Does chronic arthritic pain influence motor cortex excitability?

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in fulfilment of the requirements for the degree of
Master of Philosophy (MPhil)

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed……………………………………………………………….

Date……………………………………………………………….

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A U T E C
S E C R E T A R I A T

20 February 2013

Gwyn Lewis
Faculty of Health and Environmental Sciences

Dear Gwyn

Re Ethics Application: **13/02 How does chronic arthritic pain influence movement learning ability?**

Thank you for providing evidence as requested, which satisfies the points raised by the AUT University Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 19 February 2016.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online throughhttp://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 19 February 2016;

- A brief report on the status of the project using form EA3, which is available online throughhttp://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 19 February 2016 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

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All the very best with your research,

Dr Rosemary Godbold
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Rosaline Parker rosalindsarahparker@gmail.com

Abstract

Background: Painful hand arthritis is a major cause of disability worldwide including New Zealand, causing loss of function and reduced motor control. Arthritis is associated with changes in central nociceptive processing and cortical reorganisation. Previous studies have shown an association between chronic pain and changes in corticomotor excitability. However, few studies have assessed corticomotor excitability in people with arthritis.

Aims of the investigation: 1. To examine corticomotor and intracortical excitability in people with chronic hand pain due to arthritis. 2. To explore possible relationships between corticomotor excitability and pain variables.

Methods: Transcranial magnetic stimulation (TMS) was used to measure the excitability of the corticomotor pathway to the first dorsal interosseus muscle in 23 people with chronic painful hand arthritis (median age 71; 17 female; median pain duration 9 years) and 20 pain-free control participants (median age 70.5; 14 female). Single-pulse TMS was used to establish the resting motor threshold (RTh), stimulus-response curves, and the cortical silent period duration (CSP). Paired-pulse TMS was used to examine short- and long-interval intracortical inhibition (SICI, LICI) and short-interval intracortical facilitation (SICF). SICI was assessed using conditioning stimulus intensities of 70% and 80% RTh ($SICI_{70}$, $SICI_{80}$) and an interstimulus interval (ISI) of 2 ms. The test stimulus was set to an intensity that elicited a motor evoked potential (MEP) of 1 mV (TS_{1mV}). SICF was assessed using a conditioning stimulus of TS_{1mV}, a test stimulus of 90% RTh, and ISIs of 1.4 and 2.8 ms ($SICF_{1.4}$, $SICF_{2.8}$). Outcome measures were compared between the two groups using Mann Whitney U tests due to several of the measures being non-normally distributed. Spearman's rank correlations were used to explore the potential relationships between the corticomotor excitability measures and pain variables (pain duration, pain intensity and a measure of hand-related pain, stiffness and function).

Results: The arthritis group demonstrated significantly enhanced $SICF_{1.4}$ ($p = 0.045$) compared to the control group. RTh, stimulus-response curves, CSP duration, $SICI_{70}$, $SICI_{80}$, $SICF_{2.8}$, and LICI were not significantly different between the two groups (all $p>0.05$). Moderate strength correlations were observed between the duration of hand

pain and both measures of intracortical inhibition (SICI$_{70}$ ρ = 0.38; SICI$_{80}$ ρ = 0.434). There was a moderate strength correlation between the duration of hand pain and SICF$_{1.4}$ (ρ = 0.346).

Conclusions: This study provides evidence of enhanced facilitation in people with hand pain due to arthritis. No significant alterations in overall corticomotor excitability or inhibition were found. Relationships were observed between pain duration and intracortical excitability, with increased pain duration being associated with reduced inhibition and enhanced facilitation. This suggests that with increased hand pain duration, there is greater intracortical excitability. Similarly to other studies in assessing corticomotor excitability in chronic pain conditions, arthritic pain is associated with disinhibition of the motor cortex. Cortical disinhibition may contribute to the deficits in strength, motor control and function, which are known to impact on people with arthritic hand pain. These findings have important implications for motor learning and rehabilitation for people with hand arthritis.

Abbreviations

ATh, active motor threshold

CRPS, complex regional pain syndrome

CSP, cortical silent period

EMG, electromyographic

FDI, first dorsal interosseous

GABA, gamma-aminobutyric acid

ISI, interstimulus interval

LICF, long-interval intracortical facilitation

LICI, long-interval intracortical inhibition

MEP, motor evoked potential

OA, osteoarthritis

RA, rheumatoid arthritis

RTh, resting motor threshold

SICF short-interval intracortical facilitation

SICI, short-interval intracortical inhibition

SR curve, stimulus-response curve

TMS, transcranial magnetic stimulation

Chapter 1 Introduction

1.1 Statement of the problem

Arthritis is a major cause of disability in New Zealand. It is estimated to affect over 530,000 New Zealanders over the age of 14, at a financial cost of $3.2 billion per year (AccessEconomics, 2010). One of the most frequently affected regions are the hands. Although there are no data from New Zealand, recent estimates from Australia and Europe suggest that hand pain has a prevalence of 14 to 17%, rising to 20 to 30% in those over 50 years of age (Cole, Gill, Taylor, & Hill, 2011; Dziedzic et al., 2007). Hand pain is a frequent consequence of hand arthritis, with a recent study finding that 38.5% of people with hand pain had been diagnosed with hand arthritis (Cole et al., 2011). However, the actual prevalence may be considerably higher due to under diagnosis, as many people, even with severe disability, do not seek medical examination (Dziedzic et al., 2007; Zhang et al., 2002).

Hand pain is associated with significantly reduced quality of life (Cole et al., 2011). Females and people aged over 70 years are at the highest risk of having severe hand-related disability (Dziedzic et al., 2007), which is most likely due to the increased frequency of conditions such as hand arthritis in this population (Dahaghin, Bierma-Zeinstra, Ginai, et al., 2005). Given that the hands are essential for many activities of daily living, it is not surprising that hand arthritis is associated with a reduction in function (Bearne, Coomer, & Hurley, 2007; Cole et al., 2011). The most commonly impaired functions include those that require fine motor control, such as fastening buttons or jewellery and carrying a full pot in one hand (Allen, Jordan, Renner, & Kraus, 2006; Bellamy, Campbell, Haraoui, Buchbinder, et al., 2002). Furthermore, compared with healthy controls, patients with hand arthritis have been shown to have altered grip control and strength (Bearne et al., 2007; Cole et al., 2011; de Oliveira, Nunes, Aruin, & dos Santos, 2011).

The changes in function and motor control caused by hand arthritis may partially result from altered sensory and motor processing within the central nervous system. For example, in comparison with healthy controls, patients with painful knee osteoarthritis (OA) demonstrated a reduction in accuracy on a laterality task, whereby the participants had to judge whether photographs were of limbs of the left or right side of

the body (Stanton et al., 2012) and on a task assessing two-point discrimination (Stanton et al., 2013). This suggests there is a disruption in cortical representations in the somatosensory cortex (Pleger et al., 2006; Stanton et al., 2013). Similarly, people with hand OA pain have been shown to have an abnormally small perception of their hand when asked to estimate its size after seeing distorted images of their hand, thereby indicating that arthritis is associated with altered spatial representation of the painful region (Gilpin, Moseley, Stanton, & Newport, 2014). Furthermore, quantitative sensory testing has highlighted changes in nociceptive system function. Painful hand arthritis is associated with alterations in pain thresholds, not only in the affected hand (Farrell, Gibson, McMeeken, & Helme, 2000), but also in the opposite unaffected hand (Chiarotto, Fernandez-de-las-Peñas, Castaldo, & Villafañe, 2013) and in neighbouring unaffected regions (Wajed et al., 2012). This is indicative of a spreading of central sensitisation, a common indicator of altered central nociceptive processing (Lewis & Rice, 2014; Thakur, Dickenson, & Baron, 2014). In addition, several studies using magnetic resonance imaging have shown the occurrence of structural cortical reorganisation and altered connectivity in patients with painful arthritis (Buffington, Hanlon, & McKeown, 2005; Gwilym, Filippini, Douaud, Carr, & Tracey, 2010; Gwilym et al., 2009; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009).

One of the key cortical areas known to undergo structural and functional reorganisation in chronic pain conditions is the primary motor cortex (Maihofner et al., 2007; Tsao, Galea, & Hodges, 2008). Neuroplastic changes within the primary motor cortex and the connecting cortical regions can alter aspects of corticomotor excitability (Ljubisavljevic, 2006), which can be examined using transcranial magnetic stimulation (TMS). Depending on the TMS paradigm used, different aspects corticomotor excitability and intracortical circuits can be assessed. Overall, chronic pain is associated with a reduction in short-interval intracortical inhibition (Massé-Alarie, Flamand, Moffet, & Schneider, 2012; Mhalla, de Andrade, Baudic, Perrot, & Bouhassira, 2010; Schwenkreis et al., 2010) and a reduction in the duration of the cortical silent period (Lefaucheur, Drouot, Ménard-Lefaucheur, Keravel, & Nguyen, 2006; Maier et al., 2011; Turgut & Altun, 2009), suggesting that there is a reduction in the efficacy of both $GABA_A$ (gamma-aminobutyric acid) and $GABA_B$ mediated inhibitory intracortical circuits. Furthermore, several studies have found significant correlations between the

severity of pain and cortical inhibition, indicating that higher pain intensity is associated with a greater reduction in cortical inhibition (Lefaucheur et al., 2006; Schwenkreis et al., 2010). However, less consistent findings have been observed regarding intracortical facilitation, with studies in chronic pain patients finding opposing results (Mhalla et al., 2010; Salerno et al., 2000; Siniatchkin, Kröner-Herwig, Kocabiyik, & Rothenberger, 2007) or not detecting significant differences between people with pain and healthy controls (Brighina et al., 2005; Eisenberg et al., 2005; Lefaucheur et al., 2006; Schwenkreis et al., 2010; Schwenkreis et al., 2003).

Given the strong evidence for both cortical changes and altered motor control in arthritic conditions, very few studies have used TMS to assess corticomotor excitability in patients with arthritis. In addition, those studies that have been conducted show conflicting results (Kittelson, Thomas, Kluger, & Stevens-Lapsley, 2014; Salerno et al., 2000; Schwenkreis et al., 2010). To date, only one study has assessed corticomotor excitability in participants with hand arthritis and found no significant differences between hand arthritis and healthy controls (Schwenkreis et al., 2010). However, more research is needed to verify these findings. Moreover, no previous study has systematically examined a range of corticomotor excitability measures, including the less frequently assessed stimulus response curve or short-interval intracortical facilitation, in an arthritic population. These latter measures will provide further insight into the excitability and synaptic efficacy of the corticospinal pathway and intracortical facilitatory processes, respectively (Reis et al., 2008; Rossini & Rossi, 2007).

1.2 Purpose of the study

The purpose of this study was:

1. To systematically compare a series of corticomotor and intracortical excitability measures between participants with painful hand arthritis and pain-free aged-matched controls.

2. To explore the relationship between the corticomotor and intracortical excitability measures and measures of pain and function, specifically, the duration of painful symptoms, the Short-Form McGill Pain Questionnaire Version 2, and the Australian/Canadian Osteoarthritis Hand Index in the participants with hand arthritis.

1.3 Significance of the study

This study will have significance for health professionals and researchers involved in the rehabilitation of people with hand arthritis, as it will strengthen our understanding of the underlying mechanisms for altered motor control and function in these patients. Arthritis is associated with central sensitisation of the nervous system and can be considered a form of chronic pain. If arthritic pain is similar to chronic pain conditions, it may be anticipated that there could be alterations in corticomotor excitability and reduced intracortical inhibition. Hence, this would provide valuable information as it could facilitate the development of novel treatment strategies targeting cortical excitability and may enable improved treatment outcomes for people with hand arthritis. Previously treatment for arthritis has mainly focused on the joint itself, whereas this would provide rationale to examine the efficacy of treatments targeting the central nervous system. For example, treatments such as repetitive TMS, transcranial direct current stimulation and motor imagery have all previously been shown to influence corticomotor excitability and reduce chronic pain. The current study would provide evidence on whether to pursue this type of treatment for arthritic conditions. Additionally, findings from this study could lead to further important studies that aim to progress understanding of pain and corticomotor excitability changes. For example, arthritis related impairments in function and motor learning may be associated with altered corticomotor excitability.

Chapter 2 Literature Review

2.1 Introduction

This chapter will outline the relevant literature pertaining to the main themes of this project: arthritis, the assessment of corticomotor excitability using TMS and the effects of chronic pain on corticomotor excitability. The first section will summarise the problem of hand arthritis and the effects of arthritic pain on the central nervous system. Secondly, there will be a brief review of the main TMS techniques used to study the motor cortex and what is currently known about the underlying neurophysiological mechanisms that can be examined. The final section will be a systematic review evaluating the current research, comparing corticomotor excitability in patients with chronic pain and pain-free control participants.

2.2 Prevalence and impact of hand pain and hand arthritis

Chronic hand pain is highly prevalent and a major cause of disability worldwide. According to recent estimates from Europe and Australia, it has a prevalence of 14 to 17%, rising to 30% in those aged over 50 years and most often affects females (Cole et al., 2011; Dahaghin, Bierma-Zeinstra, Reijman, et al., 2005; Dziedzic et al., 2007). Hand pain is a common clinical manifestation of arthritis. In a recent study, 38.5% of people with hand pain had been diagnosed with hand arthritis (Cole et al., 2011), though the actual prevalence may be considerably higher as many people, even with severe disability, do not seek medical examination, possibly resulting in under diagnosis (Dziedzic et al., 2007; Zhang et al., 2002). The most common forms are OA and rheumatoid arthritis (RA) which both affect joint structures predominantly, but by different pathways and time frames. OA is characterised by cartilage degeneration and osteophyte formation within joints, whereas RA is an autoimmune disease resulting from inflammation of the synovial membrane and secondary cartilaginous and osseous changes.

Hand pain is associated with significantly reduced quality of life (Cole et al., 2011). Females and people aged over 70 years are at the highest risk of having severe hand-related disability (Dziedzic et al., 2007), which is most likely due to the increased frequency of conditions such as hand arthritis in this population (Dahaghin, Bierma-

Zeinstra, Ginai, et al., 2005). Both OA and RA have been linked to reduced function (Bearne et al., 2007; Cole et al., 2011), with the most commonly impaired functions including those that require fine motor control, such as fastening buttons or jewellery and carrying a full pot in one hand (Allen et al., 2006; Bellamy, Campbell, Haraoui, Buchbinder, et al., 2002).

2.3   Sensorimotor and pain processing changes in arthritis

The impaired function caused by hand arthritis may partially result from altered sensory and motor processing. For example, grip strength is known to be impaired in patients with OA and RA (Bearne et al., 2007; Cole et al., 2011). Strength deficits in arthritis are thought to result from complex interactions between pain and swelling, with spinal reflex pathways and alterations in cortical drive, as well as disuse atrophy (Rice & McNair, 2009). These interactions can manifest as altered sensorimotor processing. For instance, patients with hand OA have been shown to apply elevated grip forces when undertaking submaximal level tasks, and have increased latencies between grasping and lifting an object compared with healthy controls (de Oliveira et al., 2011). Grip control impairment is significantly correlated with poorer hand function (Nunes, de Oliveira, Aruin, & dos Santos, 2012). Furthermore, altered proprioception has been observed in patients with RA, which can also influence motor control and function (Bearne et al., 2007; Ferrell, Crighton, & Sturrock, 1992).

There is also evidence of nociceptive system plasticity in patients with arthritis. It is not simply that the severity of the disease causes pain and functional impairment. For instance, patients with RA may continue to experience painful symptoms even when disease related joint swelling and systemic inflammation have remitted (Morris, Cruwys, & Kidd, 1997). Likewise, there is discordance between what observed radiographically and the symptoms experienced by the patient with OA (Bedson & Croft, 2008; Lluch, Torres, Nijs, & Van Oosterwijck, 2014). Dahaghin and colleagues (2005) noted that the severity of radiographic hand OA was only modestly correlated with pain and weakly correlated with function. Moreover, Zhang et al. (2002) conducted a study comparing participants with painful symptomatic hand OA and those with asymptomatic hands, but all of whom demonstrated radiographic OA changes. It was found that the symptomatic group experienced significantly greater impairment of grip strength and function, specifically with fine motor tasks and

carrying objects. This suggests that impairments in strength and function are more closely related to pain than to peripheral structural damage.

Quantitative sensory testing has also highlighted changes in nociceptive processing in patients with arthritis. Patients who experienced persistent pain had regional differences in pressure and temperature thresholds between the hand and the forearm, indicating altered pain processing in the hand (Farrell et al., 2000). Lower thermal and mechanical pain thresholds were associated with increased ratings of continuous pain (Farrell et al., 2000). Reduced pressure pain thresholds have been demonstrated in people with hand OA at not only the affected joint, but in the opposite, unaffected hand (Chiarotto et al., 2013) and in neighbouring unaffected regions (Wajed et al., 2012). This is suggestive of a spreading of sensitisation, a common indicator of altered central nociceptive processing (Lewis & Rice, 2014; Thakur et al., 2014). In fact, in a study by Moseley et al. (2008), patients with chronic hand pain (a small number of whom had hand OA) exhibited an increase in pain and swelling in the absence of any muscle activation or movement simply by visualising moving their painful hand. The authors proposed that the increase in symptoms must therefore be cortically mediated.

Evidence of somatosensory cortical reorganisation has been demonstrated in patients with OA. Stanton et al. (2012) found that knee OA pain was associated with a reduction in accuracy on a laterality task, whereby the participants had to judge whether photographs were of limbs of the left or right side of the body. The authors suggested that arthritic pain is associated with a disruption of spatial representation and processing in the somatosensory cortex, resulting in an altered body schema. In addition, participants with painful knee OA were found to have a deficit in tactile acuity using two-point discrimination (Stanton et al., 2013), which could be indicative of a disruption in cortical representation in the somatosensory cortex (Pleger et al., 2006; Stanton et al., 2013). Furthermore, altered spatial representation has recently been demonstrated in hand OA (Gilpin et al., 2014). Hand OA pain was associated with an abnormally small perception of the hand when participants were asked to estimate the size of the hand in distorted photographs. In contrast, studies involving other chronic unilateral arm pain conditions have noted increased estimates of hand size (Moseley, 2005; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011). Irrespective of

whether greater or lesser perception, these studies provide evidence of altered cortical representations in patients with painful OA.

Several studies using magnetic resonance imaging (MRI) have shown that painful arthritic symptoms are linked to altered activity and reorganisation cortical structures. For example, in patients with OA there is evidence of alterations in the activity of the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the periaqueductal grey, assessed using functional MRI (Buffington et al., 2005; Gwilym et al., 2009), which are key brain regions associated with pain perception and modulation (Tracey & Mantyh, 2007). In addition, significant changes in grey matter volume have been observed in the anterior insula, amygdala, temporal fusiform cortex, anterior cingulate cortex, the dorsolateral prefrontal cortex, and the brain stem in patients with hip OA in comparison with controls (Gwilym et al., 2010; Rodriguez-Raecke et al., 2009). Interestingly, these changes have been shown to normalise following corrective surgery, suggesting these alterations are plastic and are associated with pain (Gwilym et al., 2010; Rodriguez-Raecke et al., 2009).

