Exploring The Role of Interhemispheric Inhibition in Musculoskeletal Pain

by

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I dedicate this thesis to my mum

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In The Name of God, The Most Gracious, The Most Merciful

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STATEMENT OF AUTHENTICATION

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in text. I hereby declare that I have not submitted this material, either in full report or in part, for a degree at this or any other institution.

Ghufran Alhassani

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PUBLICATIONS, PRESENTATIONS, AND AWARDS

Journal publications

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Papers from this thesis currently under review

Alhassani G, Clothier PJ, Liston MB, Schabrun SM. Interhemispheric inhibition between primary motor cortices is not altered in individuals with chronic lateral epicondylalgia. Submitted and under review in The Journal of Pain.

Other related publications

Chang WJ, O'Connell NE, Beckenkamp PR, **Alhassani G**, Liston MB, Schabrun SM. Altered Primary Motor Cortex Structure, Organization, and Function in Chronic Pain: A Systematic Review and Meta-Analysis. The Journal of Pain. 2018;19(4):341-59 (Q1, Impact Factor = 5.383). https://doi.org/10.1016/j.jpain.2017.10.007

Peer-reviewed Conference presentations

Alhassani G, Clothier PJ, Liston MB, Schabrun SM. 2022. Individuals with chronic lateral epicondylalgia display normal interhemispheric inhibition, *International Association for the Study of Pain world congress on Pain,* Toronto, Canada, 19- 23 September.

Alhassani G, Liston MB, Clothier PJ, Schabrun SM. 2021. The effect of acute muscle pain on interhemispheric inhibition between primary sensory cortices and sensorimotor function. *Virtual Australian Pain Society 41st Annual Scientific meeting,* 19-20 April.

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Alhassani G, Liston MB, Schabrun SM. 2019. Bilateral symptom development in unilateral musculoskeletal conditions. *World Confederation of Physical Therapy Congress*, Geneva, Switzerland, 10-13 May.

Alhassani G, Liston MB, Schabrun SM. 2018. Reduced interhemispheric inhibition in the primary motor cortex in response to acute muscle pain. *Australian Pain Society 38th and New Zealand Pain Society Conjoint Annual Scientific Meeting*, Sydney, Australia, 8-11 April.

Grants and awards arising from this thesis

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LIST OF ABBREVIATIONS

AMT	Active motor threshold
BOLD	Blood-oxygen-level-dependent
CBF	Cerebral blood flow
cm	Centimetre
CNS	Central nervous system
CPM	Conditioned pain modulation
CRPS	Complex regional pain syndrome
CS	Conditioning Stimulus
ECRB	Extensor carpi radialis brevis
EEG	Electroencephalography
EMG	Electromyography
FDI	First dorsal interosseous
FHD	Focal hand dystonia
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
IASP	International Association for the Study of Pain
ICI	Intracortical inhibition
ICF	Intracortical facilitation
IHI	Interhemispheric inhibition
ISI	Interstimulus interval
iSP	Ipsilateral silent period
LBP	Low back pain
LE	Lateral epicondylalgia

LICI	Long-interval intracortical inhibition
LIHI	Long-latency interhemispheric inhibition
M1	Primary motor cortex
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
MVC	Maximum voluntary contraction
ms	Millisecond
n	Sample size
p	P-value
PET	Positron emission tomography
PMNSEP	Paired median nerve somatosensory evoked potential
PPT	Pressure pain threshold
QST	Quantitative sensory testing
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
S1	Sensory motor cortex
SD	Standard deviation
SEP	Sensory evoked potential
SICI	Short-interval intracortical inhibition
SIHI	Short-latency interhemispheric inhibition
SMD	Standardised mean difference
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TS	Test stimulus

ABSTRACT

Musculoskeletal conditions are a leading contributor to disability worldwide. Pain and sensorimotor dysfunction are common symptoms of musculoskeletal conditions that affect an individuals' quality of life and contribute to the associated psychological and economic burden. In some unilateral musculoskeletal conditions, sensorimotor dysfunction such as increased sensitivity to heat and mechanical stimulation, and reduced grip force, present at the unaffected side despite an absence of evidence of any peripheral pathology on this side (Heales et al., 2014). While bilateral sensorimotor dysfunction has been identified in some unilateral musculoskeletal conditions, the mechanism underlying this phenomenon has yet to be elucidated. One mechanism that could underpin this phenomenon is altered interhemispheric inhibition (IHI).

Interhemispheric inhibition allows one hemisphere of the brain to inhibit the opposite hemisphere via a transcallosal pathway. This mechanism can be measured using transcranial magnetic stimulation by applying a conditioning stimulus to one hemisphere which inhibits the contralateral hemisphere (Daskalakis et al., 2002). Normal modulation of IHI allows for unilateral processing, inhibiting the transfer of motor or sensory information to the opposite cortical hemisphere, thus preventing mirroring effects of the contralateral limb. Research investigating IHI has been conducted in neurological conditions such as stroke (Duque et al., 2005; Liepert et al., 2000; Murase et al., 2004) and focal hand dystonia (Beck et al., 2009; Nelson et al., 2010; Sattler et al., 2014). These studies provide preliminary evidence that impaired IHI is associated with sensorimotor deficits. For example, in some individuals with stroke, increased IHI from the unaffected primary motor cortex (M1) to the stroke affected M1 interferes with adaptive recovery of the lesioned area and of the paretic limb. In focal hand dystonia, decreased IHI from the affected to unaffected M1 is observed and this decrease is

associated with mirror movements of the unaffected limb. Musculoskeletal conditions demonstrate similar clinical features to those with neurological conditions such as ongoing pain, altered sensorimotor function, and the development of sensorimotor dysfunction at the unaffected limb. Based on the evidence from neurological conditions, a relationship between altered IHI and bilateral sensorimotor dysfunction during acute and chronic unilateral musculoskeletal pain is plausible.

Only one previous study has investigated IHI in musculoskeletal pain. Schabrun et al. (2016) demonstrated altered IHI between the primary motor cortices (M1s) in response to experimentally induced unilateral sustained elbow pain. That study showed a reduction in IHI from the affected (corresponding to the painful muscle) to the unaffected M1 that was associated with the development of bilateral sensorimotor dysfunction. Whilst the findings from Schabrun et al. (2016) suggest altered IHI may be a mechanism underpinning the development of bilateral sensorimotor dysfunction in the transition to sustained pain, no published studies have investigated IHI when musculoskeletal pain is acute (lasting minutes to hours) or when pain is chronic (lasting > 3 months). Therefore, the broad aim of this thesis was to: i) investigate whether IHI is altered in response to acute and chronic unilateral musculoskeletal pain; and ii) determine whether a relationship exists between altered IHI (if present) and the development of bilateral symptoms.

Assessment of IHI between primary motor and sensory cortices in the acute stage of musculoskeletal pain would provide insight into whether IHI is altered in response to short-lasting muscle pain and whether there is an association between IHI and bilateral sensorimotor dysfunction soon after pain onset. However, obtaining data in clinical populations soon after pain onset is challenging due to delays in individuals receiving medical attention or diagnosis and in identifying individuals for research studies. An alternate solution is to use experimental pain models that allow for the collection of data before, during, and after the induction of pain.

Thus, Studies 1 and 2 in this thesis used an experimental pain model (intramuscular injection of hypertonic saline) to investigate IHI in the acute stage of pain. Study 3 used a clinical lateral epicondylalgia population to investigate IHI in the chronic stage of pain.

In Study 1 (Chapter 2), short and long-latency IHI from the affected M1 (corresponding to the painful muscle) to the unaffected M1 was examined in response to experimentally induced unilateral acute muscle pain in 20 healthy individuals, before, immediately after the resolution of pain, and 30 minutes following the resolution of pain. This study also assessed pressure pain thresholds at the affected and unaffected limb to investigate the presence of bilateral changes in sensorimotor function. Findings demonstrated a reduction in short and long latency IHI from the affected to the unaffected M1 immediately after the resolution of pain that persisted for 30 minutes. Increased sensitivity to pressure at the affected and notably, at the unaffected limb was observed despite the absence of pain on the unaffected side. These findings suggest that a reduction in IHI from the affected to the unaffected M1 may have relevance for the development of sensorimotor dysfunction in the unaffected hand.

Study 2 (Chapter 3) investigated IHI from the affected primary sensory cortex (S1) (corresponding to the painful muscle) to the unaffected S1 in response to experimentally induced unilateral acute muscle pain. In 21 healthy individuals, IHI was examined before, immediately after the resolution of pain, and 30 minutes following the resolution of pain. Pressure pain thresholds were assessed at the affected and unaffected limbs. Contrary to our hypothesis, IHI between S1s was unaltered in response to unilateral acute muscle pain at any time point. However, decreased pressure pain thresholds were observed at the affected and unaffected limbs 30 minutes following the resolution of pain. These findings suggest that altered IHI between S1s may not be associated with the development of bilateral sensorimotor dysfunction in acute muscle pain.

Study 3 (Chapter 4) investigated short and long-latency IHI from the affected M1 (corresponding to the painful side) to the unaffected M1 in 20 individuals with chronic lateral epicondylalgia (LE) compared to 20 healthy controls. Sensorimotor function including pressure pain thresholds, grip strength, two-point discrimination and temporal summation was assessed bilaterally. The mean pain intensity in the LE group on the day of testing was 3 ± 1.8 out of 10 points on the numerical rating scale. Findings demonstrated no difference in short and long-latency IHI from the affected to unaffected M1 between individuals with LE and healthy controls. No differences in sensorimotor function (for either the affected or unaffected side) were observed between groups. These findings suggest that IHI between M1s is not altered in a group of individuals with chronic LE who did not display significant sensorimotor dysfunction when compared with healthy controls.

In summary, the body of work in this thesis provides an original contribution to the field of musculoskeletal pain that deepens our understanding of IHI, and its potential association with changes in sensorimotor function in the unaffected limb, in unilateral conditions. Study 1 demonstrated a reduction in IHI from the affected to unaffected M1 but no change in IHI from the affected to unaffected S1 was observed in Study 2. In both studies, increased sensitivity to pressure was observed on the affected and unaffected sides. No change in IHI between M1s, and no differences in sensorimotor function were observed between individuals with chronic LE and healthy controls in Study 3.

Taken together, the findings presented in this thesis suggest that IHI between M1s is reduced in response to acute muscle pain and altered IHI could contribute to the development of bilateral sensorimotor symptoms soon after pain onset. Conversely, IHI between S1s is preserved in response to acute muscle pain. In a clinical chronic musculoskeletal pain population, IHI is also preserved. However, further research is needed to determine whether

the degree of change in IHI is related to various features of clinical pain such as pain severity, or the severity of bilateral sensorimotor dysfunction.

The studies in this thesis are amongst the first to investigate: i) IHI in response to musculoskeletal pain of varying durations; and ii) the relationship between altered IHI and the development of bilateral sensorimotor dysfunction. Longitudinal studies that follow individuals from an initial episode of acute musculoskeletal pain to recovery, or to the development of chronic musculoskeletal pain, are required to further explore the relationship between IHI and the development of bilateral sensorimotor symptoms in unilateral musculoskeletal pain conditions.

CHAPTER 1	**Introduction and Literature review**
CHAPTER 2	IHI between primary motor cortices in response to acute muscle pain
CHAPTER 3	IHI between primary sensory cortices in response to acute muscle pain
CHAPTER 4	IHI between primary motor cortices in individuals with lateral epicondylalgia
CHAPTER 5	Discussion and Conclusion

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

1.1 Statement of the problem

Musculoskeletal disorders affect approximately 1.71 billion people worldwide and are the leading contributor to disability (Cieza et al., 2021). In Australia, musculoskeletal conditions are the most common chronic condition, affecting 29% of the population (Health & Welfare, 2020a). Pain is a common symptom of musculoskeletal conditions presenting on the affected side of the body (i.e., unilateral) that can be of short or long-term duration. Musculoskeletal pain disorders impact an individuals' quality of life, which affects their ability to work, potentially contributing to psychological disorders such as anxiety and depression, and in turn add to the psychosocial burden of musculoskeletal pain (Beck et al., 2011). In addition, musculoskeletal disorders are one of the costliest health problems worldwide, with an economic burden second only to cancer (Beck et al., 2011; Holden et al., 2011; Sharma et al., 2016). For example, the total cost of chronic musculoskeletal pain disorders, including direct health care costs, loss of productivity and reduced quality of life, exceeds AUD $55 billion annually in Australia alone (Arthritis and Osteoporosis Victoria, 2013).

Some individuals with musculoskeletal pain disorders experience sensorimotor dysfunction, such as increased sensitivity to heat and mechanical stimulation, altered force production, and altered movement patterns and postures (Hodges & Falla, 2015; Lund et al., 1991; Sterling et

al., 2001; Tsao et al., 2008). Indeed, some individuals with unilateral musculoskeletal pain conditions develop bilateral sensorimotor dysfunction in the absence of the condition on the unaffected side (Heales et al., 2014). One such example is lateral epicondylalgia (LE), commonly known as tennis elbow, which is a musculoskeletal condition of the upper limb affecting 1 to 3% of the population (Shiri et al., 2006). Individuals with LE exhibit reduced grip strength, increased upper limb reaction times, reduced speed of movement and decreased pressure and thermal pain thresholds at the affected side (Coombes et al., 2012b; Pienimäki et al., 2002; Chourasia et al., 2012; Bisset et al., 2006b). In some individuals with LE, these symptoms will develop at the unaffected side (Bisset et al., 2006b; Heales et al., 2014; Pienimaki et al., 1997). Despite research identifying these bilateral deficits, it is unknown how sensorimotor symptoms develop on the unaffected side in LE and other musculoskeletal conditions. The observations of bilateral sensorimotor symptoms suggest that this phenomenon is complex and cannot be explained by peripheral mechanisms alone, suggesting it may be mediated at the level of the central nervous system.

One potential mechanism that may underpin bilateral sensorimotor development is altered interhemispheric inhibition. Interhemispheric inhibition (IHI) is a neurophysiological mechanism that is mediated by transcallosal fibres of the corpus callosum where one hemisphere inhibits activity in the opposite hemisphere (Reis et al., 2008). Normal modulation of IHI allows for unilateral processing preventing unwanted mirror movements of the opposite side. Only one previously published study has investigated the relationship between IHI and sensorimotor dysfunction of the unaffected side in an induced pain model (Schabrun et al., 2016). The authors demonstrated that IHI was decreased from the affected primary motor cortex (M1) (corresponding to the painful side) to the unaffected M1 (corresponding to the non-painful side) four days following repeated intramuscular injection of nerve growth factor into the extensor carpi radialis brevis muscle to induce progressively developing sustained

muscle pain. The decrease in IHI was associated with sensorimotor dysfunction of increased sensitivity to pressure pain thresholds observed in the unaffected limb. This finding suggests a relationship between altered IHI and sensorimotor dysfunction on the unaffected side in musculoskeletal pain. However, it remains unknown how soon after pain onset IHI is altered or how IHI is altered in chronic musculoskeletal pain and whether this is related to sensorimotor changes of the unaffected side. No data are yet available on the impact of acute pain on IHI in the M1, nor on the primary sensory cortex. In addition, no data are currently available on the impact of chronic musculoskeletal pain on IHI.

