potentially indicative of altered CNS processing may offer an adjunct to treatment plans. The equipment required for TPD assessments is inexpensive and easily available. Palpation has been shown to be moderately correlated to PPT and may offer a clinical option of pressure pain assessment without the cost of an algometer (192). It is important for the clinician to be aware that a proportion of patients presenting with RC

related shoulder pain might have CNS related factors that are contributing to their persistent symptoms.

Conclusion

This study found that poorer TPD acuity was associated with higher levels of shoulder pain and an increase in sensitivity to pressure was associated with higher levels of self-reported disability in people with shoulder pain about to undergo surgery for RC related shoulder pain. No other measures indicative of CNS processing were associated with self-reported pain and disability. This offers limited preliminary data that some perceptual CNS related factors may be implicated in persistent RC related shoulder pain, but further research is required. Low numbers meant the study was underpowered to detect any meaningful associations which may exist in this population.

Study 2

Introduction

Shoulder surgery for RC related shoulder pain is often the chosen intervention for patients that don't respond to non-surgical management (334, 335). Surgery aimed at improving RC integrity and sub-acromial tissue health is one of the most common orthopaedic procedures, with between 200 000-300 000 repairs alone done each year in the USA (99). Global arthroscopic RC related surgical rates have increased significantly in recent times (99-103). Similar trends and their associated financial burden to the health system and work force have been found locally in Western Australia (26). Despite these escalating rates of surgery, not all patients benefit from RC related shoulder surgery (115). Identifying factors associated with successful outcomes would be helpful in surgical decision making.

RC pathology is prevalent and appears in keeping with age appropriate degeneration. Up to 65% of these identified with RC pathology through radiology can present asymptomatically (31, 133). Additionally people with failed RC repair can report similar pain and disability outcomes to those for whom cuff integrity has been maintained after surgery (110). A number of demographic, psychosocial and structural factors have been previously investigated, but do not account for the variance in outcome following RC related shoulder surgery (86, 114). This highlights the need to identify non-structural factors associated with pain and disability outcomes.

Furthermore, not all patients benefit from surgical procedures. Shoulder surgery is largely directed at peripheral pathology considered to be the source of nociceptive activation. However, pain mechanisms and CNS pain processing in patients undergoing surgery may differ, meaning surgery may be less effective in those with more CNS involvement, compared to those presenting primarily with peripheral pain mechanisms (117).

Factors related to pain processing within the CNS in patients undergoing RC surgery have been examined to identify whether any of these factors could be associated with poor outcome after shoulder surgery (8, 190). Gwilym et al (2011) identified that within a group of 17 patients undergoing subacromial decompression surgery, those who were categorised as having hyperalgaesia over the affected shoulder, as measured by lower punctate sharpness thresholds compared to controls, had significantly poorer outcomes of shoulder pain and disability, three months post-surgery. However, a more recent study by Valencia et al (2013), failed to find an association between preoperative measures indicative of

altered CNS processing pain and disability six months after surgery in 78 patients undergoing various forms of shoulder surgery including RC surgery, suggesting further research is needed.

Changes in nociceptive processing are not the only CNS factors that might contribute to clinical status after RC surgery. Changes in body representation or perception have been identified in people presenting with chronic musculoskeletal pain (220) and a number of mechanisms whereby this might contribute to persistent pain have been proposed (230, 231). No other studies have been identified that explore the association between measures indicative of altered body representation and self-reported pain and disability following surgery for RC disease.

Aim

To assess the predictive association between measures of body representation and nociceptive sensitivity before RC surgery, and shoulder pain and disability 12 months after surgery, adjusting for potential confounders.

Research Methods

Design

A longitudinal cohort study of people undergoing RC surgery was conducted at a tertiary hospital in Perth Western Australia. Ethical approval from both Curtin University (HR 178/2013) and Sir Charles Gairdner Hospital (HREC 2013-202) was granted, and all participants provided informed consent.

Participants

Between June 2014 and June 2015 patients on a surgical waitlist for RC surgery were invited to participate in the study. One hundred and fourteen people were screened for eligibility. Thirty-four patients who met the inclusion criteria consented to the study and partook in the cross sectional study as outlined in 0. Figure 0.1 outlines the flow of participant recruitment and 12 month follow-up.

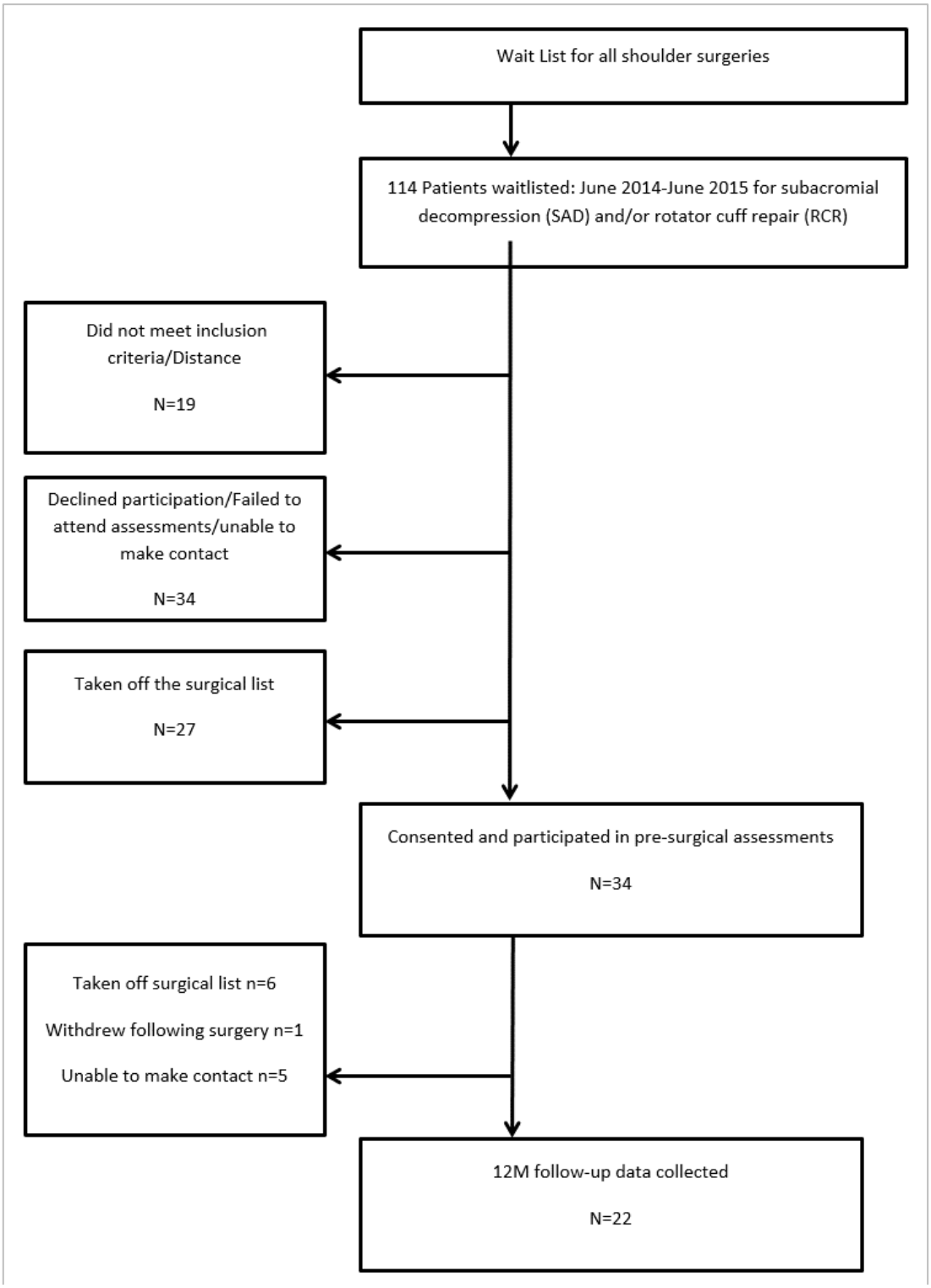

Figure 0.1 Study 2: Flowchart of participant

Procedure

Baseline data were collected at the preoperative assessment as described in 0. Twelve months after surgery, participants were mailed a paper copy of a questionnaire for completion and return.

Measures

Shoulder Pain and Disability

Shoulder specific pain and disability was evaluated 12 months after surgery using the self-administered Shoulder Pain and Disability Index (SPADI)(283), as described in 0. The responsiveness of this instrument for use in longitudinal studies has been confirmed (336).

Body representation and nociceptive sensitivity

1. The following measures were obtained at baseline and are fully described in 0:Nociceptive sensitivity to pressure and cold both locally and remotely
2. Self-reported body perception (via modified Neurobehavioural Questionnaire)
3. Left/Right Judgement Task (LRJT) accuracy and speed
4. Two point discrimination threshold

Potential confounders

Potential confounders assessed were gender(174, 191-193, 235), age (183,192,259), Body Mass Index (BMI) (273,274), waist circumference(191), duration of symptoms (273) and symptoms of depression, anxiety and stress (191-192) as described in 0.