One of the key cortical areas known to undergo pain-related structural reorganisation is the primary motor cortex (Maihofner et al., 2007; Tsao et al., 2008). The primary motor cortex is a functionally organised region of the brain which plays a central role in the integration of multiregional influences that result in the control of voluntary movements (Reis et al., 2008; Sanes & Donoghue, 2000). Influences on the primary motor cortex include the ipsilateral and contralateral motor regions as well as the parietal cortex, cerebellum and sensory afferents (Reis et al., 2008). Chronic pain has been associated with neural plasticity of the primary motor cortex, with the extent of reorganisation correlating to the degree of motor control impairment (Maihofner et al., 2007; Tsao et al., 2008). For example, Maihofner et al. (2007) found that patients with complex regional pain syndrome (CRPS) of the hand had marked enlarged activations of the motor cortex contralateral to the affected side in comparison to the ipsilateral side and to control participants. They also showed that the amount of activation correlated with the degree of motor dysfunction on a reach and grasp task. Similarly, using TMS Tsao et al. (2008) found that compared with healthy controls, patients with chronic low back pain had larger motor cortex representations of the transversus abdominis muscle and the location was more posterior and lateral.

2.4 Exploring corticomotor excitability with transcranial magnetic stimulation

Neuroplastic changes within the motor cortex and its connecting areas can alter aspects of corticomotor excitability, which can be examined using TMS. TMS was first introduced in Sheffield, England by Barker and colleagues (Barker, Jalinous, & Freeston, 1985). They found that they could excite the motor cortex through the skin and skull using a circular coil held against the scalp. By pulsing a high current through the coil, a magnetic field is generated perpendicular to the electric field which creates a current in the neural tissue underneath (Hallett, 2000; Ljubisavljevic, 2006). Unlike transcranial electrical stimulation, TMS does not induce a high current in the subcutaneous tissue or skin, making it painless and therefore more tolerable to recipients (Groppa et al., 2012). At low stimulus intensities, TMS indirectly stimulates corticospinal neurons via synaptic inputs. The resulting descending volleys are known as indirect (I) waves. The first I wave is elicited by depolarisation of neurons synapsing directly onto the corticospinal neuron. The later appearing I waves are generated from intracortical polysynaptic circuits (Reis et al., 2008). Only at higher stimulus intensities can the corticospinal neurons stimulated directly (known as D waves), though this is dependent on the type of coil used and the coil orientation (Reis et al., 2008). The descending volleys generated, which propagate along the corticospinal tract and peripheral motoneurons, can be assessed by recording the resultant muscle activity using electromyography (EMG). This response is known as a motor evoked potential (MEP).

2.4.1 Motor evoked potentials

There are a number of characteristics of MEPs that can be assessed. The MEP threshold reflects the excitability of the entire corticospinal tract, as well as the density of excitatory interneurons and corticospinal neurons within the motor cortex (Hallett, 2000; Ljubisavljevic, 2006; Rossini & Rossi, 2007). The resting motor threshold (RTh) is defined as the minimum stimulus intensity that elicits a MEP with a peak-to-peak amplitude of at least 50 µV in at least half of trials when the target muscle is totally relaxed (Rossini & Rossi, 2007). This can also be performed during a slight muscle contraction, but the required amplitude of the MEP elicited is typically increased to 100-200 µV in order for the MEP to be discernible from the ongoing EMG activity.

Another characteristic of interest is the MEP amplitude. This is typically expressed as the voltage difference between the maximal positive and negative peaks (peak-to-peak amplitude). The MEP amplitude reflects synaptic efficacy of the corticospinal pathway (Miniussi, Paulus, & Rossini, 2012). There is a sigmoidal increase in MEP amplitude with increasing stimulus intensity, which can be plotted as a stimulus response curve (SR curve) (Devanne, Lavoie, & Capaday, 1997; Pitcher, Ogston, & Miles, 2003; Ridding & Rothwell, 1997). The SR curve depicts a gradual rise in MEP amplitude followed by a more rapid increase in amplitude which has been suggested to result from increased depolarisation and recruitment of neighbouring and less excitable neurons (Rossini & Rossi, 2007). It is hypothesised that the characteristic plateau in MEP amplitude following its rapid increase is either a consequence of saturation of the available neuron pool or the concurrent activation of inhibitory circuits (Chen et al., 1998; Devanne et al., 1997; Magistris, Rösler, Truffert, & Myers, 1998).

There are several methodological considerations that can influence MEPs. Previous studies have shown that muscle activation can facilitate cortical excitability and the excitability of the motoneuron pool, increasing the MEP amplitude and lowering the motor threshold (Devanne et al., 1997; Di Lazzaro, Restuccia, et al., 1998a; Ridding, Taylor, & Rothwell, 1995). Thus, it is of paramount importance that the level of muscle activation is controlled during stimulation. Furthermore, it is important to regulate the activation of the contralateral muscles (ipsilateral to stimulation), as this has also been shown to increase MEP amplitude (Muellbacher, Facchini, Boroojerdi, & Hallett, 2000). In addition to intra-muscular factors influencing the size of responses, mental activity can also modulate corticomotor excitability (Lefebvre, Pépin, Louis, & Boucher, 2004; Master & Tremblay, 2009). For instance, there is an increase in MEP amplitude if the participant directs their attention towards the hand being assessed or imagines hand movement or muscle activation (Hashimoto & Rothwell, 1999; Master & Tremblay, 2009). The MEP amplitude can vary considerably between trials, particularly when assessed with the target muscle at rest. For this reason, it is recommended that at least at least 5 to 6 recordings are made per muscle or stimulus condition (Groppa et al., 2012).

There are also a number of factors relating to the TMS technique which can influence the elicited MEPs. The shape of the TMS pulses has been shown to affect the cortical

axons stimulated and the resulting MEP (Di Lazzaro et al., 2004; Groppa et al., 2012; Sommer et al., 2006). The most commonly used waveforms are monophasic, resulting in a single depolarising pulse, or biphasic, which has an additional second hyperpolarising phase (Miniussi et al., 2012). The type of stimulating coil influences the magnetic field induced and thus, the resulting stimulation. The figure-of-eight coil provides the most focal stimulation, whereas circular or angled (double-cone) coils can penetrate more deeply into the brain and stimulate a larger cortical volume (Groppa et al., 2012; Miniussi et al., 2012). The position and orientation of the coil are of paramount importance for reliable MEPs. The motor cortex is generally organised somatotopically, with the muscles of the hands being most accessible. The hand regions have a lower RTh than other muscles due to their location within the motor cortex, which is typically close to the surface, and the increased strength of their corticomotor projections (Chen et al., 1998; Groppa et al., 2012). In order for effective stimulation to be implemented, the coil should be systematically moved over the scalp to establish the optimal position which maximally excites the target muscle. This area, known as the hot-spot, is typically marked with a pen to allow for further consistent localisation. The orientation of the coil can impact on the direction of the induced current within the cortex and which cortical structures are stimulated (Di Lazzaro et al., 2004; Reis et al., 2008). It is therefore essential to keep this consistent during stimulation.

2.5   Assessment of intracortical excitability

There are various TMS techniques that provide insight into the excitability of different intracortical circuits. The following sections will outline the current recommended methods and summarise what is known about the underlying processes they assess.

2.5.1   Cortical silent period

The cortical silent period (CSP) refers to the sustained period of muscle inhibition in an active muscle following a single TMS pulse applied to the contralateral primary motor cortex. Overall, it appears that the CSP is predominantly a cortical inhibitory phenomenon reflecting the strength of intracortical inhibitory circuits (Groppa et al., 2012; Miniussi et al., 2012). Although, there is evidence to suggest that the initial component may be of spinal origin due to recurrent inhibition and motoneuron after-

hyperpolarisation (Chen, Lozano, & Ashby, 1999; Fuhr, Agostino, & Hallett, 1991; Inghilleri, Berardelli, Cruccu, & Manfredi, 1993). The latter part of the CSP is likely due to supraspinal influences, particularly within the motor cortex (Chen et al., 1999; Fuhr et al., 1991; Inghilleri et al., 1993; Wilson, Lockwood, Thickbroom, & Mastaglia, 1993). This is supported by research in patient populations, which highlights an association between altered CSP duration and neurological conditions affecting cortical or subcortical regions (Ahonen, Jehkonen, Dastidar, Molnár, & Häkkinen, 1998; Cantello et al., 1991; Haug, Schönle, Knobloch, & Köhne, 1992; Liepert, Storch, Fritsch, & Weiller, 2000). It is hypothesised that the cortical inhibitory mechanisms associated with the CSP are primarily $GABA_B$ mediated. There are number of studies that support this hypothesis. Firstly, $GABA_B$ receptors mediate the long-lasting component of inhibitory post-synaptic potentials, which has a similar time profile to the latter part of the CSP, whereas, the short-lasting inhibitory post-synaptic potentials are mediated by $GABA_A$ receptors (Roick, von Giesen, & Benecke, 1993). Furthermore, experimental data using drugs known to increase $GABA_B$ activity have been shown to increase the CSP duration (Siebner, Dressnandt, Auer, & Conrad, 1998; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). There are less consistent findings regarding the influence of $GABA_A$ (Groppa et al., 2012; Miniussi et al., 2012). Additionally, several other neuro-modulating neurotransmitter systems, including dopamine, have been proposed to have an effect on the CSP (Groppa et al., 2012; Miniussi et al., 2012). In summary, the CSP is largely mediated by $GABA_B$ receptors at a cortical level but it is influenced by several other physiological factors which are not yet fully understood.

The most recent recommendations from the International Federation of Clinical Neurophysiology suggest that duration of the CSP should be measured from the MEP onset until EMG activity exceeds the baseline EMG level for at least 50 ms (Groppa et al., 2012). However, the CSP may occur in the absence of a MEP, as the CSP threshold may be lower than the active motor threshold (Davey, Romaiguère, Maskill, & Ellaway, 1994). The period of inactivity typically lasts from 100 to 400 ms, increasing in duration with stimulus intensity (Haug et al., 1992; Inghilleri et al., 1993; Säisänen et al., 2008; Wilson et al., 1993). The majority of evidence suggests that the amount of muscle activation does not significantly influence the CSP duration (Haug et al., 1992; Inghilleri et al., 1993; Roick et al., 1993). However, Wilson and colleagues (1993) found a

reduction in CSP duration with increased muscle activation. Increased age is known to influence CSP duration, although conflicting results have been observed. Oliviero et al. (2006) demonstrated that older adults exhibit a significantly shorter CSP than younger individuals, whereas, a more recent study by McGinley et al. (2010) found the opposite. The length of the CSP varies considerably between individuals (Groppa et al., 2012), however it has been shown to have excellent inter-rater reliability (Kimberley et al., 2009).

2.5.2   Paired-pulse transcranial magnetic stimulation

Paired-pulse stimulation can be used to study the excitability of different intracortical circuits within the primary cortex (Reis et al., 2008). A BiStim module allows for two stimuli to be delivered in rapid succession through the same coil by connecting two TMS units. The first stimulus, known as the conditioning stimulus, influences the size of second (test) stimulus, which occurs after an interstimulus interval (ISI). Depending on the intensity of the stimuli and the ISI, different intracortical networks can be examined. The amount of inhibition or facilitation is typically expressed by comparing the MEPs elicited by the paired-pulse stimulation to single-pulse unconditioned MEPs. Paired-pulse responses have been shown to have high variability between individuals, however, the individual response is stable and has a high inter-session repeatability (Du, Summerfelt, Chiappelli, Holcomb, & Hong, 2014; Wassermann, 2002).

2.5.3   Short-interval intracortical inhibition

Kujirai et al. (1993) were the first to describe how a subthreshold conditioning stimulus followed by a suprathreshold test stimulus gives rise to a reduction in MEP amplitude. The authors found that with an ISI of 1 to 6 ms, the response was significantly inhibited, a phenomenon known as short-interval intracortical inhibition (SICI). There is considerable evidence to suggest that this inhibition occurs intracortically. This was shown indirectly by Kujirai et al. (1993), who demonstrated that there was no change in spinal reflexes with the same conditioning stimulus. Di Lazzaro (1998b) and colleagues confirmed this hypothesis by establishing that the conditioning stimulus inhibited the test stimulus descending spinal volleys, particularly the later I waves, which are thought to result from intracortical polysynaptic circuits (Reis et al., 2008). Several pharmacological studies demonstrated that these inhibitory circuits are GABA$_A$

mediated (Di Lazzaro et al., 2000; Di Lazzaro, Pilato, Dileone, et al., 2006; Ilić et al., 2002).

The intensity of the conditioning and test stimuli, as well as the duration of the ISI, have all been shown to influence the amount of inhibition. Typically, the conditioning stimulus intensity is set to 80% of RTh or lower to ensure that the stimulus does not evoke a descending spinal volley and to minimise concurrent activation of facilitatory circuits (Ilić et al., 2002; Peurala, Müller-Dahlhaus, Arai, & Ziemann, 2008). For maximal SICI to occur, the test stimulus intensity should be set in the mid-range of the SR curve and because the amount of inhibition is influenced by the test stimulus MEP size, it is important to match this when comparing over time. (Ilić et al., 2002; Müller-Dahlhaus, Liu, & Ziemann, 2008; Peurala et al., 2008). A test stimulus of this intensity allows for sufficient recruitment of later I waves but prevents D wave recruitment which occur at higher stimulus intensities and are not susceptible to SICI (Chen et al., 1998; Di Lazzaro, Oliviero, et al., 1998; Ilić et al., 2002; Peurala et al., 2008; Reis et al., 2008). To minimise contamination of SICI by facilitatory processes, the ISI should be set to 2 ms or 3 ms, as this is when facilitation is minimised (Di Lazzaro et al., 1999; Peurala et al., 2008; Ziemann, Tergau, Wassermann, et al., 1998).

2.5.4 Long-interval intracortical inhibition

There is a second inhibitory process which occurs at a much longer ISI (50 to 200 ms), known as long-interval intracortical inhibition (LICI) (Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992). A suprathreshold conditioning stimulus is used and the optimal inhibitory effects occur with an ISI of around 100 ms (Müller-Dahlhaus et al., 2008; Rogasch, Daskalakis, & Fitzgerald, 2013; Valls-Solé et al., 1992). Generally it has been thought that this process occurs intracortically (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997); though, the inhibitory circuits responsible are distinct from those that mediate SICI. Rather than resulting from transmission via $GABA_A$ receptors like SICI, transmission occurs via $GABA_B$ receptors similarly to the CSP (McDonnell, Orekhov, & Ziemann, 2006; Müller-Dahlhaus et al., 2008; Rogasch et al., 2013; Roick et al., 1993). However, more recent evidence suggests there may also be a spinal contribution to this phenomenon (McNeil, Martin, Gandevia, & Taylor, 2009).

2.5.5 Long-interval intracortical facilitation

Paired-pulse stimuli can also be used to assess intracortical facilitatory processes. It is proposed that two separate facilitatory phenomena occur (Reis et al., 2008). The first type of facilitation to be published was discovered by Kujirai and co-workers (1993). Using the same stimulus intensities as SICI (a subthreshold conditioning stimulus and a suprathreshold test stimulus), they noted that at an increased ISI of 10 to 15 ms the MEP amplitude was facilitated. Although this is termed long-interval intracortical facilitation (LICF), further investigation is warranted to determine whether it occurs purely at a cortical level (Miniussi et al., 2012; Reis et al., 2008). The current evidence suggests that LICF is cortically mediated, but only indirect evidence is available, with previous studies finding that the subthreshold conditioning stimulus did not alter spinal reflexes and does not elicit a descending volley (Kujirai et al., 1993; Reis et al., 2008; Ziemann, Rothwell, & Ridding, 1996). However, Di Lazzaro et al. (2006) did not observe changes in cervical descending volleys produced by the test stimuli, suggesting that a spinal contribution cannot be disregarded. Seemly distinct interneuronal populations mediate SICI and LICF (Ziemann, Rothwell, et al., 1996). Based on the available pharmacological evidence, it appears that LICF is glutamate mediated via N-methyl-D-aspartate receptors (Paulus et al., 2008; Schwenkreis et al., 1999; Ziemann, Chen, Cohen, & Hallett, 1998). However, there is evidence that LICF is modulated by GABA and the facilitation observed is the net effect of concurrent glutamatergic facilitation and a reduction in GABAergic inhibition (Paulus et al., 2008; Reis et al., 2008; Ziemann, Lönnecker, Steinhoff, & Paulus, 1996).

2.5.6 Short-interval intracortical facilitation

A second facilitatory phenomenon is observed using a much shorter ISI, known as short-interval intracortical facilitation (SICF). SICF occurs at specific ISIs of 1.1 to 1.5, 2.3 to 2.9 and 4.1 to 4.5 ms, between which facilitation disappears (Ilić et al., 2002; Tokimura, Ridding, Tokimura, Amassian, & Rothwell, 1996; Ziemann, Tergau, Wassermann, et al., 1998). Unlike SICI and LICF, the first stimulus is suprathreshold and the second subthreshold (Ziemann, Tergau, Wassermann, et al., 1998), or both stimuli are close to threshold intensity (Tokimura et al., 1996). It has been proposed that the facilitatory peaks are a consequence of I wave interactions occurring at a cortical level (Di Lazzaro et al., 1999; Ilić et al., 2002; Paulus et al., 2008). Current evidence suggests

SICF is mediated by disinhibition via the GABA$_A$ receptor (Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998), but further research is required to establish the possible influence of other neurotransmitter systems (Paulus et al., 2008).

Does chronic pain alter motor cortex excitability?

2.6 Search strategy

The objective of this review was to determine if chronic pain is associated with alterations in corticomotor excitability. Research articles were identified that compared measures of corticomotor excitability assessed using TMS between participants with chronic pain and pain-free control participants. Only studies directly comparing chronic pain (pain for at least three months) and pain-free populations were considered for inclusion. In addition, studies were required to apply TMS to the motor cortex and to utilise any of the following outcome measures: resting motor threshold, stimulus-response curve, cortical silent period, or short- or long-interval intracortical inhibition or facilitation. Intervention studies were included if the baseline measures were detailed, as only these measures were analysed in this review.

The initial search was performed on 15th August 2014 using the following databases: MEDLINE, CINAHL Plus, Biomedical Reference Collection, Health Business Elite, Health Source, Psychology and Behavioural Sciences Collection, SPORTDiscus and Scopus. The following search terms were used: pain AND (transcranial magnetic stimulation AND motor cortex) OR (cortical inhibition OR cortical facilitation) OR (cortical silent period OR silent period). Results were limited to journal articles published between 1985 and 15th August 2014. Included journals were also to be published in the English language, with human participants and with the full-text available. The full text of relevant studies was retrieved and reference lists were searched for additional citations.