Thus, it remains unclear what the temporal profile of IHI is in response to musculoskeletal pain and how this relates to the development of bilateral sensorimotor symptoms. Therefore, this thesis sought to answer the following questions:

1. Is IHI between M1s altered in response to acute muscle pain and is this associated with changes in sensorimotor function of the unaffected side?
2. Is IHI between primary sensory cortices altered in response to acute muscle pain and is this associated with changes in sensorimotor function of the unaffected side?
3. Do individuals with chronic LE exhibit altered IHI between M1s when compared to healthy controls?

This thesis is comprised of five chapters, beginning with an introduction (Chapter 1) that presents a review of the literature pertaining to the research questions. This is followed by three studies (Chapters 2 - 4) and a discussion (Chapter 5) that evaluates the findings, presents the research implications, makes recommendations for future research, and acknowledges the limitations of the work in this thesis. An outline of the thesis chapters and studies conducted is provided in Figure 1.1.

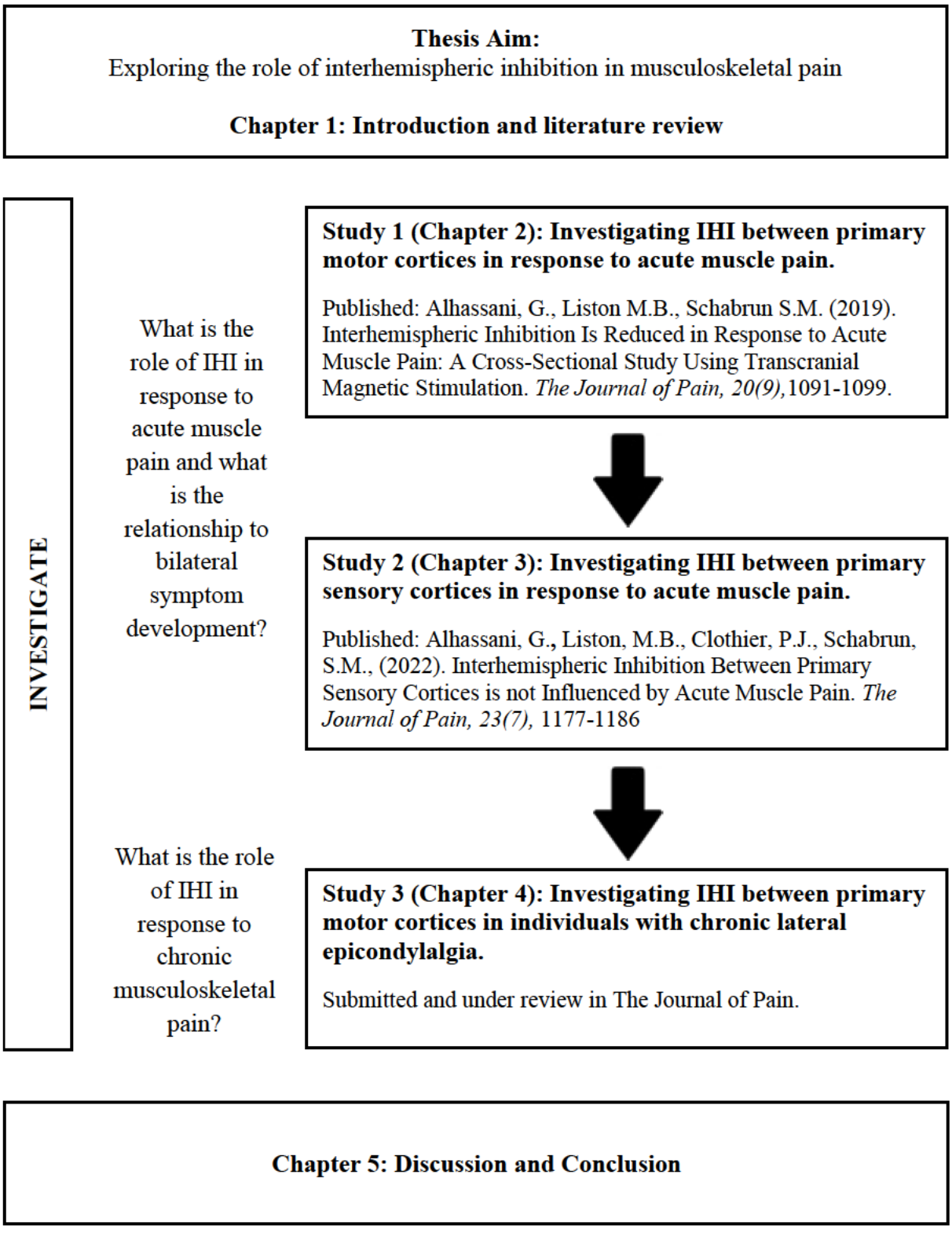

Figure 1.1. Schematic representation of the thesis structure. The flow of thesis chapters and experimental studies forming the thesis.

LITERATURE REVIEW

This section of the chapter provides an overview of the literature on musculoskeletal pain and the concept of IHI, a neurophysiological mechanism hypothesised to underpin bilateral symptom development in unilateral musculoskeletal pain conditions, such as LE. First, musculoskeletal pain is introduced and discussed, followed by a discussion of the pathophysiology of LE. A review of the literature on IHI is then presented with a review of the methods to assess IHI. This is followed by a review that details IHI in the healthy nervous system, its pathology, and presentation within musculoskeletal conditions. Finally, the chapter ends with a rationale and aim for each study included in the thesis.

1.2 Musculoskeletal pain disorders

Musculoskeletal disorders have been defined as injuries of the muscles, ligaments, and related soft tissue (Kulin & Reaston, 2011; Perrot et al., 2019). Worldwide, musculoskeletal disorders are an increasing public health problem affecting approximately 1.7 billion people (Cieza et al., 2021) and were the highest contributor to disability in 2017 (Hay et al., 2017). In Australia, musculoskeletal disorders, such as back pain, arthritis and osteoporosis, are the most common chronic conditions with 29% of the population reporting at least one musculoskeletal disorder in 2017-2018 (Health & Welfare, 2020a).

A primary symptom of most musculoskeletal disorders is pain. Pain has been defined by the International Association for the Study of Pain (IASP) as "an experience typically caused by, or resembling that caused by, actual or potential tissue injury" (Raja et al., 2020). Pain is typically described in terms of duration, and is classified as either acute, subacute, or chronic. 'Acute pain' is defined as a short-lasting physiological response to a noxious stimulus that is actually or potentially damaging to tissues (Kent et al., 2017; Schug, 2011), and of a duration lasting less than six weeks (Carlson & Carlson, 2011; Islam & Frey, 2020). Acute pain acts as a protective mechanism against further pain, injury, or both (Hodges & Tucker, 2011; Kent et al., 2017). Subacute pain is classified as the presence of pain beyond the duration of acute pain, lasting greater than six weeks but not extending past three months (Carlson & Carlson, 2011; Mariano et al., 2018). Pain that lasts beyond expected tissue healing times (> 3 months duration) is defined as 'chronic pain' (Treede et al., 2015).

Musculoskeletal pain impacts quality of life with lasting physical, psychological, social, and financial impacts on individuals, communities, and the healthcare system (Briggs et al., 2016; Health & Welfare, 2019, 2020b). In 2018-19, the estimated expenditure associated with musculoskeletal pain was $14 billion accounting for 10.3% of disease related expenditure in

Australia (Health & Welfare 2019). However, this figure does not include direct costs from outside the healthcare sector or indirect costs due to illness. This is evidenced in a 2012 report that when accounted for the estimated total cost of chronic musculoskeletal pain disorders, including direct health care costs, loss of productivity and reduced quality of life, equalled AUD $55.1 billion annually in Australia alone (Arthritis and Osteoporosis Victoria, 2013). The cost of productivity loss further increases when individuals with musculoskeletal pain experience poor mental health such as depression, anxiety, and psychological distress (Beck et al., 2011; Sharma et al., 2016). This has a greater impact on work-related absences (absenteeism) and decreased productivity while at work (presenteeism) (Holden et al., 2011), with even minor levels of depression associated with decrements in work function (Beck et al., 2011).

1.2.1 Treatments for musculoskeletal pain

Although musculoskeletal pain is a major health issue with lasting physical, psychological, social, and financial impacts, there are few effective treatment strategies. For example, pharmacological treatments such as non-steroidal anti-inflammatory drugs and opioid-based medications are discouraged or prescribed with caution, and are found to have no added benefit to the treatment of low back pain, the most common chronic musculoskeletal condition (Lin et al., 2020). Pharmacological treatments are also associated with negative side effects such as gastrointestinal (Sostres et al., 2010) and cardiovascular complications (Antman et al., 2007), as well as the risk of medication abuse or addiction (Cicero et al., 2005). Consequently, non-pharmacological treatments are considered to minimise the use of pharmacological treatments.

Non-pharmacological treatment strategies have been recommended for the management of musculoskeletal pain. These include treatment strategies such as patient education, acupuncture, ultrasound, transcranial electrical nerve stimulation and exercise amongst others

(El-Tallawy et al., 2021). However, numerous non-pharmacological strategies have demonstrated limited effectiveness in the management of musculoskeletal pain. For example, clinical practice guidelines recommend exercise-based therapy as the most promising strategy to treat musculoskeletal conditions such as chronic low back pain, knee osteoarthritis and neck pain, yet at best, the effect sizes are moderate (Geneen et al., 2017; Puljak & Arienti, 2019) with compliance to exercise complex and multifactorial (Campbell et al., 2001).

The limited effectiveness of current treatments shows the complexity of musculoskeletal pain. One area that has received increased attention in recent years in clinical practice and research is the evidence surrounding physiological mechanisms driving musculoskeletal pain. Understanding the neurophysiological mechanisms underpinning musculoskeletal pain can help us identify individuals who may transition from acute to chronic pain development following a musculoskeletal injury. Evidence suggests that altered primary motor and sensory cortical mechanisms play a role in acute and chronic musculoskeletal pain. Thus, the following section discusses evidence of primary motor and sensory system changes in musculoskeletal pain.

1.2.2 Central nervous system involvement in musculoskeletal pain:

Over the past 20-30 years there has been a plethora of neurophysiological research dedicated to explaining and understanding musculoskeletal pain (Arendt-Nielsen et al., 2011; Chang et al., 2018; Flor et al., 1997; Kuner & Flor, 2016; Schaible, 2007; Tsao et al., 2011; Wright, 1999). The vast array of evidence has led to the widely accepted conclusion that maladaptive central nervous system changes occur in the presence of musculoskeletal pain conditions (Snodgrass et al., 2014). The ability of the central nervous system (CNS) to undergo structural and functional changes is a process termed neuroplasticity (Passmore et al., 2014). However, maladaptive plasticity is suggested to contribute to the symptoms of pain and sensorimotor dysfunction in musculoskeletal conditions (Burns et al., 2016b; Chang et al., 2018; Di Pietro

et al., 2013; Flor et al., 1997; Kuner & Flor, 2016; Schabrun et al., 2016; Vartiainen et al., 2009). The body of research investigating the structural and functional changes of the brain has identified maladaptive cortical changes within regions of the brain, such as the primary motor (M1) and sensory cortices (S1) at both the acute and chronic stages of musculoskeletal pain (Treede et al., 2015). To investigate cortical reorganisation in musculoskeletal pain, both experimental pain models and clinical pain populations can be used.

Experimental pain models

The use of experimental pain models to induce muscle pain allows for the investigation of pain mechanisms (Reddy et al., 2012). Such experimental pain research allows for a controlled pain stimulus of varying duration to assess the nociceptive system before, during, and after episodes of pain, while assessing biopsychosocial factors via qualitative methods (Arendt-Nielsen & Yarnitsky, 2009). The use of acute muscle pain models to isolate muscle pain mechanisms without the confounding factors of clinical pain (e.g. psychological factors and medication use), minimises participant heterogeneity (Svensson & Arendt-Nielsen, 1995). Bridging the gap between the science of pain and clinical application is therefore possible.

Acute experimental pain

Endogenous and exogenous methods of experimental muscle pain induction in humans are commonly used by researchers. Endogenous methods induce pain by natural methods such as ischemia and exercise, while exogenous methods induce pain using external interventions such as electrical, mechanical, chemical, and thermal stimulation as presented in Table 1.1 (Graven-Nielsen & Arendt-Nielsen, 2003; Reddy et al., 2012). However, these methods are not without limitations. Limitations include the non-specificity to muscles with potential activation of skin, joints and other tissues with pain models such as ischemia, mechanical and thermal stimulation, and the concurrent activation of muscle twitching by use of electrical stimulation (Graven-

Nielsen & Arendt-Nielsen, 2003; Reddy et al., 2012). Therefore, non-limiting experimental pain that mimics acute musculoskeletal pain is required to better examine and understand the development of musculoskeletal pain. One such experimental pain model is the chemical induction of muscle pain via hypertonic saline.

Table 1.1. Experimental pain models used to induce muscle pain in humans

Experimental pain model	Description
Ischemia	Tonic pain induced via application of torniquet ⟶ induced widespread pain
Exercise	Induced via eccentric muscle work ⟶ induced delayed onset muscle soreness with peak soreness after 24 to 48 hours
Mechanical	Induced via application of pressure algometry ⟶ induces pain in skin and muscle
Chemical	Intramuscular injections of algesic substances to induce muscle pain ⟶ induces muscle hyperalgesia via activation of C fibres
Electrical	Induced via intramuscular electrical stimulation ⟶ induces muscle pain via activation of muscle nociceptor afferents
Thermal	Induced via heat or cold through isotonic saline at different temperatures ⟶ activates nociceptors in deeper structures targeting muscle; Induced via contact heat or cold stimulation ⟶ induces muscle pain by activation of A-delta and C fibres.

Injection of hypertonic saline to induce acute muscle pain

Hypertonic saline is a type of chemical stimulation that is used to induce muscle pain and is comparable to clinical acute muscle pain (Gibson et al., 2006; Slater et al., 2003). Injection of hypertonic saline is deemed safe as minimal side effects have been reported and it does not cause muscle toxicity (Svendsen et al., 2005). This model produces short-lasting, high pain intensity with pain qualities described as aching, drilling, and taut as well as producing referred pain, cutaneous, muscular and sensory changes comparable to clinical acute muscle pain (Graven-Nielsen et al., 1997). The saline solution is commonly administered as a bolus injection producing pain that rises rapidly, lasts approximately 10 minutes and then pain

completely resolves (Jensen & Norup, 1992). The mechanism of action of hypertonic saline is thought to occur by activation of groups III and IV nociceptive afferents (Kumazawa & Mizumura, 1977) and the release of glutamate (Gibson et al., 2009), which contributes to nociception and hyperalgesia.

Hypertonic saline provides a clinically relevant model and nociceptive method of pain induction, while also having the same effects of pain on motor performance (Hodges et al., 2003; Stohler & Kowalski, 1999) and exhibiting local and referred pain patterns (Arendt-Nielsen & Graven-Nielsen, 2008; Kellgran, 1938). In referred pain areas following injection, somatosensory modulations have been observed such as decreased sensitivity to light touch and thermal hypoesthesia (Leffler et al., 2000b), consistent with acute clinical muscle pain. Hypertonic saline injection has demonstrated reproducible intra-individual scores for pain intensity, quality, and distribution, with cutaneous changes also demonstrated (Graven-Nielsen et al., 1997).