Statistical Analysis

Correlation analysis was used to assess the association between SPADI pain and disability scores at 12 months and demographic measures, duration of symptoms, psychological distress measures and the baseline value of the SPADI score. Pearson's, Spearman's and point biserial correlation coefficients were used for continuous, ordinal and categorical data respectively. For subsequent regression analysis CPS and the Neurobehavioural questionnaire scores were transformed to binary indicator variables, due to the floor effects, indicating a score of 0 versus >0, and PPT, LJT reaction time and TPD were log-transformed to normalise skew. Multivariable regression analysis was used to examine the association of each body representation and nociceptive sensitivity measures with SPADI scores 12 months after surgery, adjusted for the baseline value of the outcome. Statistically this equates to identifying if body representation and nociceptive sensitivity measures are associated with change in pain or disability over the 12 month follow-up period, and this method is the most

statistically efficient method for examining associations of independent variables with change in score over time (337). Analyses were adjusted for potential confounding variables. Results are presented as standardised and unstandardised regression coefficients with associated 95% confidence intervals. As SPADI pain and disability scores at 12 months follow-up were right-skewed, bootstrapped standard errors (1000 replications) were used to estimate 95% confidence intervals and associated p-values.

A priori power analysis indicated a sample of 100 will give 83% power to detect R^2 changes in multivariable regression models of at least 7%. (i.e. correlation coefficient for independent associations of 0.26 or more). All data were analysed using the IBM SPSS statistical package (version 22).

Results

Of the 34 participants consented and included in the cross sectional study, 12 participants did not complete the 12 month follow-up questionnaires. Of these, six participants were removed from the surgical waitlist after recruitment into the study, one participant withdrew during the follow up period and five participants did not return their follow up questionnaires and did not respond to reminders.

Table 0.1 compares baseline measures between those participants who participated in the 12 month follow-up to those who did not. There was a significant difference for self-reported SPADI disability (P=.035), with the group not completing follow-up reporting significantly higher levels of disability. In addition, this group had significantly lower PPT scores (P=.045). There was no significant difference between the two groups for any other of the variables.

In the 22 participants with 12 month data, SPADI pain score improved from 61.7 to 24.9, with a mean change score mean of 32.2, 95% CI [18.1, 46.3]. SPADI disability score improved from 49.9 to 18.8 with a mean change score of 25.0, 95% CI [12.1, 38.0], more than the minimal detectable change of 18 points (338). Table 0.2 displays the correlations between baseline variables considered as potential confounders and 12 month SPADI pain and disability scores. No variables were significantly associated with 12 months SPADI pain or disability scores.

Table 0.1 General characteristics of patients lost to 12 Month follow-up

Characteristic	Participants completed 12m follow-up (N=22) *% or mean (SD)*	Participants lost to follow up (N=12)	P value
Demographics			
Gender n males (%)	13 (59.1%)	8 (66.7%)	.664
Age years	61.6 (17.3)	60.3 (17.2)	.795
Body mass index	29.8 (7.6)	29.9 (6.3)	.952
Waist circumference(cm)	103.1 (16.2)	105.9 (19.5)	.649
Duration of symptoms* n (%)			
0-3M	1 (4.5%)	1 (11.1%)	.640
>3-6M	3 (13.6%)	0	
>6-12M	3 (13.6%)	2 (22.2%)	
>12-24M	5 (22.7%)	1 (11.1%)	
>24M	10 (45.5%)	5 (55.6%)	
Psychological distress (DASS total)[#]	13.7 (17.3)	23.0 (29.8)	.331
Clinical Measures			
SPADI[ǂ]			
Pain score	57.7 (17.7)	72.2 (24.4)	.088
Disability score	44.4 (20.2)	62.7 (22.1)	.035
Neurobehavioral Q[Δ] (0-25)	2.4	1.6	.504
LJT			
Reaction (Sec)	1.9	2.4	.064
Accuracy (%)	88.9	85.8	.235
TPD (mm)	53.2	59.6	.504
PPT (KPascals)			
Shoulder	579.4	363.3	.045
Leg	811.0	767.2	.726
CPS (VAS 0-10)			
Shoulder	2.8	1.8	.436
Leg	1.5	1.2	.766

Abbreviations: Abbreviations: SD, standard deviation; IQR, interquartile range; N, number; SPADI, Shoulder Pain and Disability Index; JLT, laterality judgement task; TPD, two-point discrimination; PPT, pressure pain threshold; CPS, Cold Pain Sensitivity; DASS, Depression Anxiety Stress Scale.
*Data missing 3 cases; [ǂ] Data missing 5 cases; [#] Data missing 8 cases; [Δ]Data missing 4 cases

Table 0.2 Associations between SPADI Pain and Disability Scores 12 months post-surgery with baseline demographics, duration of symptoms, psychological distress and SPADI scores

	SPADI	
	Pain 12 months	**Disability 12 months**
Gender	.262[c] p=.238	.118[c] p=.602
Age	.043[a] p=.849	.115[a] p=.611
Body mass index	-.167[a] p=.456	-.029[a] p=.899
Waist circumference	-.282[a] p=.204	-.049[a] p=.830
Duration of symptoms	.211[b] p=.347	.235[b] p=.292
DASS total	.214[b] p=.378	.298[b] p=.215
Baseline SPADI score	.128[a] p=.581	.302[a] p=.183

[a]Pearson's correlation coefficient
[b]Spearman's correlation coefficient
[c]Point-biserial correlation coefficient
Abbreviations: SPADI, Shoulder Pain and Disability Index; DASS, Depression Anxiety Stress Scale

Table 0.3 displays the results of the series of linear regression models of 12 month post-surgery SPADI pain and disability scores regressed on each independent variable, adjusted for baseline values of pain/disability. Although gender and waist circumference were not found to be significantly associated with 12 month SPADI pain and disability, these were considered as potential confounding variables due to the association with baseline SPADI, PPT and CPS in the larger sample from 0, and thus models with PPT and CPS as independent variables were also estimated adjusted for gender and waist circumference. In unadjusted analysis, having CPS > 0 at the shoulder was significantly associated with a higher SPADI pain score at 12 months (25.2 points, 95%CI:3.7 to 46.8) but this association was not statistically significant after adjustment for waist circumference (21.7 points, 95%CI:-5.1 to 48.4). No other measures of nociceptive sensitivity nor any measures of body representation were significantly associated with change in either SPADI pain or disability in other unadjusted or adjusted analyses.

Table 0.3 Associations between body representation and nociceptive sensitivity variables and SPADI pain and disability at 12 months post-surgery adjusted for baseline score (Model 1), and additional potential confounding variables (Model 2)

		SPADI Pain 12 months			SPADI Disability 12 months		
		Regression Coefficient (95%CI)	P-value	Standardised coefficient	Regression Coefficient (95%CI)	P-value	Standardised coefficient
PPT Shoulder (ln)	Model 1	-7.1 (-25.7–11.5)	.412	-.18	-8.1 (-30.8-14.6)	.485	-.21
	Model 2[a]	-11.5 (-35.3-12.3)	.342	-.28	-9.8 (-34.6-15.1)	.442	-.25
PPT Leg[c]	Model 1	-1.8 (-5.5-1.7)	.311	-.24	-1.1 (-6.1–2.8)	.585	-.15
	Model 2[b]	-1.8 (-7.0-3.4)	.491	-.24			
CPS Shoulder[d]	Model 1	25.2 (3.7-46.8)	**.022**	.46	8.8 (-15.1-32.7)	.371	.17
	Model 2[a]	21.7 (-5.1-48.4)	.112	.40	7.5(-17.5-32.5)	.558	.14
CPS Leg[d]	Model 1	5.3 (-30.3-40.9)	.770	.08	6.7 (-17.3-30.7)	.585	.11
Neglect[e]	Model 1	-1.1 (-26.6-24.3)	.931	-.02	7.9 (-17.3-33.2)	.538	.15
Laterality Reaction(ln)	Model 1	-36.7 (-82.5-9.1)	.117	-.34	-25.0 (-67.4-17.4)	.248	-.24
Laterality Accuracy	Model 1	-1.0 (-3.1-1.1)	.353	-.19	-1.3 (-3.4-0.8)	.226	-.26
TPD (ln)	Model 1	-15.1 (-37.5-7.3)	.187	-.25	-13.7 (-31.6-4.1)	.132	-.24

adjusted for [a]waist circumference, [b]gender

[c]Regression Coefficient represents expected increase in SPADI score for 100Pa

[d]Regression Coefficient represents difference in SPADI score between those with CPS=0 versus CPS>0

[e]Regression Coefficient represents difference in SPADI score between those with Neglect=0 versus Neglect>0

Abbreviations: SPADI, Shoulder Pain and Disability Index; TPD, two-point discrimination; PPT, pressure pain threshold; CPS,Cold Pain Sensitivity; DASS, Depression Anxiety Stress Scale.

Discussion

This study aimed to identify whether measures of body representation and nociceptive sensitivity before surgery are associated with shoulder pain and disability 12 months after surgery. Participants undergoing surgery for RC related shoulder pain or RC tear reported a decrease in overall self-reported pain and disability at 12 months following surgery compared to before surgery. No measures of body representation and nociceptive sensitivity before surgery were identified to be associated with pain and disability scores 12 months following RC surgery.

