Afferent inhibition and cortical silent periods in shoulder primary motor cortex and effect of a suprascapular nerve block in people experiencing chronic shoulder pain

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Highlights

- Novel sensorimotor integration, a cortical silent period and their interaction were demonstrated in shoulder primary motor cortex in healthy adults.
- Cortical neurophysiology was aberrant in patients with chronic shoulder pain.
- Suprascapular nerve block injection immediately normalised sensorimotor integration and reduced pain while further modulation of the CSP by sensory input was apparent one week later

Abstract

Objective: To characterise short afferent inhibition (SAI) and the cortical silent period (CSP) in primary motor cortex representations of the infraspinatus muscle in healthy adults and people experiencing chronic shoulder pain, to determine the impact of suprascapular nerve block (SSNB).

Methods: Neurophysiological measures were obtained in 18 controls and 8 patients with chronic shoulder pain, pre and post SSNB and one week later. Pain intensity was assessed by a visual analogue scale.

Results: SAI was observed in controls (all $P < 0.03$) and there was a CSP which reduced in the presence of SAI (all $P < 0.0001$). Compared to controls, shoulder pain patients demonstrated higher active motor threshold ($P = 0.046$), less SAI ($P = 0.044$), a longer CSP ($P = 0.048$) and less modulation of the CSP by SAI ($P = 0.045$). Higher motor thresholds were related to higher pain scores ($P = 0.009$). The SSNB immediately restored SAI ($P = 0.013$), with a positive relationship between increased SAI and reduced pain ($P = 0.031$). The SSNB further reduced modulation of CSP by SAI at one week post injection ($P = 0.006$).
Conclusions: SAI and the CSP were present and demonstrated robust interaction in controls, which was aberrant in patients. The SSNB transiently restored SAI but had no effect on the CSP; however CSP modulation by SAI was further attenuated one week post injection.
Significance: The current findings improve understanding of shoulder motor cortex neurophysiology, its modulation by chronic pain and the effect of SSNB. Interventions that target cortical inhibition might increase efficacy for chronic shoulder pain.

Keywords: Transcranial magnetic stimulation, short afferent inhibition, cortical silent period, chronic shoulder pain, infraspinatus, suprascapular nerve block

1.Introduction

Chronic shoulder and upper limb pain is a highly prevalent and recalcitrant condition affecting health-related quality of life in many patient populations (Pope et al., 1997, Hill et al., 2010, Gill et al., 2013). There is emerging evidence that painful musculoskeletal disorders of the upper limb are accompanied by aberrant cortical neurophysiology (Krause et al., 2004, Krause et al., 2006, Alexander, 2007, Berth et al., 2009, Berth et al., 2010, Schabrun et al., 2014). It is unclear whether this aberrant neurophysiology normalises in response to interventions targeting upper limb pain. If so, cortical measures might provide intervention targets and useful markers for the impact of treatments targeting pain. A suprascapular nerve block (SSNB) has shown efficacy for rheumatologic (Shanahan et al., 2003, Shanahan et al., 2004) and post-stroke shoulder pain (Adey-Wakeling et al., 2013), with high patient acceptability and few adverse effects (Shanahan et al., 2012, Shanahan and Smith, 2012). The mechanisms contributing to the clinical efficacy of SSNB are unclear, but might arise from modification of cortical networks innervating shoulder musculature. It is well known that sensory input influences excitability of cortical networks by modulating intracortical connections within primary motor cortex (M1) (Chen et al., 1999, Tokimura et al., 2000). Furthermore, an ischemic nerve block produces rapid cortical reorganisation and increases corticomotor excitability in upper limb M1 representations in healthy adults (Brasil-Neto et al., 1993). An investigation into the effect of SSNB on cortical mechanisms is hampered by limited knowledge of neurophysiology of proximal upper limb muscles. The infraspinatus muscle is an important dynamic stabiliser of the shoulder, active throughout all shoulder movements (Arwert et al., 1997). Motor control of the infraspinatus is degraded in painful musculoskeletal conditions (Magarey and Jones, 2003). The cortical representations of infraspinatus have been mapped (Ngomo et al., 2013) and its task-dependent neural control investigated in healthy adults using transcranial magnetic stimulation (TMS) (Roberts et al., 2008, Bradnam et al., 2010b). A study of infraspinatus cortical neurophysiology in people with chronic rotator cuff tears revealed higher active motor thresholds in M1 contralateral to the painful shoulder compared to the non-painful side (Ngomo et al., 2014), with thresholds related to pain duration. Cortical maps and corticomotor excitability were similar between hemispheres in these chronic shoulder pain patients.