Whilst hypertonic saline provides a suitable model to investigate acute muscle pain, some potential limitations do exist. The main limitations are controlling parameters such as pain intensity, duration, and rate of administration with a bolus injection. To counteract this, infusion of hypertonic saline by mechanical infusion pumps, whereby the rate of infusion is controlled, allows for standardisation of these parameters (Graven-Nielsen et al., 1997). Another limitation is that hypertonic saline is associated with interindividual variability (Reddy et al., 2012), possibly due to the distribution of pain and individually perceived pain intensity. However, hypertonic saline demonstrates good intra-individual reproducibility with reproducible scores of pain intensity, quality, distribution and cutaneous changes over time (Graven-Nielsen et al., 1997). A further limitation is injection of surrounding tissues besides the intended muscle, such as fascia. This may be mitigated by performing ultrasound guided injection (Tsao et al., 2010).

Despite the limitations identified above, hypertonic saline has gained the most acceptance as an experimental pain model to induce acute muscle pain due to its short-lasting nature and quality to mimic clinical acute musculoskeletal pain (Graven-Nielsen et al., 1997). The qualities of hypertonic saline provide a realistic model to investigate the onset and resolution of muscle pain while allowing for baseline data to be collected prior to pain onset and controlling for confounders that compromise data quality.

Cortical reorganisation in response to acute experimental muscle pain

Experimental pain models have been used extensively to explore corticomotor reorganisation in response to acute pain. In acute pain, data from transcranial magnetic stimulation (TMS) and electroencephalography (EEG) studies have shown reduced S1 and corticomotor excitability during and following the resolution of acute experimental muscle pain (Burns et al., 2016b). A systematic review of acute experimental pain models (pain lasting minutes to hours) acquired data from 25 studies on 257 participants that used TMS, EEG and functional magnetic resonance imaging (fMRI) (Burns et al., 2016b). The most common method of inducing experimental pain was hypertonic saline (n = 17 studies). The findings of the review by Burns et al. (2016b) demonstrated reduced S1 and M1 excitability contralateral to the painful and pain-free muscles in the same body segment during and post-pain resolution compared to baseline. The reductions in excitability were hypothesised to reflect a defensive adaptive response to protect the injured body part from the threat of further pain and / or injury. Evidence for reduced corticomotor excitability is further supported by a recent systematic review by Chowdhury et al. (2022) of 49 studies that showed corticomotor excitability is reduced in response to acute experimental pain (minutes to hours) and this was associated with lower pain severity, hypothesised to be a beneficial short-term strategy required for muscle adaptation (Chowdhury et al., 2022).

Limited evidence is available from the review by Burns et al. (2016b) for the effect of acute pain on the ipsilateral hemisphere derived from fMRI studies only. The findings provided evidence of a bilateral reduction in regional cerebral blood flow (rCBF) at S1, which negatively correlated with pain ratings (Owen et al., 2010), and increased blood-oxygen-level-dependent (BOLD) contrast bilaterally at S1 (Nash et al., 2010a; Nash et al., 2010b; Niddam et al., 2002) and bilateral deactivation of S1/M1 activity (Loggia et al., 2012). However, findings from this systematic review need to be interpreted carefully. Due to inconclusive findings of synthesis of fMRI data and the lack of studies investigating excitability of ipsilateral M1/S1, insufficient evidence is available to draw a definitive conclusion regarding the effect of acute experimental pain on the ipsilateral hemisphere in M1 and S1.

Cortical reorganisation in clinical chronic musculoskeletal pain

Organisational, structural, and functional changes of M1 in chronic musculoskeletal pain have been explored. A systematic review by Chang et al. (2018) identified studies in musculoskeletal pain that used TMS to measure corticomotor excitability by eliciting motor evoked potentials (MEPs). The conditions evaluated included fibromyalgia, low back pain (LBP), knee pain, shoulder pain, LE, neck pain, osteoarthritis, rheumatoid arthritis and myofascial pain. Data demonstrated no difference in corticomotor excitability between individuals with and without chronic pain (resting motor threshold: SMD 0.01 [95% CI -0.29 to 0.31]). There was no further difference observed during subgroup analysis for any of the musculoskeletal conditions included. These findings are consistent with an earlier review of chronic pain that also showed no significant difference in corticomotor excitability between those with and without chronic pain (Parker et al., 2016). Such findings contrast with those observed in acute pain and suggest corticomotor excitability is intact in chronic musculoskeletal pain populations.

Whilst no changes in corticomotor excitability have been shown, maladaptive corticomotor reorganisation has been demonstrated in chronic musculoskeletal pain. For example, in chronic unilateral LE, increased cortical excitability of muscle representations, larger overlapping of the centre of gravity (the amplitude-weighted centre of a M1 representation) of muscle representations, and a reduced number of discrete peaks (representing the areas of greatest excitability) of the muscle representations are demonstrated. Further, these changes are positively associated with pain severity (Schabrun et al., 2015a). Similarly, fewer discrete peaks are demonstrated in low back pain (Schabrun et al., 2017a) and in patellofemoral joint pain (Te et al., 2017). However, conflicting evidence exists for map volume (the total excitability of an entire representation). Increased map volume is demonstrated in the transverse abdominis muscles in low back pain (Tsao et al., 2008) and the wrist extensors in LE (Schabrun et al., 2015a). In contrast, reduced map volume in of deep multifidus and longissimus erector spinae muscles in LBP (Tsao et al., 2011) and quadriceps in patellofemoral pain (Te et al., 2017) have also been demonstrated. These differences are suggested to be due to sample sizes and methodology including coil size, electromyography electrodes and grid size used to measure the map. Despite this, it is hypothesized that overlap of muscle representations and reductions in discrete peaks are associated with the severity of pain and the degree of movement deficits, such as postural control deficits in LBP (Tsao et al., 2008). Whilst this is beneficial in the short-term as a protective mechanism, in the long term this may contribute to the maintenance of maladaptive motor strategies and movement dysfunction in musculoskeletal pain.

Primary sensory cortex structural and organisational changes have been demonstrated in chronic musculoskeletal pain (Table 1.2). For example, the S1 representation of the back in chronic LBP is shifted more than 2.5 cm medially towards the leg representation with a significant relationship between the degree of S1 reorganisation and duration of pain (average

duration of pain 12.8 years) (Flor et al., 1997). Enhanced S1 excitability characterised by a larger sensory evoked potential (SEP) component 80 milliseconds after stimulation in chronic LBP has been observed and this was positively correlated with increased sensitisation to painful stimuli (Diers et al., 2007). In complex regional pain syndrome (CRPS), it is widely accepted that S1 reorganisation characterised by shrinkage of representation contralateral to the CRPS affected side occurs (Di Pietro et al., 2013; Maihöfner et al., 2003). However, a systematic review reported that although the CRPS affected hand representation is smaller compared to the unaffected hand in the CRPS group, the S1 representation of the unaffected hand in CRPS is enlarged compared to the hand representations of healthy controls (Di Pietro et al., 2015), with individuals experiencing high pain levels presenting with the most distinctive representational differences between sides (Maihöfner et al., 2003; Pleger et al., 2004). These findings suggest that there is a possible link between cortical reorganisation changes and pain characteristics (pain duration and severity) that contributes to the experience of chronic musculoskeletal pain.

Table 1.2. Altered S1 cortical organisation and function in chronic pain

Author (year)	N	Pain Duration (mean ± SD months)	Diagnosis	Outcome Measure	Finding
Flor et al. (1997)	10*	153.6 ± 44.4	CLBP	SEF	S1 representation shifted 2.5cm medially
Diers et al. (2007)	14*	224.4 ± 173.9	CLBP	SEP	↑ SEP response 80 ms after stimulation
Maihöfner et al. (2003)	12	3.4 ± 2.4	CRPS	SEF	↓ affected cortical hand representation and shifted to lip representation
Pleger et al. (2004)	7*	5.7 (NR)	CRPS	SEP mapping	↓ affected cortical hand representation
Di Pietro et al. (2015)	17*	56.7 ± 78.7	CRPS	Hand spatial representation	↑ representation of healthy hand compared to HC

Note: *, age and gender matched healthy controls; N = pain group sample size; CLBP = chronic low back pain; CRPS = complex regional pain syndrome; field; SEP = somatosensory evoked potential; SEF, somatosensory evoked field; (↓), represents reduced; (↑) represents increased; NR, not reported; HC, healthy control

Intracortical mechanisms

Intracortical mechanisms are also reported to be altered in musculoskeletal conditions. Intracortical inhibition (ICI) and facilitation (ICF) are thought to maintain M1 reorganisation. Short (SICI) and long (LICI) interval intracortical inhibition can be probed using TMS and are thought to reflect gamma-aminobutyric acid type A ($GABA_A$) and gamma-aminobutyric acid type B ($GABA_B$) receptor systems respectively (McDonnell et al., 2006; Werhahn et al., 1999), whilst ICF is thought to reflect the glutamatergic system (Ziemann et al., 1998). The systematic review and meta-analysis by Chang et al. (2018) investigated changes in M1 function and found evidence for an increase in LICI in the M1 of people with chronic pain conditions including LE, fibromyalgia and arthritis (3 studies, 102 participants SMD = 0.78 [95% CI 0.37 to 1.19]). Sub-group analysis demonstrated a moderate reduction of SICI in CRPS (4 studies, 100

participants, SMD = − 0.77 [95% CI = −1.21 to – 0.34]), and reduced ICF in people with non-neuropathic pain (6 studies, 151 participants, SMD = − 0.53 [95% CI = − 0.94 to – 0.13]). This increased $GABA_B$ and $GABA_A$ receptor systems, reflected in increased LICI and decreased SICI respectively, are hypothesised to contribute to motor dysfunction (Burns et al., 2016a).

Structural and functional changes of the cortical hemisphere corresponding to the injured body part are commonly investigated., However, research is increasingly demonstrating the transfer of sensorimotor symptoms such as sensitivity and weakness of muscles to the opposite uninjured side. Specifically, individuals with unilateral tendinopathies have demonstrated development of bilateral sensorimotor dysfunction on the unaffected side. This suggests the cortical hemispheres are integrated and interact between each other and may be involved in the transfer of symptoms to the uninjured side (Bloom & Hynd, 2005; Borich et al., 2015; Carson, 2005; Vecchio et al., 2014). The following sections introduce tendinopathies and discuss the literature pertaining to the development of bilateral sensorimotor dysfunction in tendinopathy.

1.2.3 Tendinopathies

Types of musculoskeletal pain disorders are related to muscle, bone, joint and tendon/ligaments. Within these disorders are tendinopathies, a clinical condition associated with pain and disability that is increasing in prevalence (Abat et al., 2017). Characterised by degenerative changes in tendon structure, changes at the tendon-bone junction i.e., enthesopathy, and inflammation (Cardoso et al., 2019; Cook et al., 2016), tendinopathies are commonly observed in working populations. They account for approximately 30% of musculoskeletal pain consultations in general practice and 30 – 50% of sporting injuries (Lipman et al., 2018; Shiri et al., 2006). Tendinopathies commonly present in the upper and lower extremities of the body within the elbow, knee, shoulder, and ankle. Major types of

regional tendinopathies include lateral epicondylalgia, patella tendinopathy, rotator cuff tendinopathy and Achilles tendinopathy (Hopkins et al., 2016).

Tendon pathology can exist without pain. Further, the evidence between tendon pain and tissue pathology is variable (Rio et al., 2014). As pain is the key feature of tendinopathy, it is suggested that tendon pathology alone cannot explain the source of pain and is likely driven by a spinal, peripheral, or central nervous system mechanism (Rio et al., 2016). Tendon pain can also manifest in the opposite healthy limb with the development of sensorimotor symptoms in some tendinopathies, further supporting a central mechanism of pain (Heales et al., 2014; Rio et al., 2016; Rio et al., 2014). The following section briefly discusses the development of bilateral sensorimotor dysfunction in unilateral tendinopathies.

Bilateral sensorimotor dysfunction in unilateral tendinopathies

Sensorimotor changes of the affected arm in musculoskeletal conditions are well documented. However, research has demonstrated significant differences in sensorimotor function of the healthy uninjured limb in individuals with musculoskeletal pain compared to healthy controls. A systematic review conducted by Heales et al. (2014) confirms findings of bilateral sensorimotor dysfunction in unilateral tendinopathies. Twenty studies were investigated including studies in LE (n = 17 studies), patella tendinopathy (n = 1 study), Achilles tendinopathy (n = 1 study), and rotator cuff tendinopathy (n = 1 study). Meta-analysis of the LE studies provided evidence of bilateral sensorimotor dysfunction including lower pressure and thermal pain thresholds, slower simple and two-choice reaction time, and slower speed of movement. These findings were also shown to align with findings of bilateral symptom development from studies of other tendinopathies, such as chronic wrist pain as summarised in Table 1.3 (Smeulders et al., 2002; Alburquerque-sendin et al., 2013)

Table 1.3. Bilateral sensorimotor dysfunction in unilateral tendinopathies

Author (year)	N	Pain Duration (mean ± SD months)	Diagnosis	Outcome Measure	Finding
Smeulders et al. (2002)	18*	NR	Chronic wrist pain	Motor control	↓ fine motor control at unaffected side
Alburquerque-Sendin et al. (2013)	27*	44.3 ± 54.0	SIS	Trigger points, PPT	Bilateral trigger points. ↓ PPT Bilaterally
Coronado et al. (2014)	58*	17.2 ± 18.8	Shoulder pain	PPT	↓ PPT bilaterally
Hidalgo-Lozano et al. (2010)	12*	8.5 (NR)	SIS	PPT	↓ PPT at local and referred areas

Note: *, age and gender matched healthy controls; N = pain group sample size; SIS, shoulder impingement syndrome; PPT, pressure pain threshold; ↓, decreased; ↑, increased; NR, not reported

As the development of bilateral sensorimotor dysfunction is prevalent in unilateral LE, and the musculoskeletal disorder being investigated in this thesis is LE, the remainder of this section is focused on that condition.

Lateral epicondylalgia is a highly prevalent musculoskeletal disorder of the upper limb that may be compounded by the development of sensorimotor dysfunction at the unaffected limb in individuals with unilateral LE (Heales et al., 2014). As with other musculoskeletal conditions, LE impacts quality of life with lasting physical, psychological, social, and wide-ranging individual, community, and healthcare system financial impacts (Aben et al., 2018; Bisset & Vicenzino, 2015; Coombes et al., 2015; Walker-Bone et al., 2012). Hence, prioritising research to enhance our understanding and the treatment of LE will help lessen the burden and potentially assist in the management of other tendinopathies. The sections below describe the key features of LE including its aetiology, prevalence, and pathophysiology using a model that describes the three interrelated components of LE.

1.2.4 Lateral epicondylalgia (LE)

Lateral epicondylalgia, commonly termed ‘tennis elbow’, is a musculoskeletal disorder described as an overuse injury that affects 1 - 3% of the general population (Shiri et al., 2006; Walker-Bone et al., 2012). The disorder was first described by Runge in 1873 as a painful condition affecting the attachment of the wrist extensors at the lateral epicondyle of the humerus (Runge, 1873), with the extensor carpi radialis brevis (ECRB) muscle suggested to be the most commonly affected (Vicenzino, 2003). Lateral epicondylalgia is prevalent in individuals over 35 years of age who perform repetitive forceful movements (Sanders et al., 2016; Shiri et al., 2006). The prevalence of LE does not differ between males and females (Shiri et al., 2006; Vaquero-Picado et al., 2016), but the incidence increases with age and the amount of exposure to forceful repetitive movement (Shiri et al., 2006). In a survey of the general population in Minnesota (USA) between 2000 and 2012, the annual incidence of LE was 3.4 per 1000 people with rates slightly lower in males than females and a recurrence rate within two years of 8.5% (Sanders et al., 2016).