Association between measures of nociceptive sensitivity before surgery and SPADI scores 12 months after surgery

There is some emerging evidence for the use of various QST measures prior to surgery to predict outcomes following surgery. These measures include measures of thresholds as used within the current study, which are static measures of pain processing. Neither PPT nor CPS was found to be predictive of pain and disability 12 months after surgery in the current study. The only other study to make use of static QST to investigate nociceptive processes in patients awaiting RC surgery investigated the relationship between mechanical pain threshold measures at baseline and patient reported outcomes three months after subacromial decompression surgery. This group divided the baseline mechanical pain thresholds into binary values using the mean value (high and low sensitivity) and found a significant difference with the high sensitivity group having poorer self-reported pain and disability scores as measured by the Oxford Shoulder Scale (OSS) (8).

Other studies include dynamic measures of pain processing, which give insight into facilitatory or inhibitory pain modulation. There is no consensus within the literature as to the optimal battery of testing, and whether the cluster of tests chosen should be specific to pain region or condition. Dynamic measures of nociceptive processing at baseline and three months following surgery have been explored as predictors of pain and disability six months after arthroscopic shoulder surgeries for RC repair, adhesive capsulitis, acromioplasty and labral tears (190). Baseline measures did not predict pain and disability six months following surgery. Although baseline QST measures in the aforementioned study were not predictive of pain and disability six months after surgery, the change score (baseline measures compared to QST measures three months post-surgery) of suprathreshold heat pain responses were predictive of pain and disability six months after surgery (190). Unlike

the current study, the aforementioned study identified changes in the CNS facilitatory functioning as measured by suprathreshold heat pain to be predictive of outcome post-surgery. This may indicate that a decline in facilitatory pain mechanisms after surgery could be predictive of less pain and less disability at later time points after surgery. However, overall the literature reporting on associations of nociceptive sensitivity prior to surgery and outcomes of pain and disability following RC surgery is limited.

Widespread hyperalgaesia has been previously identified in patients undergoing knee and hip replacement, and these measures of nociceptive sensitivity have been shown to normalise following surgery (178, 186, 207). Additionally both static and dynamic measures of pain processing prior to knee and hip surgery have been explored for their predictive utility for risk of chronic post-surgical pain and disability. Widespread hyperalgaesia identified by significantly lower PPT scores at the forearm of participants awaiting total knee replacement compared to healthy controls have also been found to be predictive of pain and disability 12 months post-surgery in people undergoing knee replacement (176). Similarly, reduced pain thresholds to electrical stimuli tested remotely to the knee, indicating widespread hyperalgaesia, measured prior to knee replacement have also been found to be significantly associated with greater pain levels 18 months after surgery (208). Conversely a number of studies have refuted the use of PPT testing either locally or remotely prior to surgery to predict pain and disability following surgery. Lower PPT locally and remotely prior to knee replacement has been found to not be associated with the amount of pain relief reported (difference between mean VAS prior and following surgery) 12 months following surgery(181). Additionally no correlation has been found between reported pain 12 months following surgery and the preoperative local and remote PPT measures in people undergoing knee replacement (207). However, Wylde et al (2013)(176) found a positive correlation between remote but not local PPT measures and pain and disability 12 months following knee replacement. In a study of people undergoing hip or knee replacement, remote PPT measures prior to surgery indicating widespread hyperalgaesia were associated with pain 12 months following surgery only in the hip group (279). Dynamic pain processing measures (conditioned pain modulation and temporal summation) were not significantly associated with pain and disability 12 months after knee replacement surgery when considered independently, but people with both facilitated temporal summation and impaired conditioned pain modulation reported significantly higher pain than other participants (181). Compared to these previous studies where participant numbers ranged between 69- 322, the current study had less power to detect significant associations between pre-surgical

measures of nociceptive sensitivity and outcome after surgery. Although many static and dynamic measures, in isolation or combination, indicating either facilitated or inhibited pain modulation, have been investigated for their predictive utility for outcome after surgery for various conditions, the evidence of an association between these and pain and disability following surgery varies. The lack of consistent findings, varied protocols, the use of local and remote sites, and the lack of understanding of the exact neurophysiological mechanisms of each measure highlights that further research is required and may need to be site specific.

Association of measures of body representation before surgery with SPADI scores after surgery

Neither physical measures of body representation (TPD and left/right judgement tasks), nor self-reported body perception, were found to be associated with pain and disability 12 months following RC surgery in this study. This finding is at odd to the growing evidence of a link between altered body representation and pain (220). For shoulder pain, evidence is still emerging, but to date some studies have provided evidence, albeit indirect, that like many other chronic musculoskeletal presentations RC related pain is also linked to changes to body representation. Brain mapping using MRI and transcranial magnetic stimulation have identified altered activation patterns within the motor cortex whereby affected RC muscles showed decreased excitability on the affected compared to unaffected side (339) and deltoid muscles on the affected and unaffected side compared to healthy controls showed increased excitability, which was argued to be a compensatory mechanism commonly found in RC disease (340). Several studies have reported that people with shoulder pain present with suboptimal motor control (341, 342) and proprioception (247, 248). In people with altered motor control and proprioception, improved proprioception was observed after surgery for RC disease (248, 249). Although changes in body representation have been suggested in people with RC related pain, there is little to suggest an association with outcomes after surgery. This study assessed left/Right judgement tasks, TPD and self-reported body perception, as representative measures of body representation. A relationship between these measures of altered body representation at baseline and pain and disability following surgery could not be established in this study either. The neurobehavioral questionnaire used in this study has been previously utilised in a study of people three and six weeks after knee joint replacement surgery to identify the presence of perceptual alterations, but it has not been assessed prior to surgery as a predictive tool for pain and disability after surgery (258). In the aforementioned study, patients who reported

specifically motor perceptual deficits rather than cognitive deficits three and six weeks following surgery had significantly more post-surgical pain at these time periods. Surgery itself may induce perceptual changes that are greater indicators of outcome of pain and disability at 12 months following the procedure. Further research is required to identify whether these measures of body representation measured prior to surgery or at various stages after surgery may also be linked to pain and disability following surgery.

Associations between SPADI scores, demographics and psychological distress before surgery and SPADI scores after surgery

Female gender, untreated depression and high baseline pain intensities have been found to be associated with an increased risk in developing chronic post-surgical pain in general (343). There was however no evidence in the current study for an association between any demographic factors, pain and disability measured at baseline or psychological distress and the final outcome of patient reported pain and disability 12 months following RC surgery.

Age has previously been identified as a significant prognostic factor of post-surgical pain and disability following RC surgery (113, 114, 344). Age was not significantly associated with self-reported pain and disability at 12 months in this current study and some previously published studies (345-347).

In this study gender was not associated with pain and disability after surgery, similar to previous studies investigating pain and disability outcomes post RC surgery (345, 348-350). Conversely, a number of studies have identified a significant association with female gender and greater self-reported pain and disability six to twelve months after shoulder surgery (347, 351-353).

There is limited evidence investigating the association between patient reported pain and disability prior to and 12 months following RC surgery, and this study did not identify an association between the two. Previous studies have corroborated this finding for various outcome measures including the Constant Score (351), ASES (American Shoulder and Elbow Surgeon score) (354), DASH (disabilities of arm, shoulder and hand) (355) and WORC (Western Ontario rotator cuff index) (355). Of the 64 studies found within a systematic review investigating prognostic factors influencing outcome following RC related surgery, only eight reported using baseline outcome measures of pain and disability to predict pain and disability following surgery. Based on these limited studies they reported five studies to have found a significant correlation between pre-surgical and post-surgical patient reported

pain and disability outcome measures (113), but only one matched a similar population and surgical interventions to our current study (356). In contrast to the current study, this aforementioned study included 118 participants compared to the 22 participants in the current study that completed 12 month data. It is likely that the participant numbers limited finding any association, but further studies with large participant numbers would be required to identify if this association truly exists.

The role of duration of symptoms prior to RC surgery is not frequently reported on in studies investigating association of factors before surgery and post-surgical pain and disability. Considering that 50% of the population over the age of 60 present with asymptomatic RC tears (135), reporting of duration of symptoms may be difficult to assess as RC pathology presents as a continuum and the onset of symptoms is gradual and subjective. This current study did not identify a significant association with duration of symptoms before surgery and pain and disability after surgery, similar to several reported studies (114, 345, 357).

Obesity has been identified to be associated with significantly worse functional outcomes 12 months post RC repair, although both obese and non-obese patients reported significant improvements in pain and disability (358). The current study found neither BMI nor waist circumference to have a significant relationship with pain and disability 12 months after surgery. This finding has also been previously corroborated in a longitudinal study following RC repair (359). Existing literature suggests RC related surgery can be effective in both obese and non-obese populations, but maintaining a healthy weight may improve pain and disability even further.