Intracortical mechanisms contributing to aberrant cortical neurophysiology in people experiencing shoulder pain can be explored using TMS. One method with potential relevance is known as short afferent inhibition (SAI). SAI is the result of inhibition of corticomotor

excitability by sensory input and is assessed by pairing TMS and peripheral nerve stimulation. Short AI was originally described in hand motor cortex following stimulation of the median nerve at the wrist (Tokimura et al., 2000). The SAI pathway is only partially elucidated, but is likely to traverse from the periphery directly to the thalamus and M1 (Tokimura et al., 2000), via primary somatosensory cortex (SI) (Tsang et al., 2014). It is known that SAI is reliant upon cholinergic mechanisms (Di Lazzaro et al., 2000, Sailer et al., 2003) interacting with γ-amino butyric acid (GABA) inhibitory interneurons (Di Lazzaro et al., 2005). Afferent inhibition is deficient in neurological disorders including stroke (Di Lazzaro et al., 2012), Alzheimer's disease (Di Lazzaro et al., 2002) and Parkinson's disease (Sailer et al., 2003, Yarnall et al., 2013). In contrast, SAI is normal in complex regional pain syndrome affecting the hand (Turton et al., 2007). There has been limited use of TMS to measure SAI outside of hand motor cortex; accordingly SAI in chronic shoulder pain has not yet been investigated. We recently described suppression of corticomotor excitability of infraspinatus by stimulation of the suprascapular nerve (Hendy et al., 2014), facilitating exploration of SAI of shoulder motor cortex in patient populations.

Intracortical inhibition mediated by GABAergic interneurons within M1 can also be explored using TMS. One measure is the cortical silent period (CSP), a transient period of electromyography (EMG) suppression following TMS during a voluntary muscle contraction. The late period of the CSP is attributed to GABA-mediated intracortical inhibition (Fuhr et al., 1991, Inghilleri et al., 1993, Roick et al., 1993, Uncini et al., 1993). Modulation of cortical excitability by GABAergic interneurons is critical to the integrity and normal function of neural networks (Jacobs and Donoghue, 1991). Aberrant intracortical inhibition impacts on cortical reorganisation and motor learning, with negative consequences for recovery of function. Accordingly, the CSP is altered in neurological diseases such as Parkinson's and Alzheimer's disease, Dystonia and Schizophrenia (Khedr et al., Curra et al., 2011, Lang et al., 2011, Trompetto et al., 2011). The CSP has not been previously described in shoulder motor cortex or tested in a chronic shoulder pain population. The CSP may elucidate whether GABAergic inhibition within shoulder motor cortex is altered in people with chronic pain or if modulation of GABA receptor-mediated inhibition contributes to the effect of SSNB. Finally, sensory inputs mediating SAI also modulate GABA receptor-mediated inhibition, exposed previously by paired-pulse TMS (Udupa et al., 2009, 2014). Intracortical inhibition is reduced when SAI is present. The interaction between SAI and

GABAergic inhibition has not been explored using the CSP or in shoulder M1 in healthy adults or adults experiencing chronic shoulder pain.

The aim of this study was to characterize SAI and CSP in M1 representations of infraspinatus in healthy adults, to compare these measures to people experiencing chronic shoulder pain, and to determine the impact of SSNB. We formed an *a priori* hypothesis that SAI and CSP are present in healthy adults and SAI attenuates the CSP (Udupa et al., 2009, 2014). Our second hypothesis was that SAI is reduced and the CSP lengthened in people with chronic shoulder pain. Our third hypothesis was these measures are normalised following SSNB, associated with a reduction in subjective pain intensity. These findings will further the understanding of cortical neurophysiology in people with chronic shoulder pain and may explain the clinical efficacy of SSNB in this population.

2. Methods

2.1 Participants

Twenty-six participants included eighteen healthy controls (9 male, 8 female) aged 20-68 years (mean 41.3), without history of musculoskeletal or neurological conditions affecting the upper limb or neck and eight patients with chronic shoulder pain (1 male, 7 female, 49 - 75 years old, mean 64.9) recruited from a rheumatology clinic. The dominant hand for each control participant was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). All patients had been diagnosed with rotator cuff pathology at least one year prior to the study and were identified as suitable candidates for SSNB by the rheumatologist (MS). Ethical approval for the study was provided by the local ethics committee and all participants provided written informed consent.