Recreational sports and instrument playing are known causes of LE (Gruchow & Pelletier, 1979; Lee et al., 2013). However, only 5% of individuals with LE are tennis players. In contrast, LE affects between 2 and 23% of the working population, particularly where the work includes forceful, repetitive actions of the upper limb such as office and administration jobs, construction jobs, factory work and work in the meat and fish processing industries (Chiang et al., 1993; Kurppa et al., 1991; Linaker et al., 1999; McCormack Jr et al., 1990; Ranney et al., 1995; Shiri et al., 2006). In addition to exposure to forceful and repetitive activities, other risk factors for developing LE include age, smoking, and obesity (Herquelot et al., 2013; Shiri et al., 2006).

Worker productivity is reduced in individuals with LE due to physical restrictions associated with pain and disability (Shiri & Viikari-Juntura, 2011; Shiri et al., 2006). Absenteeism in individuals diagnosed with LE has been reported up to 5%, estimated to be an absence of 29 days in a year (Walker-Bone et al., 2012). In Queensland, Australia, LE accounted for 18% of WorkCover-related insurance claims from 2009 to 2013 (Workcover Queensland, 2013) with high healthcare costs related to the treatment and therapy of LE including doctor's visits, physiotherapy visits, and outpatient care (Bisset & Vicenzino, 2015; Coombes et al., 2015; Struijs et al., 2006).

A hallmark symptom of unilateral LE is the development of bilateral sensorimotor dysfunction. Signs of sensorimotor dysfunction in the local area on the unaffected side have been identified including reduced grip force, increased upper limb reaction time, reduced speed of movement and a wrist posture that is 11 degrees less extended bilaterally than healthy controls (Bisset et al., 2006b; Heales et al., 2014; Pienimaki et al., 1997). Clinical implications associated with bilateral sensorimotor dysfunction include increased disability of individuals with musculoskeletal pain (Coombes et al., 2012b). Hence, the development of bilateral sensorimotor dysfunction influences the treatment of LE, requiring consideration of the unaffected side when developing a treatment plan. The personal and broader community impacts of LE have been clearly established. To explore LE in greater depth, the pathophysiological changes associated with LE, including bilateral deficits, are discussed below.

1.2.5 Pathophysiology of LE

Historically, LE has been considered to result from local inflammation of the ECRB tendon following repetitive overuse of the forearm (Vicenzino & Wright, 1996; Waugh, 2005). However, a new pathophysiological model suggests LE comprises three interrelated components: i) local tendon pathology; ii) impairment in the motor system; and iii) central changes in the pain system (Coombes et al., 2009b), with different proportions of these mechanisms explaining the heterogeneous clinical presentation of LE (Figure 1.2). Understanding the proportional contributions of these three components in an individual's LE clinical presentation may help develop effective management strategies and techniques.

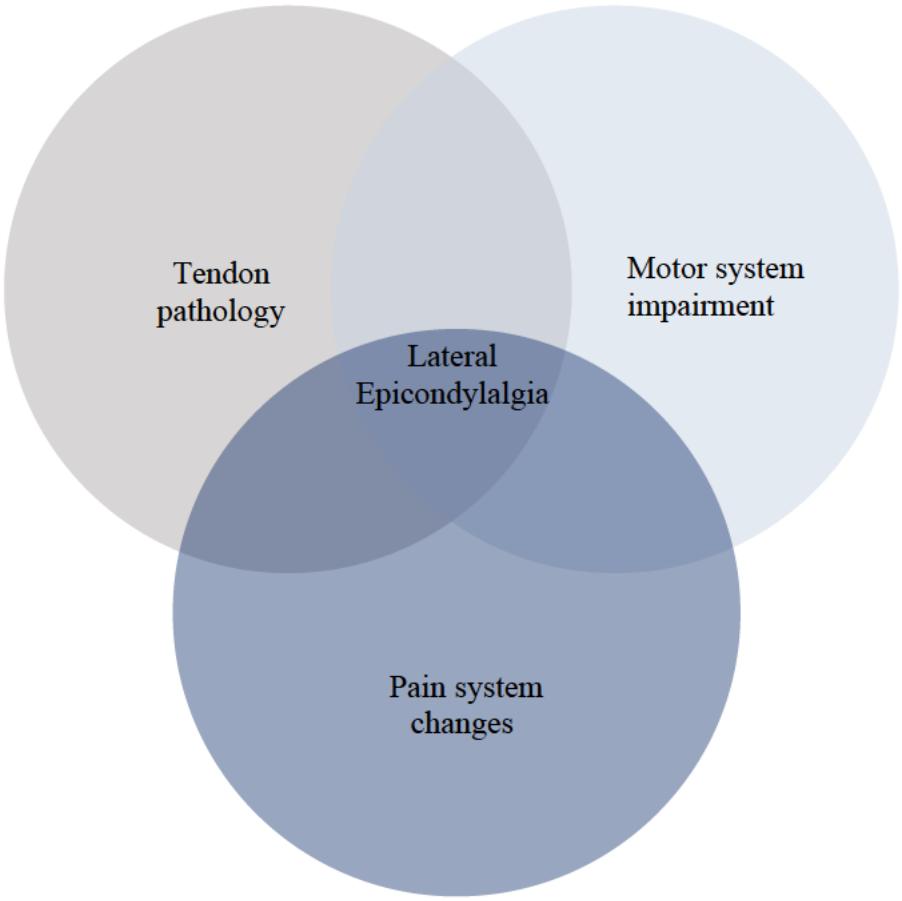

Figure 1.2. A pathophysiological model of LE with three interrelated components, i) tendon pathology; ii) motor impairments; and iii) pain system changes. Source: Adapted from Coombes et al. (2009b).

Evidence for local tendon pathology

There is strong evidence of local tendon pathology changes identified in LE. Histological examination of tissue biopsies obtained from individuals undergoing surgery for LE reveal four key changes in tendon structure: i) an increased number of tenocytes and increased ground substance; ii) the presence of vascular hyperplasia; iii) increased concentration of neurotransmitters such as substance P and glutamate; and iv) a pattern of disorganised and immature collagen (Abate et al., 2009; Bass, 2012; Heales et al., 2014; Kraushaar & Nirschl, 1999). Further, imaging by magnetic resonance imaging (MRI) and ultrasound show loss of collagen, tendon thickening and thinness, partial tears, neovascularisation, and mucoid degeneration (Heales et al., 2014; Jaén-Díaz et al., 2010; Steinborn et al., 1999; Vaquero-Picado et al., 2016). Collectively, these changes are termed angiofibroblastic hyperplasia and are thought to result due to a 'degenerative' process of the tendon, also described as repeated cycles of 'dysfunctional, immature healing' (Nirschl, 1992; Tosti et al., 2013; Vicenzino, 2003; Waugh, 2005), rather than from local inflammation.

The precise mechanism driving chronic tendon degeneration is unclear but is thought to be related to mechanical load. Increased loading that exceeds the mechanical strength of the tendon is shown to induce histopathological changes in tendon structure (Maganaris et al., 2004; Rees et al., 2009). This leads to ingrowth of blood vessels and nerves that may occur in the tendon with a partial or complete tear, rendering a dysfunctional repair response of the tendon that can manifest through pain (Fredberg & Stengaard-Pedersen, 2008; Maffulli et al., 2010; Nirschl, 1992). While excessive mechanical stress is a predominant clinical focus, the absence of or lower than usual mechanical stimulus termed 'stress shielding' could similarly compromise tendon structure and thus contribute to pathology (Ahmad et al., 2013; Maganaris et al., 2004). Ultimately, stress-shielding predisposes the tendon to structural weakening, increasing susceptibility to overload and injury. It is plausible that stress shielding occurs due

to fear-avoidance of pain, i.e., pain related inhibition, contributing to modified biomechanics, altered motor control, and subsequent structural weakening of the tendon (Leeuw et al., 2007; Vlaeyen & Linton, 2000). However, pathological changes noted by ultrasound and MRI do not correlate with measures of self-reported pain and function assessed by the pain-rated tennis elbow evaluation (PRTEE) (Chourasia et al., 2012; Levin et al., 2005; Potter et al., 1995). As tendon pathology does not correlate with pain and function, this reflects the complex nature of tendon pain and the requirement for further comprehensive clinical assessment to determine the relationship between tendon pathology and, pain and function.

In addition to structural and pathological changes of the tendon, similar maladaptation of the tendon enthesis i.e., the insertion site on bone, termed enthesopathy or insertional tendinopathy have been identified (Milz et al., 2004). Pathological changes demonstrated at the ECRB enthesis in LE include fibrovascular proliferation, focal calcification, and mucoid degeneration (Apostolakos et al., 2014; Milz et al., 2004). The ECRB enthesis is responsible for transferring mechanical load from tendon to bone, contributing to the dissipation of stress from a small point across a large area (Weinreb et al., 2014). As the shear, tensile and compressive forces transported across the enthesis are suggested to determine the fibrocartilaginous composition of the ECRB enthesis (Wang, 2006), the total mechanical stress placed upon it likely contributes to pathology.

Evidence for motor system impairment

Motor system impairments in LE encompass deficits in grip strength, motor control, muscle strength and muscle morphological changes. These motor deficits have been demonstrated locally (Alizadehkhaiyat et al., 2007; Heales et al., 2016) and bilaterally (Bisset et al., 2006b; Heales et al., 2021; Slater et al., 2005) and contribute to the pathophysiology of LE. The following discussion represents a review of common motor system impairments found in LE.

Deficits in grip strength

Pain over the lateral epicondyle during gripping is the most common symptom of LE affecting grip strength (Chourasia et al., 2012; Pienimäki et al., 2002; Tosti et al., 2013; Wyn Lim, 2013). The grip strength test is used to objectively assess the amount of force generated as an indicator of grip strength. Grip strength is measured using a dynamometer and is commonly performed with the patient seated, their elbow flexed to 90 degrees and the forearm and wrist in neutral positions. Pain-free grip strength is measured as the amount of force generated prior to the onset of lateral epicondylar pain until the patient feels discomfort (Vicenzino et al., 2003; Wyn Lim, 2013). Maximal grip strength is measured as the maximum force generated regardless of pain. Pain-free grip strength is considered a more sensitive measure for detecting changes in grip strength compared to maximal grip strength testing (Stratford, 1987; Stratford & Balsor, 1994) and has been demonstrated to be reliable and valid (Stratford & Balsor, 1994).

In individuals with unilateral LE, clinical tests display diminished pain-free grip strength of the affected and unaffected limb with a flexed wrist posture (i.e., reduced wrist angle) when compared to healthy controls (Bisset et al., 2018; Chourasia et al., 2012; Bisset et al., 2006b) (Table 1.4). Reduced maximal and pain-free grip strength are demonstrated on the LE affected side when compared to the contralateral unaffected arm and healthy individuals (Alizadehkhaiyat et al., 2007; Coombes et al., 2012b; Ucurum et al., 2019). Interestingly, three studies demonstrate lower pain-free and maximal grip strength (Bisset et al., 2018; Slater et al., 2005) with longer electromechanical delay and rate of force development (Chourasia et al., 2012) during gripping on the unaffected side of patients with unilateral LE compared to the corresponding side of healthy controls. In addition, wrist position during gripping in LE is demonstrated to be 11 degrees more flexed than controls bilaterally, likely affecting maximal grip force output (Bisset et al., 2006b). In contrast, Bisset et al. (2006b) demonstrated greater grip strength on the contralateral side of patients with unilateral LE

compared to the corresponding side of healthy controls. There are several possible explanations for this finding including: i) a compensatory strategy of the contralateral unaffected limb so as to protect the injured arm; and ii) the LE group was stronger than the control group in grip strength prior to developing LE (Bisset et al., 2006b; Heales et al., 2014). Nonetheless, the majority of studies demonstrate reduced grip force production suggested to be driven by alterations in the CNS that affect muscle activity and consequently affect grip strength (Manickaraj et al., 2018). This ultimately contributes to altered motor function and motor system organisation in individuals with LE.

Muscle strength deficits

In addition to local and bilateral deficits in grip strength, widespread bilateral strength deficits in unilateral LE have been demonstrated. Flexion and extension strength deficits of the elbow and wrist joints are observed in LE compared to healthy controls (Coombes et al., 2012a). Both wrist extension and flexion strength are reported to be approximately 30% weaker in the LE affected limb compared to controls (Alizadehkhaiyat et al., 2007; Lucado et al., 2012; Slater et al., 2005). Weaker wrist extensor strength is further demonstrated bilaterally in LE when compared to the corresponding arm of controls, suggesting the involvement of the peripheral and central nervous systems (Slater et al., 2005). Widespread strength deficits have also been demonstrated in LE. Shoulder movements are reported as 25 - 35% weaker and metacarpophalangeal flexion strength 36% weaker than controls (Alizadehkhaiyat et al., 2007). Strength deficits in the upper trapezius and serratus anterior muscles have been demonstrated in the affected limb with reduced strength of the lower trapezius demonstrated at the unaffected limb relative to the control group (Heales et al., 2021). These findings indicate the extent of these deficits beyond the local site of injury with widespread and global upper limb muscle weakness. However, strength deficits have not been demonstrated during metacarpophalangeal joint extension suggesting that they may compensate for the weakness of the wrist extensors

(Alizadehkhaiyat et al., 2007). These changes may be explained by peripheral mechanisms in the muscles and mechanisms within the CNS. One such peripheral change is local morphological changes of the muscles.

Morphological changes of muscle

Morphological changes of muscle fibres have been identified in the ECRB muscle of LE patients. Examination of the ECRB tendon revealed changes including moth-eaten fibres with 80% found in LE patients compared to 11% in controls, degenerated and regenerated muscle fibres (muscle fibre necrosis), increase distribution in oxidative fibre types and loss of fast twitch fibres (Ljung et al., 1999). These changes are thought to contribute to motor system dysfunction affecting motor performance and muscle strength, thus contributing to the impairment of the motor system.