The participants in this study presented with very low levels of psychological distress at baseline, and psychological distress was not associated with pain and disability following RC surgery. Three recent studies have also evaluated this association and similarly found little association between anxiety and depression scores measured at baseline and self-reported pain and disability 12 months after RC surgery (345, 360, 361). Similar to our current study the number of more severely distressed participants was very low (11%) in the Potter et al study, making it difficult to conclude on the effects of severe levels of distress and their effects on RC surgery outcomes. It is unclear if this reflects a low level of distress generally in those with RC problems or a reluctance by surgeons to list highly distressed individuals for surgery, this is clearly an issue that requires further investigation. Conversely a recent study has identified that higher levels of psychological distress before shoulder surgery is

associated with higher levels of pain and disability following RC surgery (362). What remains unclear though is the effect of the surgery on psychological distress itself and how this changes with surgery.

Strengths and Limitations

To our knowledge, this is the first longitudinal study to explore not only nociceptive sensitivity, but also measures of body representation, as predictors of pain and disability following RC surgery. However, this study was unable to provide any evidence for factors indicative of altered CNS processing being associated with outcome after surgery. A major limitation of this study was the low participant numbers at baseline and subsequent drop-out rate prior to the 12 month follow-up analysis. This study had aimed to recruit 110 participants allowing for 10% attrition, to give adequate power to detect R^2 changes of 7%, which corresponded to partial correlations of the magnitude 0.26. Only 34 of the 114 total patients that were waitlisted consented to participate in this study, and only 22 provided follow-up data (35% drop out). With this small a sample, the study was only powered to detect moderately strong associations between CNS processing and pain and disability outcomes (partial correlations of the magnitude 0.5 or greater), which is unlikely to exist given the multidimensional nature of pain and disability. A larger sample size would also allow for more confounding factors to be used in statistical models. A further consideration is the fact that those participants who did not provide 12 month data presented with significantly higher levels of nociceptive sensitivity to pressure and reported being significantly more disabled than those participants who contributed 12 month data, which meant that associations may have been biased towards the null due to loss of more sensitised and more disabled participants. Not all patients undergoing RC surgery will present with measures indicating altered pain processing and body representation. It is possible that the patients in this study who did not complete the 12 month questionnaire were those more affected by CNS influences and resultant nociceptive hypersensitivity and body representation changes. Lastly it is important to acknowledgement that not having an RCT including “no surgery” versus “surgery” means that it cannot be dissected out if a factor is just prognostic of outcome in general or predictive of benefit from surgery.

Implications for Future Research

This preliminary study sought to explore altered CNS processing and its association with pain and disability 12 months following surgery. This study failed to show any associations, most likely due to the limited participant numbers and the high, non-random loss to follow up.

Conclusion

Measures considered to be potentially indicative of altered CNS processing were not found to be predictive of shoulder pain and disability 12 months following RC surgery. No definitive conclusions can be drawn from this study regarding the presence or absence of an association between altered CNS processing before surgery and pain and disability 12 months following RC surgery because of limited participant numbers at baseline and the loss of a further 12 participants prior to 12 month data collection. Further studies with larger participant numbers are needed to determine if associations exist.

Discussion

This discussion presents a summary and discussion of the findings of this study. A summary of the findings with regard to each aim is presented, and a comparison to the previous literature is made. The strengths, limitations and implications for clinical practice of this body of work are discussed. Finally, a conclusion of the thesis is presented.

Study 1

This first study of this thesis investigated cross-sectional associations between pressure pain thresholds (PPT), cold pain sensitivity (CPS), measures of body representation (TPD, left/right judgement tasks and the neurobehavioural neglect questionnaire) and levels of pain and disability reported by people with RC related shoulder pain about to undergo shoulder surgery.

Main findings in this study

1. Increased sensitivity to pressure (lower PPTs) was associated with higher levels of disability.
2. Poorer Two Point Discrimination (TPD) was associated with higher levels of pain.
3. No other measures indicative of nociceptive sensitivity or altered body representation were associated with either pain or disability levels.

Prior to discussing observed findings in context of the available evidence, the limited sample size needs to be further highlighted and discussed. This study was powered to require a sample size of 100, to detect correlation coefficients for independent associations of 0.26 or more. The sample of 34 participants has meant that this study is only able to identify strong associations, and is also vulnerable to chance findings. Only 117 people were waitlisted for RC related shoulder surgery in a public hospital over the study recruitment period. Of these 34 consented and continued to be participants in this study. The remainder did not meet inclusion criteria (n=19), were subsequently taken off the waitlist (n=27) or declined to participate (n=34) on the basis of time and expense. Recruitment in the public hospital sector is challenging and recommendations to improve on recruitment numbers will be discussed later in this chapter.

Comparison to previous literature:

Association between measures of nociceptive sensitivity before surgery and SPADI scores before surgery

An increase in nociceptive sensitivity to pressure i.e. decreased PPT at the affected shoulder was associated with higher levels of reported disability in this study. This finding is in line with previous studies of RC disease cohorts that reported decreased PPT at the painful site to be associated with higher levels of reported disability (154, 205).

Alburquerque-Sendin et al. (2013) similarly found that lower PPTs over six separate shoulder muscle locations, were significantly associated with higher levels of Disabilities of the Arm, Shoulder and Hand scores indicating greater disability. The strengths of the associations detected were of moderate size (r=0.5-0.6) and slightly larger than those reported in this study. However, the study by Alburquerque-Sendin et al. pooled the affected and unaffected sides of a RC-related shoulder pain group (n=27) and a control group (n=20) for analysis, which likely inflated the size of these correlations by a lack of consideration for repeated data from two sides in the same individual. Additional reasons for potential bias are the use of a control group which had a severe floor effect for the DASH score, and that the analyses were not adjusted for any potential confounders.

Uddin et al. (2016) reported that higher PPT scores (indicating less nociceptive sensitivity) at both the deltoid and tibialis anterior of the affected side were associated with less disability as measured by the SPADI disability subscale (deltoid; r= -0.36, p<.05,tibialis anterior; r=-0.32, p<.05). This study by Uddin et al. (2016) can be more directly compared with the current study as disability was similarly measured using the SPADI, and PPT was similarly measured directly over the same sites (deltoid and tibialis anterior muscles) and both studies were drawn from a similar population (participants awaiting RC related surgery). However, although multivariable models were evaluated, these only included multiple sensory variables, so the comparison of estimates adjusted for potential confounding by factors, such as age and adiposity, is not possible. Uddin et al. (2016) found associations between PPT and disability at both the remote and local site, which differs from the current study. A likely explanation for this remote association between PPT and disability is that Uddin et al. (2016) found PPT scores over both sites to be quite similar in values (8.4 versus 7.2 with no report of measurement unit), compared to the current study where the mean local shoulder PPT (458KPa) showed greater sensitivity compared to the mean of the PPT measured at the remote site (796KPa).

Lower PPT scores at the affected shoulder site indicate nociceptive sensitivity and may be a manifestation of peripheral and central nervous system changes. Although the current study identified an association between PPT at the affected shoulder and disability, a significant association with PPT measured remotely over the tibialis anterior muscle and disability was not detected. Disability may be more closely associated with local pathology and associated tissue sensitisation. In shoulder pain-related disability, the relationship between local tissue sensitivity may be more direct, meaning that local rather than central changes in sensitisation may be predominant in this condition. The limited sample size and consent rate may mean that the sample included in this study is not representative of the underlying population of people undergoing RC related shoulder surgery. It is possible that those who did not consent experienced greater levels of pain and disability, and/or may have exhibited higher levels of central nociceptive sensitivity.

Similar to the findings of this study, significant associations between PPT measured at various sites local to the affected knee and disability have been reported in people diagnosed with osteoarthritis of the knee. Lower PPT scores were associated with higher levels of disability (R^2=0.608), greater stiffness and poorer quality of life (R^2=0.611) scores in two studies investigating knee osteoarthritis (363, 364).

The findings of this study and those studies in knee osteoarthritis are in contrast to a meta-analysis of 43 studies of people experiencing chronic spinal pain, which concluded that PPT scores are not correlated with decreased function and disability in chronic spinal pain (r=-0.17, 95%CI; -0.24 to -0.10) (204). This may indicate that nociceptive sensitisation is differently moderated in spinal pain and is not a significant factor in spinal pain related disability compared to people experiencing chronic peripheral joint pain.

This study failed to find an association between higher levels of pain and lower PPT measures at the shoulder or over the tibialis anterior site. The previous evidence in the shoulder literature is divided, with some studies reporting lower PPTs to be associated with higher levels of pain (153-155), while others report no association (157, 205, 291).

As previously discussed, Uddin et al (205), the most aligned protocol to this study, also found no association between PPT measured over the deltoid muscle and the pain sub-score of the SPADI questionnaire (205). Valencia et al. (2011) and Coronado et al. (2014) also reported no association between PPT and pain, although a direct comparison is difficult as they used the acromion as their pressure application site. Both studies used the validated Brief Pain Inventory questionnaire for measures of pain with the Valencia et al.

study only using the present pain component and the Coronado et al. study using an average of present, least and worst pain. Using these tools that capture spontaneous pain and pain with provocation would cover both centrally mediated pain responses as well as peripherally driven pathological responses. Despite this, no significant association between nociceptive measures of PPT and reported pain was identified by these studies.