2.2 Experimental Design

Control participants attended a single session to assess cortical neurophysiology. The patients attended two sessions, separated by one week. At the first session, baseline TMS measures and visual analogue scale (VAS) for pain intensity were collected (PRE), followed by a SSNB delivered by the rheumatologist (MS). A second set of measures were taken 30 minutes later (POST1). Cortical neurophysiology and VAS for pain intensity was assessed again at the second session one week later (POST2).

2.3 Motor Tasks

Upper limb tasks were used to pre-activate the infraspinatus prior to TMS because MEPs are difficult to evoke in this muscle without voluntary activation (Bradnam et al., 2010b). Participants were seated with their dominant or painful upper limb positioned in approximately 5º of shoulder flexion, 10º of abduction and 45º of external rotation with the elbow flexed to 120º and the forearm midway between supination and pronation. The limb was supported under the elbow. Prior to testing, participants were trained to perform a consistent level of external rotation of the shoulder using visual EMG biofeedback. Activity of infraspinatus was carefully monitored by the experimenters by observation of prestimulus, root mean square (rms) EMG activity throughout the experiment. Participants were verbally encouraged to maintain a consistent contraction. Data were collected over three periods separated by a short break (approximately 5 minutes) to prevent muscle fatigue.

2.4 Electromyography

Surface electromyography (EMG) was recorded from the infraspinatus muscle of the dominant upper limb for controls and the affected shoulder in patients. Two 10mm-diamter Ag/AgCl adhesive electrodes (Ambu, Ballerp, Denmark) were positioned approximately 3cm below the midpoint of the spine of scapula, 1cm apart, and aligned with the direction of underlying muscle fibres of the infraspinatus (Roberts et al., 2008, Bradnam et al., 2010b). A 20mm-diameter Ag/AgCl electrode was fixed over the acromion process as a reference. Electrodes were positioned on the upper trapezius and biceps brachii to aid localization of the optimum stimulation point for peripheral nerve stimulation (PNS). Electromyography signals were sampled at a frequency of 2000Hz (CED1401; UK), amplified and band-pass filtered (20-1000Hz) (CED1902; UK) and stored for offline analysis (Signal v 5.07).

2.5 Transcranial magnetic stimulation

Single pulse TMS was applied over M1 using a hand-held flat 70mm figure of eight-coil Magstim 200² stimulator (Magstim Company, Dyfed, UK). The coil was positioned tangentially 45° to the central sulcus over M1 to elicit motor-evoked potentials (MEPs) in the infraspinatus muscle (Roberts et al., 2008, Bradnam et al., 2010b, Ngomo et al., 2013). The stimulation site evoking the largest amplitude MEP was determined and marked on the head. The maximal MEP response (MEP$_{MAX}$) was obtained and used to establish the stimulus intensity (% maximum stimulator output, MSO) to evoke an MEP of approximately half the maximal response (50%MEP$_{MAX}$). Active motor threshold (AMT) was determined as the

lowest stimulus intensity producing an MEP above 100uV in five of ten consecutive single pulses (Rossini et al., 1994). TMS intensity was set to 120% of AMT and sixteen MEPs were recorded to assess corticomotor excitability. To determine SAI and the CSP, PNS was delivered prior to TMS using three different ISIs (20, 30 and 40ms) (Hendy et al., 2014). Sixteen non-conditioned MEPs were collected along with sixteen conditioned MEPs for each ISI, delivered in random order by the computer software (Signal v 5.07, CED, UK).

2.6 Conditioning peripheral nerve stimulation

A constant current stimulator (DS7A, Digitimer, Hertfordshire, UK) delivered a square wave, 1-ms duration pulse every 5 seconds via an anode (Ambu, Ballerp, Denmark) positioned on the skin over the suprascapular nerve. The nerve was first located using a pen electrode, superior and lateral to Erb's point just above the clavicle (Hendy et al., 2014). Optimum anode position was determined by observing an EMG response in the infraspinatus with minimal activation of upper trapezius and biceps brachii muscles, to avoid stimulation of spinal or musculocutaneous nerves (Figure 1). Stimulus intensity was set to 80% of motor threshold to preferentially stimulate group I sensory afferents (Nicolas et al., 2001).