2.7 Quality assessment

Selected studies were assessed for methodological quality and reporting using the TMS checklist devised by Chipchase and colleagues (2012) (Appendix A). This checklist consists of 30 criteria assessing variables relating to the participants, the experimental methodology and the analysis. The checklist was devised to allow critical appraisal of TMS studies of the motor system. Studies were required to both report and control for

potential bias in each of the criteria and a point was issued for each when the criteria were met. Four of the criteria are only applicable to studies using paired-pulse techniques and, therefore, only studies using paired-pulse stimulation were evaluated using these criteria. In addition, the checklist was adapted by removing the criterion relating to the time between testing days and adding the requirement for studies to control the gender of participants by matching the patient and control groups (Pitcher et al., 2003). The study quality score was calculated as a percentage of the criteria met out of the total applicable criteria.

2.8 Results

The initial search yielded 588 studies, of which 571 remained when duplicates were removed. A further 541 were removed after reviewing titles and abstracts. The full text was examined for 30 studies of which nine were excluded (**Figure 1**, see below). The most common reasons for exclusion were not including a chronic pain population or not performing a direct comparison between patients and control participants. A total of 21 studies met the inclusion criteria.
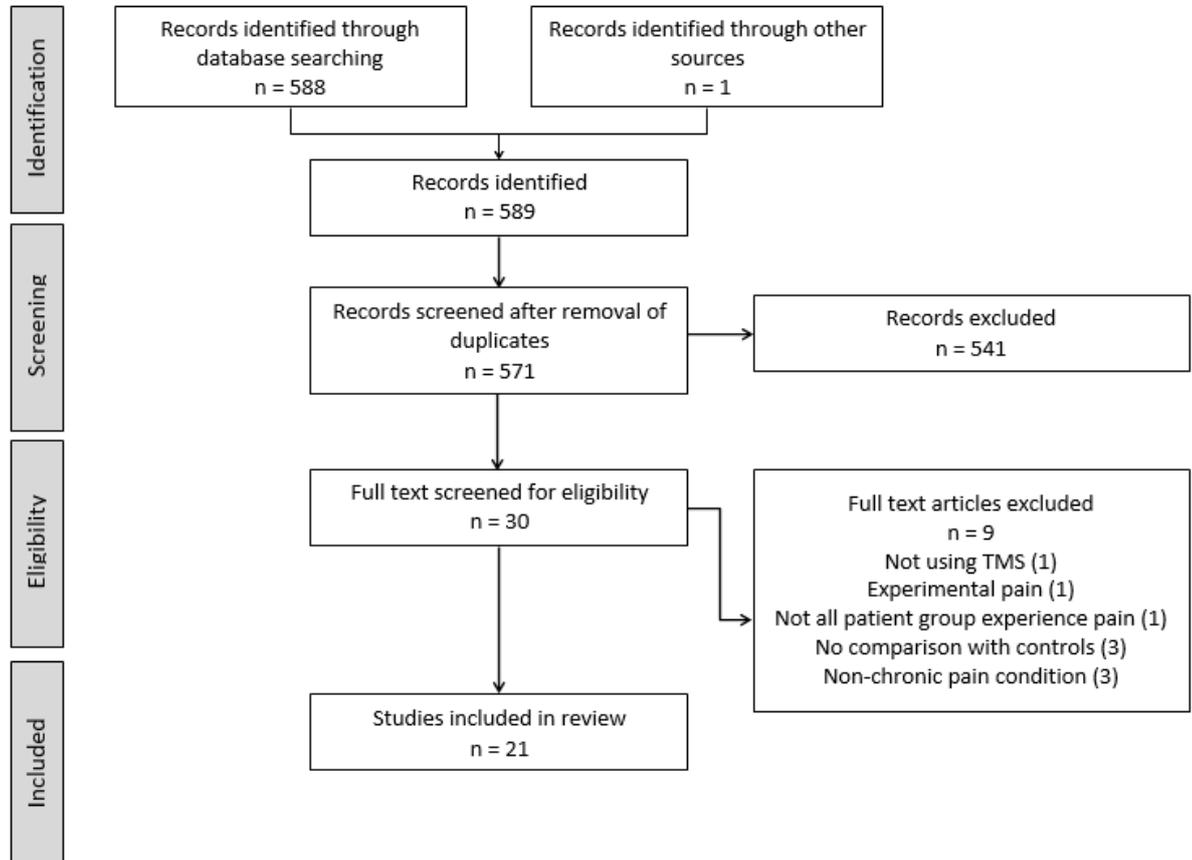
Figure 1: Flow diagram showing the study selection process.

2.9   Participant characteristics

In total, there were 431 participants with chronic pain and 363 control participants.
Participant characteristics are summarised in Table 1. Sample sizes ranged from 9 to 46
and from 7 to 30 in the patient and control groups, respectively. The age of the
included participants varied across studies, with the average age ranging from 24.2 to
63.9 in the patients and from 24.9 to 58.8 in the controls. Overall, more women than
men were included; two studies assessed female participants exclusively (Mhalla et al.,
2010; Siniatchkin et al., 2007) and for 92 of the participants their gender was not
reported. The most frequently studied chronic conditions were migraine (nine studies),
neuropathic pain (four studies), CRPS (three studies), chronic low back pain (two
studies) and fibromyalgia (two studies). Additional conditions were chronic neck pain,
RA and OA.

2.10 Methodological quality

Table 1 displays summarised quality scores. The mean (SD) percentage of criteria
fulfilled was 66% (12.7) and ranged from 39% (Curra et al., 2007) to 96% (Marker,
Stephenson, Kluger, Curran-Everett, & Maluf, 2014). All studies met the criteria
relating to reporting and controlling for age except for one study (Strutton, Catley,
McGregor, & Davey, 2003). However, six studies neglected to report the gender and/or
the handedness of the participants (Aurora, Al-Sayeed, & Welch, 1999; Curra et al.,
2007; Khedr, Ahmed, & Mohamed, 2006; Krause, Foerderreuther, & Straube, 2005;
Salerno et al., 2000; Strutton et al., 2003). Another frequently missed participant
criterion was not reporting the participants' other medical conditions, with the
exception of two studies (Eisenberg et al., 2005; Marker et al., 2014). Furthermore,
only one study stated whether the participants had a history of specific repetitive
motor activity (Marker et al., 2014). Regarding the TMS methodology, all studies met
the criteria concerning the reporting of the type of stimulator used, the intensity of
stimulation and inter-stimulus intervals used for the paired-pulse measures. However,
several important methodological factors were frequently overlooked. Only four
studies reported whether the TMS pulse used was mono- or bi-phasic (Aurora et al.,
1999; Conte et al., 2010; Maier et al., 2011; Marker et al., 2014) and just six studies
reported the time between TMS trials (Brighina et al., 2011; Brighina et al., 2005;
Conte et al., 2010; Cosentino et al., 2011; Eisenberg et al., 2005; Marker et al., 2014).

Additionally, controlling the attention of participants during stimulation was only reported by Marker et al. (2014).

2.11 Study set up

The studies utilised a variety of TMS methods. All of the studies used surface EMG, which was typically used to assess MEPs in hand muscles (15/20 studies), most commonly the first dorsal interossei (FDI) but also the abductor pollicis brevis and abductor digiti minimi muscles. The remaining studies recorded MEPs from the lumbar erector spinae, the lower abdominals, the lower leg muscles, the perioral muscles and the forearm extensors. Most studies conducted TMS testing in supported sitting with the target muscle at rest (18/21 studies), with the exception of the CSP. The magnitude of the MEPs was predominantly calculated from the peak-to-peak amplitude, aside from the study by Eisenberg et al. (2005) who calculated the paired-pulse measures from the area under the rectified MEP curve. In addition, a range of coil types were used. Most commonly this was a figure-of-eight design (10/21 studies), with the remaining studies using circular or the double-cone type coil. The latter coil design was mainly used in the studies targeting abdominal, lumbar and lower limb musculature. Of the studies that reported the shape of the TMS pulses, half were monophasic (Maier et al., 2011; Marker et al., 2014) and half were biphasic (Aurora et al., 1999; Conte et al., 2010).

Table 1: Summary of included studies

Study	Participants (mean age, number female participants)	Outcomes Measures	Results	Summary (Patients compared with controls)	TMS Checklist Criteria met
Aurora (1999)	9 migraine with aura (35.9, ?), 9 controls (37.6, ?)	RTh, CSP	No difference in RTh. Shorter CSP in migraine.	Reduced inhibition	71%
Brighina (2005)	9 migraine with aura (35.1, 6), 8 controls (30.4, 5)	RTh, SICI, LICF	No difference in RTh or LICF. Reduced SICI in migraine.	Reduced inhibition	70%
Brighina (2011)	18 migraine with aura (33.8, 13), 18 controls (31.8, 13)	RTh, CSP	No difference in RTh or CSP.	No difference	65%
Conte (2010)	37 migraine(19 with aura (40.3, 13), 18 without aura (37, 15)), 19 controls (38, 13)	RTh, CSP	No difference in RTh or CSP.	No difference	73%
Cosentino (2011)	12 migraine with aura (35.3, 8), 8 controls (28.8, 5)	RTh, SR curve	No difference in RTh. Increased MEP recruitment in migraine.	Increased corticomotor excitability	63%
Curra (2007)	26 migraine (39.5, 18) (12 with aura, 14 without aura), 15 controls (44.7, ?)	CSP	CSP shorter in migraine.	Reduced inhibition	39%
Eisenberg (2005)	12 CRPS1 (6 upper limb (33, 2), 6 lower limb(32, 1)), 14 controls (31, 4)	RTh, ATh, SICI, SICF, LICF, LICI	SICI reduced in upper limb CRPS1. No differences in other measures or in patients with lower limb CRPS1.	Reduced inhibition (upper limb CPRS1). No difference (lower limb CRPS1)	72%
Khedr (2006)	28 migraine (33.7, 17) (18 with aura, 10 without aura), 20 controls (30.5, ?)	RTh, CSP, SR curves	Reduced RTh, shorter CSP in migraine. No difference in SR curves.	Increased corticomotor excitability. Reduced inhibition	69%
Krause (2005)	12 CRPS1 (48.2, 10), 10 controls (42.4, ?)	RTh, MEP size 110%, CSP	Reduced MEPs amplitude in CRPS1. No difference in CSP or Rth	Reduced corticomotor excitability	49%
Lefaucheur (2006)	22 chronic neuropathic hand pain (56.5, 10), 22 controls (54.8, 12)	RTh, CSP, MEP 140%/120% ratio, SICI,L ICF	No difference in RTh, MEP 140%/120% ratio, or LICF. Shorter CSP and reduced SICI in neuropathic pain.	Reduced inhibition	61%
Maier (2011)	30 migraine(15 with aura (37.1, 13), 15 without aura (28.4, 12)), 18 controls (30.8, 11)	RTh, CSP	No difference in RTh. Shorter CSP in migraine with aura than controls or migraine without aura.	Reduced inhibition in migraine with aura but not without aura	76%

Table 1: Summary of included studies (continued)

Study	Participants (mean age, number female participants)	Outcomes Measures	Results	Summary (Patients compared with controls)	TMS Checklist Criteria met
Marker (2014)	9 chronic neck pain (42.4, 7), 8 controls (31.5, 4)	RTh, ATh, SICI, MEP size 120%	No difference in RTh, ATh, SICI and MEP size 120%.	No difference	96%
Massé-Alarie (2012)	9 chronic low back pain (53.7, 5), 13 controls (48.7, 6)	ATh, SICI, CSP	Reduced SICI in chronic low back pain. No difference in ATh or CSP	Reduced inhibition	67%
Mhalla (2010)	46 fibromyalgia (50.8, 46), 21 controls (46.7, 21)	RTh, MEP 140%/120% ratio, SICI, LICF	Increased RTh, reduced MEP 140%/120% ratio, reduced SICI and reduced LICF in fibromyalgia.	Reduced corticomotor excitability, inhibition and facilitation	68%
Salerno (2000)	13 fibromyalgia (50.1, 13), 5, RA (50.0, 5), 13 controls (49.1, ?).	RTh, CSP, SICI, LICF, LICI	Increased RTh, shorter CSP, reduced LICF and reduced LICI in patients. No differences in SICI.	Reduced corticomotor excitability, inhibition and facilitation	58%
Schwenkreis (2003)	25 CRPS1 (49.1, 16), 20 controls (49, 10)	RTh, SICI, LICF	No difference in RTh or LICF. Reduced SICI in CRPS1.	Reduced inhibition	85%
Schwenkreis (2010)	20 neuropathic pain due to neuralgia (50.9, 12), 20 hand OA (56.6, ?), 14 controls (58.8, 8)	RTh, SICI, LICF	No difference in RTh or LICF. Reduced SICI in neuropathic pain but not in OA.	Reduced inhibition in neuropathic pain but not OA	70%
Siniatchkin (2007)	16 migraine without aura (24.2, 16), 15 controls (24.9, 15)	RTh, ATh, CSP, LICI, LICF	LICF increased in migraine. No differences in other measures.	Increased facilitation	72%
Strutton (2003)	9 unilateral sciatica (?), 7 controls (?)	RTh, ATh, CSP, CSPTh	Increased RTh, ATh and CSPTh in sciatica. No difference in CSP.	Reduced corticomotor excitability	45%
Strutton (2005)	24 low back pain (39.1, 9), 11 controls (35.9,4)	ATh, CSP, CSPTh	Increased ATh and CSPTh in low back pain. No difference in CSP.	Reduced corticomotor excitability	55%
Turgut (2009)	20 diabetic with neuropathic pain (63.9, 15), 50 diabetic without neuropathic pain (59.2, 24), 30 controls (58.3, 16)	RTh, CSP	Reduced RTh and shorter CSP in diabetic neuropathic pain.	Increased corticomotor excitability and reduced inhibition	64%

Note: ?, data not found; ATh, active motor threshold; CRPS1, complex regional pain syndrome type 1; CSP, cortical silent period duration; CSPTh, cortical silent period threshold; LICF, long-interval intracortical facilitation; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; OA, osteoarthritis; RA, rheumatoid arthritis; RTh, resting motor threshold; SICF short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; SR curve, stimulus-response curve

2.12 Study outcome measures and findings

2.12.1 Motor thresholds

The RTh or active motor thresholds (ATh) were assessed in all studies except one (Curra et al., 2007). For the most part, the threshold was defined as the minimum stimulus intensity that elicited a MEP in 50% of trials, with the exception of one study which required five consecutive MEPs (Siniatchkin et al., 2007). Typically, the peak-to-peak amplitude was required to be of at least 50 µV in order for the MEP to be included. Although, in the two oldest studies, the MEPs were required to be at least 100 µV (Aurora et al., 1999; Salerno et al., 2000) and three studies simply required that the MEPs were identifiable (Siniatchkin et al., 2007; Strutton et al., 2003; Strutton, Theodorou, Catley, McGregor, & Davey, 2005). Assessment of the ATh was conducted with a low level of target muscle activation, normally between 5-20% of maximum. Half of the studies required the MEP amplitude to be 100 µV, while the remaining studies stated that MEPs should be discernable. Few of the studies specified the actual method used to establish the RTh or ATh and no studies used the standardised algorithm suggested by International Federation of Clinical Neurophysiology (IFCN) committee (Groppa et al., 2012).

Thirteen of the studies showed no significant differences in RTh between participants with chronic pain and healthy control participants (Table 1). No significant differences were found between the groups in four of the six studies assessing ATh, with the exception of Strutton et al. (2003; 2005) who found ATh was higher in patients with chronic sciatica or low back pain. Four of the remaining studies demonstrated that motor thresholds were increased in patients with chronic pain conditions, including RA (Salerno et al., 2000), chronic sciatica (Strutton et al., 2003), and two studies investigating fibromyalgia (Mhalla et al., 2010; Salerno et al., 2000). Conversely, two studies found that the RTh was lower in participants with migraine (Khedr et al., 2006) and diabetic neuropathic pain (Turgut & Altun, 2009). Thus, overall it seems that there is little change in RTh in chronic pain conditions and significant have been inconsistent.

2.12.2 Motor evoked potential amplitude

Two studies assessed MEP amplitudes at a set stimulus intensity. Krause et al. (2005) found that at a stimulus intensity of 110% of RTh that participants with CRPS type 1

had significantly reduced MEP amplitudes. Whereas, at a stimulus intensity of 120% no differences in MEP amplitude were observed between participants with chronic neck pain and controls (Marker et al., 2014). Two studies examined the ratio of the MEP amplitudes at stimulus intensities of 140% RTh /120% RTh. In comparison with controls, the MEP amplitude 140%/120% ratio was significantly reduced in participants with fibromyalgia (Mhalla et al., 2010), but not in patients with chronic neuropathic hand pain (Lefaucheur et al., 2006).

2.12.3 Stimulus response curves

Only two studies assessed stimulus response curves. Both studies compared patients with migraines to healthy participants but found differing results. Both studies compared the peak-to-peak MEP amplitudes at a range of stimulus intensities and used a repeated-measures ANOVA to compare the groups. Khedr et al. (2006) found no significant differences between the groups, whereas Cosentino et al. (2011) found that the patients had significantly enhanced MEP recruitment. Consentino and colleagues also found that patients demonstrated a significant rise in MEP amplitude at 120% RTh, rather than 140% RTh control group, indicating that the migraine patients had enhanced corticospinal recruitment at a lower stimulus intensity.

2.12.4 Cortical silent period

Fourteen studies measured the CSP using a range of methods. The CSP was assessed during a low level (15-30% of maximum) of muscle contraction in eight of the studies, whereas five of the studies conducted stimulation during maximal voluntary contractions (Curra et al., 2007; Khedr et al., 2006; Lefaucheur et al., 2006; Salerno et al., 2000; Turgut & Altun, 2009). In addition, the intensity of stimulation was also variable; it was typically between 100 and 150% of RTh, although, one study used the maximum stimulator output (Curra et al., 2007) and another did not specify the stimulation intensity (Strutton et al., 2003). The duration of the CSP was calculated from the end of the preceding MEP, with the exception of four studies which either calculated it from the start of the MEP (Aurora et al., 1999; Krause et al., 2005; Salerno et al., 2000) or did not give sufficient details (Strutton et al., 2003). The criteria for the end of the CSP were also highly variable. Most commonly it was determined as the resumption of EMG activity (six studies) or the when EMG activity reached the

prestimulus baseline level (four studies). The most accurate methods of CSP calculation were by Maier et al. (2011) and Conte et al. (2010), who both determined the start and end of the CSP from when the EMG signal dropped below a set percentage or standard deviation of the baseline EMG activity until activity had surpassed this value.