Three studies that did identify an association between lower PPT measures and higher levels of pain used different pain self-report instruments to this study. The SPADI, used in this thesis, questions pain at its worst and with provocative positions or activities. Coronado et al. (2011), used an average of current, worst pain over 24 hours and best pain over 24 hours, and reported a significant correlation between shoulder PPT and average pain ($r=-0.284$, $p=.029$). This 2011 study differed from their 2014 study mentioned in the previous paragraph by the use of three shoulder sites for the pressure assessment compared to only one in their 2014 study. This suggests that location of PPT yields different findings, and as shoulder pain can be heterogeneous in regards to site, the use of multiple sites may be indicated. Alburquerque-Sendin et al. (2013), found associations between the greatest level of pain experienced in the last week and PPT for four of the six shoulder muscles tested, but the association between PPT over the deltoid (as measured in this study) and greatest level of pain experienced in the last week was not significant. Deltoid PPTs and the lowest level of pain experienced in the last week were associated ($r=-0.422$, $p=.029$), but this is not captured by the SPADI. The third study to report a significant association between pain and PPT was Hidalgo-Lozano et al. (2010), in which the only measure of pain evaluated was pain at rest. PPT was measured at four sites, namely supraspinatus, infraspinatus, subscapularis and levator scapulae muscles. Significant correlations were found between pain at rest and PPT over levator scapulae ($r=-0.637$, $p=.025$) and supraspinatus muscles ($r=-0.577$, $p=.045$). In contrast to measuring pain at rest or spontaneous pain, the SPADI captures pain at its worst and with provocative positions or activities. CNS changes may lead to pain augmentation, less provocation required to elicit a pain response and subsequently a generation of spontaneous pain responses. It may be that people with CNS mediated pain augmentation therefor report more pain at rest. Reported pain with provocation may indicate simple activation of peripheral nociceptors (Aδ and C fibres) and not be as influenced by CNS changes. Including validated measures that capture pain at both rest and with provocative activities may yield useful information separately.

Similar to the present study in studies investigating spinal pain and whiplash associated pain, the correlation between lower PPT scores and higher levels of pain has not been confirmed

(204, 290). Conversely in osteoarthritis related knee pain a meta-analysis of 2126 participants showed pain lower PPT scores to be associated with higher levels of pain (365). These findings would suggest that sensitisation to mechanical stimuli is linked to pain severity in knee osteoarthritis. However, there is a poor understanding of how this links in with pathology. Radiological evidence of more severe osteoarthritis is not associated with lower scores of PPT (187), indicating that pathology is not the only factor to take into consideration when considering pain sensitisation. Normalisation of PPT following knee joint replacements has been reported, indicating pain sensitisation must be at least party driven by peripheral inputs in people with knee osteoarthritis (178).

There may be two reasons this study did not identify an association between PPT and reported pain. Firstly, the use of only static measures of quantitative sensory testing may not be sufficient to assess nociceptive sensitisation, and dynamic QST measures are needed to capture the CNS modulation of pain. Identifying if there is an increase or decrease in the facilitatory and inhibitory functioning of the pain pathways may be an important component linking in to the reported pain experience, which is not captured by static threshold measures. Secondly, because pain is a self-reported phenomenon which is complex and multifactorial, associations between PPT and reported pain may be difficult to detect. Pain is difficult to define, with studies using different questionnaires which capture different aspects of pain: resting pain, average pain, presenting pain, pain on particular activities and worst pain. A study by Parks et al (2011), assessing the difference in brain activity between provoked pain and spontaneous pain identified that spontaneous pain in knee osteoarthritis provoked greater pre-frontal limbic region activity illustrating a greater emotional component to pain perception compared to provoked pain. This is an important construct to take into account when considering the choice of pain outcome measure for studies investigating associations between quantitative sensory testing and self-reported pain (366).

Finally, the limitation of the small sample size of this study needs to be reiterated. If only a small proportion people with RC related shoulder pain exhibit significant levels of nociceptive sensitivity, larger sample sizes will be needed to detect an association.

This study indicated significant levels of shoulder pain and disability, yet these were not associated with increased cold pain sensitivity This study found a lack of evidence to support significant nociceptive hypersensitivity to cold stimuli over the affected shoulder or at remote sites, with only six participants presenting with CPS scores indicating cold pain sensitivity, making finding any association between increased cold pain sensitivity and

increased pain and disability unlikely. Cold pain sensitivity over the affected shoulder in RC related shoulder pain has not been previously investigated.

The underlying neurophysiological mechanisms of CPS and PPT are not fully understood. The difference in these processes may explain why PPT scores were associated with disability scores but not CPS. CPS relies on input from cutaneous receptors, while PPT is dependent on input from deep structures (11). PPT is a deeper assessment and may be influenced by local tissue inflammation responses, compared to the superficial cutaneous assessment of CPS. Nociceptive sensitivity at the skin may indicate greater CNS augmentation of pain compared to pressure over inflamed shoulder structures which may be more indicative of peripheral changes. Most of the participants included in this study presented with low level of sensitivity to CPS testing, indicating that this sample did not have significantly altered nociceptive processing with respect to cold stimuli. This may be specific to this sample or may be a consistent finding amongst people with RC related shoulder pain, but no other studies can confirm this.

A meta-analysis of pain sensitivity in knee osteoarthritis, concluded that there was no evidence for the presence of cold pain sensitivity in this population (365). However, a subsequent study identified increased cold pain sensitivity in people with knee osteoarthritis, with between 37.5- 47.5% of participants identified as cold pain sensitive when compared to controls. These cold pain sensitive participants demonstrated significantly lower levels of function (WOMAC and SF36 scores) compared to participants who were categorised as not cold pain sensitive (293). Increased cold pain sensitivity has also been associated with increased symptom severity (combined pain and disability) in lateral epicondylalgia (292). Conversely, a meta-analysis of five spinal pain studies including whiplash associated pain could only identify a weak correlation between cold pain sensitivity and disability scores (204).Further studies with larger sample sizes investigating cold sensitivity in RC related shoulder pain are required to identify if cold sensitivity is associated with disability outcomes in people with shoulder pain.

This study also found no association between cold pain sensitivity and reported pain. An increase in sensitivity to cold stimuli and its' association with increased pain has been previously reported in many different musculoskeletal pain populations though including lateral epicondylalgia (174, 292), spinal pain (197), knee osteoarthritis (186, 293) and whiplash associated pain (294).

Cold pain sensitivity testing using an ice block has been previously validated in spinal pain (203) as a reliable method of assessing sensitivity to cold, but no previous validation studies have been undertaken in the shoulder or other peripheral joints, and perhaps assessing cold pain thresholds using a thermode would be more accurate measure of cold sensitivity in people with shoulder pain.

Association between measures of body representation before surgery with SPADI scores before surgery.

This study did not identify any associations between reported pain and disability and disturbances in self-reported body representation as measured by the Neurobehavioural questionnaire. Participants' Neurobehavioural questionnaire scores were very low, with more than half being zero. This potentially means that the majority of people with RC related shoulder pain do not present with significant disturbances in body perception.

Conversely, CRPS and low back pain cohorts present with significantly higher levels of neurobehavioural neglect indicative of distorted or disrupted body representation (141, 257, 296). Chronic pain has been identified to induce changes in the sensory cortex, leading to a smudging of these sensory representations (367). There is no clear understanding of the extent of cortical changes that exist in shoulder pain. Two transcranial magnetic stimulation studies have been reported in people with unilateral RC related shoulder pain. One identified a bilateral central motor activation deficit in the deltoid muscle (340) and the other decreased excitability on the affected side compared to unaffected side when a RC muscle (infraspinatus) was stimulated (339). These mapping studies offer limited evidence of changes in the motor cortex in people with RC pathology.

Although changes in the sensory cortex have been identified in people with low back pain and CRPS, only two studies have assessed whether a relationship exists between the self-report of neglect like symptoms and pain and disability. Measures indicating disruptions of body representation using a modified Neurobehavioural questionnaire have been previously associated with an increase in average pain ($r=.265$ $p<.001$) and increased disability ($r=.319$ $p<.001$) in a sample of people with low back pain (141). Another study of people with upper limb CRPS (296) reported that those participants who reported neglect-like symptoms reported greater pain at rest, but did not perform any statistical evaluation of this relationship. Those participants who reported neglect-like symptoms had an average of 5.9mm on a VAS scale for pain at rest compared 3.8mm for those participants who did not. CRPS and low back pain studies have identified a link between cortical changes,

variables indicating changes in body representation and reported pain. As studies linking RC related shoulder pain to cortical changes and changes in body representation are lacking we can make two hypotheses from our findings. Firstly that perceptual changes do not occur, or occur only in a small proportion, of people with chronic RC related shoulder pain, or secondly, that potential associations exist between self-reported body representation and pain and disability, but that a true representation of people with RC related shoulder pain was not captured due to the small sample size of this study.

This study did not detect an association between reaction time or accuracy in the left/right judgement task and shoulder pain and disability. Reaction times have been previously found to be associated with reported pain in CRPS (235, 260, 300) and accuracy with reported pain in low back pain(298) and disability in patients with cervical pain (301).