2.7 Data analysis

Motor EPs were rectified using Signal software (v5.07) and the area measured between the MEP onset and offset (MEP_{AREA}). To account for any differences in prestimulus EMG, EMG_{AREA} was calculated from the prestimulus EMG over a period equivalent in duration to that used to calculate MEP_{AREA}. MEP size was calculated for individual traces using the formula: $MEP_{SIZE} = (MEP_{AREA} - EMG_{AREA}) \times 1000$ as described previously (Bradnam et al., 2010b). The average MEP_{SIZE} was calculated for each individual using the same window across time where relevant. A ratio of conditioned to non-conditioned MEP_{SIZE} (C/NC) was used to determine SAI at each ISI, so that a ratio of less than one indicated inhibition. To determine the duration of the CSP, the period of EMG silence was measured (ms) from the stimulus artefact to the point where the unrectified EMG activity returned to 50% of prestimulus value (Silbert and Thickbroom, 2013). To determine the influence of SAI on the CSP (Udupa et al., 2009), conditioned responses were expressed relative to non-conditioned (C/NC) so that a ratio of less than 1 indicated a reduction in CSP (i.e. less inhibition) when conditioned by SAI (CSP^{SAI}). To determine effect of SSNB in patients, pain scores and neurophysiological measures were expressed relative to baseline (post-pre = Δ) and compared using linear regression.

2.8 Statistical Analysis

Statistical analysis was performed using SPSS v14 (IBM). Data were tested for normality using the Shapiro-Wilks test. Consistent with our *a priori* hypothesis, SAI and CSP^{SAI} were characterised in control participants for each ISI using one sample t- tests. For both groups, ISI was separately compared using repeated measures ANOVA (rmANOVA). Independent sample t-tests compared the control and patient (baseline) groups for AMT, MEPSIZE, SAI, CSP, CSP^{SAI} and NC MEPs. Prestimulus rmsEMG was compared across conditioned and non-conditioned responses and between groups by rmANOVA. In patients, linear regression was used to compare baseline pain scores to the neurophysiological variables. To assess the effect of SSNB, SAI and CSP^{SAI} were separately analysed using a 3 ISI x 3 TIME rmANOVA. VAS pain intensity scores, MEPSIZE, CSP and NC MEPs (for SAI) were compared using a 3 TIME (PRE, POST1, POST2) rmANOVA, while AMT at PRE and POST2 was compared with a paired t-test. Prestimulus rmsEMG was tested with a 3 TIME by 4 CONDITION (conditioned and non-conditioned responses) rmANOVA. Finally, ΔVAS at POST1 and POST2 were compared to ΔSAI and ΔCSP^{SAI} using linear regression. Post hoc paired t-tests were used to explore main effects and Bonferroni corrections were applied to multiple comparisons. Where data did not conform to sphericity, Greenhouse-Geisser corrections were utilised. Significance was set at $P < 0.05$. Data are reported as mean ± standard error mean (SEM).

3.Results

All patients tolerated the nerve block injection and there were no adverse events during TMS reported by any participants. Baseline characteristics for patients with chronic shoulder pain are provided in Table 1. Figure 2 shows EMG traces of conditioned and non-conditioned responses for SAI and CSP in a representative control and shoulder pain patient.

3.1 Characterisation of SAI and CSP in controls

The one sample t-tests revealed SAI was demonstrated by controls at all ISI's (ISI20, 0.85 ± 0.04; ISI30, 0.82 ± 0.059; ISI40 0.83 ± 0.072, all $P < 0.03$). There was a CSP present in controls (mean 98.34 ± 4.6ms) and the CSP was reduced in the presence of SAI (CSP^{SAI}) at all three ISI's (ISI20, 0.86 ± 0.014; ISI30, 0.86 ± 0.023; ISI40 0.85 ± 0.026, all $P < 0.0001$, Figure 3). In line with these data, there was no main effect of ISI for SAI or CSP^{SAI} (both $P >$

0.91). Likewise, there was no difference between ISI's for SAI or CSP^{SAI} in patients (both $P > 0.94$), so data were collapsed across ISI for analysis of GROUP.