Table 1.4. Studies demonstrating grip strength deficits in unilateral LE

	LE			Controls			
Author (year)	N	Age Mean ± SD	Symptom duration (mean ± SD months)	N	Age Mean ± SD	Protocol	Results
Slater et al. (2005)	20	48.25 (NR)	6.5 ± 1.1	20	47.45 (NR)	MG	↓ MG and wrist extension in LE affected arm compared to contralateral arm and compared to both arms for healthy controls. Unaffected arm was weaker than matched arm of controls
Bisset et al. (2006b)	40	49.5 (NR)	7.7 ± 10	40	48.4 (NR)	PFG + MG	↓ PFG on LE affected side; 11° less extended wrist posture bilaterally during gripping; ↑ MG on unaffected side compared to controls
Alizadehkhaiyat et al. (2007)	16	49 (NR)	NR	16	40 (NR)	MG	↓ MG of the LE affected side compared to controls
Coombes et al. (2012b)	164	49.6 ± 9.0	5.7 ± 7.1	62	49.6 ± 8.7	PFG	↓ PFG of the LE affected arm compared to controls
Chourasia et al. (2012)	28 (13 unilateral ; 15 bilateral)	48.2 ± 8.4	24 (NR)	13	44.6 ± 8.1	PFG	↓ PFG of LE side compared to unaffected side ↓ Rate of force and electromechanical delay bilaterally compared to controls
Bisset et al. (2018)	25	50.4 ± 8.7	3 (NR)	15	49.3 ± 6.5	PFG	↓ PFG bilaterally compared to control group
Ucurum et al. (2019)	51	44.88 ± 9.66	12 (NR)	51	42.71 ± 9.72	MG	↓ MG of the LE affected side compared to the contralateral unaffected side and compared to controls

Note: MG, maximum grip strength; PFG, pain-free grip strength; NR, not reported; ↓, indicates decreased; ↑, indicates increased

Motor control deficits

In unilateral LE, the development of bilateral motor control deficits has been identified compared to healthy controls. Increased reaction times of the upper limb and reduced speed of movement have been demonstrated in the affected limb in individuals with unilateral LE and the contralateral unaffected side (Bisset et al., 2006b; Chourasia et al., 2012; Kauranen & Vanharanta, 1996). In the contralateral side, weighted pooled mean differences demonstrated reaction time to be 37.8 ms slower, the two-choice reaction time 36 ms slower and speed of movement 20 cm/s slower when compared to the corresponding side of controls (Bisset et al., 2006b; Heales et al., 2014; Pienimaki et al., 1997). This finding could be due to poor proprioception which can affect motor activity (Juul-Kristensen et al., 2008). Proprioception is the perception of movement and position of the body in relation to each other without the aid of vision (Proske & Gandevia, 2012). Proprioception is poorer in the elbows of LE patients than in controls, with LE patients showing greater errors in threshold detection of passive movement, and greater error in detecting joint position sense (Juul-Kristensen et al., 2008). Poor proprioception can be influenced centrally, indicating potential involvement of the CNS. Additionally, local mechanisms can contribute such as altered muscle activity, leading to altered motor function (Juul-Kristensen et al., 2008; Rissén et al., 2000).

In addition to motor control deficits, deficits in forearm muscle activity have been observed in LE compared to pain-free controls. The literature demonstrates that neuromuscular control and coordination of forearm muscles measured by electromyography (EMG) differs between LE and healthy control groups (Heales et al., 2016). These changes in motor activity include: i) altered amplitude and duration properties of motor unit action potentials during resisted wrist extension (Calder et al., 2008; Heales et al., 2016); ii) a delay in time from the onset of muscle EMG to grip force development (Chourasia et al., 2012; Heales et al., 2016); iii) increased EMG amplitude of forearm muscles during single-handed backhand tennis strokes (Bauer &

Murray, 1999; Kelley et al., 1994); and iv) motor cortex reorganisation including overlapping cortical representations of ECRB muscles and greater peak-to-peak amplitudes indicating increased cortical excitability (Schabrun et al., 2015a). One explanation for altered forearm muscle activity is that increased tension in the forearm flexors occurs to compensate for reduced activity of extensor muscles (Alizadehkhaiyat et al., 2007; Edgerton et al., 1996). This results in an imbalance of forearm muscle activity as some muscles are overactive and others underactive, which subsequently alters movement patterns (Alizadehkhaiyat et al., 2007; Edgerton et al., 1996). Another explanation is thought to be due to the experience of pain during gripping (Heales et al., 2016). Increased contribution of EMG of the extensor digitorum communis muscle relative to the total amount of muscle activity was associated with increased pain and disability and reduced pain free grip force (Manickaraj et al., 2018). Further, the level of maximum voluntary contraction alters the magnitude of muscle activity whereby at 15% maximum voluntary contraction there was lesser contribution of ECRB and greater contribution of the extensor carpi ulnaris in individuals with LE compared to healthy controls (Mackinaraj et al., 2018). Alternatively, as neuromuscular control is a measure of the output of the processes in the CNS, impairments in muscle activity may provide evidence of altered CNS function which are consequently affecting the motor system.

In summary, strong evidence suggests that individuals with LE display impaired motor function bilaterally. Changes include grip strength deficits, altered muscle activity, deficits in extensor and flexor muscle strength of the wrist and upper arm, and morphological muscle changes. The presence of motor function control and impairment bilaterally further suggests that a CNS component is involved. However, additional research into specific central processing mechanisms that contribute to motor system changes is needed to further our understanding of the development of bilateral dysfunction in unilateral musculoskeletal pain conditions, including LE.

Evidence for pain system changes

There is growing evidence that supports pain system changes in LE. Musculoskeletal pain, in particular chronic pain, involves changes in the peripheral nervous system (PNS) and CNS. This encompasses changes in nociceptive and non-nociceptive sensory afferents, the release of chemical mediators, and alterations of CNS processing such as the sensitisation of neurons causing local and widespread hypersensitivity (Gangadharan & Kuner, 2013). Collectively, these alterations are referred to as "pain system changes" (Coombes et al., 2009b). In LE, demonstrated pain system changes include neurochemical imbalances at the ECRB tendon (Alfredson et al., 2000; Ljung et al., 2004; Ljung et al., 1999), central sensitisation of pain (Nijs et al., 2021) and alterations in sensory function (Coombes et al., 2012b; Fernández-Carnero et al., 2009a; Fernández-Carnero et al., 2009b; Jespersen et al., 2013; Ruiz-Ruiz et al., 2011). These changes in the nervous system have clinical implications for the assessment and treatment of LE.

Peripheral sensitisation

Altered pain processing by the peripheral nervous system, commonly referred to as peripheral sensitisation, is a mechanism believed to contribute to chronic LE. Peripheral sensitisation is defined by the IASP as "increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields" (International Association for the Study of Pain, 2011). Neurochemical imbalance of the ECRB tendon in the absence of inflammation in individuals with chronic LE is linked to the pathophysiology of chronic LE (Coombes et al., 2012b). The neurotransmitter glutamate, and neuropeptides substance P and calcitonin gene-related peptide (CRGP) are released into the tendon contributing to nociception (the neural process of encoding noxious stimuli) (International Association for the Study of Pain, 2011) and mediating pain (Jensen & Olesen, 1991). For example, significantly higher concentrations of glutamate at the ECRB tendon of people with LE of at least six months

duration have been detected compared to healthy controls, with no difference in the concentration of prostaglandin (a substance involved in inflammatory reactions) detected between the groups (Alfredson et al., 2000). As glutamate is known to mediate pain, these findings suggest that glutamate mediates pain in LE and confirms no signs of inflammation are evident at a chronic stage of LE (Alfredson et al., 2000).

Similarly, neuropeptides substance P and CRGP, and their receptor neurokinin-1 have shown to be distributed amongst small blood vessels and nerve bundles at the proximal ECRB tendon of individuals with LE (Ljung et al., 2004; Ljung et al., 1999). Mechanical stress due to high levels of tension in eccentric contraction at the ECRB muscle stimulate the release of substance P and CGRP and consequently the sensitisation and excitation of nociceptors. Therefore, the release of these neuropeptides results in increased sensitisation of the fibres they are found in and contribute to the pathophysiology of LE. These findings are in line with several other studies that confirm that substance P and CGRP are associated with pain modulation and hyperalgesia (Gibson et al., 2009). In LE, the presence of substance P and CGRP are believed to be involved in mediating pain (Fedorczyk, 2006) associated with a process of inflammation, that results from nociceptor activation, causing the release of neuropeptides known as neurogenic inflammation (Haker et al., 1998; Jensen & Olesen, 1991; Littlejohn & Guymer, 2018; Ljung et al., 2004; Ljung et al., 1999; Matsuda et al., 2019; Waugh, 2005) and greater tendon degeneration (Han et al., 2021). Collectively, the current research indicates LE is characterised by the presence of neurochemicals within the ECRB tendon implicating peripheral sensitisation mechanisms that mediate pain in LE, thus contributing to alterations of the pain system.

Central sensitisation

In addition to altered neurochemical levels at the periphery, altered pain processing of the central nervous system known as central sensitisation is observed in LE. Central sensitisation is a process that occurs due to altered pain system processing in the CNS (Simons et.al 1999). Central sensitisation is defined by the IASP as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (International Association for the Study of Pain, 2011). This may include increased responsiveness due to the dysfunction of endogenous pain control systems. Changes in function occur in central neurons despite normal functioning of peripheral neurons (International Association for the Study of Pain, 2011).

Central sensitisation is characterised by the presence of hyperalgesia and allodynia. Hyperalgesia is an enhanced or prolonged pain response to a noxious stimulus that normally provokes pain. Where this occurs locally at the site of musculoskeletal pain it is referred to as primary hyperalgesia; beyond the site of injury, it is known as secondary hyperalgesia (Pavlaković & Petzke, 2010). Allodynia is increased sensitivity to normally non-noxious stimuli. Several proposed mechanisms of central sensitisation have been suggested and are explored below.

Mechanisms of central sensitisation

Mechanisms of central sensitisation involve altered pain processing in supraspinal centres and the spinal cord (Figure 1.3). One such mechanism suggests that peripheral noxious input initiates central sensitisation, but at a chronic stage of pain this can be sustained in the absence of peripheral noxious input (Fernández-de-las-Peñas et al., 2009). Following this initiation, excitation and sensitisation of nociceptors results in sensitisation of the spinal dorsal horns, which alter the somatosensory system (Graven-Nielsen & Arendt-Nielsen, 2010; Woolf, 2011;

Wright, 1999). When this occurs, neuronal function in the CNS is altered and any pain generated occurs in response to sensory input rather than the presence, intensity, or duration of peripheral noxious stimuli (Latremoliere & Woolf, 2009).

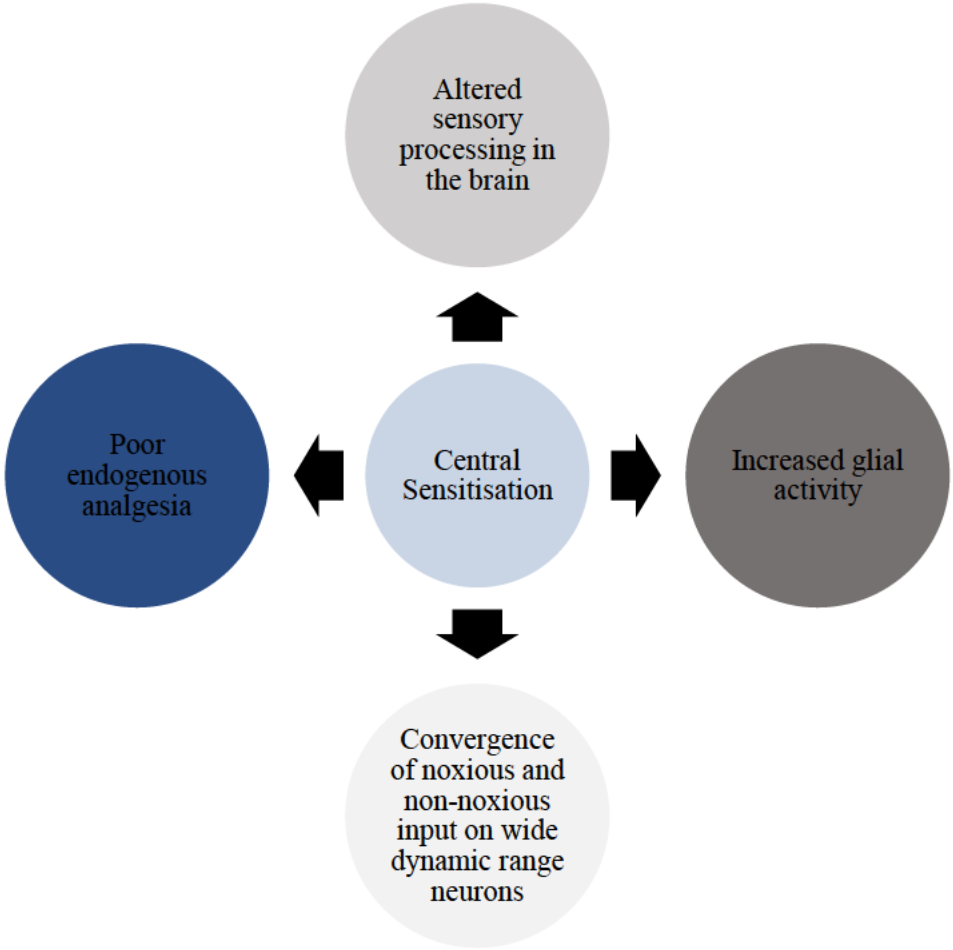

Figure 1.3. Contributing mechanisms of central sensitisation.

Poor functioning of the endogenous analgesic system, referred to as descending inhibitory pain control, is another proposed mechanism of central sensitisation. In LE, endogenous pain inhibition is impaired, and this impedes the ability to suppress pain (Lim et al., 2017). Assessed using a conditioned pain modulation (CPM) paradigm, also described as the 'pain inhibits pain' method, CPM provides information on the net balance between endogenous facilitatory and inhibitory mechanisms (Arendt-Nielsen et al., 2018). A painful stimulus such as cold or heat pain applied to a remote area of the body (conditioning stimulus) inhibits pain sensation, i.e.,

reduces pain perception, of another noxious stimulus (test stimulus) applied to another part of the body (Arendt-Nielsen & Yarnitsky, 2009; van Wijk & Veldhuijzen, 2010). When this occurs, ascending projections to supraspinal structures trigger descending inhibitory projections to the dorsal horn (Cruz-Almeida & Fillingim, 2014). Unlike pain-free individuals, in chronic pain, altered endogenous pain modulation results in an imbalance between descending facilitation and inhibition where inhibition is reduced, or facilitation is enhanced (Arendt-Nielsen et al., 2018; Arendt-Nielsen et al., 2015).

Increased glial activity also contributes to the mechanism of central sensitisation. Glia are non-neuronal cells within the CNS supporting neuronal function. Activated glia leads to production of proinflammatory cytokines and chemokines that mediate neuroinflammation (Matsuda et al., 2019). This increased glial activation is associated with hyperalgesia and allodynia and drives central sensitisation, contributing to the pathophysiology of chronic pain conditions (Matsuda et al., 2019; Nijs et al., 2019). As the presence of neurochemicals has been established in the pathophysiology of LE, increased glial activity is a highly likely mechanism of pain mediation in LE.

Several other mechanisms within the CNS may also contribute to central sensitisation. These include the convergence of noxious and non-noxious input on wide dynamic range neurons that increases their excitability (Woolf, 1989) and receptive field size (Cook et al., 1987), and changes in somatic withdrawal reflexes (Wall & Woolf, 1984). This subsequently increases sensitivity to painful or non-painful stimuli. Reduced withdrawal reflex thresholds have been demonstrated in LE, strengthening the evidence of central sensitisation and more specifically, spinal cord hyperexcitability in LE (Lim et al., 2012). Further evidence suggests sensitisation of myelinated afferents contribute to altered central processing and mechanical hyperalgesia (Wright et al., 1994), which is also demonstrated in LE (Smith & Wright, 1993). The

mechanisms of central sensitisation can be evaluated using quantitative sensory testing and will be discussed in the following section.

Quantitative sensory testing

Central sensitisation can be reflected in altered somatosensory function and may be evaluated by quantitative sensory testing (QST). Quantitative sensory testing is a psychophysical method of assessing and quantifying somatosensory pathways (Backonja et al., 2013; Uddin & MacDermid, 2016). The QST methods provide insight into the functional status of the entire sensory neuroaxis, from peripheral receptors by assessing small (A-delta, C) and large (A-beta) afferent nerve fibre function, to the cerebral cortex by assessing their pathways in the central nervous system (Arendt-Nielsen & Yarnitsky, 2009; Gruener & Dyck, 1994; Yarnitsky & Granot, 2006; Zaslansky & Yarnitsky, 1998). Quantitative sensory testing involves a battery of tests that can include the following methods: detection threshold (the minimum amount of stimulus required to perceive a stimulus), tolerance threshold (the maximum amount of stimulus a person can tolerate) or a rating (a rating of the intensity or magnitude of a standardised stimulus) (Curatolo et al., 2000; Uddin & MacDermid, 2016). When performed, QST can identify sensory gain (e.g., allodynia, hyperalgesia) or sensory loss (e.g., hypoesthesia, hypoalgesia) in response to stimuli.