Left /right judgement tasks have not previously been assessed in RC related shoulder pain. Studies have reported normative data for reaction time and accuracy of the left/right judgement task as applied to the shoulder (237, 297), and the current study found similar reaction times, but poorer accuracy, compared to this normative data. Previous studies of people with knee osteoarthritis and low back pain have similarly found a compromise of accuracy but not reaction time (142, 236, 298). A recently published meta-analysis concluded that reaction times and accuracy are compromised in CRPS but not consistently in axial pain and other non-CRPS limb pain(368). Accuracy in left/right judgement tasks is thought to be a reflection of the accuracy of cortical proprioceptive maps, although clear causal relationships between pain and deficits in reaction time or accuracy have not been found though.

The current study found a poorer ability to TPD to be associated with increased reported pain levels. This association has been previously corroborated in some CRPS cohorts (302). Evidence of similar associations or lack thereof, have not been previously reported in RC related shoulder pain. No statistically significant associations have been identified in people with in low back pain (245, 267), or people with knee osteoarthritis (267).

TPD thresholds depend on the density of innervation of touch receptors of the overlying skin, accurate somatosensory representation and finally on an efficient lateral sensory inhibitory system. Lateral inhibition enhances identification of a tactile stimulus by suppressing input from surrounding areas. In chronic pain, lateral inhibitory mechanisms can be compromised (369). A lack of tactile sensory inhibition in the case of chronic pain may explain why in part pain levels and TPD changes are associated. TPD measures in this study and previous studies have shown large variability (237, 297), indicating that the construct may be complex and also highly individualised.

TPD measures over the shoulder were not associated with self-reported disability in the current study. No other studies of self-reported disability and TPD have been conducted on people with shoulder pain.

Study 2

This second study of this thesis investigated longitudinal associations between baseline measures of pressure pain thresholds (PPT), cold pain sensitivity (CPS), measures of body representation (TPD, left/right judgement tasks and the neurobehavioural neglect questionnaire) and levels of pain and disability reported by people with RC related shoulder pain 12 months following surgery.

Main findings in this study

1. Measures of nociceptive sensitivity (PPT and cold pain sensitivity) prior to surgery were not associated with shoulder pain and disability 12 months following surgery.
2. Measures of body representation (neurobehavioural neglect, TPD and left/right judgement tasks) prior to surgery were not associated with shoulder pain and disability 12 months following surgery.

Comparison to previous literature:

Associations between measures of nociceptive sensitivity before surgery and pain and disability 12 months after surgery

Baseline measures of PPT in this study were not associated with levels of pain and disability 12 months following surgery. Only one other study of 17 people undergoing arthroscopy for RC related shoulder pain has previously reported on this association in RC related shoulder surgery (8). This study claims to identify an association between increased mechanical pain thresholds (punctate sharpness) measured before surgery with increased disability and pain scores as measured by the Oxford Shoulder scale (p= .04) three months following surgery. However, despite reporting no association between pre-operative mechanical pain thresholds and Oxford Shoulder scale three months after surgery (r=0.03, p=0.92), they also report an analysis of the mechanical pain thresholds data dichotomised at the median which suggested weak evidence for a poorer Oxford Shoulder Score three months after surgery in those below the median. These results are potentially biased due to the use of arbitrary dichotomisation, a small sample rendering chance findings more likely, and a poor reporting

of the study selection procedure. The final outcome measures were taken at three months compared to 12 months in this study, and the additional nine months in this study may offer an opportunity for other external factors to influence this association more significantly. Alternatively, lost to follow-up of those participants with greater levels of nociceptive sensitivity and disability may explain the lack of associations at 12 months in this thesis.

With regard to the association of PPT measures with pain after surgery, the study by Gwilym et al (8) discussed above is the only shoulder surgery study to report on this association. However, this study used the Oxford Shoulder Scale so the results are difficult to interpret as the two separate constructs of pain and disability cannot be separated. The current study used separate pain and disability scales as they are different constructs and previous literature has reported different associations with QST measures and pain and disability independently. Studies have been conducted in people undergoing surgery in other peripheral joints however, and results show variable evidence both in favour and refuting an association. PPT measures before surgery at the affected knee of people with diagnosed knee osteoarthritis were not associated with peak pain intensity at baseline, or change in peak pain intensity from baseline to 12 months following knee replacement surgery (181, 207). Wylde et al. (2013) found lower PPT measures over the forearm but not over the affected knee were correlated with the WOMAC pain score 12 months following surgery (176) . The authors hypothesised that lower forearm PPT is an indicator of central sensitisation compared to local knee PPT sensitivity, which is more an indicator of peripheral sensitisation. The current study found no evidence of either local (deltoid) or remote (tibialis anterior muscle) PPT being associated with pain outcomes 12 months following RC related shoulder surgery. Wylde et al. (2015) further investigated the association between widespread pain sensitivity (PPT measured at the forearm) before surgery and pain 12 months following both knee and hip replacement surgery with larger cohorts (THR: n=322, TKR: n=316). Decreased PPT measures over the forearm were associated with greater pain with movement at 12 months following hip replacement surgery. Forearm PPT measures however were not associated with either movement pain or resting pain 12 months following knee replacement surgery in this study.

Dynamic measures of temporal summation and conditioned pain modulation using pressure stimuli have also been found to predict pain relief 12 months following knee replacement (206). Petersen et al. went on to subgroup baseline measures of temporal summation and conditioned pain modulation and found the group with increased temporal summation and impaired conditioned pain modulation reported the least amount of pain

relief 12 months following surgery, suggesting both facilitatory and inhibitory functions are important. As previously discussed above in relation to the cross-sectional findings of this study, dynamic measures of QST may be more predictive of pain and disability after shoulder surgery because they may better capture the CNS modulation of pain, and both facilitatory and inhibitory functions may need to be considered.

This study found no association between increased cold pain sensitivity measured before surgery and pain or disability 12 months following surgery. Comparison with available literature is difficult due to limited studies investigating the association of thermal QST with outcomes following surgery. In the only other study pertaining to shoulder surgery, dynamic measures of thermal nociceptive processing at baseline and three months following surgery were explored by Valencia et al (2013) (190) as potential predictors of pain and disability six months following surgery for RC related shoulder pain. Although baseline measures were similarly not found to be predictive of outcome six months following surgery the change in suprathreshold heat pain responses (indicating a decline in pain facilitatory capacity) from baseline to three months after surgery were predictive of pain intensity and disability at 6 months after surgery . Unlike the current study which only made use of static measures of thermal QST, understanding the capacity of the CNS to modulate pain, as is captured by more dynamic measures of QST, may have a better association with pain and disability following surgery. Additionally, capturing a change score in QST, indicative of a change in the CNS modulation of pain before and after surgery, may also offer a greater association with pain and disability following surgery.

Associations between measures of body representation before surgery and pain and disability 12 months after surgery

In this study no measures of body representation (neurobehavioural neglect, TPD and left/right judgement tasks) prior to surgery were associated with shoulder pain and disability 12 months following surgery. No previous studies have investigated the association between measures of body representation, and pain and disability following surgery for RC related shoulder pain.

Changes in measures of body representation occur with pain and have been measured through a number of constructs as previously outlined in section 1.4.3.6. Even in other musculoskeletal conditions, there have been no studies that have investigated the association of pre-surgery measures of body representation with outcomes after surgery, or whether surgery itself induces changes in body representation. At this stage there is

insufficient literature to confirm if changes in body representation are common in RC related shoulder pain, and if these changes are associated with pain and disability following surgery.

Strengths of the thesis

This thesis included both cross-sectional and longitudinal studies, potentially identifying any associations between measures indicative of altered CNS processing at baseline with shoulder pain and disability both at baseline and 1 year following shoulder surgery.

No standardised protocol for QST testing in shoulder pain exists. However, more than one modality of QST is recommended in the literature, due to the low correlation between various measures, which indicates that each measures different neuro-physical mechanisms within the CNS (180). Both thermal and pressure QST pain stimulus were utilised in this study.

The additional use of measures of body perception in addition to nociceptive sensitivity in this study is novel in RC related shoulder pain. Changes in body representation have been identified in other chronic musculoskeletal conditions. Investigating whether changes in body representation exist in people with RC related shoulder pain and whether these are associated with levels of pain and disability may provide a potential target for interventions. Graded motor imagery has already been identified as a potentials means of targeting disturbances in body image and associated pain (282).

Finally, the relationship between reported pain, pathology and nociceptive sensitivity is unclear. Nociceptive sensitisation is commonly found in an osteoarthritic knee population. Glenohumeral arthritis was not the focus of this study of RC related shoulder pain, and by excluding people with radiological evidence of glenohumeral osteoarthritis this study allowed for findings to be more applicable to RC related shoulder pain, which has poorly identified pain pathoanatomical mechanisms.

Limitations and recommendations for future research

The largest limitation to this study was the low initial participant numbers (n=34) and subsequent dropout rate (35%). The study was therefore underpowered to identify any meaningful associations between measures indicative of CNS processing and shoulder pain and disability. Additionally, the participants who failed to complete the study presented with significantly higher levels of disability and significantly more pressure pain sensitivity, introducing a possible selection bias to the study. Future recommendations would include a

protocol that allows for baseline assessment to occur at the same time and location as routine clinical pre-surgical assessments to minimise cost and time requirements for the participants. In the current study, participants were required to attend an additional session without any compensation for their time or costs.