Half of the studies found that the CSP was shorter in the chronic pain patients compared with control participants (Aurora et al., 1999; Curra et al., 2007; Khedr et al., 2006; Lefaucheur et al., 2006; Maier et al., 2011; Salerno et al., 2000; Turgut & Altun, 2009). The remaining studies found no significant differences between the groups (Brighina et al., 2011; Conte et al., 2010; Krause et al., 2005; Massé-Alarie et al., 2012; Siniatchkin et al., 2007; Strutton et al., 2003; Strutton et al., 2005).

2.12.5 Intracortical inhibition

Nine studies included measures of intracortical inhibition (Table 1), predominantly assessing SICI. To assess SICI, all studies used a conditioning stimulus below ATh (80% RTh – 95% ATh) and suprathreshold test stimulus (most commonly 120% RTh or 1 mV amplitude) with an ISI of either 2 or 4 ms, except Marker et al. (2014) who had an interval of 2.5 ms. Overall, chronic pain was associated with a reduction in SICI (Brighina et al., 2005; Eisenberg et al., 2005; Lefaucheur et al., 2006; Massé-Alarie et al., 2012; Mhalla et al., 2010; Schwenkreis et al., 2010; Schwenkreis et al., 2003), with only two studies finding no significant differences between groups (Marker et al., 2014; Salerno et al., 2000).

Three studies evaluated LICI. Suprathreshold test and conditioning stimuli were used by two of the studies, but the study by Eisenberg et al. (2005) used a conditioning stimulus of 80% RTh. A range of different ISIs were used by all three studies ranging from 55 to 355 ms. Salerno et al. (2000) found significant differences between groups when the ISI was 155 and 200 ms, demonstrating reduced LICI in patients with fibromyalgia and RA in comparison with control participants. The remaining two studies did not observe significant differences between the groups (Eisenberg et al., 2005; Siniatchkin et al., 2007).

2.12.6 Intracortical facilitation

The studies assessing LICF demonstrated less consistent results (Table 1). To test LICF, the majority of studies employed subthreshold test stimuli (typically 80% RTh) and suprathreshold conditioning stimuli (either 120 % RTh or 1 mV amplitude) with an ISI of 10 or 15 ms. The exceptions were Siniatchkin et al. (2007) and Salerno et al. (2000), who used a longer ISI of 20 and 25 ms, respectively. Also, Siniatchkin et al. (2007) was the only study to use a suprathreshold conditioning stimulus (110% RTh). The majority of studies found no significant differences in LICF between participants with and without chronic pain (Brighina et al., 2005; Eisenberg et al., 2005; Lefaucheur et al., 2006; Schwenkreis et al., 2010; Schwenkreis et al., 2003). The remaining studies found differing results, with a reduction in LICF being observed in participants with fibromyalgia and RA (Mhalla et al., 2010; Salerno et al., 2000) but increased LICF in participants with migraine (Siniatchkin et al., 2007). Only one study assessed SICF, finding no significant differences between people with CRPS and healthy age-matched controls (Eisenberg et al., 2005).

2.13 Discussion

The aim of this review was to investigate whether there is an association between chronic pain and changes in corticomotor excitability. Twenty-one studies met the inclusion criteria, encompassing a wide range of chronic pain conditions and TMS methods. The main finding was that chronic pain was associated with a reduction in cortical inhibition. The strongest evidence is for a reduction in inhibition at an intracortical level, as 89% of studies measuring SICI found it to be significantly reduced in patients compared with controls, including the predominantly high and moderate quality studies (quality scores of ≥70% or 60-70% respectively). SICI is dependent on $GABA_A$ mediated interneurons, which modulate corticomotor outputs (Di Lazzaro, Pilato, Dileone, et al., 2006; Müller-Dahlhaus et al., 2008; Rossini & Rossi, 2007). Therefore, these findings suggest that people with chronic pain have impaired efficacy of $GABA_A$ interneuronal circuits within the motor cortex.

The findings regarding the CSP also support a reduction in inhibition in people with chronic pain. Half of the studies assessing the CSP found a significant difference between the groups. The studies that found significant results were of higher quality

and all found that the CSP duration was reduced in the participants with chronic pain. Interestingly, all the studies that assessed the CSP during maximal voluntary contractions found significant differences. The CSP duration reflects the GABA_B mediated cortical and spinal inhibitory mechanisms influencing the corticomotor pathway (Groppa et al., 2012; Rossini & Rossi, 2007). Thus, together with the SICI results, it is concluded that chronic pain is associated with a reduction in both GABA_A and GABA_B cortical inhibition.

LICI is also mediated by GABA_B receptors (McDonnell et al., 2006; Müller-Dahlhaus et al., 2008; Rogasch et al., 2013; Roick et al., 1993), yet only one low quality study found that LICI was reduced in chronic pain (Salerno et al., 2000). The higher quality studies found there were no significant differences between groups (Eisenberg et al., 2005; Siniatchkin et al., 2007). Based on the current evidence it may be suggested that LICI is not affected in chronic pain, but given the lack of studies using this paradigm and the different stimulation parameters used in each of the studies, further research is needed.

The RTh assesses the resting membrane threshold and the excitability of corticomotor pathways, including excitatory interneurons, corticospinal neurons and motoneurons (Groppa et al., 2012; Rossini & Rossi, 2007). The current research does not support a strong influence of chronic pain on the overall excitability of the corticomotor pathway. It is difficult to draw conclusions regarding the effect of chronic pain on RTh and ATh. The majority of studies found no significant differences between the groups (70%), and the remaining studies demonstrated conflicting results. However, certain chronic pain conditions showed more consistent results. In studying participants with migraine, eight out of the nine studies found non-significant results. Whereas both studies that included patients with fibromyalgia found the RTh was higher in patients than controls (Mhalla et al., 2010; Salerno et al., 2000), indicating reduced corticomotor excitability in this group of patients. This indicates that results may vary between chronic pain conditions, perhaps due to differing pathophysiological processes.

Another measure of corticomotor excitability is the SR curve. The MEP amplitude is indicative of the synaptic efficacy of the corticospinal pathway (Miniussi et al., 2012),

and the input-output characteristics typically show a sigmoidal increase in MEP amplitude with increasing stimulus intensity (Devanne et al., 1997; Pitcher et al., 2003). It is suggested that the increase in the size of the MEPs is a consequence of increased recruitment of neighbouring or less excitable neurons (Rossini & Rossi, 2007), which plateau when the inhibitory neurons (which are concurrently recruited) negate further increases in MEP size (Devanne et al., 1997). Only two studies assessed SR curves, both of which compared participants with migraines to healthy controls. Consentino et al. (2011) found that the patients demonstrated significantly increased responsiveness with increased stimulus intensity, implying increased cortical excitability in patients with migraines. Khedr and colleagues (2006) observed a similar trend to Consentino et al. (2011) though the findings did not reach significance. Further research is needed to deduce whether findings in other chronic pain conditions are similar. No previous studies have examined this phenomenon in people with arthritis. If similar to the findings by Cosentino et al. (2011) this may be indicative of enhance corticospinal depolarisation and recruitment (Rossini & Rossi, 2007).

For the most part, LICF appeared to be unaffected by chronic pain, as five out of the eight articles found no differences between the groups. The physiological mechanisms underlying LICF are currently inconclusive. However, it is thought to be glutamate mediated via N-methyl-D-aspartate receptors and to be of cortical origin (Di Lazzaro, Pilato, Oliviero, et al., 2006; Paulus et al., 2008; Rossini & Rossi, 2007; Schwenkreis et al., 1999; Ziemann, Chen, et al., 1998; Ziemann, Tergau, Wischer, et al., 1998). Interestingly, both studies assessing LICF in people with fibromyalgia observed a significant reduction in LICF (Mhalla et al., 2010; Salerno et al., 2000) but enhanced LICF was demonstrated in participants with migraine (Siniatchkin et al., 2007). This supports the notion that the processes underlying fibromyalgia and migraine have differing effects on the motor cortex. Although, it should be noted that Siniatchkin et al. (2007) used quite different stimulation techniques, using a suprathreshold conditioning stimulus and a longer 20 ms ISI, which could have also influenced the result. In summation with the RTh and SR curve findings, these studies imply an overall reduction in corticomotor excitability in fibromyalgia and an increase in migraine. Further research is required to establish the influence of arthritic conditions on LICF, as the two studies which investigated arthritic participants reported conflicting results.

Schwenkreis et al. (2010) found no significant difference between participants with hand OA and healthy controls, while Salerno and colleagues (2000) showed reduced LICF in participants with RA. Only one study assessed SICF, which is known to be mediated by distinct neural populations to LICF (Reis et al., 2008). Eisenberg et al. (2005) found that SICF was not altered in participants with CRPS. Although this study was of high quality, further studies including other conditions are needed to extrapolate the findings to the wider chronic pain population.

There were a number of common methodological limitations highlighted by this review. In studies involving TMS, the controlling and/or reporting of key participant characteristics is imperative. Not reporting or matching the participants' gender, handedness or whether they had history of specific repetitive motor activity were frequently neglected participant factors known to influence corticomotor excitability (Chipchase et al., 2012). The attention of the participants during TMS stimulation has also been shown to alter corticomotor excitability (Abbruzzese, Assini, Buccolieri, Marchese, & Trompetto, 1999; Lefebvre et al., 2004; Master & Tremblay, 2009; Stinear, Byblow, Steyvers, Levin, & Swinnen, 2006), yet only one study sought to control attention (Marker et al., 2014). The shape of TMS pulse is also known to influence MEPs (Chipchase et al., 2012). The waveforms used are typically either monophasic or biphasic, which are believed to recruit differing cortical neurons depending on the coil orientation (Di Lazzaro et al., 2004). In spite of this, only four of the included studies reported this important methodological factor (Aurora et al., 1999; Conte et al., 2010; Maier et al., 2011; Marker et al., 2014). To improve the quality of future TMS studies, researchers should use the TMS checklist during methodology design and reporting to address the weaknesses brought to light by this review.

2.13.1 Limitations

There are a number of limitations which apply to the results of this review. Due to the heterogeneous TMS methods utilised, some of the inconsistencies found may relate to the variance in the stimulation techniques, such as the intensity of the conditioning and test stimuli and the duration of the ISI. This could be a consequence of the older studies predating more recent guidelines, though so far these guidelines have focused more on the clinical application and safety aspects of TMS (Groppa et al., 2012; Rossi,

Hallett, Rossini, & Pascual-Leone, 2009). For direct comparability of studies, further efforts are required to standardise TMS protocols, particularly pertaining to paired-pulse studies, which show the greatest variability.

The majority of the studies did not use the methods recommended by the IFCN committee (Groppa et al., 2012) for calculating the RTh and CSP. Most studies stated that the RTh was the minimum stimulus intensity that elicited a MEP with an amplitude of at least 50 μV in 50% of trials, but very few detailed whether an algorithm was used. The CSP is recommended to be measured from MEP onset but only three studies used this (Aurora et al., 1999; Krause et al., 2005; Salerno et al., 2000), the remaining studies measuring from the end of the MEP, which can be disadvantageous as it can be more difficult to discern. In addition, during the CSP it is common to have short bursts of EMG activity before returning to silence and it is therefore recommended that studies specify the criteria for the end of the CSP, detailing the required duration and amount of EMG activity. For example they suggest that it is when EMG activity reaches or exceeds the pre-TMS baseline level and lasted for at least 50 ms (Groppa et al., 2012). However, no studies reported the required duration of EMG resumption. To improve the reliability of TMS measures, studies should use the IFCN recommendations.

The conclusions in this review are limited to the included chronic pain conditions. The majority of these conditions are commonly associated with maladaptive changes within the central nociceptive system, such as migraine, neuropathic pain, CRPS and fibromyalgia. Thus, the findings may not be generalised to other chronic pain populations. Very little research has been conducted on chronic pain conditions traditionally thought to be peripherally driven and nociceptive in nature, such as arthritis (Schwenkreis et al., 2010). To date, only two studies have examined cortical excitability in people with arthritis. Schwenkreis et al. (2010) found no significant differences in SICI, LICF or RTh between participants with painful hand OA and pain-free controls. Whereas, Salerno and colleagues (2000) demonstrated that RA was associated with a significant reduction in both cortical inhibition and facilitation. However, the TMS parameters used in this study are no longer typical with regard to the intensities and intervals between stimuli and that a double-cone type coil was used to stimulate hand muscles. Moreover, there was a very small sample of only five

participants in the RA group. Thus the current study sought to investigate the influence of arthritic pain on corticomotor excitability but with a larger sample and using recent standard TMS techniques.

2.14 Conclusion

Overall, there is high quality evidence that chronic pain is associated with a reduction in both GABA$_A$ and GABA$_B$ mediated intracortical inhibition. There are less consistent results regarding the influence of chronic pain on corticomotor excitability and LICF, which may vary depending on the chronic pain condition being examined. To improve the quality and reliability of TMS studies, more work is needed to standardise TMS protocols and reporting methods. Further research is needed to investigate the lesser studies paradigms, such as SR curve, SICF and LICI are affected in chronic pain conditions. Only two studies have explored whether corticomotor excitability is influenced by arthritic pain which found conflicting results. Only one poor quality study has examined the CSP, SICI and LICI. Given the recent evidence suggesting the cortical reorganisation occurs in arthritis, further research on this topic is needed.

Chapter 3 Methods

3.1 Introduction

The purpose of this study was to systematically compare a series of corticomotor and intracortical excitability measures between participants with hand arthritis and pain-free aged-matched controls. In addition, the relationship between these excitability measures and measures of pain and function in the participants with hand arthritis was established. This chapter will outline the methods used including the study design, the participants, the procedure and the data processing and analysis.

3.2 Study setting and design

All testing was performed at the Health and Rehabilitation Research Institute, Auckland University of Technology (AUT), Auckland, New Zealand. A cross-sectional case-control study design was used to compare corticomotor excitability between cases with hand arthritis and pain-free controls. The independent variable was the group (arthritis and pain-free control). The dependent variables were the corticomotor excitability measures: stimulus-response curve characteristics (max, s50 and slope), SICI, SICF, LICI and CSP duration. To determine the relationship between corticomotor excitability measures and pain and function measures in the case group, a correlational study design was used.

3.3 Ethical and cultural considerations

Ethical approval was gained from the Auckland University of Technology Ethics Committee (AUTEC 13/02) (see page vii). Informed, voluntary and written consent was gained and participants were notified that at any time during the study they were free to withdraw. Participants were informed of the purpose of the study and any potential risks or side effects associated with TMS. To ensure people with contraindications to TMS were excluded, participants were screened prior to enrolment and completed a written TMS safety checklist (Rossi et al., 2009) (see Appendix B). Throughout the study design and completion, the Treaty of Waitangi principles of partnership, participation and protection were adopted. This included the requirement of head touching for TMS being discussed prior to participant enrolment and participants were encouraged to discuss and attend the study with their family members/whanau, care-

givers, or friends if preferable. No participants of specific ethnicities were preferentially recruited, as all potential participants meeting the inclusion and exclusion criteria had equal opportunity of involvement.

3.4 Participants

3.4.1 Sample size

The sample size was determined with a power calculation using G*Power 3.1.3 software (Faul, Erdfelder, Lang, & Buchner, 2007) and was based on a comparable study by Schwenkreis et al. (2010). They found that intracortical inhibition was significantly reduced in participants with neuralgia (relative amplitude 69.1% ± 53.4%) compared to pain-free controls (relative amplitude 26.9% ± 13.0%). The calculated effect size was 1.09. According to Cohen (1988b) this would be considered a large effect size and may be expected to be clinically meaningful. For the sample size calculation, the alpha level was set at 0.05 with a power of 0.9. A sample size of 38 was required, including 19 participants with hand arthritis and 19 age- and sex-matched controls.

3.4.2 Recruitment

Participants were recruited between March 2013 and January 2014 through an advertisement placed in the North Shore Times (see Appendix C), via advertisements on the Arthritis New Zealand website, using posters placed around the AUT North Shore Campus, and in the waiting areas of hand clinics and hospital outpatient physiotherapy departments in the Auckland region (see Appendix D). These advertisements included the title of the study, a brief description of its aims and what would be involved, and invited the participants to contact the researchers. Participants who expressed interest in the study were sent an information sheet (see Appendix E) giving a more detailed description of the study, including the inclusion and exclusion criteria and any risks involved. A follow-up phone call was made one week after receiving the information sheet to answer questions and enrol those who consented to participate. The flow of participants through the study and the data collection procedure are shown in Figure 2.
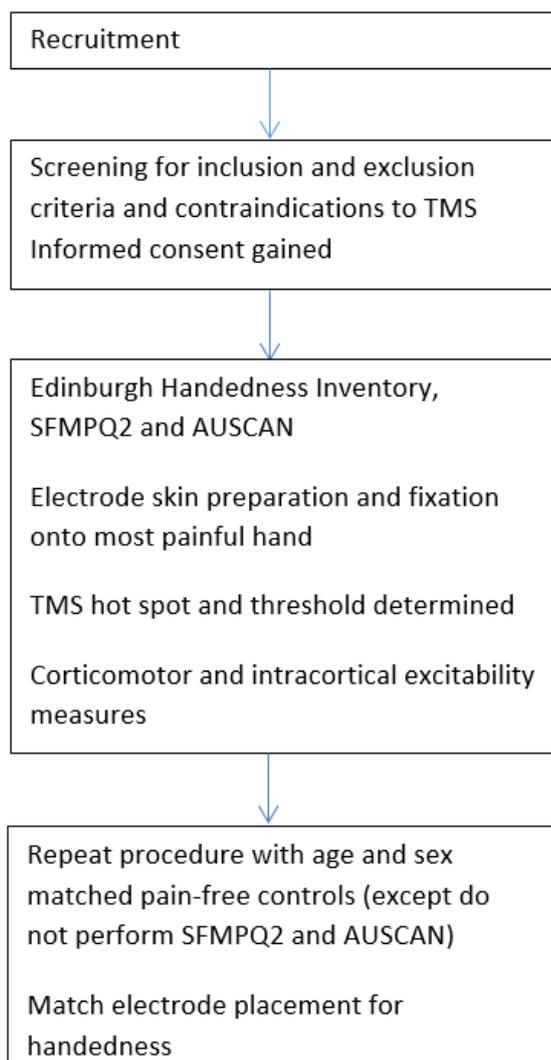
Figure 2: Data collection flowchart.

Note: AUSCAN, Australian/Canadian Osteoarthritis Hand Index; SFMPQ2, Short-Form McGill Pain Questionnaire Version 2; TMS, transcranial magnetic stimulation

3.4.3 Inclusion criteria

To be included in the arthritis group, participants must have experienced pain of at least three out of ten on the pain numeric rating scale (NRS) at least every other day for the preceding month and have received a previous diagnosis of hand arthritis by a medical doctor. Participants were included in the control group if they were matched in age (+/-8 years) and gender to a participant in the arthritis group. This was of particular importance as age has been shown to influence corticomotor and intracortical excitability (Oliviero et al., 2006; Peinemann, Lehner, Conrad, & Siebner,

2001; Rossini, Desiato, & Caramia, 1992). All participants were required to be at least 18 years old and fluent in English.