3.2 Comparison of control and patient groups

The AMT was higher in patients at baseline (42.38 ± 3.73 MSO) than controls (33.78 ± 2.17 MSO, $P = 0.046$, figure 4a). SAI was decreased in patients compared to control participants (patients 0.94 ± 0.031; controls 0.83 ± 0.034; $F_{1,73} = 5.73$, $P = 0.044$, figure 4b). The CSP was longer in patients (118.03 ± 9.8mm) than controls (98.34 ± 4.6mm, $P = 0.048$, figure 4c) and there was less CSP^{SAI} in patients (0.90 ± 0.012) than controls (0.86 ± 0.013, $F_{1,73} = 3.60$, $P = 0.045$, figure 4d). The groups did not differ for MEPSIZE ($P = 0.25$). Non-conditioned MEPs used to probe SAI/CSP were similar for both groups (patients 1.84 ± 0.65 mV, controls 1.68 ± 0.25; $P = 0.52$), as was prestimulus rmsEMG for SAI/CSP (patients 0.028 ± 0.0043mV, controls 0.03 ± 0.003mV; all $P > 0.91$).

3.3 Effect of SSNB in patients

Mean VAS for pain intensity in patients with chronic shoulder pain was 4.4 ± 1.2. There was a relationship between VAS pain intensity score and AMT at baseline ($R^2 = 0.71$, $P = 0.009$), so that higher pain scores were associated with higher AMT (Figure 5A).There was no relationship between VAS and SAI, CSP, CSP^{SAI} or MEPSIZE at baseline (all $P > 0.22$). Patients reported reduced pain following the SSNB (POST1, 2.9 ± 0.58; POST2, 3.9 ± 0.81), but this did not reach statistical significance ($P = 0.26$, Figure 5b). The rmANOVA for SAI revealed no main effects or an interaction (all $P > 0.13$). Data were collapsed across ISI to explore the impact of SSNB. The normalised SAI revealed a main effect of TIME ($F_{2,46} = 4.23$, $P = 0.022$). Post hoc paired t-tests found SAI was increased from baseline to Post 1 (Pre, 0.94 ± 0.031; POST1, 0.86 ± 0.021; $P = 0.013$) and decreased from Post 1 to Post 2 (POST1, 0.86 ± 0.021; POST2, 0.94 ± 0.028; $P = 0.017$, Figure 5c). There was no difference between baseline and Post 2 ($P = 0.86$). Data were collapsed across TIME to explore ISI. There was no main effect ($P = 0.82$). For CSP^{SAI} there were no main effects or interactions (all $P > 0.21$). Data were collapsed across ISI to explore the impact of SSNB. There was a main effect of TIME ($F_{2,46} = 3.91$, $P = 0.03$). Paired t-tests revealed a reduction in CSP^{SAI} between baseline and Post 2 (PRE, 0.90 ± 0.12; POST2, 0.95 ± 0.18; $P = 0.006$) and between Post 1 and Post 2 (POST1, 0.91± 0.03; POST2, 0.95 ± 0.18; $P = 0.047$, Figure 5d). Data were

collapsed across TIME to further explore ISI. There was no main effect ($P = 0.77$).There was no effect of SSNB for CSP ($P = 0.54$), AMT ($P = 0.72$) or MEPSIZE ($P = 0.55$). The NC MEP used to calculate SAI/CSP was consistent ($P = 0.52$), as was rmsEMG recorded during SAI/CSP and MEP collection (both $P > 0.49$).

There was a positive linear relationship between ΔSAI and ΔVAS at post 1 ($R^2 = 0.57$, $P = 0.031$), where an increase in SAI was associated with a decrease in pain (Figure 6). There was no relationship for ΔSAI and ΔVAS between baseline and post 2 or between post 1 and post 2 (both $P > 0.23$). There was no relationship between ΔCSP^{SAI} and ΔVAS at any time point (all $P > 0.15$).

4.Discussion

The present study investigated short afferent inhibition, the cortical silent period and their interactions in shoulder M1 in healthy adults and people experiencing chronic shoulder pain before and after a SSNB. There were several findings of interest. First, SAI was demonstrated equally at all three ISIs in both participant groups. A CSP was recorded from the infraspinatus muscle and was shortened in the presence of SAI in controls. Second, patients with shoulder pain demonstrated different cortical neurophysiology compared to controls, including reduced SAI, an increased CSP duration and less CSP suppression by SAI in the M1 contralateral to the pain affected shoulder. Active motor threshold was higher in patients compared to controls and higher AMT in patients was associated with greater pain intensity. Third, the SSNB immediately normalised SAI, and an increase in SAI was associated with reducted pain intensity, but the effects were transient. Modulation of CSP in the presence of SAI, already reduced in patients, was further attenuated one week after the SSNB. The SSNB did not influence CSP duration or corticomotor excitability assessed by AMT or MEPSIZE. The implications of these findings for understanding cortical contributions to chronic shoulder pain and treatment by SSNB are discussed below.