There is no clear indication of how nociceptive sensitivity changes over time and the effects of surgery on these thresholds. This study only measured nociceptive sensitivity before surgery and thus any change in nociceptive sensitivity from before to after surgery is unknown. The change in nociceptive sensitivity thresholds from before to after surgery may be more indicative of CNS functioning and a better predictor of outcome 12 months following surgery.

Normative data for the shoulder for cold pain sensitivity and self-perception measures are lacking, and existing normative values for PPT, TPD and left/right judgement tasks are limited. Some RC related shoulder pain studies have reported significant nociceptive sensitivity in those with pain (decreased PPT compared to matched controls) both locally and remotely and interpreted this as indicative of central sensitisation (8, 155-157), while others have refuted this (8, 155-157). Waller et al. (2016) reported sex, hip-waist ratios, mental health and smoking status to be significantly associated with PPT and CPT in a pain free community sample of 22 year olds. Including a pain free control sample matched for these potential confounding factors would have allowed better interpretation of the levels of nociceptive sensitivity and body representation reported measures in this study (191). However, this does not invalidate the primary aim which was to estimate the association between levels of nociceptive sensitivity and altered body representation with pain and disability within the population of people with RC related shoulder pain. The lack of an association between measures indicative of CNS processing and pain and disability in this study may be due to there being limited numbers of participants with altered CNS processing, due to the sample not being representative of the population of people undergoing surgery for RC related shoulder pain. This concern is supported by the loss to follow-up of those participants with higher disability and lower PPTs, and the large number of people (n=34, Figure 3.1) who declined participation or failed to attend the baseline assessments despite eligibility.

Two-point discrimination is a combined measure of receptor field innervation, accurate somatosensory representation and functional lateral inhibition. It appears to be highly individualised as large variations of this measure have been reported in all studies reviewed in a meta-analysis (272). As only the painful shoulder was measured in this study, it is unknown

whether the level of TPD was representative of receptor field function in general or if the measurement was altered just at the shoulder due to the presence of pain, and differed from the unaffected shoulder. Capturing values on the unaffected sides would help to clarify this.

This study focused on RC related shoulder pain, which is commonly seen in primary care. Surgical rates and related costs for RC related shoulder pain are escalating (26), so identifying characteristics of those individuals that are likely to have limited benefits from surgery is important. Many psychosocial and biological factors associated with outcomes following RC related surgery have been investigated, and evidence of CNS changes that may be moderating the pain experience are emerging (8, 190). Lastly it is important to acknowledgement that not having an RCT including "no surgery" versus "surgery" means that it cannot be dissected out if a factor is just prognostic of outcome in general or predictive of benefit from surgery. Ongoing investigation into the role of CNS changes in RC related shoulder pain may assist to direct surgical and non-surgical care.

Implications for clinical practice

This study contributes some evidence that increased sensitivity to pressure and a poorer ability to two-point discriminate may be associated with shoulder pain and disability prior to, but not 12 months after, RC surgery. Chronic pain induces change in nociceptive thresholds and body representation, but this study casts doubt on how useful these values are and does not offer a clear association between these values and post-surgical outcomes at 12 months. However further studies are needed to confirm these findings. No direct clinical considerations can be made from this study with regards to associations of measures considered to be potentially indicative of CNS pain processing with pain or disability levels after surgery, as the small sample size meant there was limited power to identify any meaningful associations. Should consistent and meaningful associations be identified in future studies, people with altered CNS processing of pain could potentially be directed to non-surgical interventions targeting normalisation of pain processing, rather than, or prior to, shoulder surgery.

Conclusion

Increased sensitivity to pressure was associated with higher levels of self-reported disability and decreased TPD acuity was associated with higher levels of shoulder pain in people awaiting RC related shoulder surgery. However, no baseline measures of nociceptive

sensitivity or body representation were predictive of pain or disability 12 months following RC surgery. The sample size of this study was limited and larger studies are required to confirm the presence or absence of these associations.

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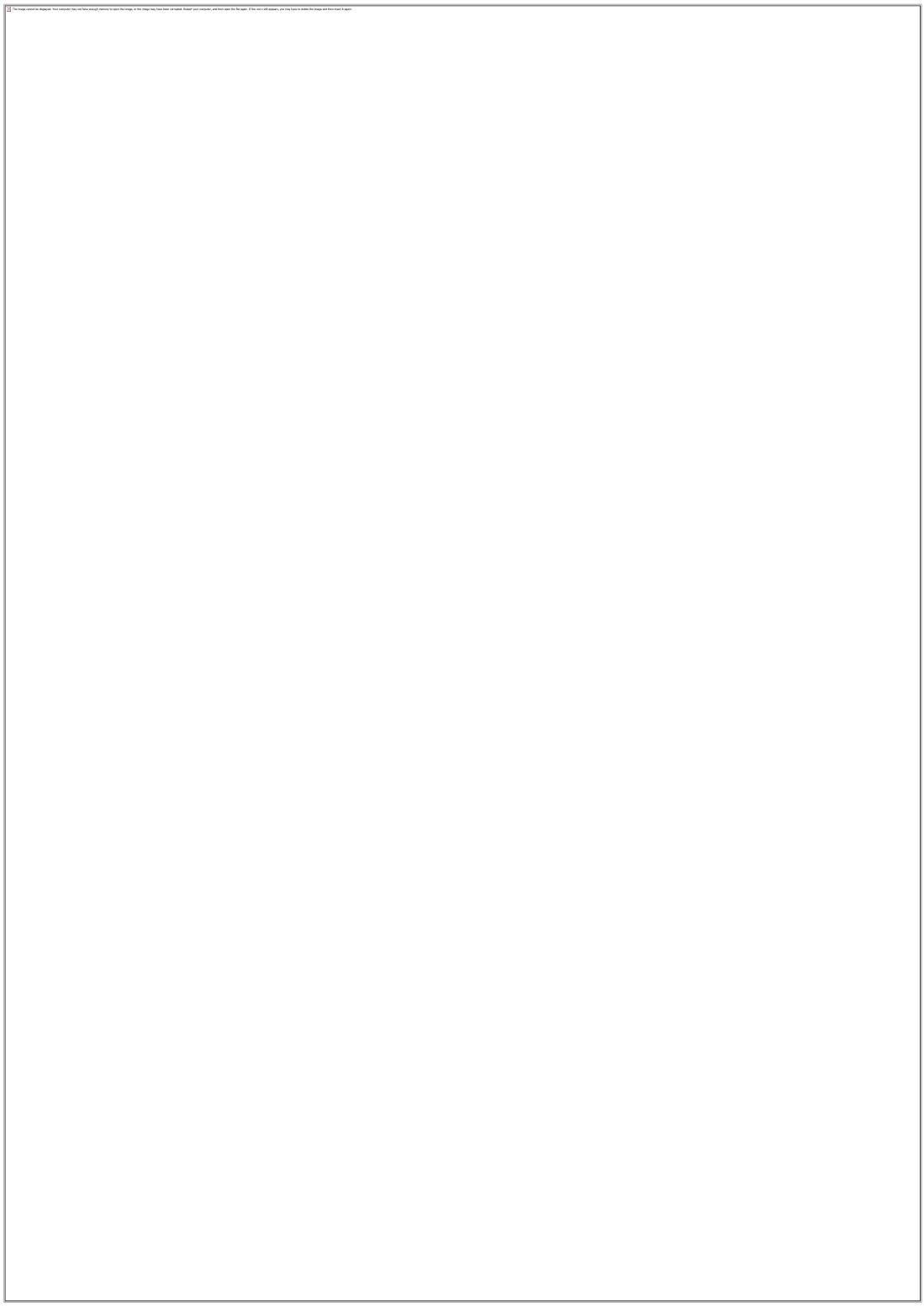
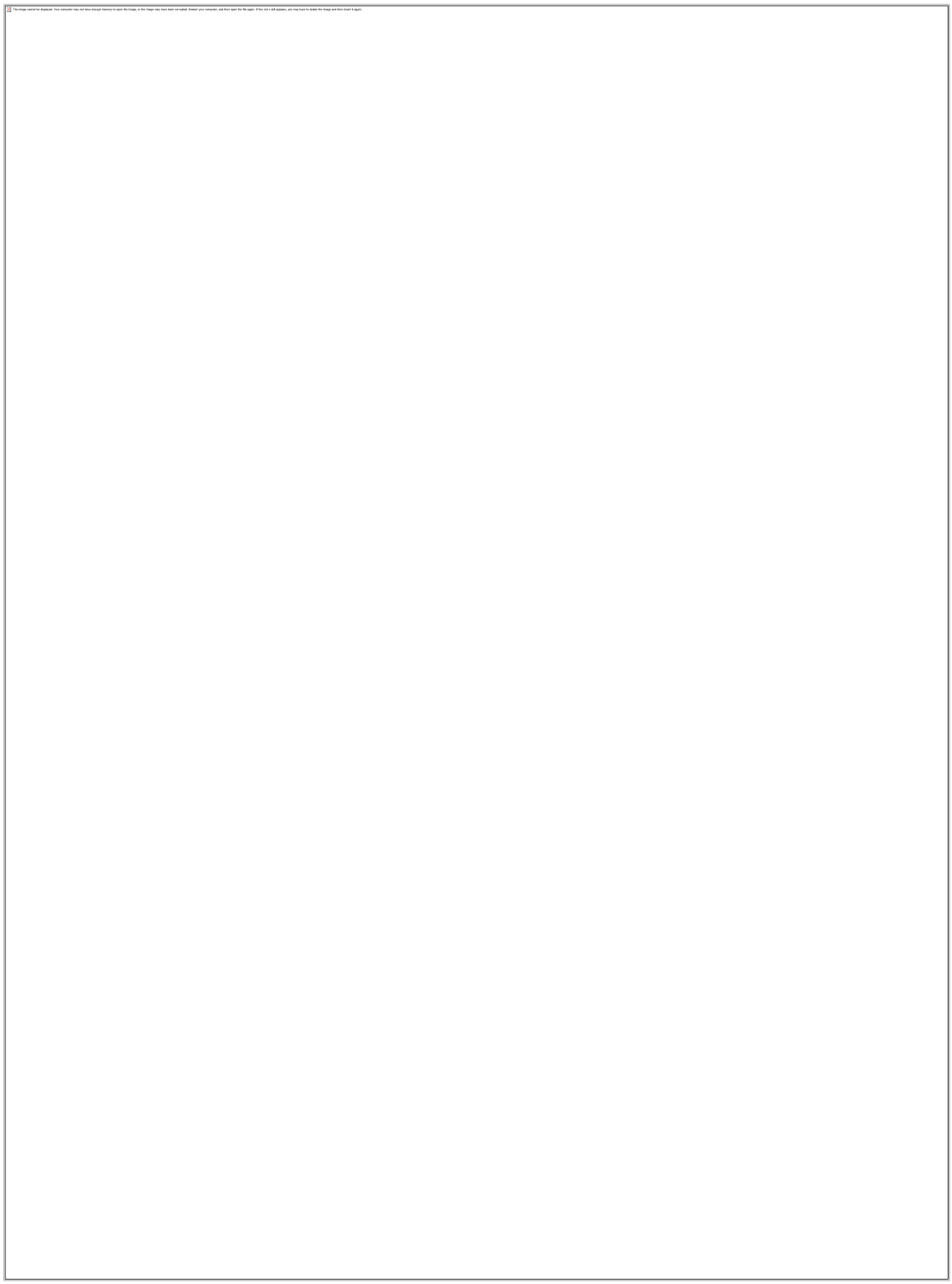
APPENDICES