3.4.4 Exclusion criteria

To reduce confounding factors affecting corticomotor excitability and to minimise potential risk of harm, the following exclusion criteria were applied. Participants were excluded if they had known contraindications to TMS including: metal implants in head (excluding fillings), known skull defects, concussion within the last 6 months, history of epilepsy or seizures, pacemaker or artificial heart valve, intracardiac lines, history of unexplained recurring headaches, taking medication that could lower seizure threshold or current pregnancy (Rossi et al., 2009). Also, if participants had a neurological condition, a musculoskeletal condition affecting the upper limb (other than arthritis) or a history of chronic pain (other than arthritis) they were excluded from the study. In addition, participants were excluded if they took CNS active drugs such as antidepressants. Participants were permitted to take other analgesics, however, they were asked to refrain from taking them on the day of testing. Participants in the control group were excluded if they had experienced any condition causing significant pain greater than two out of ten on the NRS anywhere in their upper limbs in the previous six months or had any current upper limb pain.

3.5 Screening, demographic information and questionnaires

At the start of the testing session, participants were required to complete a screening checklist assessing contraindications to TMS (see Appendix B) and to provide written informed consent (see Appendix F). Demographic data such as height, weight, years of hand pain, diagnosis, history of specialist hand use, other medical conditions including other pain sites and details of current medications were collected.

The Edinburgh Handedness Inventory was completed to determine hand dominance (Oldfield, 1971) (see Appendix G), in order for the arthritis and control groups to be matched for handedness. This was performed to control for the possible influence of handedness on corticomotor excitability (Macdonell et al., 1991; Triggs, Calvanio, Macdonell, Cros, & Chiappa, 1994).

3.5.1 Pain intensity

The Short-Form McGill Pain Questionnaire Version 2 (SFMPQ2) was used to assess pain intensity (Dworkin et al., 2009) (see Appendix H). The SFMPQ2 is 22 item scale, designed to assess the multi-dimensional qualities of pain, including sensory and affective qualities. Participants were asked to rate their average pain over the past week for each of the 22 descriptors on a visual analogue scale from 0 to 10, with the anchors 'none' and 'worst possible', respectively. Participants were instructed to rate their pain as 0 if a descriptor did not represent a dimension of their pain. The SFMPQ2 has been previously validated for use with arthritis pain (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012) and is significantly correlated with several other pain measures, demonstrating excellent construct validity (Dworkin et al., 2009; Lovejoy et al., 2012). The SFMPQ2 has been shown to have high internal consistency reliability (Dworkin et al., 2009; Lovejoy et al., 2012).

3.5.2 Hand-related pain, stiffness and function

The Australian/Canadian Osteoarthritis Hand Index (AUSCAN) is a self-reported measure designed to assess hand arthritis related pain, stiffness and function (Bellamy, Campbell, Haraoui, Buchbinder, et al., 2002) (Appendix I). Participants rated their pain, stiffness or difficulty on a 0 to 10 visual analogue scale for specific activities that have been shown to be affected by hand arthritis. The AUSCAN has high construct validity (Allen, DeVellis, Renner, Kraus, & Jordan, 2007; Bellamy, Campbell, Haraoui, Gerecz-Simon, et al., 2002), in addition to face and content validity (Bellamy, Campbell, Haraoui, Gerecz-Simon, et al., 2002). The AUSCAN is a reliable measure, with previous studies indicating it has high internal consistency and adequate test-retest reliability (Allen et al., 2007; Bellamy, Campbell, Haraoui, Buchbinder, et al., 2002; Bellamy, Campbell, Haraoui, Gerecz-Simon, et al., 2002).

3.6 Laboratory procedures

Each participant was seated in a comfortable chair with their neck supported by a neck rest. The hand and elbow were supported on a pillow beside the participant (see Figure 3). Throughout the experiment participants were encouraged to be as relaxed as possible, particularly in the muscles of the hand and upper limb.
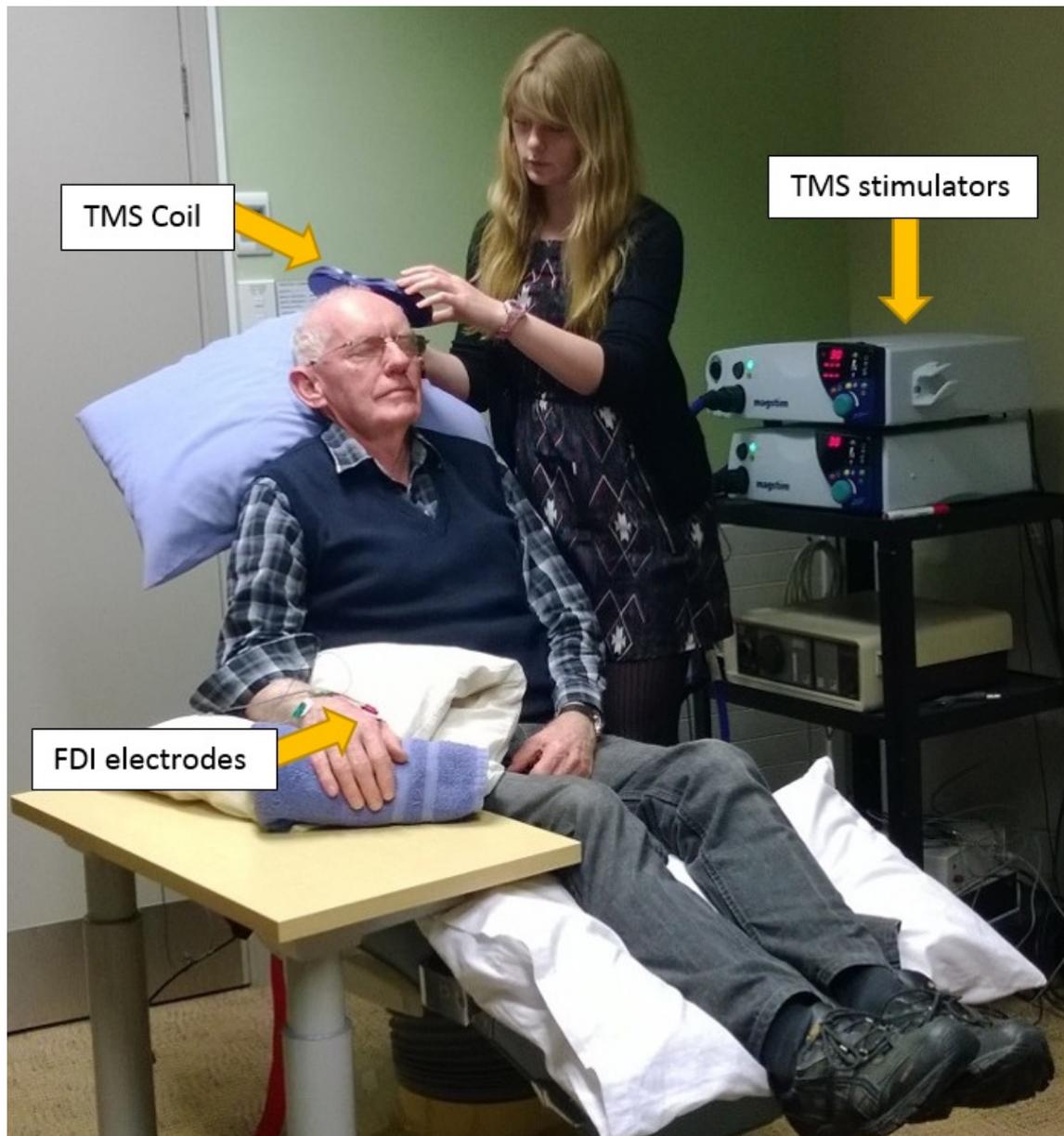
Figure 3: Participant set-up for transcranial magnetic stimulation. Permission granted for display of photograph.

3.6.1 Electromyography

Electromyographic (EMG) activity in the FDI was measured using a Norotrode20™ bipolar Ag/AgCl 22mm self-adhesive surface electrode (Myotronics Inc, Kent, WA) placed parallel with the muscle fibres (Masquelet, Salama, Outrequin, Serrault, & Chevrel, 1986). The muscle belly of FDI was palpated during active second finger abduction by the participant. Standard skin preparation techniques of shaving to remove hair, exfoliating, and cleansing with an alcohol wipe were applied to minimise impedance between the electrode and FDI muscle activity. The ground electrode was placed over the ulnar styloid process. EMG data were amplified and filtered (10-1000

Hz) using an AMT-8 (Bortec Biomedical Ltd, Canada). Data were sampled at 5000 Hz and signals were transmitted to a Micro 1401 MKII data acquisition system controlled by Signal software version 4.06 (both Cambridge Electronic Design, Cambridge, UK). The sampling window was from 100 ms pre-stimulus until 200 ms post-stimulus for the SR curve and paired-pulse measures, and until 400 ms post-stimulus for CSP assessment. The FDI on the most painful hand was assessed for the arthritis group and this was matched for handedness in the control group.

3.6.2   Transcranial magnetic stimulation

The recently devised recommendations for TMS methodology were used during the development and reporting for this study (Chipchase et al., 2012) (See Appendix J for details). Corticomotor and intracortical excitability were assessed using single and paired pulse TMS with a Bistim module connecting two Magstim 200^2 stimulators (Magstim Co. Ltd, Dyfed, UK). A standard 70 mm figure-of-eight coil was used for stimulation. This type of coil has been shown to elicit more focal stimulation than other types of coil, making it most appropriate for selectively stimulating a distinct cortical region (Groppa et al., 2012), such as the FDI representation. Throughout the study monophasic pulses were delivered.

In order to assess the neural pathways most affected by pain, the TMS coil was placed over the motor cortex contralateral to the target hand (see Figure 3). The optimal location to stimulate the FDI was established by placing the coil at 45° to the sagittal plane approximately 5 cm lateral and 1 cm anterior to the vertex to produce a posterior to anterior current (Groppa et al., 2012). From this position the coil was systematically moved over the scalp delivering suprathreshold stimuli until the site eliciting the largest MEP was located. This site, known as the hotspot, was marked with a pen and the remaining stimuli were delivered with the coil located in the same position. During all stimulation, care was taken to constantly monitor coil position and orientation to ensure consistency. The time interval between stimuli was 6 seconds ± 15%. This was varied to prevent predictability.

Previous studies have shown that muscle activation can alter cortical excitability (Devanne et al., 1997; Ridding et al., 1995). To ensure muscles remained quiescent during stimulation, participants were asked to relax in a well-supported position and

EMG activity was monitored via observation of continuous traces on an oscilloscope (TDS2014B, Tektronix Inc, Beaverton, OR). The participant's level of attention during TMS stimulation has been suggested to be an important variable to control (Chipchase et al., 2012), with previous studies demonstrating that corticomotor excitability was affected when mental activity or attention towards the hand being assessed were manipulated (Lefebvre et al., 2004; Master & Tremblay, 2009). During stimulation, participants were asked to focus on counting each stimulus in their head and to inform the researcher when they had counted 20, 40, 60 and 80 stimuli.

3.6.3   Resting motor threshold

RTh was defined as the minimum stimulus intensity that elicited a MEP with a peak-to peak amplitude of at least 50 µV in a minimum of four out of a train of eight stimuli with the target muscle at rest (Rossini & Rossi, 2007). This was recorded as a percentage of maximal stimulator output (MSO)(Groppa et al., 2012). The technique used to determine RTh was based on the IFCN committee standardised algorithm (Groppa et al., 2012). Starting from a subthreshold stimulus intensity, the intensity was increased by 5% MSO increments until MEPs of at least 50 µV peak-to peak amplitude were elicited by at least four out of eight stimuli. Stimulus intensity was then decreased by 1% MSO until less than four out eight responses were positive. Assessment of the MEP amplitude of hand muscles has been shown to be reliable using similar techniques in healthy adults (Lefebvre et al., 2004; Livingston & Ingersoll, 2008; Malcolm et al., 2006) and in older adults (Christie, Fling, Crews, Mulwitz, & Kamen, 2007).

3.6.4   Stimulus response curve

A stimulus response curve was obtained by delivering single stimuli at different intensities. A total of 80 stimuli were randomly delivered at intensities of 90%, 100%, 110%, 120%, 130%, 140%, 150% and 160% of RTh, with 10 stimuli delivered at each intensity. Previous studies have demonstrated that 5 trials are sufficient to obtain reliable MEPs from hand muscles in healthy adults and older adults (Christie et al., 2007; Malcolm et al., 2006).

3.6.5 Intracortical inhibition and facilitation

SICI, SICF, and LICI were assessed using paired pulse stimulation. A block of 60 randomised stimuli were delivered over the hot spot. Ten stimuli were delivered for each of six conditions; these included two measures of SICI and SICF, and one measure of LICI and one single pulse non-conditioned measure. The non-conditioned stimulus was set to elicit a response of approximately 1 mV in size (Müller-Dahlhaus et al., 2008; Peurala et al., 2008; Ziemann, Tergau, Wassermann, et al., 1998). The stimulus intensity to obtain a response of 1 mV was determined by reviewing the mean responses in the stimulus response curve and selecting the intensity that was closest to eliciting a response of 1 mV. This stimulus intensity (TS1mV) was utilised for the intracortical measures. Two measures of SICI were assessed. In both of these, the test stimulus was TS1mV with an ISI of 2 ms. This was preceded by a conditioning stimulus set at either 70% ($SICI_{70}$) or 80% ($SICI_{80}$) of RTh (Kujirai et al., 1993). Two measures of SICF also were assessed. The conditioning stimulus was TS1mV with an ISI of either 1.4 ms ($SICF_{1.4}$) or 2.8 ms ($SICF_{2.8}$) before a test stimulus set to 90% of RTh (Peurala et al., 2008; Ziemann, Tergau, Wassermann, et al., 1998). For assessment of LICI, the conditioning stimulus of 120% of RTh was followed by a test stimulus of TS1mV with an ISI of 99 ms (Müller-Dahlhaus et al., 2008; Valls-Solé et al., 1992; Wassermann et al., 1996).

3.6.6 Cortical silent period

The CSP is the period of muscle inhibition following a MEP during a sustained voluntary contraction (Rossini & Rossi, 2007). The CSP was calculated from the average of 10 stimuli using a stimulus intensity of 120% RTh. These were performed while the participant sustained a low muscle activation level (approximately 10% of maximum voluntary contraction (MVC)) of FDI in the hand contralateral to the test hemisphere. To obtain the desired level of muscle contraction, the participant was asked to lightly abduct the second finger against gravity with the forearm in a neutral position (mid-way between pronation and supination) and aim for a level of 10% of MVC contraction. EMG activity was monitored by both the researcher and the participant to assist with achieving consistent activity.

3.7 Data processing and analysis

3.7.1 Data management

All written data were stored in a locked cabinet in the Neurophysiology Research laboratory at AUT. Electronic data were stored on a password protected laboratory computer with an additional copy saved to a memory stick. To ensure participant confidentiality, all electronic files were saved using a numerical code allocated to the participant on entry to the study.

3.7.2 Motor evoked potential processing

Processing of corticomotor and intracortical excitability MEPs was performed using Signal software version 4.06 (CED, Cambridge, UK, 2009). All frames were visually screened for background muscle activity, and if present were removed prior to processing. For the SR curve and paired pulse measures, the individual MEP peak-to peak amplitude was calculated and then averaged over the 10 trials.

To construct the SR curve, the mean MEP peak to peak amplitudes were plotted against stimulus intensity for each participant. SPSS software version 19 (SPSS, 2010) was used to fit the data with the Boltzmann equation (Carroll, Riek, & Carson, 2001; Devanne et al., 1997). Using this equation, MEP amplitude at stimulus intensity s is determined by:

$$MEP_s = MEP_{max} / (1 + exp((s50 - s) / m))$$

where MEP_{max} is the maximum MEP amplitude defined by the function, m is a slope parameter ($1/m$ is proportional to the slope), and $s50$ is the stimulus intensity where the MEP size would be 50% of the MEP_{max} (Carroll et al., 2001; Devanne et al., 1997).

Paired-pulse responses were processed by dividing the mean conditioned peak-to peak MEP amplitude by the mean non-conditioned TS1mV response. Thus, responses < 1 indicate inhibition of the test MEP and >1 indicate facilitation (Kujirai et al., 1993).

The duration of the CSP was measured from the MEP onset, when the EMG exceeded the baseline level, and ended when EMG activity reached or exceeded 3 standard deviations of the re-TMS EMG baseline level, lasting for at least 50ms (Groppa et al., 2012).
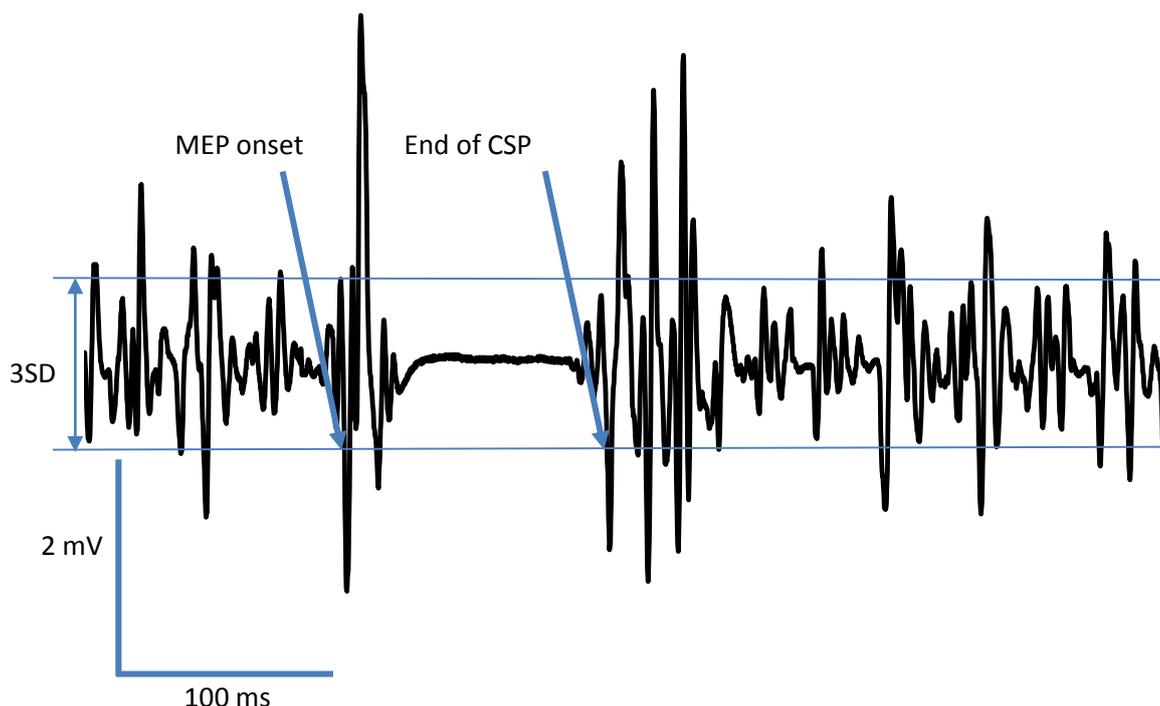
Figure 4: Example of a cortical silent period.