4.1 Afferent inhibition and cortical silent periods in shoulder motor cortex

Knowledge of the cortical control of proximal muscles in healthy humans is increasing (MacKinnon et al., 2004, Alexander et al., 2007, Bradnam et al., 2010a, Bradnam et al.,

2010b, Alexander, 2011, Bradnam et al., 2011, Perez et al., 2014, Tazoe and Perez, 2014). This is the first study to describe sensorimotor integration and characterize cortical silent periods in the M1 innervating a proximal upper limb muscle to our knowledge. A CSP of just less than 100ms was recorded in the infraspinatus M1 representations in control participants. For SAI, the MEP was suppressed by suprascapular nerve stimulation at all three ISIs. The observation of SAI at an ISI of 30ms contrasts with our preliminary report in fewer subjects (Hendy et al., 2014). The difference may simply be due to greater statistical power in the current study. However, the similar effects observed at all ISIs is interesting and warrants discussion. Observation of SAI at each ISI may arise from the method used to evoke SAI in shoulder motor cortex. By necessity, the infraspinatus muscle must be pre-activated for TMS. The degree of SAI assessed from the active infraspinatus (Hendy et al., 2014) is less than that reported in resting hand muscle representations but similar to the reduction in SAI prior to and during movement to facilitate corticomotor drive to working hand muscles (Voller et al., 2006, Asmussen et al., 2013). Interestingly, finger muscle contractions attenuate SAI in hand M1 (Voller et al., 2006, Asmussen et al., 2013) by modulation of both cortical and spinal excitability (Asmussen et al., 2014). The latter finding has implications for our study. If the degree of SAI is modulated by the contracting infraspinatus, the question is raised as to whether the observed SAI is primarily a cortical or spinal response. Strong support for SAI as a cortical phenomenon is provided by the finding of robust CSP attenuation in the presence of SAI in healthy adults in the current study, indicating sensory inputs were acting upon cortical GABAergic circuits. The CSP duration provides a measure of inhibitory $GABA_B$ (Siebner et al., 1998) and $GABA_A$ receptor-mediated inhibition (Silbert and Thickbroom, 2013). In hand muscles, the latter portion of EMG silence is considered a cortical phenomenon (Fuhr et al., 1990, Inghilleri et al., 1993, Ziemann et al., 1993, Wilson et al., 1995). The significant attenuation of the CSP in the presence of SAI observed in the current study indicates neurons mediating SAI in M1 suppressed GABAergic inhibitory interneurons. This finding is consistent with interactions between SAI and GABA-receptor mediated inhibition using paired pulse TMS described in hand motor cortex (Udupa et al., 2009, 2014). In the latter studies, short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI), both cortical phenomena, were reduced in the presence of SAI in hand M1. However, we cannot rule out that SAI assessed from the contracting infraspinatus muscle is not, at least partially, mediated in the spinal cord. There are robust reticulospinal descending pathways to spinal motoneurons innervating proximal muscles in the non-human primate (Davidson and Buford, 2006, Davidson et al., 2007) and this pathway could increase spinal excitability of

the contracting infraspinatus. It might be that descending drive from the reticulospinal tract modified the effect of cortically-evoked SAI once that descending volley had reached the spinal cord. Such an effect might explain why we observed SAI at all 3 ISIs tested. Regardless, our findings for SAI, the CSP and their interactions in shoulder M1 adds to the growing understanding of the neural control of the proximal upper limb in healthy adults.

4.2 Comparison of cortical neurophysiology between controls and patients

There were several differences in TMS-evoked measures between controls and shoulder pain patients in the current study. These findings support the presence of aberrant cortical neurophysiology in musculoskeletal disorders presenting with pain (Flor, 2003). Our primary measure of interest SAI, was reduced in infraspinatus M1 representations in the chronic pain group compared to controls. While the reason for reduced SAI in patients cannot be determined from the current study, we suggest it might result from lower activity in inhibitory projections from S1 to M1 interneurons mediating SAI. It is known that S1 excitability is important for normal SAI, as in healthy adults repetitive TMS to suppress S1 reduced SAI in hand motor cortex (Tsang et al., 2014). It is also known that primary sensory cortex is suppressed by acute nociceptive afferent input (Schabrun et al., 2013). If chronic pain also produces ongoing S1 suppression, then S1 drive to M1 circuits mediating SAI would be reduced in turn attenuating the SAI response. While this idea is speculative, it is known that activity in S1 is modulated by peripheral inputs and S1 modulation is closely associated with M1 excitability (Schabrun et al., 2012). The aberrant mechanisms may also include a reduction in brain acetylcholine levels as SAI is decreased or abolished in the presence of acetylcholine blockers (Knikou, 2008), or an increase in levels of GABA, also known to reduce SAI (Di Lazzaro et al., 2005).