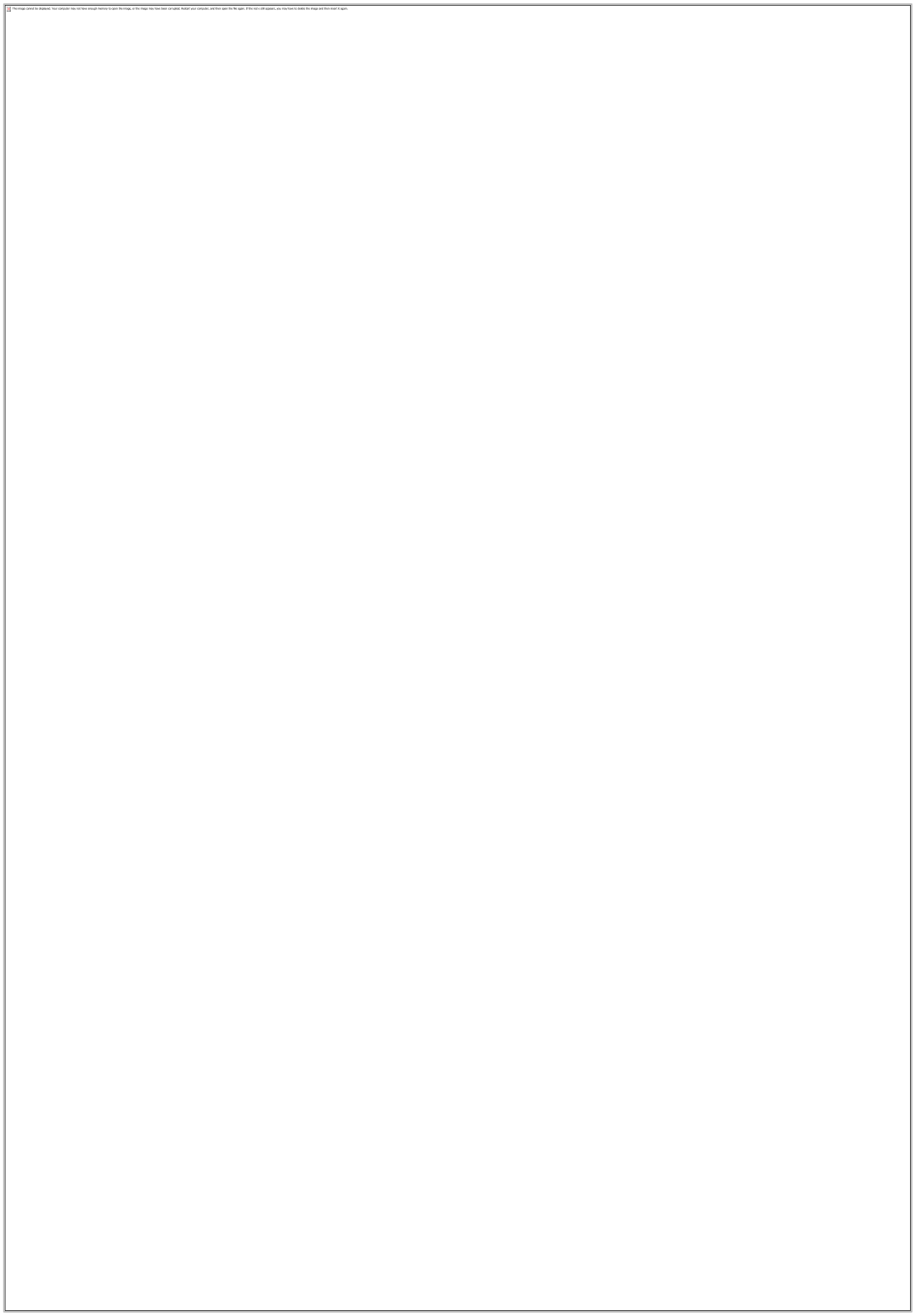
Appendix A Patient information flyer



Appendix B Patient information sheet



Appendix C Shoulder Pain and Disability Index (SPADI)



Shoulder Pain and Disability Index (SPADI)

Please place a mark on the line that best represents your experience during the last week attributable to your shoulder problem.

Pain scale

How severe is your pain?

Circle the number that best describes your pain where: 0 = no pain and 10 = the worst pain imaginable.

At its worst?	0	1	2	3	4	5	6	7	8	9	10
When lying on the involved side?	0	1	2	3	4	5	6	7	8	9	10
Reaching for something on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Touching the back of your neck?	0	1	2	3	4	5	6	7	8	9	10
Pushing with the involved arm?	0	1	2	3	4	5	6	7	8	9	10

Disability scale

How much difficulty do you have?

Circle the number that best describes your experience where: 0 = no difficulty and 10 = so difficult it requires help.

Washing your hair?	0	1	2	3	4	5	6	7	8	9	10
Washing your back?	0	1	2	3	4	5	6	7	8	9	10
Putting on an undershirt or jumper?	0	1	2	3	4	5	6	7	8	9	10
Putting on a shirt that buttons down the front?	0	1	2	3	4	5	6	7	8	9	10
Putting on your pants?	0	1	2	3	4	5	6	7	8	9	10
Placing an object on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Carrying a heavy object of 10 pounds (4.5 kilograms)	0	1	2	3	4	5	6	7	8	9	10
Removing something from your back pocket?	0	1	2	3	4	5	6	7	8	9	10

Appendix D Neurobehavioural Questionnaire

Neurobehavioral Questionnaire

Using the following scale, please indicate the degree to which your shoulder feels this way **when you are experiencing pain**

0 = Never feels like that
1 = Rarely feels like that
2 = Occasionally, or some of the time feels like that
3 = Often, or a moderate amount of time feels like that
4 = Most of the time feels like that
5= Always feels like that

	Never	Rarely	Occasionally	Often	Mostly	Always
1. If I don't focus my attention on my painful limb it would lie still, like dead weight.	0	1	2	3	4	5
2.My painful limb feels as though it is not part of the rest of my body.	0	1	2	3	4	5
3.I need to focus all of my attention on my painful limb to make it move the way I want it to.	0	1	2	3	4	5
4.My painful limb sometimes moves involuntarily, without my control.	0	1	2	3	4	5
5.My painful limb feels dead to me	0	1	2	3	4	5

V. If you have further comments with regard to these questions, please comment:

_____

_____

_____

Appendix E Pre-operative Physiotherapy physical assessment