Note: CSP, cortical silent period; MEP, motor evoked potential; SD, standard deviations

3.7.3 Data analysis

Data were statistically analysed using SPSS software version 19 (SPSS, 2010). Data were screened for normality using Shapiro-Wilk tests (Razali & Wah, 2011). Due to several of the data sets being non-normally distributed, non-parametric tests were used. Statistical significance was set at an alpha-level of 0.05. The independent variable was the group (arthritis and pain-free control). The dependent variables were the corticomotor measures (RTh, stimulus-response curve parameters, SICI, SICF, and CSP duration) and the baseline variables (age, gender, BMI, and hand dominance). Mann-Whitney U tests were used to compare dependent variables between groups, with the exception of the nominal measures (gender and hand dominance) where the Chi squared test was utilised.

An exploratory analysis was also performed to determine whether there were relationships between the corticomotor measures and the pain variables (pain duration, SFMPQ2, and AUSCAN total score) in the arthritis group. Spearman's Rank tests were used to calculate the strength of association between variables. These were interpreted using criteria suggested by Cohen with ≥ .1 being considered a small

association, ≥.3 a medium association, and ≥.5 representing a large association (1988a).

Chapter 4 Results

4.1 Introduction

This chapter will present the study results. The purpose of this study was to systematically compare a series of corticomotor and intracortical excitability measures between participants with hand arthritis and aged-matched controls, and to explore how these measures relate to pain and function in the participants with hand arthritis. This chapter will outline the results of recruitment and the participant characteristics. The focus of this chapter will be the between group comparisons of the corticomotor excitability measures (RTh, SR curve parameters, $SICI_{70}$, $SICI_{80}$, $SICF_{1.4}$, $SICF_{2.8}$, LICI and CSP). To conclude, this chapter will detail the exploratory correlational analysis between the corticomotor excitability measures and pain duration, the SFMPQ2, and the AUSCAN for the participants with hand arthritis.

4.2 Recruitment and data collection

Twenty-three participants with painful hand arthritis and twenty age-matched control participants met the inclusion criteria. Data collection took place between April 2013 and March 2014. All participants completed the data collection session. The MEP_{max}, m (a slope parameter) and s50 could not be calculated from the SR curve data for one of the participants with hand arthritis and for two of the control participants and were therefore not included in the analysis of those variables. The paired-pulse measures for one of the control participants were not included in the analysis due to a measurement error of the test stimulus intensity causing all measures to be inaccurate. The CSP could not be calculated for one arthritis participant due to inconsistent muscle activation and one of the control participants could not be included due to excessive EMG noise. Several participants in both groups found it difficult to maintain a resting state of their FDI muscle. All frames showing muscle preactivation were excluded from the analysis. Extra stimuli were delivered for participants when more than 30% of responses had preactivation. For all of the corticomotor excitability measures, there were at least seven useable responses collected for each participant. The highest intensities of the SR curve could not be obtained for two participants in each group due to the intensities exceeding the

maximum stimulator output. For these participants, the curves were assessed based on the intensities collected, which ranged from five to seven intensities.

4.3 Sample characteristics

The participants' characteristics are presented in Table 2. There were no statistically significant differences between the groups in age, gender, BMI or test hand dominance ($p > 0.05$). The majority of the participants were female (74% and 70% for the arthritis and control groups, respectively). Most participants with arthritis experienced pain in bilateral hands, with the dominant hand being most painful in 65% of participants. The majority of the participants with hand arthritis had been diagnosed with OA (n = 17). Three participants had a diagnosis of RA and the three remaining participants were diagnosed with psoriatic arthritis, systemic lupus erythematosus and polymyalgia rheumatica. The majority of the participants in both groups did not have a history of a specific hand motor activity, with the exception of one person in each group who were piano players. No participants in either group had a history of neurological or psychiatric disorders. The participants' other medical conditions are summarised in Table 3. In both groups, around half of participants had cardiovascular conditions that were controlled with medication. The hand arthritis group had an increased number other painful musculoskeletal conditions, which were typically other arthritic joints in their lower limbs. No participants were taking central nervous system active drugs. Table 3 summarises the participants' prescribed medications, which were mainly for controlling hypertension and hypercholesterolemia, or analgesics and anti-inflammatories in the arthritis group.

Table 2: Participant characteristics

	Arthritis group Median (IQR)	Control group Median (IQR)	p value
Age (years)	71 (5.5)	70.5 (10.5)	.442
Gender (female: male)	n = 17:6	n = 14:6	.606
BMI	26.4 (7.0)	25.5 (2.7)	.263
Test hand (dominant: non-dominant)	n = 15:8	n = 11:9	.348
Pain duration (years)	9 (12.5)		
SFMPQ2	39 (33)		
AUSCAN	90 (32.5)		
Arthritis Type			
• Osteoarthritis	n = 17		
• Rheumatoid	n = 3		
• SLE	n = 1		
• Psoriatic	n = 1		
• Polymyalgia rheumatica	n = 1		

Note: AUSCAN, AUSCAN Osteoarthritis Hand Index; BMI, body mass index; IQR, interquartile range; SFMPQ2, Short-Form McGill Pain Questionnaire 2; SLE, systemic lupus erythematosus

Table 3: Participant medical conditions and medications

Medical Condition	Arthritis group (n/23)	Control group (n/20)
Musculoskeletal conditions affecting other regions (not upper limbs) (e.g. knee/ hip osteoarthritis, mechanical low back pain)	18	8
Hypertension (controlled)	10	8
Asthma	3	2
Cardiac condition (controlled)	1	1
Hypothyroidism (controlled)	3	1
Lymphoedema (controlled)	1	1
Glaucoma	1	1
Psoriasis	1	0
Diabetes (controlled and not affecting sensation)	1	0
Haemochromatosis	1	0
Medication type	**Arthritis group (n/23)**	**Control group (n/20)**
Antihypertensives (e.g. metoprolol, cilazapril)	10	8
Statins	6	8
Anti-coagulants	7	4
NSAIDs	7	1
Digestive/Reflux medication (omeprazole)	6	2
Asthma medication (e.g. seretide, ventolin)	3	2
Analgesics (paracetamol +1 person taking codeine)	5	0
Thyroid medication	3	1
Diuretics	2	2
Osteoporosis medication (fosamax, odanacatib)	2	0

Note: NSAID, non-steroidal anti-inflammatory drug

4.4   Cortical excitability measures

4.4.1   Introduction

The results of the corticomotor excitability measures are summarised in Table 4, including the RTh, the stimulus response curve parameters (m, $s50$, MEP_{max}), the paired-pulse states ($SICI_{70}$, $SICI_{80}$, $SICF_{1.4}$, $SICF_{2.8}$, and LICI) and the CSP duration.

4.4.2   Corticomotor excitability measures

There were no significant differences between the arthritis and control groups for any of the corticomotor excitability measures (Table 4) The results were similar between the groups for the RTh and all of the parameters relating to the SR curve, including MEP_{max}, m, and $s50$ (p > 0.05).

4.4.3   Intracortical excitability measures

Intracortical measures were compared between groups as an expression of the conditioned MEP amplitude relative to the non-conditioned MEP amplitude (Table 4). There was a statistically significant difference between groups in SICF with an ISI of 1.4 seconds ($p = 0.045$), with the arthritis group demonstrating enhanced facilitation compared with the control group (see Figure 5B). The responses to $SICF_{1.4}$ were extremely variable between participants in the arthritis group, with responses ranging from 1.05-27.09 (see Figure 6C). There were no other statistically significant differences observed between groups for any of the other intracortical measures including $SICI_{70}$, $SICI_{80}$, $SICF_{2.8}$ and LICI ($p > 0.05$). The patients with hand arthritis demonstrated minimal $SICI_{80}$, while the groups were not significantly different, the patients had an average reduction in MEP amplitude of 3% compared with 47% in the controls.

4.4.4   Cortical silent period

The CSP median duration was similar for the arthritis and control groups (Table 4). There were no significant differences between the groups ($p = 0.896$).

Table 4: Corticomotor and intracortical excitability

	Arthritis group Median (IQR)	Control group Median (IQR)	*p* value
RTh (% of stimulator output)	50 (14.5)	50 (8.3)	.705
MEP_{max}	3.14 (4.39)	2.58 (1.86)	.654
*s*50	127.56 (15.94)	132.52 (21.88)	.271
m	9.36 (5.35)	9.81 (4.52)	.295
Test stimulus 1mV (mV)	0.46 (0.74)	1.02 (0.95)	.109
$SICI_{70}$	0.56 (0.43)	0.49 (0.37)	.318
$SICI_{80}$	0.64 (0.91)	0.49 (0.37)	.133
$SICF_{1.4}$	2.71 (4.29)	1.65 (1.33)	.045*
$SICF_{2.8}$	1.76 (1.56)	1.42 (0.68)	.139
LICI	0.34 (0.87)	0.39 (0.51)	.733
CSP (s)	0.134 (0.032)	0.139 (0.032)	.896

Note: * = $p < 0.05$ CSP, Cortical silent period; LICI, IQR, interquartile range; long-interval intracortical inhibition; MEP, motor evoked potential; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; RTh, resting motor threshold.

A
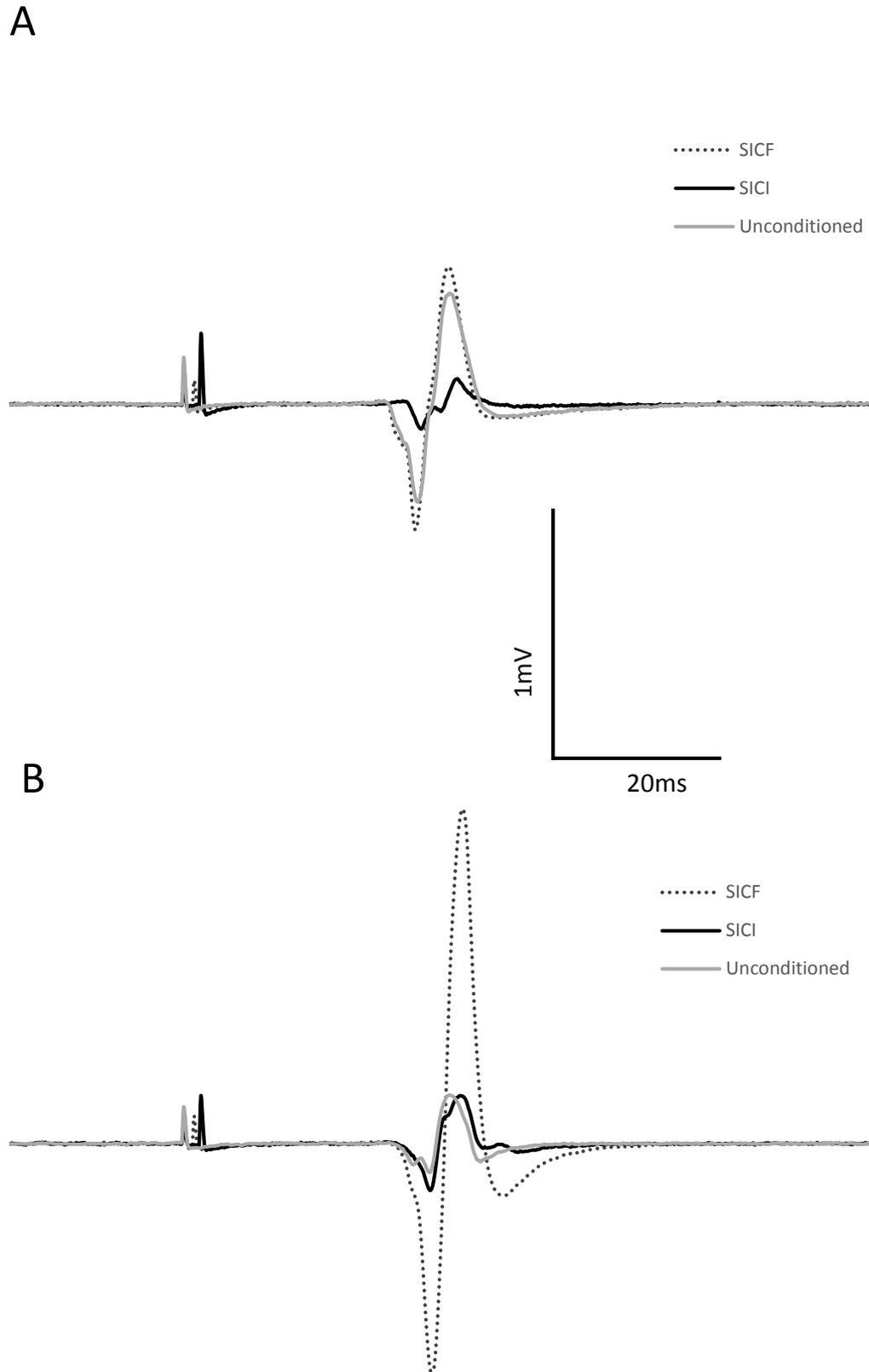
Figure 5: Examples of conditioned motor evoked potentials in a control participant (A) and a participant with hand arthritis with reduced $SICI_{70}$ and enhanced $SICF_{1.4}$ (B). Each trace is an average of the 10 responses in each condition. Note: SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition

4.5   Correlations between corticomotor excitability and pain

Spearman's rank correlations were used to explore potential relationships between the corticomotor excitability measures and pain variables (Table 5, below). The correlations were interpreted using values suggested by Cohen (1988a) for the strength of the relationships. Medium strength correlations were observed between the duration of hand pain and both measures of intracortical inhibition ($SICI_{70}$ ρ = 0.38, n = 23, p = 0.074; $SICI_{80}$ ρ = 0.434, n = 23, p = 0.038), with longer pain duration being associated with a reduction in SICI (Figure 6A and B). Increased pain duration was also associated with increased intracortical facilitation (Figure 6C). There was a medium strength correlation between the duration of hand pain and $SICF_{1.4}$ (ρ = 0.346, n = 23, p = 0.106). There were no large or medium strength correlations observed between the RTh, $SICF_{2.8}$, LICI, CSP or the SR curve parameters and the pain measures (Table 5).

Table 5: Spearman's rank correlations between corticomotor excitability and pain variables

	Pain Duration	SFMPQ2	AUSCAN
RTh (% of stimulator output)	-.029	-.217	-.080
MEP_{max}	.207	.138	.012
$s50$	.195	.258	.198
m	-.002	.036	-.046
$SICI_{70}$	.380[+]	.203	-.071
$SICI_{80}$	.434[+*]	.183	-.030
$SICF_{1.4}$	.346[+]	.132	.023
$SICF_{2.8}$	.090	-.005	.001
LICI	.022	-.038	-.157
CSP	.247	-.048	.100

*Correlation is significant at the 0.05 level (2-tailed). [+] Correlation is of medium strength. *Note:* CSP, Cortical silent period; IQR, interquartile range; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; RTh, resting motor threshold; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition
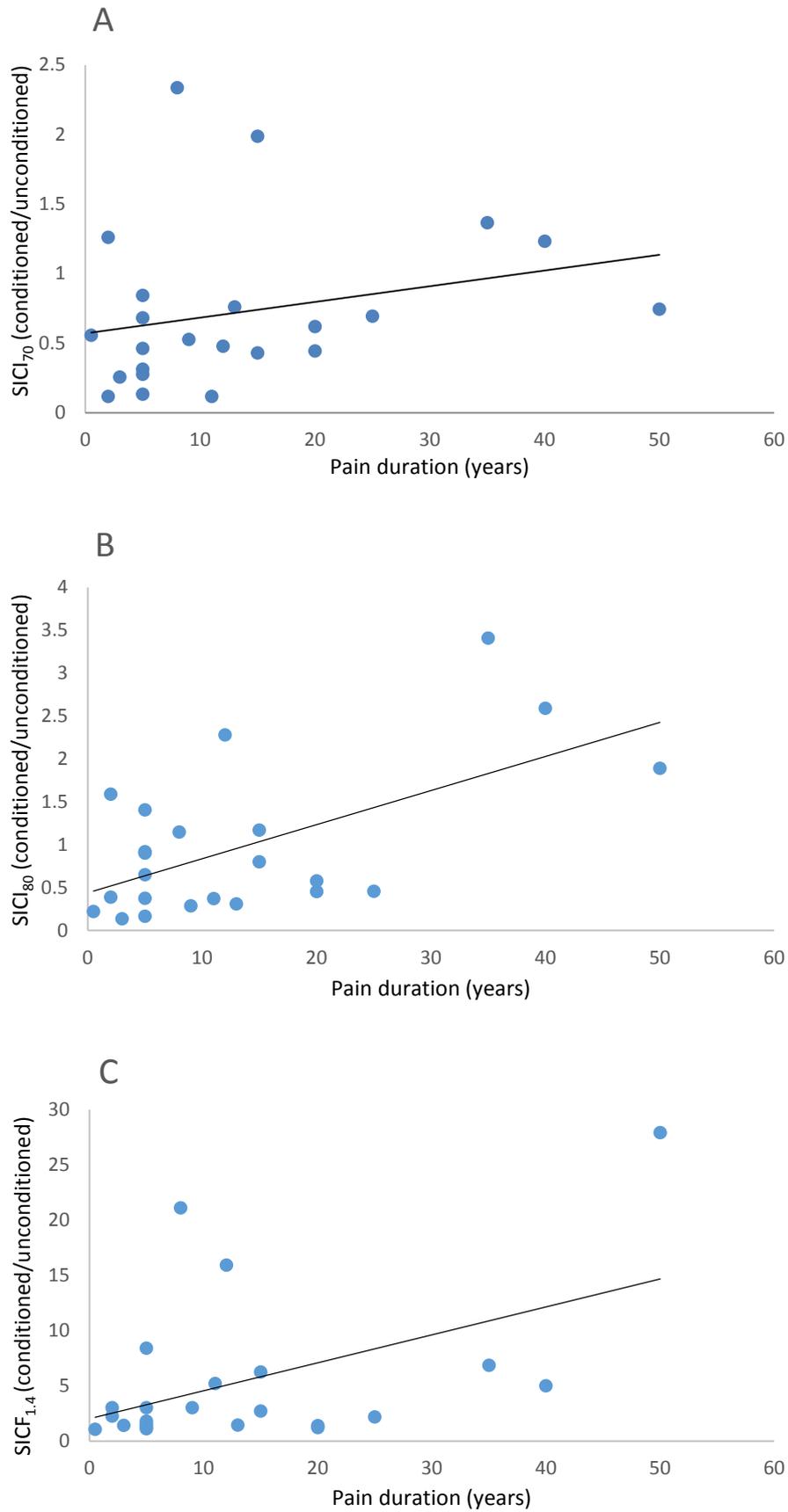
Figure 6: Moderate strength correlations between pain duration and SICI$_{70}$ (A), SICI$_{80}$ (B), SICF$_{1.4}$ (C). Note: the positive correlation in 2A and 2B demonstrate that with increased pain duration there was less of a reduction in MEP amplitude due to SICI.