The latter mechanism is supported by our finding that the CSP was lengthened in chronic shoulder pain patients compared to controls, indicating an increase in GABA-receptor mediated inhibition. An increase in GABAergic inhibition has implications for recovery of motor function in conditions presenting with chronic pain (Boudreau et al., 2010), as a reduction in GABA receptor-mediated inhibition is necessary for cortical reorganization and motor learning (Perez et al., 2004; Stagg et al., 2011). Furthermore, suppression of the CSP by SAI was deficient in patients, indicating a reduction of the modulatory effect of sensory inputs on intracortical GABA circuits in chronic shoulder pain. The mechanism to explain this observation could be that activity in SAI interneurons is too weak to influence the

stronger GABA inhibitory circuits or the increase in GABA receptor-mediated inhibition is of such magnitude that it cannot be suppressed by SAI. Regardless, the impact in patients with chronic shoulder pain is disruption in cortical control of a crucial dynamic stabilizer of the glenohumeral joint, potentially exacerbating shoulder pathology and impeding functional recovery.

Motor thresholds were higher in patients than controls in the current study, in agreement with previous findings in chronic shoulder pain (Alexander, 2007, Berth et al., 2009) and between painful and non-painful hemispheres in patients (Ngomo et al., 2014). Motor threshold reflects intrinsic neuronal membrane excitability dependent upon metabolically driven ion pumps and ion channel conductivity (Ziemann et al., 1996). Pain may affect these cellular mechanisms and raise depolarization threshold. Interestingly, higher active thresholds were associated with pain intensity in the current study; in contrast to a previous study where higher thresholds were associated with pain duration (Ngomo et al., 2014). There was no difference in MEP amplitude, normalized for background muscle activity, between groups in the current study. This finding differs from a previous report where corticomotor excitability of the contracting deltoid muscle in people with a rotator cuff injury was reduced in comparison to healthy controls (Berth et al., 2009). However, in agreement with our study, people with chronic rotator cuff tendinopathy had no difference in corticomotor excitability between hemispheres controlling the painful and painless shoulders (Ngomo et al., 2014). Furhtermore, in that study cortical maps were no different in each hemisphere. Cortical reorganisation has been observed in other musculoskeletal pain conditions such as persistent elbow pain (Schabrun et al., 2014) and recurrent low back pain (Tsao et al., 2008, Tsao et al., 2011). These data suggest AMT along with SAI and the CSP could provide biomarkers and cortical targets for future interventions for chronic shoulder pain rather than corticomotor excitability assessed by MEP amplitude.

The SSNB has been found to reduce pain in chronic musculoskeletal and post-stroke shoulder pain (Shanahan et al., 2003, Shanahan et al., 2004, Adey-Wakeling et al., 2013), although we did not observe a longer term effect in the current study. Therapeutic benefits might be due to an influence of the SSNB at the level of the cortex by an increase in cortical excitability (Brasil-Neto et al., 1993). In the current study, SAI was increased immediately following SSNB and was associated with less pain. These findings indicate reduced nociceptive afference may have driven restoration of SAI, possibly by influencing excitability of S1. If