For LE and other pain conditions, QST provides an understanding of the underlying pain processing mechanisms occurring at the central and peripheral nervous systems that contribute to the development of musculoskeletal pain conditions (Uddin & MacDermid, 2016). An understanding of potentially altered mechanisms may facilitate the application of treatments specific to the mechanism of action to improve pain and sensorimotor function outcomes. Types of QST assessed in LE include pressure pain thresholds, thermal pain and detection thresholds, vibratory detection thresholds and temporal summation.

Although QST is widely used and is deemed reliable and valid, it is influenced by individual characteristics such as age, sex, ethnic or racial status and body site of measurement (Nijs et al., 2021; Rolke et al., 2006). These factors influence central sensitisation and should be controlled for to allow reduced variability in responses to stimuli. Further, because these tests involve a psychological component, QST can be affected by participant concentration, attention, and disposition (Cruz-Almeida & Fillingim, 2014). Thus, using standardised protocols is important in reducing variability of responses. In LE, QST has been widely used to evaluate somatosensory function to better understand pain processing mechanisms. The following paragraphs examine altered somatosensory function in LE via QST methods.

Altered bilateral pain processing in LE

Altered QST has been demonstrated in the LE affected side of individuals, with increasing evidence demonstrating altered QST at the contralateral unaffected side as summarised in Table 1.5. Individuals with unilateral LE have demonstrated decreased pressure pain thresholds (PPTs) over the ECRB muscle belly (Ruiz-Ruiz et al., 2011; Wright et al., 1992) and the lateral epicondyle (Coombes et al., 2012b; Fernández-Carnero et al., 2009a Pienimäki et al., 2002; Sran et al., 2001) of the affected and unaffected side (Heales et al., 2014), when compared to the corresponding sides of healthy controls. These bilateral deficits demonstrate mechanical secondary hyperalgesia, a manifestation of central sensitisation. Evidence demonstrates similar findings at the affected and unaffected sides for thermal pain thresholds in LE with cold hyperalgesia (Coombes et al., 2012b; Ruiz-Ruiz et al., 2011; Wright et al., 1992). Findings of bilateral cold pain hyperalgesia support the involvement of a central pain mechanism, mainly central sensitisation that implies alterations of the spinothalamic pathways of the CNS. However, evidence of altered sensitivity to heat stimuli in LE is inconsistent. Reduced heat pain thresholds in LE have been demonstrated unilaterally (Coombes et al., 2012b; Fernández-Carnero et al., 2009b), bilaterally (Ruiz-Ruiz et al., 2011) and in the area of pain referral

(Leffler et al., 2000a). In contrast, some studies report no difference in heat pain thresholds between the LE affected and unaffected sides (Fernández-Carnero et al., 2009b; Wright et al., 1994). These inconsistencies may be due to the heterogeneity of study design, such as the duration of LE and sample size. These contrasts in findings support the need for robust methodologies and consistent study designs to determine the reproducibility of results so that clear conclusions about heat pain thresholds in LE can be made. Heat hyperalgesia has been associated with peripheral sensitisation (Coombes et al., 2012b; Woolf, 2011), thus implicating local physiological mechanisms. However, as cold pain threshold results are consistent and suggestive of central pain mechanism involvement, this provides further evidence for the hypothesis that altered central pain processing mechanisms are involved in the development of bilateral tendinopathy.

Table 1.5. Studies demonstrating bilateral sensory dysfunction in unilateral LE

Author (Year)	N	Current Pain Intensity at rest (mean ± SD)	Pain duration (mean ± SD Mo)	Outcome Measure	Finding
Slater et al. (2005)	20*	3.2 ± 0.4	6.5 ± 1.1	PPT	↓ bilaterally
Fernández-Carnero et al. (2009b)	12*	4.4	25 ± 16	PPT, CPT, HPT, VDT	↓ PPT bilaterally ND for CPT, HPT, VDT between sides
Fernández-Carnero et al. (2009a)	26*	1.0 (NR)	20.3 (NR)	PPT	↓ PPT bilaterally
Fernández-de-las-Peñas et al. (2010)	16*	1.1 ± 1.0	21.6 ± 14.4	PPT	↓ PPT bilaterally
Ruiz-Ruiz et al. (2011)	16*	1.6 ± 0.6	19.2 ± 95	PPT, CPT, HPT	↓ PPT, HPT and ↑ CPT bilaterally
Coombes et al. (2012b)	164*	1.1 ± 1.41	5.7 ± 6.9	PPT, CPT, HPT	↓ CPT and PPT bilaterally ↓HPT affected side only
Bisset et al. (2018)	25*	3.9 ± 1.7	3.0 ± 1.4	PPT, CPT	↓ PPT bilaterally, ↓CPT affected side only

Note: *, age and gender matched healthy controls; N = pain group sample size; NR, not reported; PPT, pressure pain threshold; CPT, cold pain threshold; HPT, heat pain threshold; VDT, vibration detection threshold; ND, no difference; Mo, months; (↓), represents reduced; (↑), represents increased

In addition to the above QST methods, facilitated temporal summation of pain is demonstrated in the affected side of individuals with LE compared to controls, and at the lower leg in LE compared to controls suggesting generalised hyperalgesia in LE (Bisset et al., 2018; Jespersen et al., 2013). However, neither of these studies compared temporal summation between the affected and unaffected sides between LE and control groups. Similarly, while few studies have examined vibration detection threshold in LE, two studies have shown elevated vibration detection threshold (i.e., poorer detection) on the affected side in LE patients (Fernández-Carnero et al., 2009b; Palaniswamy et al., 2018). Although, the findings from Fernández-Carnero et al. (2009b) were not statistically significant, likely due to the small sample size. Taken together, there is insufficient data to conclude whether vibration detection threshold is impaired in LE.

When combined, the findings of sensory dysfunction in the affected and unaffected limbs of individuals with unilateral LE suggest that altered central pain processing is a feature of chronic LE. The contribution of central pain processes to pain is important for understanding the underlying mechanism of the diagnosis and treatment of LE. However, the mechanism underlying bilateral sensory dysfunction in musculoskeletal pain has not been investigated and remains unclear.

Maladaptive cortical reorganisation in LE

Sensorimotor cortical adaptations have also been reported in chronic lateral epicondylalgia. Evidence of increased excitability of wrist extensor muscles ECRB and extensor digitorum (i.e., increased map volume), with smudging of M1 representations of affected muscles was associated with higher pain severity scores at rest and in the preceding 6 months (Schabrun et al., 2015a). Altered intracortical networks including reduced SICI, ICF and LICI have been demonstrated in the M1 contralateral to the LE affected side, however, no changes were found for the M1 contralateral to the unaffected side in the LE group (Burns et al., 2016a).

Interestingly, corticomotor excitability of the affected and unaffected M1 remain unaltered (Burns et al., 2016a; Dessureault, 2008). Whilst the data on cortical reorganisation in LE is limited, it suggests altered cortical reorganisation of the M1 contralateral to the affected side in chronic LE is associated with high pain severity (Schabrun et al., 2015a). However, as these studies investigate cortical hemispheres individually, we are unable to discern the interaction between cortical hemispheres and how this may influence the development of bilateral sensorimotor dysfunction.

Evidence of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain has prompted further investigation into interhemispheric communication as a possible mechanism. Interhemispheric communication via cross-education is one mechanism proposed to explain bilateral sensorimotor deficits (Heales et al., 2014). Cross-education is when unilateral reduction in activity is transferred to the contralateral unaffected side causing bilateral deficits. Cross-education is thought to involve cortical interhemispheric interactions where ipsilateral corticospinal fibres project to the contralateral muscles during unilateral movement (Camus et al., 2009; Perez et al., 2007). Therefore, interhemispheric interactions present as an alternate mechanism of the central nervous system to central sensitisation that may underpin bilateral symptom development.

Taken together, strong evidence suggests altered peripheral and central nervous system function contributes to the pathophysiology of LE. Such changes to the pain system include the detection and imbalance of neurochemicals, somatosensory changes including mechanical and thermal hyperalgesia, impaired vibration detection thresholds and facilitated temporal summation, and altered cortical reorganisation. Further, the presence of bilateral dysfunction in unilateral LE suggests maladaptive central pain processing such as central sensitisation. At present, research surrounding interhemispheric interactions in response to pain is limited. Therefore, further investigation into the role of this mechanism from an acute to chronic stage

of pain could provide further insights into the development of bilateral sensorimotor dysfunction in unilateral pain conditions such as LE.

Summary of the pathophysiological model of LE

The pathophysiological model of LE suggests that three interrelated components (local tendon pathology, motor system and pain system) are involved in LE. The extent of involvement of each component varies and may differ depending on the severity of the condition. Treatment strategies used to manage clinical symptoms due to these three components include: pharmacotherapy to manage sensitisation processes and motor impairment e.g. corticosteroid injections and non-steroidal anti-inflammatory drugs (Bisset et al., 2006a; Coombes et al., 2009b); physiotherapy to target local tendon pathology e.g. manual therapy (Bisset et al., 2005; Vicenzino, 2003); exercise to target tendon pathology and motor system impairments (Kjaer, 2004; Langberg et al., 2007; Pienimäki et al., 1996); and a multimodal management approach e.g. combining exercise with electrophysical therapy (Bisset et al., 2006a; Smidt et al., 2002). However, the development of sensorimotor dysfunction on the unaffected side suggests that the pathophysiology is more complex and likely involves changes of the central nervous system and cortical reorganisation (Figure 1.4).

As mentioned earlier, some studies suggest the underlying mechanism may be due to cortical interhemispheric interactions where activity in one hemisphere projects onto and influences the opposite hemisphere. A neurophysiological mechanism that may be relevant to the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions is interhemispheric inhibition. The following section describes the anatomical and physiological components of the interhemispheric inhibition mechanism.

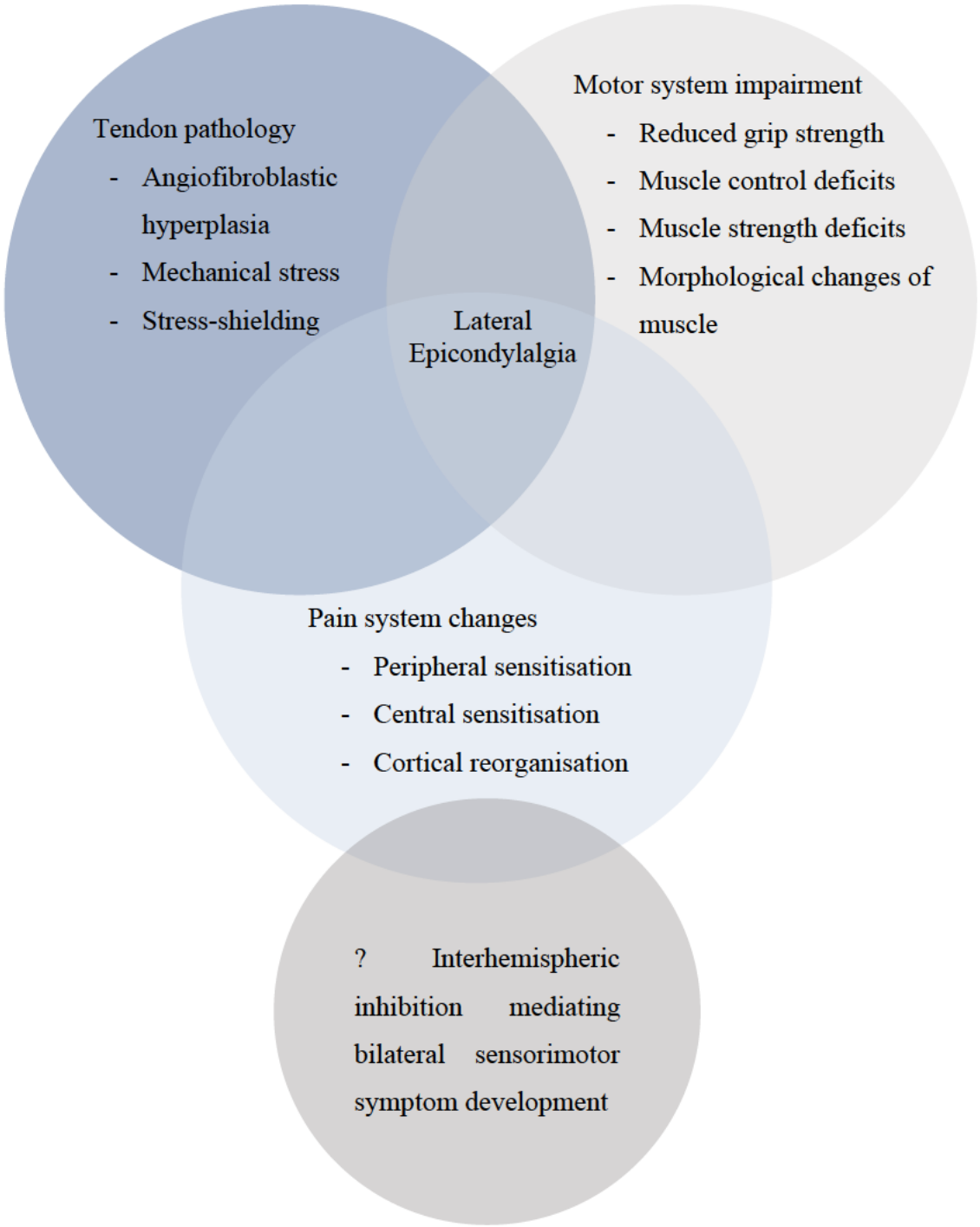

Figure 1.4. The three interrelated components of LE. The mechanism mediating bilateral sensorimotor symptoms in unilateral LE remains to be understood. Interhemispheric inhibition is a neurophysiological mechanism suggested to underpin this phenomenon. Adapted from Coombes et al. (2009b).

1.3 Interhemispheric inhibition (IHI)

Most individuals who suffer from musculoskeletal conditions experience common symptoms of pain and sensorimotor dysfunction that are restricted to one side of the body (i.e., they are unilateral). However, some individuals develop sensorimotor dysfunction bilaterally despite the absence of the condition on the contralateral side (Heales et al., 2014; Pelletier et al., 2017). The pathophysiological mechanism that underpins bilateral symptom development is not well understood. A neurophysiological mechanism, known as interhemispheric inhibition (IHI), has been postulated to contribute to the development of bilateral sensorimotor dysfunction. This section discusses the research that has characterised the anatomical and physiological components of IHI.

1.3.1 The role of the corpus callosum in IHI

There has been extensive investigation into the anatomy of interhemispheric connections and interactions. Interhemispheric interactions are proposed to occur via transcallosal fibres of the corpus callosum, the largest white matter structure in the brain (Cook, 1984; Kinsbourne, 1975). The transcallosal fibres connect homologous cortical areas of the right and left cerebral hemispheres to allow communication between the two hemispheres (Bloom & Hynd, 2005). The corpus callosum is divided into the rostrum, genu, truncus or midbody, isthmus and splenium (Figure 1.5). Specifically, the posterior midbody connects the primary and secondary somatosensory and motor areas (van der Knaap & van der Ham, 2011).