Chapter 5 Discussion

5.1 Introduction

The purpose of this study was to systematically compare a series of corticomotor and intracortical excitability measures between participants with painful hand arthritis and pain-free aged-matched controls. This study provides evidence of enhanced intracortical facilitation in people with hand pain due to arthritis. Although we found no evidence of alterations in corticomotor excitability or intracortical inhibition, relationships were observed between pain duration and intracortical excitability, with increased pain duration being associated with reduced inhibition and increased facilitation. In this chapter, these results will be discussed in relation to the current evidence. Thereafter, the limitations of this study and areas for future research are outlined.

5.2 Pain and corticomotor excitability

This is the first study to show a link between pain and SICF. Patients with arthritic hand pain demonstrated significantly enhanced facilitation compared with age-matched controls. Although this facilitatory phenomenon is not fully understood, it is suggested that this results from interactions between I waves at an intracortical level (Di Lazzaro et al., 1999; Ilić et al., 2002; Paulus et al., 2008; Ziemann, Tergau, Wassermann, et al., 1998). The term 'I waves' refers to the descending volleys generated when TMS indirectly stimulates corticospinal neurons, the first of which results from stimulation of the axons of excitatory interneurons which synapse onto corticospinal neurons, whereas the subsequent I waves are generated by local polysynaptic interneuronal circuits (Ziemann, Tergau, Wassermann, et al., 1998). It is hypothesised that the conditioning stimulus makes the excitatory interneurons that mediate the later I waves hyperexcitable, so when they interact with the I waves generated by the test stimulus, the size of the response is enhanced (Ilić et al., 2002; Reis et al., 2008). The increase in MEP amplitude may reflect the increased excitability of the excitatory interneurons at the time of the second stimulus (Ilić et al., 2002). On the other hand, there is evidence that SICF is controlled by inhibition via the $GABA_A$ receptor, thus the increase in SICF may be due to a reduction in inhibition (Ilić et al., 2002; Ziemann, Tergau, Wischer, et al., 1998). The current finding provide some evidence for a link between arthritic pain

and the intracortical facilitatory processes that influence I waves. Additionally, this may be in part due to a reduction in $GABA_A$ receptor mediated inhibition. Demonstrating enhanced SICF in people with hand arthritis has important ramifications for motor learning and possible new rehabilitation strategies which will be discussed at the end of this Chapter.

Only one previous study has examined the effects of chronic pain on SICF. Eisenberg et al. (2005) found that SICF was not significantly different between people with CRPS and healthy age-matched controls. However, in this study the sample sizes were extremely small, with six patients with CRPS in each group for the analysis. Additionally, there was no justification of the sample size and it was not specified whether a power calculation had been performed. This may partly account for their non-significant result. Interestingly, they did observe significantly enhanced facilitation in the hemisphere associated with the painful limb, compared with the contralateral side in the patients with upper limb CRPS (Eisenberg et al., 2005). This study also found that there was significantly less inhibition in the affected hemisphere by assessing SICI.

SICI is suspected to result from $GABA_A$ mediated intracortical inhibitory circuits (Di Lazzaro et al., 2000; Di Lazzaro, Pilato, Dileone, et al., 2006; Ilić et al., 2002). Overall, chronic pain is associated with a reduction in SICI or, put another way, disinhibition of the primary motor cortex (Brighina et al., 2005; Eisenberg et al., 2005; Lefaucheur et al., 2006; Massé-Alarie et al., 2012; Mhalla et al., 2010; Schwenkreis et al., 2010; Schwenkreis et al., 2003). However, similarly to the previous studies involving people with arthritis (Kittelson et al., 2014; Salerno et al., 2000; Schwenkreis et al., 2010), the current study did not find significant evidence that arthritic pain affected motor cortex disinhibition. While the groups were not significantly different, the patients with hand arthritis demonstrated minimal inhibition, particularly when the conditioning stimulus was set to 80% of RTh, with an average reduction in MEP amplitude of just 3% compared with 47% in the controls. This finding is in contrast with a study by Schwenkreis et al. (2010), who found that patients with hand OA had an approximately 75% reduction in MEP amplitude, using an identical protocol for assessing SICI. The current study supports the notion that musculoskeletal-based pain may differ from other painful conditions in its effect on inhibitory intracortical processes. Previous research has mainly focused on conditions that are commonly associated with

maladaptive central nervous system neuroplasticity, such as migraine, neuropathic pain, CRPS and fibromyalgia, which demonstrate greater reorganisation of inhibitory intracortical circuits (see literature review section, p. 20). It may be that these pain-related neuroplastic changes in the motor cortex occur to a lesser extent in arthritis.

The effects of chronic pain on LICI have been less comprehensively examined. Similarly to studies by Siniatchkin et al. (2007) and Eisenberg et al. (2005), which investigated people with migraine and CRPS, respectively, this study did not find any significant differences in LICI between the patient and control groups. Collectively, these finding suggest that chronic pain conditions are not associated with changes in the intracortical circuits that mediate LICI. These circuits are distinct from those that mediate SICI and SICF, with pharmacological studies demonstrating that LICI transmission occurs via $GABA_B$ receptors rather than $GABA_A$ receptors (McDonnell, Orekhov, & Ziemann, 2006; Müller-Dahlhaus et al., 2008; Rogasch, Daskalakis, & Fitzgerald, 2013; Roick et al., 1993).

The CSP is also suggested to be predominantly mediated by $GABA_B$ intracortical inhibition (Groppa et al., 2012; Miniussi et al., 2012). Similarly to the results for LICI, there was no evidence of altered $GABA_B$ inhibitory mechanisms in the patients with hand arthritis when assessed via the CSP. This is in accordance with around half of the previous studies investigating the CSP in patients with chronic pain (see literature review section, p. 20). However, the remainder of the studies suggest there is a reduction in $GABA_B$ cortical inhibition associated with chronic pain, including the only other previous study to investigate the CSP in a group of patients with arthritis (Salerno et al., 2000). Salerno et al. (2000) found that patients with either RA or fibromyalgia had significantly less $GABA_B$ mediated inhibition in comparison with age-matched control participants, with the patients demonstrating shorter CSPs and reduced LICI. There are a number of possible explanations for the discrepancy with the results from the current study. Firstly, Salerno et al. (2000) only included participants with RA, whereas a number of different arthritic conditions were included in the current study, primarily patients with OA, which could differentially influence intracortical circuits. The sample size in the study by Salerno et al. (2000) was small, with five people in the arthritis group and with no justification or evidence of a sample size calculation. Finally, the stimulation protocols were quite different between the

studies. Salerno et al. (2000) used a higher conditioning and lower test stimulus intensity than the current study and they found LICI was significantly reduced with an ISI of 150 and 200 ms, whereas the current study had an ISI of 99 ms. Further research using recent standard TMS protocols would be needed to establish if the type of arthritis influences cortical inhibition.

This study found no significant differences between the participants with painful hand arthritis and control participants in their RTh or any of the measures relating to the SR curve. Together, these findings suggest that the pain resulting from hand arthritis is not associated with a change in the overall excitability or synaptic efficacy of the corticospinal pathway (Miniussi et al., 2012). These findings are in agreement with the previous literature examining the relationship between chronic pain and overall corticomotor excitability, with the majority of studies observing no significant differences between participants with pain and controls (see literature review section, p. 20). This may be a consequence of the non-specific nature of these measures, which are influenced by both spinal and cortical level processing (Hallett, 2000; Ljubisavljevic, 2006; Rossini & Rossi, 2007). Thus, even if there are changes in certain regions of the central nervous system, such as the motor cortex, it may not be sufficient to alter the overall excitability of the pathway, which is influenced by excitatory interneurons, corticospinal neurons and motoneurons (Groppa et al., 2012; Rossini & Rossi, 2007).

5.3   Correlations between corticomotor excitability and pain

Medium strength associations were observed between the measures of intracortical excitability and the duration of painful symptoms. Intracortical inhibition decreased with increasing pain duration. As previously discussed, chronic pain is typically associated with a reduction in the activity of GABA$_A$ mediated inhibitory circuits. The relationships observed in this study are consistent with the notion that cortical disinhibition occurs in patients with chronic pain, suggesting that intracortical reorganisation progresses with the course of the disease. Furthermore, enhanced facilitation was also associated with increased duration of hand pain. This provides some indirect evidence that over time there may be greater cortical plasticity of GABA$_A$ activity within the motor cortex. It may be hypothesised that this is linked to other changes in spinal and supraspinal nociceptive processing which occur in arthritis, such

as central sensitisation (Finan et al., 2013; Lluch et al., 2014; Meeus et al., 2012). With increased duration of pain, the persistent firing of nociceptors in arthritic joints can result in neuroplasticity of the dorsal horn and the supraspinal descending modulating systems, resulting in enhanced central nociceptive processing and pain amplification (Lluch et al., 2014; Millan, 2002; Thakur et al., 2014; Woolf, 2011). Though the time over which these processes are observed is likely to be quite varied, central sensitisation processes have been shown to occur in both OA and RA (Lluch et al., 2014; Meeus et al., 2012). Furthermore, Thakur et al. (2014) proposed that there is a subgroup of patients with OA that demonstrate neuropathic pain features who may respond differently to medications or corrective surgeries due to the changes within the central nervous system. Central sensitisation was not assessed in the current study, therefore future studies should establish whether the presence of neuropathic pain features or the degree of central sensitisation are associated with changes in corticomotor and intracortical excitability.

Previous studies have also found a relationship between pain and changes in intracortical excitability, although, the associations were with pain intensity rather than pain duration. Schwenkreis et al. (2010) found that SICI was significantly more reduced in neuralgia patients with moderate to severe pain compared with those experiencing mild pain. Similarly, Lefaucheur et al. (2006) observed a negative correlation between the CSP duration and pain intensity in patients with chronic neuropathic hand pain. Collectively, these studies indicate that high pain intensity is associated with a reduction in cortical inhibition. In a recent study, Kittelson et al. (2014) investigated corticomotor excitability in patients with knee OA. Although they found no significant differences between the patients and controls, a large negative association was observed between RTh and pain intensity, suggesting that patients with higher pain intensity have increased excitability of the corticospinal pathway. Increased pain intensity and corticomotor excitability were also associated with reduced quadriceps strength. They hypothesised that the cortical changes may be a neurophysiological adaptation to the reduction in strength in arthritis. Although, in the current study, there was minimal association between corticomotor or intracortical excitability measures and the measure of hand-related pain, stiffness and function ($\rho \leq$ 0.3).   As highlighted by Kittleson et al. (2014), longitudinal studies are required to

unravel this association, in order to determine whether the corticomotor changes contribute to the disease process or if they are an adaptation to the disease. In addition, Kittelson et al. (2014) found that there was a medium strength association between LICF and pain intensity, observing that facilitation was reduced in the patients with higher pain, which provides further evidence of a relationship between pain and cortical plasticity. This was in the opposite direction to the enhanced SICF observed in the current study. However, LICF is thought to be mediated by separate intracortical mechanisms to SICF (Paulus et al., 2008; Reis et al., 2008). Overall, what can be taken from the current evidence is that there is a link between chronic pain (including arthritic conditions) and changes within the motor system, particularly the $GABA_A$ mediated inhibitory intracortical circuits.

Although this study has extended the link between chronic pain and cortical disinhibition to include arthritic conditions, it remains unclear as to how or if the changes in excitability of cortical circuits relate to the motor control deficits and reduced function observed in this population (Bearne et al., 2007; Cole et al., 2011; de Oliveira et al., 2011; Nunes et al., 2012). In addition, these findings have important implications for motor learning, which is also associated with cortical disinhibition (Ljubisavljevic, 2006). Lefaucheur et al. (2006) found that people with chronic neuropathic pain respond differently to an intervention aimed at altering cortical excitability due to altered baseline cortical excitability. This suggests that patients with chronic pain may not have the same capacity for learning-induced cortical reorganisation because cortical inhibition is already reduced and it has been shown that the brain has limited capacity to reorganise in response to interventions (Wolters et al., 2003). Previous studies using experimental pain models have shown that pain can alter motor learning induced neuroplasticity (Boudreau et al., 2007; Rittig-Rasmussen, Kasch, Fuglsang-Frederiksen, Svensson, & Jensen, 2014) and reduce the capacity to acquire novel motor skills (Boudreau et al., 2007). In contrast, there is evidence which suggests that pain may improve motor performance during a learning task (Dancey, Murphy, Srbely, & Yielder, 2014) or have no effect (Ingham, Tucker, Tsao, & Hodges, 2011). These contradictory findings make it difficult to discern the impact of pain on motor learning and neural plasticity. Additionally, all of these studies have used acute experimental pain models and it is not yet known if chronic pain

influences motor learning. Future research should explore whether the changes in cortical excitability in patients with arthritic pain influence motor learning and neuroplasticity.

It is currently unknown whether the alterations in corticomotor excitability result as adaptation to pain or the way people move differently in pain, or conversely, whether the cortical changes themselves play a role in mediating the pain and motor control deficits. The interactions among pain, motor control and corticomotor excitability are clearly complex and may be multidirectional. For instance, previous studies found that pain relief following a repetitive TMS intervention was correlated with normalisation of SICI in patients with fibromyalgia and neuropathic pain (Lefaucheur et al., 2006; Mhalla et al., 2011). Furthermore, in a case report by Hunt et al. (2011), a gentleman with painful unilateral knee OA had reduced corticomotor excitability and strength compared with his unaffected side. Following an eight week muscle strengthening intervention, his corticomotor excitability increased in line with improvements in strength and reductions in pain.

These studies provide some evidence, albeit weak due to being based on association in a cross-sectional study, that there is a temporal relationship among pain, motor function, and corticomotor excitability. This suggests that other interventions that are known to alter cortical excitability may be beneficial in chronic pain populations. For example, motor imagery has been shown to modulate cortical excitability, with studies demonstrating that it is associated with increased corticomotor excitability and intracortical facilitation and reduced intracortical inhibition (Abbruzzese et al., 1999; Fadiga et al., 1998; Kasai, Kawai, Kawanishi, & Yahagi, 1997; Läppchen et al., 2012; Stinear & Byblow, 2003, 2004). Additionally, in conditions characterised by chronic pain and loss of movement, such as CRPS and phantom limb pain, interventions utilising motor imagery have been shown to reduce pain (Beaumont, Mercier, Michon, Malouin, & Jackson, 2011; Lagueux et al., 2012; MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008; Moseley, 2004, 2006), which may partly result from normalisation of corticomotor excitability (Läppchen et al., 2012). Improvements in pain may also be related to normalisation of the body schema in the somatosensory cortex and sensorimotor processing (Maihofner, Handwerker, Neundorfer, & Birklein, 2004). Evidence of cortical reorganisation has also been demonstrated in the somatosensory

cortices in patients with OA (Gilpin, Moseley, Stanton, & Newport, 2014; Stanton et al., 2013; Stanton et al., 2012). These regions have high connectivity with the motor cortex and have been shown to modulate intracortical excitability (Reis et al., 2008). Future studies should investigate whether interventions that target normalisation of the somatosensory cortex, such as sensory retraining techniques (Maihofner et al., 2004; Moseley, Zalucki, & Wiech, 2008; Pleger et al., 2006; Pleger et al., 2005) and motor imagery (Moseley, 2004, 2006), are of benefit in patients with arthritic pain.

5.4 Limitations

There are a number of limitations that require consideration. A heterogeneous group of patients was recruited for the painful arthritis group. The majority of participants had been diagnosed with OA, but a small number of participants with RA, psoriatic arthritis, systemic lupus erythematosus and polymyalgia rheumatica were also included. It is not yet known whether specific pathological processes may have differing effects on corticomotor excitability. It seems unlikely, as there is significant overlap in pathophysiological features across OA and RA including their phenotypic, cellular and molecular characteristics and the effective therapies (de Lange-Brokaar et al., 2012; Murphy & Nagase, 2008; Reines, 2004; Woetzel et al., 2014). In addition, recent systematic reviews have shown that central sensitisation plays a role in both diseases, including changes at both spinal and supraspinal levels (Lluch et al., 2014; Meeus et al., 2012). The inclusion criteria were kept deliberately broad because the main symptom of interest was the presence of hand pain, and the aim was to determine the effects of pain on corticomotor excitability. Participants in the arthritis group were required to have been diagnosed by a medical doctor as having hand arthritis, but an X-ray was not performed in all patients. It is well established that there is a discordance between pain and radiographic findings, and hence the relevance of the information gained from a radiograph is questionable (Bedson & Croft, 2008; Finan et al., 2013; Lluch et al., 2014).

Another possible limitation was the location of pain. In the participants with hand arthritis pain, the location of maximal pain was not always close to the 2nd finger, which was where MEPs were collected. The FDI muscle was selected as it is easily stimulated using TMS and it is commonly chosen in both the clinical and research

setting. Furthermore, it is easily localised and identifiable by palpation (Groppa et al., 2012), and has been used in similar studies (Schwenkreis et al., 2010). It is unlikely that the site of hand measurement would have had a large influence on the results, as similar results have been found when assessing paired-pulse measures in various small hand muscles, including abductor pollicis brevis, adductor digiti minimi and FDI (Liepert, Classen, Cohen, & Hallett, 1998; Zoghi, Pearce, & Nordstrom, 2003). It has also been shown that this muscle is weakened in individuals with hand arthritis (Oldham & Stanley, 1989). This study did not control for pain in regions other than the upper limbs. It was necessary to include participants with pain in other areas as the majority of participants were aged 60 to 80 years, and typically had some form of musculoskeletal pain. However, the presence of pain in other regions was low in magnitude and less regular, and did not have the more distinctive characteristics of chronic pain. Finally, not all participants with arthritis had pain at the time of testing. Whether patients have incidental or continuous hand pain can influence the response to quantitative sensory testing (Farrell et al., 2000), but it is unknown if this influences cortical excitability.

Finally, it must be acknowledged that the size of the test stimulus (TS1mV) was smaller in the arthritis group compared with the controls and this has the potential to influence the results. However, the test stimulus was not significantly different between the groups. Based on the difficulties experienced in this study to match the test stimulus using this method, future studies should evaluate whether choosing a mid-point on the SR curve such as 120% RTh may allow for a more accurate test stimulus assessment.