the SSNB transiently reversed S1 suppression so that cortico-cortical drive to M1 interneurons mediating SAI was restored SAI would normalise, as we observed in our patients. However, the effect of the SSNB was short-lived as SAI was attenuated again at one week follow up. Therefore, an increase in SAI cannot explain ongoing therapeutic benefits of SSNB reported in clinical populations. There was no change in corticomotor excitability after the SSNB, in contrast to a previous report where corticomotor excitability was increased immediately following a forearm nerve block (Brasil-Neto et al., 1993). However, that study was conducted in healthy participants with normal cortical function. Intracortical inhibition was increased in our chronic shoulder pain group, which may have prevented an increase in corticomotor excitability. In support, SSNB did not reduce the longer CSP in patients in the current study, indicating SSNB does not influence GABA receptor-mediated inhibition in M1. This finding agrees with those in healthy adults where an ischaemic nerve block did not reduce GABAergic intracortical inhibition measured by paired-pulse TMS (Vallence et al., 2012). The effect of a nerve block on the cortex does not appear to include direct modification of GABA inhibitory circuits. In contrast, the modulation of CSP by SAI in shoulder M1 may be influenced by the SSNB. While modulation of CSP by SAI was unaffected immediately after SSNB (when SAI was normalised), reduced suppression of the CSP by SAI in patients was further attenuated one week later (when SAI had reverted to baseline). This finding indicates SSNB may affect the longer term interaction between GABAergic and SAI circuitry within M1 by an independent and unknown mechanism. Further exploration of inhibitory interactions in shoulder motor cortex may be useful to explain longer term clinical benefits of SSNB for chronic shoulder pain. The lack of any other robust finding at the one week follow up means it is likely cortical mechanisms underlying longer term effects are outside of those currently investigated and future studies should investigate other TMS measures.

5. Limitations

There are several limitations to the study. First, the patient cohort and healthy controls were not age and gender matched and the average age of the control group was much younger than the shoulder pain group. Therefore, difference in cortical neurophysiology may be associated with aging as well as pain. This can be explored further using a carefully age and gender matched control group. Second, the chronic shoulder pain group was likely underpowered to detect all effects of SSNB, and while all had diagnosed rotator cuff pathology of greater than one year, the mechanism of injury, specific diagnosis and duration of symptoms was not

standardised. Third, by chance this cohort had relatively low pain scores at baseline providing a smaller margin for change and limiting application to the wider population. However, the current findings indicate a larger, fully powered study in a homogeneous group of chronic shoulder pain patients is warranted. Finally, future studies should investigate cortical neurophysiology in both hemispheres, as proximal muscles are known to be bilaterally controlled (Bradnam et al., 2010a, Bradnam et al., 2010b, Bradnam et al., 2011, McCambridge et al., 2011) and differences in some cortical measures between hemispheres have been reported in chronic shoulder pain (Ngomo et al., 2014).

6.Conclusions

Sensorimotor integration, intracortical inhibition and their interactions can be studied in infraspinatus motor cortex by pairing TMS and suprascapular nerve stimulation. Deficits in cortical function were identified in people experiencing chronic shoulder pain compared to controls in the current study, where intracortical inhibitory mechanisms were aberrant. Short term clinical effects of a suprascapular nerve block might be explained by modulation of sensorimotor integration, while longer term effects might be related to interactions between inputs from somatosensory cortex and inhibitory GABA circuits within M1. The SSNB did not influence active motor thresholds or the cortical silent period, two neurophysiological markers that differentiated patients from controls. It may be of value to assess the effect of other interventions for shoulder pain on these cortical biomarkers. Further studies using larger numbers of homogeneous patients and a wider range of TMS measures are needed to further elucidate the effects of SSNB in chronic shoulder pain.

Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed

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Figure Legends

Figure 1. Location of the suprascapular nerve for peripheral nerve stimulation. The suprascapular nerve was located superiorly and laterally from Erb's point (B). The anode was positioned on the skin overlying the suprascupular nerve (A) and the cathode over the clavicle (C).

Figure 2. Electromyography traces showing condition and non-conditioned MEPs used to calculate SAI and CSPs in A. a representative control participant and B. a chronic shoulder pain patient. The onset of the CSP is indicated by the arrow. Smaller MEPs and shorter CSPs are noted for conditioned responses compared to non-conditioned responses in controls but not patients.

Figure 3. A. SAI and B. CSP^{SAI} in control participants. There was SAI and CSP^{SAI} at all three ISIs. Significance with one sample t-test is signified by asterisks (*). There was no difference between ISIs for either measure (both $P > 0.91$).

Figure 4. A comparison between control and patient participants. A. AMT, B. SAI, C. CSP, D. CSP^{SAI}. The significant difference between groups is signified by asterisks (*) at $P < 0.05$.

Figure 5. A. The relationship between AMT and self-reported pain at baseline in patients. B. Effect of SSNB on SAI, C. Effect of SSNB on CSP, D. Effect of SSNB on CSP^{SAI}. Significance differences are signified by asterisks (*) at $P < 0.05$.

Figure 6. The relationship between a reduction in pain at POST1 and an increase in SAI, where restoration of SAI was associated with greater pain reduction.

Table 1. Characteristics of patients with chronic shoulder pain.