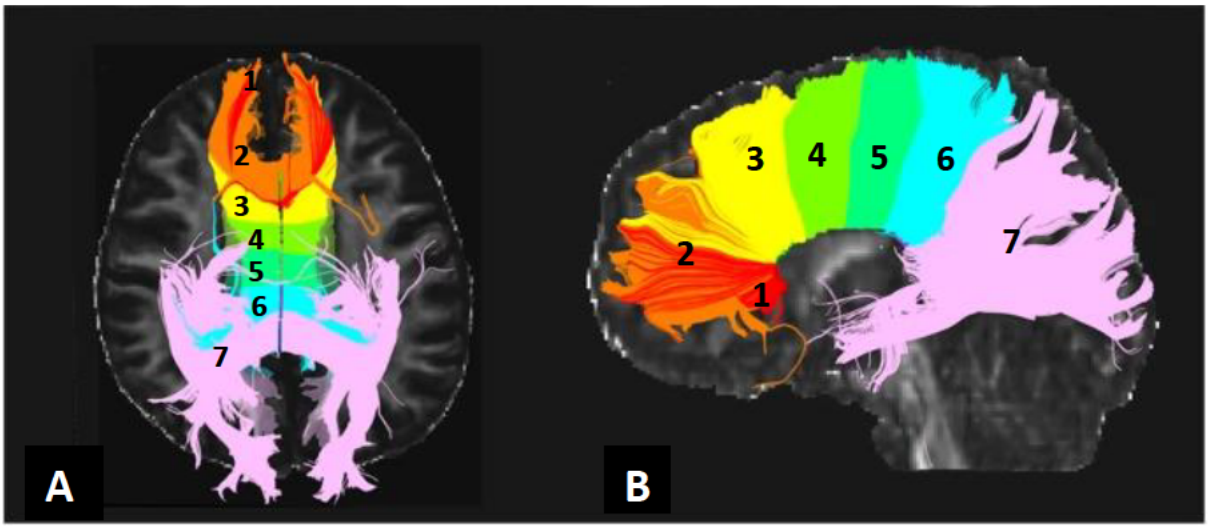

Figure 1.5. Diffusor tract imaging of the corpus callosum in a human brain with the seven major divisions of the corpus callosum labelled. Presented is an axial (A) and sagittal section (B) of the corpus callosum. (1) rostrum; (2) genu; (3) rostral body; (4) anterior midbody; (5) posterior midbody; (6) isthmus; (7) splenium.
Adapted from https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-019-2079-6

Comparisons between human and animal species of the structure of the corpus callosum suggest increases in brain size reflects hemispheric lateralisation processes (Ringo et al., 1994). The corpus callosum contributes to the lateralisation of brain function and is responsible for the exchange of information between the hemispheres of the brain, playing a crucial role in interhemispheric interactions (Takeuchi & Izumi, 2012).

There are two types of interhemispheric interactions: inhibition and facilitation. Interhemispheric inhibition is the neurophysiological mechanism that allows one hemisphere to inhibit the opposite hemisphere. This allows for the processing of unilateral information and the execution of unilateral movements without coactivation of contralateral muscles (Ni et al., 2009). In IHI, excitatory neurons from one hemisphere synapse on inhibitory neurons in the opposite hemisphere, causing a decrease in the firing rate of the neurons (Figure 1.6a). Conversely, interhemispheric facilitation (i.e., excitation) supports the performance of bilateral

movements and the exchange of bilateral information. In interhemispheric facilitation, an increase in the firing rate of a neuron from one hemisphere causes the neuron on which it synapses in the opposite hemisphere to increase in firing (Figure 1.6b) (Bloom & Hynd, 2005).

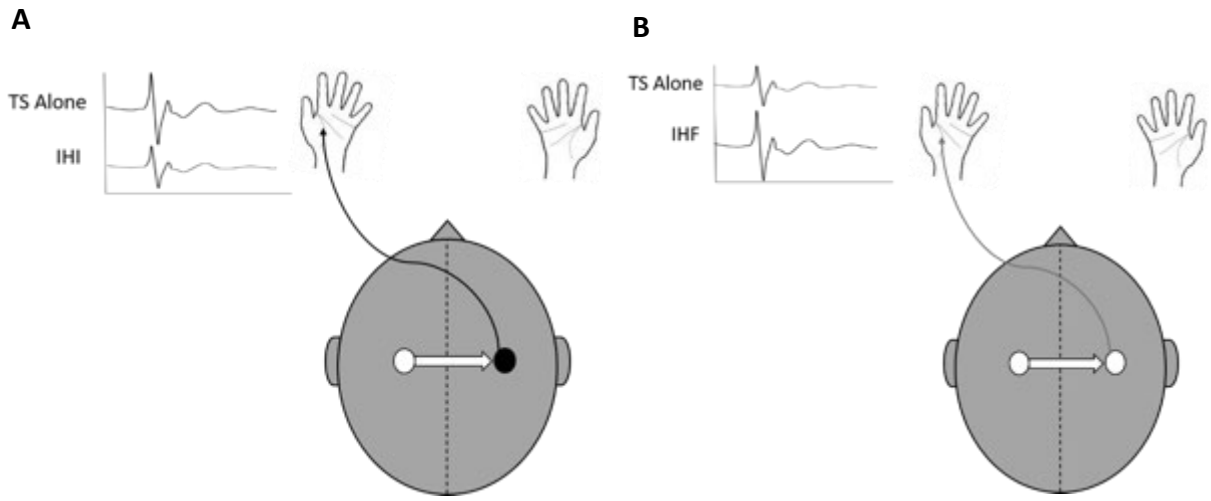

Figure 1.6. Schematic diagram of IHI (A) and IHF (B). The white circle represents excitation, and the black circle represents inhibitory interactions. The arrows denote the flow of the interaction. TS, test stimulus; IHI, interhemispheric inhibition; IHF, interhemispheric facilitation.

Interhemispheric sensorimotor transmission times between cortical areas in humans has been determined by Poffenberger (1912). Through a series of reaction time experiments, the time required for the transfer of information from one hemisphere to the opposite hemisphere was evaluated. Stimuli were presented to the left or right visual hemifield contralateral or ipsilateral to the responding hand, and participants were required to press a button as fast as possible after the stimuli were presented. The study findings demonstrated faster reaction times when the visual stimuli were presented ipsilateral to the responding hand due to intrahemispheric processing of sensory input and motor execution i.e., sensorimotor information being processed

within the same hemisphere. Reaction times were slower when the visual stimuli were presented contralateral to the responding hand, suggested to be due to the interhemispheric transfer of the sensory information via the corpus callosum to the hemisphere that controls the motor response, thus, leading to longer reaction times. The interhemispheric transfer time of sensorimotor information across the corpus callosum was proposed to be between 2 - 6 ms (Aboitiz et al., 1992; Poffenberger, 1912; Tamè & Longo, 2015). Subsequent research demonstrated IHI in humans occurs at short latencies of 6 - 15 ms and long latencies of 40 - 50 ms (Chen et al., 2003; Ferbert et al., 1992; Ni et al., 2009). Short and long latency IHI is discussed later in this section.

Studies investigating the functions of the corpus callosum in both animals and humans extended the findings of Poffenberger (1912) and informed a more detailed understanding of interhemispheric interactions, specifically IHI. These studies are reviewed in the following section.

1.3.2 Animal research investigating IHI via the corpus callosum

The majority of investigations studying the corpus callosum and IHI in animal models have examined visual functioning and simple tasks that provided foundational knowledge. Animal studies have investigated the role of the corpus callosum in the transfer of information between hemispheres using a process called callosotomy (Gavalas & Sperry, 1969; Gazzaniga, 1966; Myers & Sperry, 1953; Pearce, 2019; Sperry, 1961; Stamm & Sperry, 1957). Callosotomy is a procedure that involves partial or complete sectioning of the corpus callosum. Table 1.6 summarises the findings of several studies that have investigated callosotomy in animals.

Table 1.6. Studies investigating the role of the corpus callosum in animal species

Author (Year)	N	Population	Method	Outcome Measure	Finding
Myers and Sperry (1953)	NR	Sectioning of the corpus callosum in cats	Visual discrimination task	Correct responses for pattern discrimination	Interhemispheric transfer of sensory information between hemispheres was blocked. The corpus callosum is required for transfer of sensory information between hemispheres.
Myers (1956)	6	Cats with optic chiasm and corpus callosum sectioned	Visual discrimination task	Number of correct responses	Interocular transfer of visual information from the trained eye to the untrained eye failed when the corpus callosum was sectioned but not when the optic chiasm was sectioned. The corpus callosum is important in integrating interhemispheric information.
Myers and Sperry (1958)	14	Cats with optic chiasm and cortical removal	Visual discrimination tasks	Number of correct responses	Cats with sectioned corpus callosum failed to transfer the complex visual pattern learnt with the trained eye to the opposite untrained eye
Gazzaniga (1966a)	10	Macaca nemestrina monkeys with sectioning of the corpus callosum, ant and hippocampal commissures and optic chiasm	Visual discrimination task	90% correct responses in consecutive visual discrimination task trials	Interhemispheric transfer of visual discrimination patterns did not occur immediately.
Gazzaniga (1966b)	5	Macaca nemestrina monkeys with sectioning of the corpus callosum, ant and hippocampal commissures and optic chiasm	Visual discrimination task	90% correct responses in consecutive visual discrimination task trials	One hemisphere of split-brain monkeys was distracted by stimuli presented to the opposite hemisphere if exposure was prolonged. If stimuli presented was brief the opposite hemisphere was unaffected. Thought to be affected by subcortical mechanisms or intracortical mechanisms.
Gavalas and Sperry (1969)	4	Macaca nemestrina monkeys with sectioning of the optic chiasm and corpus callosum	Visual pattern task	Number of correct trials	Integration of visual patterns projected separately to right and left sides was achieved but not interocular transfer of visual pattern training i.e. training in one eye was not transferred to the other eye due to corpus callosum sectioning
Trevarthen (1962)	2	Monkeys with optic chiasm, corpus callosum, and anterior and hippocampal learning	Contradictory pattern discrimination tasks	Number of correct trials	Simultaneous learning of contradictory pattern discriminations occurred in split-brain monkeys
Glickstein and Sperry (1960)	7	Three normal rhesus monkeys and four monkeys with anterior, hippocampal and corpus callosum sectioning	Somesthetic discrimination tasks	Number and percentage of correct trials	Collosum-sectioned monkeys failed to transfer learning of somesthetic tasks from the trained hand to untrained hand.

Note: N, sample size; NR, not reported.

Callosotomy studies in cats have found the transfer of visual information from one hemisphere to another is inhibited (Myers, 1956; Myers & Sperry, 1953, 1958). Myers (1956) investigated interocular transfer of visual information in cats to better understand the role of the corpus callosum by presenting a visual discrimination task to one eye. Myers (1956) demonstrated that cats that had undergone callosotomy were unable to transfer the visual pattern information from the trained eye to the untrained eye. In contrast, the control cats with an intact corpus callosum could perform the pattern taught to the first eye with the second eye. This is due to interhemispheric transfer of visual information from the hemisphere of the trained eye to the hemisphere of the untrained eye via the corpus callosum fibres. Interestingly, when the corpus callosum in the control cats was cut following training of the first eye, they could still perform the pattern with the second eye. This finding demonstrated that the corpus callosum is important in providing interhemispheric facilitation of visual information to be duplicated in the opposite hemisphere.

In monkeys, callosotomy studies show visual information is processed independently by each hemisphere as interhemispheric transfer of information is abolished (Gavalas & Sperry, 1969; Gazzaniga, 1966a, 1966b; Glickstein & Sperry, 1960; Trevarthen, 1962). Studies with callosotomised monkeys demonstrate that sensory information presented to the divided hemispheres can be separately controlled (Glickstein & Sperry, 1960; Sperry, 1961; Trevarthen, 1960). Trevarthen (1960) studied callosotomised monkeys to understand if the hemispheres operate one at a time or have two separate processes operating simultaneously. Using a visual discrimination exercise, they presented patterns to one eye and the same pattern in reverse to the other eye. Trevarthen (1960) found that the different patterns could be processed with each eye independently (i.e., one hemisphere would process a pattern and the opposite hemisphere would process the pattern in reverse simultaneously). Furthermore, when

the monkeys were made to process complex-coloured patterns, the eye contralateral to the responding hand learned the pattern better than the opposite eye.

These animal studies demonstrate lateralisation of the brain as each hemisphere processed visual information independently. The findings show that without the corpus callosum, interhemispheric integration of information is absent and interhemispheric inhibition of visual information that allows strictly unilateral performance is also deficient. These animal studies highlight the importance of the corpus callosum in the interhemispheric transfer of information, where interhemispheric facilitation would allow for the integration of information to the opposite side and allow both hemispheres to work in unity on one task in normal circumstances. Conversely, IHI would increase to allow unilateral processing of one hemisphere while the opposite hemisphere remains aware of the task being performed. While these findings are significant, their applicability to humans, who can perform more complex tasks and exhibit higher cognitive function, is limited. A review of studies in humans investigating the corpus callosum to understand IHI is presented below.

1.3.3 Human studies investigating IHI via the corpus callosum

In humans, the transcallosal response across the corpus callosum was first measured by Cracco et al. (1989). They applied a unilateral magnetic coil over the right hemisphere and recording electrodes over the left hemisphere. The results showed that following the stimulation of the right hemisphere, evoked transcallosal responses had a minimum onset of 8 – 12 ms, a duration of 7 – 15 ms and an amplitude of 20 μV with high focal specificity. These findings suggested a direct transcallosal connection between homologous areas of the hemispheres. Interhemispheric interactions between M1s were further characterised by Ferbert (1992) (detailed in section 1.4).

However, theories and understandings of IHI in humans were developed from studies of split-brain individuals that had undergone callosotomy. Callosotomy was often performed in individuals with intractable epilepsy to prevent epileptic seizures from spreading to the opposite hemisphere. Callosotomies have allowed researchers to investigate cerebral lateralisation in humans more effectively with key studies conducted by Sperry and Gazzinga. Their research demonstrated split-brain patients independently processed information presented to each hemisphere such as visual, perceptual, and sensory information (Gazzaniga, 1967; Gazzaniga & Sperry, 1967; Sperry & Gazzaniga, 1967; Sperry et al., 1969). For example, a visual discrimination task was presented to patients that required them to identify patterns of light presented to one eye only or to each individual eye simultaneously. The patients showed they could process visual information to each eye simultaneously in the same amount of time as it took to process information in one eye. This indicated the hemispheres separately processed the information due to the lack of interhemispheric transfer and integration of information (Gazzaniga & Sperry, 1966). In another study, Gazzaniga et al. (1963) showed sensory input was more impaired when presented to the contralateral hemisphere compared to the minimal impairment when sensory input was presented to the ipsilateral hemisphere. Further, results showed tactile stimulation of the left side could be pointed to by the left hand but not the right hand, whilst temperature and pain discrimination could not be discerned correctly between the right and left sides of the body due to the abolished interhemispheric integration of sensory information. These studies showed how callosotomy affected the transfer of visual, sensory, and attentional information from one hemisphere to the other. They also demonstrated lateralisation of the hemispheres and the importance of the corpus callosum in interhemispheric transfer of information. Table 1.7 summarises studies that have investigated interhemispheric communication in split-brain patients.