5.5 Conclusion and clinical implications

This was the first study to show a link between arthritic hand pain and heightened SICF. This finding suggests that there are changes in the intracortical facilitatory processes that influence I waves in hand arthritis. Very little research has been conducted assessing the relationship between pain and SICF or evaluating corticomotor excitability in patients with arthritis. The few studies that have been performed generally found non-significant results, although this may be a consequence of the sample sizes used in some cases. Overall, chronic pain is

associated with a reduction in SICI when compared to control participants. Similarly to previous studies on arthritic pain, this was not observed in this study, suggesting that different pain conditions could have distinct effects on the motor cortex. However, there were medium strength correlations between the measures of intracortical excitability and the duration of hand pain. These relationships suggest that the disease process is associated with a gradual reduction in the efficacy of $GABA_A$ mediated inhibitory circuits within the motor cortex, another novel finding. These findings have important implications for our understanding of the effects of arthritis on the brain. Cortical disinhibition may contribute to the deficits in strength, motor control and function, which are known to impact on people with arthritic hand pain. Furthermore, motor learning is also associated with cortical disinhibition and has been shown to be affected by experimental pain. However, it is not known how chronic pain conditions influence learning-induced cortical reorganisation. These findings have important clinical implications for health professionals and researchers involved in rehabilitation. This study provides evidence that interventions which modulate corticomotor excitability, such as repetitive TMS, transcranial direct current stimulation and motor imagery could be of benefit for people with hand arthritis.

5.6 Future research

There are a number of questions that relate to future research that have become apparent in the course of this study. These include:

- Does the type of arthritis influence corticomotor excitability?
- How does corticomotor excitability relate to strength, motor control and motor learning in people with chronic arthritic pain?
- What is the time course of changes in pain, function, strength and corticomotor excitability in patients with arthritis and are they related?
- Does the degree of central sensitisation of the nociceptive system influence corticomotor excitability in patients with arthritis?
- Can interventions that are known to influence motor cortex excitability, such as non-invasive brain stimulation and motor imagery, influence arthritic pain and function?

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Appendix A

	Reported	Controlled
Title:		
Author:		
Year:		
Participant Factors		
1. Age of subjects		
2. Gender of subjects		
3. Handedness of subjects		
4. Subjects prescribed medication		
5. Use of CNS active drugs (e.g. anti-convulsants)		
6. Presence of neurological/ psychiatric disorders when studying healthy subjects		
7. Any medical conditions		
8. History of specific repetitive motor activity		
Participant Factors section score /8		
Methodological Factors		
9. Position and contact of EMG electrodes		
10. Amount of relaxation/contraction of target muscles		
11. Prior motor activity of the muscle to be tested		
12. Level of relaxation of muscles other than those being tested	N/A	
13. Coil type (size and geometry)		
14. Coil orientation		
15. Direction of induced current in the brain		
16. Coil location and stability (with or without a neuronavigation system)		
17. Type of stimulator used (e.g. brand)		
18. Stimulation intensity		
19. Pulse shape (monophasic or biphasic)		
20. Determination of optimal hotspot		
21. The time between MEP trials		
22. Time between days of testing	N/A	N/A
23. Subject attention (level of arousal) during testing		
24. Method for determining threshold (active/resting)		
25. Number of MEP measures made		
26. Paired pulse only: Intensity of test pulse		
27. Paired pulse only: Intensity of conditioning pulse		
28. Paired pulse only: Inter-stimulus interval		
Methodological Factors section score /20		
Analytical factors		
29. Method for determining MEP size for analysis		
30. Paired pulse only: Size of unconditioned MEP		
Analytical factors section score /2		

Appendix B

Participant Checklist for using Transcranial Magnetic Stimulation

Volunteer Name: _____

Volunteer D.O.B.: _____   Date: _____

Has the volunteer ever been diagnosed with epilepsy or
suffered from epileptic seizures?   Yes / No

Does the volunteer currently take medication that may   Yes / No
reduce their threshold for seizure? (e.g. antidepressants)

Does the volunteer wear a pacemaker?   Yes / No

Does the volunteer have a metal implant in any part of their
body including the head (except tooth fillings)?   Yes / No

Has the volunteer ever had a skull fracture?   Yes / No

Does the volunteer have any known skull defects?   Yes / No

Does the volunteer suffer from recurring headaches?   Yes / No

Has the volunteer suffered a head injury or concussion
within the last 6 months?   Yes / No

Does the volunteer suffer from anxiety associated with
medical procedures, needles etc.?   Yes / No

Checklist completed by: _____

Signature: _____

Appendix C

How Does Pain Influence Movement? A New Research Study at AUT University

The Health and Rehabilitation Research Institute at AUT University (North Shore Campus) is running a series of research studies investigating the effect of pain on the ability to learn new skills. In New Zealand a common cause of chronic pain and disability is arthritis, which is estimated to effect 16% of the population aged fifteen or over, or around 1 in 6 people. The hand is one of the most frequently affected parts of the body. Hand arthritis causes altered muscle strength and control, leading to difficulties with activities requiring fine hand skills, such as fastening buttons or jewellery.

Studies have shown that people with long-term pain conditions often have changes in the part of the brain that controls movement. These pain-related changes in the brain may result in altered movement and a reduced ability to learn new movement tasks. However, it is not yet known how arthritic pain affects the brain or how this may influence skilled movement learning.

A study is about to begin at AUT's Health and Rehabilitation Research Institute investigating how arthritic pain influences the ability to learn a new movement skill by comparing people with painful hand arthritis to people who are pain-free. The study involves measuring the nerve pathways from the brain to the finger muscles using a painless and safe magnetic stimulation technique. This will be followed by a 30 minute skilled learning task, then retesting the nerve pathways to see if they have changed. This study will tell us more about whether arthritis influences movement learning. This may provide us with ideas on how to improve movement learning and function in people with chronic pain conditions such as arthritis.

If a doctor has diagnosed you with arthritis in your hand or fingers causing regular pain we would like hear from you. If you would like to be involved or wish to obtain more information please contact:

Rosalind Parker on 0211247028 or email rosalindsarahparker@gmail.com or call Dr Gwyn Lewis on 921 9999 x7621 or email gwyn.lewis@aut.ac.nz.

Appendix D

VOLUNTEERS WITH HAND ARTHRITIS REQUIRED

How Does Pain Influence Movement?

We are looking for **people with painful hand arthritis** to participate in a research project. The study involves measuring the nerve pathways from the brain to the finger muscles using a painless and safe magnetic stimulation technique. This will be followed by a 30 minute skilled learning task, then retesting the nerve pathways to see if they have changed. This study will tell us more about whether arthritic pain influences movement learning and may help to improve the rehabilitation of people who have chronic pain conditions such as arthritis.

Testing will take approximately **two and a half hours** of your time and will take place at the AUT University North Shore Campus. You will be reimbursed for your time and travel costs.

If you wish to obtain more information about this study, please contact **Rosalind Parker** at the Health and Rehabilitation Research Institute on **0211247028** *rosalindsarahparker@gmail.com* **or Dr Gwyn Lewis (09) 921 9999 ext 7621** *gwyn.lewis@aut.ac.nz*

HEALTH & REHABILITATION RESEARCH INSTITUTE
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Appendix E

Participant Information Sheet

Date Information Sheet Produced:

15 November 2012

Project Title

How does chronic arthritic pain influence movement learning ability?

An Invitation

My name is Rosalind Parker and I work in the Health and Rehabilitation Research Institute at AUT University. I would like to invite you to participate in our research project called *How does chronic arthritic pain influence movement learning ability?* Your participation in this project is voluntary and you may withdraw at any time prior to the completion of data collection.

What is the purpose of this research?

The purpose of this project is to determine if pain due to arthritis influences the ability to learn a new movement skill. People with long-term pain conditions often have abnormal brain excitability and show a reduced ability to learn new movement tasks, but we do not know if these are related. This project will compare people with painful hand arthritis to people who are pain-free to determine if this influences the ability to learn a movement skill involving the hand. The project will be written up for publication in an international journal and will be used for a Masters thesis.

How was I identified and why am I being invited to participate in this research?

You have been identified because you have either arthritis of the hand causing pain of at least 3 out of 10 at least every other day, or you have no pain in your hand and you are matched in age to someone who does have hand pain. You may be excluded from participating if you have a neurological condition, musculoskeletal condition affecting your hand other than arthritis, current pain or a history of chronic pain other than arthritis, metal implants in your head (excluding fillings), skull defects, concussion within the last 6 months, history of epilepsy or seizures, pacemaker or artificial heart valve, history of unexplained recurring headaches, medication that lowers seizure threshold, or pregnancy. You may be excluded from the pain-free group if you have experienced hand pain in the last year.

What will happen in this research?

If you participate in this project you will be asked to attend a single data collection session at the Health and Rehabilitation Research Institute, AUT University North

Shore Campus. During this session, we will assess the excitability of the neural pathways from your brain to your finger muscles and you will perform a finger training task for 25 minutes.

During the session, you will be seated in a comfortable chair and place your hand into a device that allows measurement of the forces generated by your index finger. The excitability of the neural pathways from your brain to your finger muscles will then be assessed. This will involve recording responses in your finger muscles to magnetic stimulation over your scalp and will involve touching your head. Following this you will complete a training task where you twitch your index finger in a specific direction as quickly as possible for 25 minutes. You will be given feedback on your performance during this task. Once you have completed the training, the excitability of the neural pathways from your brain to your finger muscles will be assessed again and then repeated every 10 minutes for 30 minutes.

What are the discomforts and risks?

There is a minimal risk of seizure using magnetic brain stimulation. However, this has been in most cases in people with a history of epilepsy or taking medications which increase the risk of seizures. There is a small risk that you may have a headache following brain stimulation. There is a risk that you may have minor skin irritation over your finger muscles where the electrodes are placed.

How will these discomforts and risks be alleviated?

You will complete a magnetic brain stimulation safety checklist that will be used to screen out anyone with a risk of seizure, such as if you have a family history of seizures or take certain medications. If you frequently experience headaches it is recommended that you do not take part in this project or take preventative medication if headaches are only occasional. The skin over your finger muscles will be thoroughly wiped with alcohol before applying electrodes to reduce the chance of skin irritation. There will also be aloe vera cream available in the laboratory.

What are the benefits?

You will receive no direct benefit from participating in this research. The project outcomes will tell us more about the relationship between pain, brain excitability and movement learning, and may provide us with ideas on how to improve movement learning in people with chronic arthritic pain.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, providing the incident details satisfy the requirements of the law and the Corporation's regulations.

How will my privacy be protected?

You will be given a code upon entry to the study and your name will not be used. The Consent Form that contains your name and your code will be stored in a locked filing cabinet. No individual results will be identifiable in the study.

What are the costs of participating in this research?

The cost of participating in this project will be your time. The data collection session is expected to last approximately 2 hours.

What opportunity do I have to consider this invitation?

You will have one week to consider this invitation after receiving the Information Sheet. We will call you at the end of the week to see if you would like to participate.

How do I agree to participate in this research?

You will need to complete a Consent Form that will be provided at the data collection session. This session will be scheduled after you have told us that you would like to participate.

Will I receive feedback on the results of this research?

You will have the opportunity to receive a one page summary of the study results at the conclusion of the project. There will be a section in the Consent Form to indicate if you would like to receive this summary.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Researcher, Miss Rosalind Parker, rosalindsarahparker@gmail.com, 0211247028.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Dr Rosemary Godbold, *rosemary.godbold@aut.ac.nz* , 921 9999 ext 6902.

Whom do I contact for further information about this research?

Researcher Contact Details:

Miss Rosalind Parker, AUT University North Shore Campus

Ph: 0211247028

Email: rosalindsarahparker@gmail.com

Project Supervisor Contact Details:

Dr Gwyn Lewis, Rm AB112, AUT University North Shore Campus

Ph: 921 9999 x7621

Email: gwyn.lewis@aut.ac.nz

Appendix F

# Consent Form	**AUT** UNIVERSITY TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Project title: **How does chronic arthritic pain influence movement learning ability?**

Project Supervisor: **Dr Gwyn Lewis**

○ I have read and understood the information provided about this research project in the Information Sheet dated 15 November 2012.

○ I have had an opportunity to ask questions and to have them answered.

○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.

○ I do not have a neurological condition, musculoskeletal condition affecting my hand other than arthritis, current pain or a history of chronic pain other than arthritis, metal implants in my head (excluding fillings), skull defects, concussion within the last 6 months, a history of epilepsy or seizures, a pacemaker or artificial heart valve, a history of unexplained recurring headaches, take medication that lowers seizure threshold, or current pregnancy. I have not experienced hand pain in the last year (pain-free participants only).

○ I agree to take part in this research.

○ I wish to receive a copy of the report from the research (please tick one): Yes○ No○

○ I would like to be contacted in regard to other studies conducted at the Health and Rehabilitation Research Institute (please tick one): Yes ○ No ○

Signature: ………………………………………………………………………………………………

Name: ………………………………………………………………………………………………

Contact details (if appropriate):

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………………………………………………………………………………………………

Date:

Appendix G

EDINBURGH HANDEDNESS INVENTORY

Name ....

Date of Birth ....   Sex ....

Please indicate your preference for the use of the left or right hand in the following tasks. If you have such a strong preference for one hand that you would never try to use the other hand unless forced to, place "++" in the column. If you would mostly use one hand but may sometimes use the other hand, place "+" in the column of the hand you would mostly use. If you would perform the task with either hand place "+" in both columns.

Some of the tasks require both hands. In these cases the part of the task, or object, for which hand preference is wanted is specified.

Please try to answer all of the questions. Only leave a blank if you have no experience of the task or object.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking match (match)		
10	Opening jar (lid)		
11	Which foot do you prefer to kick with?		
12	Which eye do you use when using only one?		

Total

Please leave blank   EHI = (R–L)/(R+L)

Appendix H

Short-form McGill Pain Questionnaire 2

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the number that best describes the intensity of each of the pain and related symptoms you felt during ***the past week***. Use **0** if the word **does not describe** your pain or related symptoms.

	None										Worst possible
Throbbing pain	0	1	2	3	4	5	6	7	8	9	10
Shooting pain	0	1	2	3	4	5	6	7	8	9	10
Stabbing pain	0	1	2	3	4	5	6	7	8	9	10
Sharp pain	0	1	2	3	4	5	6	7	8	9	10
Cramping pain	0	1	2	3	4	5	6	7	8	9	10
Gnawing pain	0	1	2	3	4	5	6	7	8	9	10
Hot-Burning pain	0	1	2	3	4	5	6	7	8	9	10
Aching pain	0	1	2	3	4	5	6	7	8	9	10
Heavy pain	0	1	2	3	4	5	6	7	8	9	10

Tender	0	1	2	3	4	5	6	7	8	9	10
Splitting pain	0	1	2	3	4	5	6	7	8	9	10
Tiring-Exhausting	0	1	2	3	4	5	6	7	8	9	10
Sickening	0	1	2	3	4	5	6	7	8	9	10
Fearful	0	1	2	3	4	5	6	7	8	9	10
Punishing-Cruel	0	1	2	3	4	5	6	7	8	9	10
Electric-Shock pain	0	1	2	3	4	5	6	7	8	9	10
Cold-Freezing pain	0	1	2	3	4	5	6	7	8	9	10
Piercing	0	1	2	3	4	5	6	7	8	9	10
Pain caused by light touch	0	1	2	3	4	5	6	7	8	9	10
Itching	0	1	2	3	4	5	6	7	8	9	10
Tingling or "Pins and Needles"	0	1	2	3	4	5	6	7	8	9	10
Numbness	0	1	2	3	4	5	6	7	8	9	10

Appendix I

AUSCAN Osteoarthritis Hand Index

Name: **Date:**

Pain Subscale

Please rate your pain you have experience in your hand in the past 48 hours:

	No pain										Extreme pain
1. At rest	0	1	2	3	4	5	6	7	8	9	10
2. Gripping	0	1	2	3	4	5	6	7	8	9	10
3. Lifting	0	1	2	3	4	5	6	7	8	9	10
4. Turning	0	1	2	3	4	5	6	7	8	9	10
5. Squeezing	0	1	2	3	4	5	6	7	8	9	10

Stiffness Subscale

6. Please rate your stiffness after first wakening in the morning in the past 48 hours:

No stiffness										Extreme stiffness
0	1	2	3	4	5	6	7	8	9	10

Physical Function Subscale

Please rate your difficulty doing the following activities due to your hand in the past 48 hours:

	No difficulty									Extreme difficulty	
7. Turning taps/faucets on	0	1	2	3	4	5	6	7	8	9	10
8. Turning a round doorknob or handle	0	1	2	3	4	5	6	7	8	9	10
9. Doing up buttons	0	1	2	3	4	5	6	7	8	9	10
10. Fastening jewellery	0	1	2	3	4	5	6	7	8	9	10
11. Opening a new jar	0	1	2	3	4	5	6	7	8	9	10
12. Carrying a full pot with one hand	0	1	2	3	4	5	6	7	8	9	10
13. Peeling vegetables/fruits	0	1	2	3	4	5	6	7	8	9	10
14. Picking up large heavy objects	0	1	2	3	4	5	6	7	8	9	10
15. Wringing out wash cloths	0	1	2	3	4	5	6	7	8	9	10

Appendix J

TMS Checklist for Does chronic arthritic pain influence corticomotor excitability

Participant factors

Age of subjects Controlled (matched) and reported

Gender of subjects Controlled (matched) and reported

Handedness of subjects Controlled (matched) and reported

Subjects prescribed medication Reported

Use of CNS active drugs (e.g. anti-convulsants) Controlled and reported

Presence of neurological/ psychiatric disorders when studying healthy subjects Controlled and reported

Any medical conditions Reported

History of specific repetitive motor activity Controlled (matched) and reported

Methodological factors

Position and contact of EMG electrodes Controlled and reported

Amount of relaxation/contraction of target muscles Controlled and reported

Prior motor activity of the muscle to be tested Controlled and reported

Level of relaxation of muscles other than those being tested Controlled

Coil type (size and geometry) Controlled and reported

Coil orientation Controlled and reported (45 degrees)

Direction of induced current in the brain Controlled and reported

Coil location and stability (with or without a neuronavigation system) Controlled and reported

Type of stimulator used (e.g. brand) Controlled and reported

Stimulation intensity Controlled and reported

Pulse shape (monophasic or biphasic) Controlled and reported

Determination of optimal hotspot Controlled and reported

The time between MEP trials Controlled and reported

Time between days of testing N/A

Subject attention (level of arousal) during testing Controlled and reported

Method for determining threshold (active/resting) Controlled and reported

Number of MEP measures made Controlled and reported

Paired pulse only: Intensity of test pulse Controlled and reported

Paired pulse only: Intensity of conditioning pulse Controlled and reported

Paired pulse only: Inter-stimulus interval Controlled and reported

<u>**Analytical factors**</u>

Method for determining MEP size during analysis Controlled and reported

Size of unconditioned MEP Controlled and reported