Table 1.7. Studies investigating the role of the corpus callosum in humans.

Author (Year)	N	Population	Method	Outcome Measure	Finding
Gazzaniga et al. (1963)	1	Patient with seizures undergone surgical sectioning of the cerebral commissures	Somatosensory tests	Correct responses to somatosensory tests	Somatosensory tests revealed separation of the right and left extremities and right and left sides of the trunk. Severe impairment during right-left cross integration
Gazzaniga and Sperry (1966)	4	Individuals with epilepsy undergone callosotomy	Visual discrimination tasks	Time taken to respond to stimuli a single or double discrimination task in the visual field	Callosotomy patients completed the double discrimination task as fast as they did for the single discrimination task. Healthy subjects took 40% longer to complete the double discrimination task than the single task
Meyer et al. (1995)	10	Individuals with abnormalities of the corpus callosum	Transcranial magnetic stimulation	Silent period (ms)	EMG activity was not suppressed, with delayed onset latency in individuals with abnormalities of the anterior section of the corpus callosum compared to healthy controls
Eliassen et al. (1999)	1	Individuals with callosotomy	Completion of drawing presented	Total response time, directional variability and movement initiation synchrony	Following posterior callosotomy mirror image drawings become less symmetrical. The posterior corpus callosum plays an important role in meditating hand coordination during bimanual movements
Roland et al. (2017)	22	Individuals with epilepsy undergone partial or complete surgical sectioning of the corpus callosum	Resting state-fMRI	BOLD – functional connectivity	Interhemispheric functional connectivity was reduced showing callosal connections are required in interhemispheric functional connectivity

Note: N, sample size; fMRI, functional Magnetic Resonance Imaging; Bold, Blood-Oxygen-Level-Dependent; ms, millisecond; EMG, electromyography

Research on humans has also confirmed direct evidence of the cortical origin of IHI. Di Lazzaro et al. (1999) measured from the epidural space of the cervical spinal cord in healthy humans, descending corticospinal volleys (I-waves) produced by transcranial stimulation in one hemisphere and measured how MEPs were affected by a preceding magnetic stimulus over the opposite hemisphere. Their findings showed that the conditioning stimulus had a significant inhibitory effect on the later (I3) descending volleys, which originates from the indirect activation of pyramidal tract neurons of the cerebral cortex. Whereas, for the earlier volleys, I2 was less inhibited and I1 was not inhibited. Thus, IHI is thought to originate predominately at a cortical level (Boroojerdi et al., 1996; Ferbert et al., 1992; Meyer et al., 1995).

Investigations of IHI on spinal excitability demonstrating no inhibition of the H-reflex further confirms IHI is of cortical origin (Ferbert et al., 1992; Gerloff et al., 1998; Harris-Love et al., 2007; Ni et al., 2009). H-reflex is a measure of spinal α-motoneuron excitability. It assesses the modulation of monosynaptic reflex activity in the spinal cord (Palmieri et al., 2004). Several studies have demonstrated magnetic stimulation has no effect on the peak-to-peak amplitude of H-reflexes in proximal and distal arm muscles, confirming that spinal inhibitory mechanisms do not contribute to IHI and that it occurs at a cortical level (Ferbert et al., 1992; Gerloff et al., 1998; Harris-Love et al., 2007; Ni et al., 2009).

The fibres of the corpus callosum that mediate IHI are predominantly made up of excitatory neurons that synapse onto inhibitory neurons in the opposite hemisphere. This occurs at two phases of IHI i.e., short and long latency IHI that are mediated by different cortical inhibitory neurons. The following section describes the physiological origins of short and long latency IHI pathways.

1.3.4 The physiological origins of SIHI and LIHI

In humans, there are two distinct phases of IHI, short and long latency IHI. Short latency IHI (SIHI) occurs between 6 – 15 ms and long latency IHI (LIHI) occurs between 40 – 50 ms (Chen et al., 2003; Ni et al., 2009; Reis et al., 2008). Theories of neurotransmitter systems mediating IHI developed from animal studies that suggested $GABA_A$ neurons mediate SIHI and $GABA_B$ neurons mediate LIHI (Chowdhury et al., 1996a; Chowdhury et al., 1996b; Kawaguchi & Kubota, 1997). Palmer et al. (2012) comprehensively described the microcircuitry underlying IHI by studying the rat somatosensory cortex. Their findings showed $GABA_B$ receptors mediate LIHI. The authors further demonstrated that callosal input activates cortical layer 1 and projects to cortical layer 5 where pyramidal neurons were inhibited for hundreds of milliseconds when ipsilateral stimulation was applied to the somatosensory cortex after contralateral stimulation. They concluded that LIHI is mediated predominately through direct postsynaptic mechanisms in the apical dendritic shafts of pyramidal neurons (Palmer et al., 2013; Palmer et al., 2012). The findings that $GABA_B$ mediated LIHI were further replicated in mice studies of the primary visual cortex (He et al., 2015) and motor area (Spalletti et al., 2017).

In humans, Irlbacher et al. (2007) sought to characterise the neurotransmitter system mediating SIHI and LIHI. They examined the effects of $GABA_B$ and $GABA_A$ agonist medication on LIHI and SIHI, respectively. Their findings demonstrated that $GABA_B$ agonist medication did not significantly enhance SIHI, but significantly strengthened LIHI. However, $GABA_A$ was not shown to influence SIHI. They concluded that LIHI is mediated by post-synaptic $GABA_B$ receptors similar to previous animal studies, however the results remained inconclusive regarding receptors mediating SIHI. This demonstrates a gap in the literature as the SIHI pathway is not yet fully understood.

Various methodological techniques have been used to assess IHI in humans. In earlier studies, transcranial magnetic stimulation (TMS) was used to assess IHI and has since remained a popular method of IHI assessment with two paradigms being used to assess IHI between primary motor cortices. Further, electroencephalography (EEG) is becoming increasingly popular in measuring IHI between primary sensory cortices. The following section discusses the methods of TMS and EEG used to measure IHI.

1.4 Assessment of IHI in Humans

1.4.1 Assessing IHI between primary motor cortices (M1)

The following section outlines the different methods of assessing IHI between primary motor cortices using TMS. An overview of TMS is presented first followed by a discussion of paired-pulse stimulation and the ipsilateral silent period (iSP) that are the common paradigms used to assess M1 IHI. The advantages and limitations of each paradigm are then discussed.

Transcranial magnetic stimulation (TMS)

Non-invasive brain stimulation techniques can be used to assess IHI in humans. One such non-invasive brain stimulation technique is TMS. Transcranial magnetic stimulation is a safe, painless neurophysiological technique that is commonly used to assess human brain activity in healthy and patient populations (Klomjai et al., 2015).

Transcranial magnetic stimulation is based on Faraday's law of electromagnetic induction. A magnetic stimulator produces a current that is transmitted through the TMS coil which induces a magnetic field. A figure-of-eight shaped coil is most used, which produces a more focal magnetic field. The TMS coil is placed over the scalp and the magnetic field from the coil penetrates the scalp and skull generating an electrical current within the underlying brain tissue. In response to this trigger stimulus, corticospinal neurons are depolarised, thus activating a series of waves referred to as descending corticospinal volleys. These volleys are activated either directly (D waves) as a result of direct activation of pyramidal neurons, or indirectly (I waves) as a result of indirect activation of pyramidal neurons and travel down the corticospinal tract to the target muscle and elicit a muscle response (Figure 1.7) (Barker et al., 1985; Di Lazzaro et al., 2001; Di Lazzaro et al., 2018). The muscle response is recorded as a MEP using surface or intramuscular EMG.

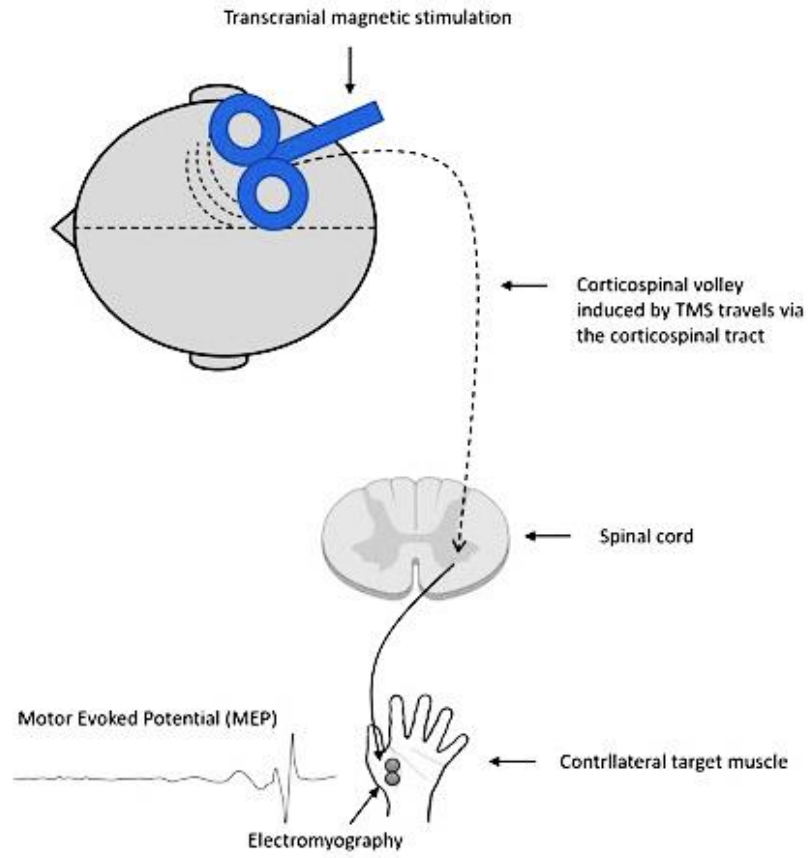

Figure 1.7. A schematic representation of transcranial magnetic stimulation. A figure of 8 coil is applied to the primary motor cortex. Corticospinal volleys are generated and travel down the corticospinal tract through the spinal cord to the target muscle. A resulting motor-evoked potential is produced recorded by electromyography.

Motor evoked potentials (MEP)

The MEP is the most common TMS measure used to assess the excitability of the corticospinal motor system providing information on the reactivity and response of stimulated neurons (Hallett et al., 2017). The MEP is expressed as the peak-to-peak amplitude which is a measure of the number of pyramidal tract neurons activated along the corticospinal tract (Figure 1.8) (Kobayashi & Pascual-Leone, 2003). The MEP amplitude consists of cortical and spinal contributions resulting from direct and indirect activation of descending corticospinal volleys. Hence, the MEP provides a measure of corticomotor excitability, also known as corticomotor output.

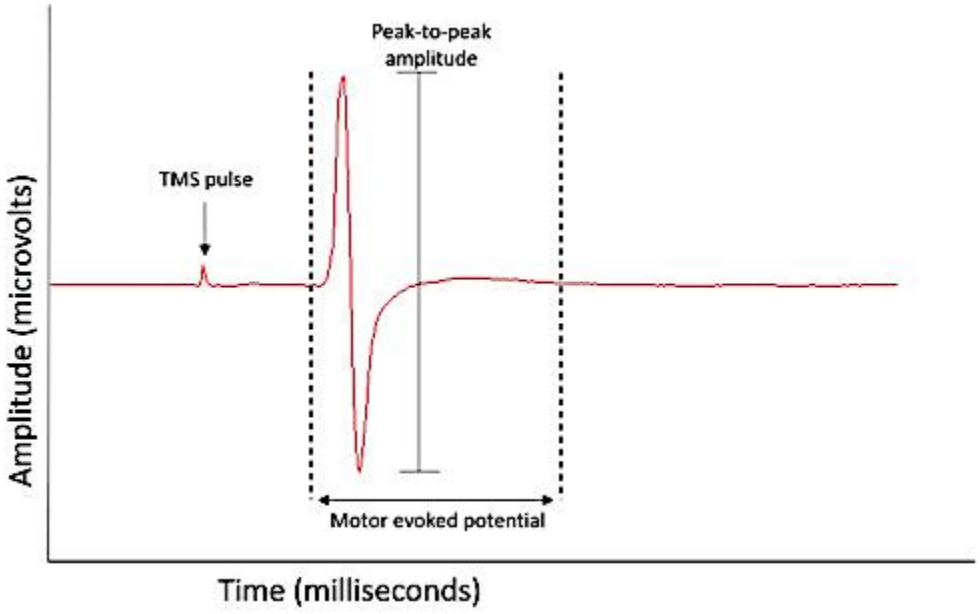

Figure 1.8. Image of a motor evoked potential following transcranial magnetic stimulation (extracted and edited from Chapter 2, Study 1).

There is evidence suggesting MEPs are variable and can be influenced by methodological factors such as stimulation intensity, coil position and EMG background activity (Rossini et al., 2015; van der Kamp et al., 1996). Despite this, when these factors are accounted for, the MEP amplitude is a measure that provides a specific indication of the integrity and excitability of the corticospinal tract and local cortical circuits in individuals with disease or following an intervention (Barker et al., 1987; Barker et al., 1985; Reis et al., 2008; Rossini et al., 2015).

Transcranial magnetic stimulation can be delivered as a single pulse (termed single-pulse TMS), which can assess cortical output of a single cortical region (Rossini et al., 2015). Transcranial magnetic stimulation can also be delivered in pairs of stimuli separated by an interval (interstimulus interval) and is termed paired-pulse TMS. Paired-pulse TMS can be used to assess a single cortical region by delivering two pulses, a subthreshold pulse and a suprathreshold pulse, through the same coil. Paired-pulse TMS can also assess two different cortical regions by delivering a suprathreshold pulse through one TMS coil and a second

suprathreshold pulse through a second TMS coil. The former paired-pulse method allows for the investigation of intracortical circuits of facilitation and inhibition, and the latter paired-pulse paradigm measures interhemispheric circuits of inhibition and facilitation (Ferbert et al., 1992; Reis et al., 2008; Valls-Solé et al., 1992; Wassermann et al., 1996).

1.4.1.1 Using TMS to measure IHI

The following section is focused on the application of TMS to assess IHI between cortical regions of the two hemispheres. To assess IHI, two main paradigms using TMS are used: paired-pulse TMS and the ipsilateral silent period.

1.4.1.2 Paired-pulse paradigm

The paired-pulse paradigm assesses IHI by delivering two suprathreshold pulses via two separate TMS coils. Ferbert et al. (1992) conducted a seminal study whereby IHI in a healthy cohort of participants was measured using the application of the paired-pulse paradigm. This paradigm involves applying a suprathreshold pulse called the conditioning stimulus (CS) delivered over a cortical region of one hemisphere that precedes and is inhibited by a second suprathreshold pulse, the test stimulus (TS), delivered over the homotopic site in the opposite hemisphere (Daskalakis et al., 2002; Ferbert et al., 1992) (Figure 1.9). In the study by Ferbert et al. and since confirmed by other authors, inhibition of the test MEP at conditioning-test intervals is demonstrated between 6 - 50 ms when muscles are at rest or active, consistent with transcallosal conduction times of the corpus callosum (Chen et al., 2003; Di Lazzaro et al., 1999; Ferbert et al., 1992). Interhemispheric inhibition can be assessed between the left and right hemispheres in either direction. However, from the left to right hemisphere is reported to be the dominant IHI direction for individuals with dominant right-hand function and visa-versa (Bäumer et al., 2007; Netz et al., 1995).

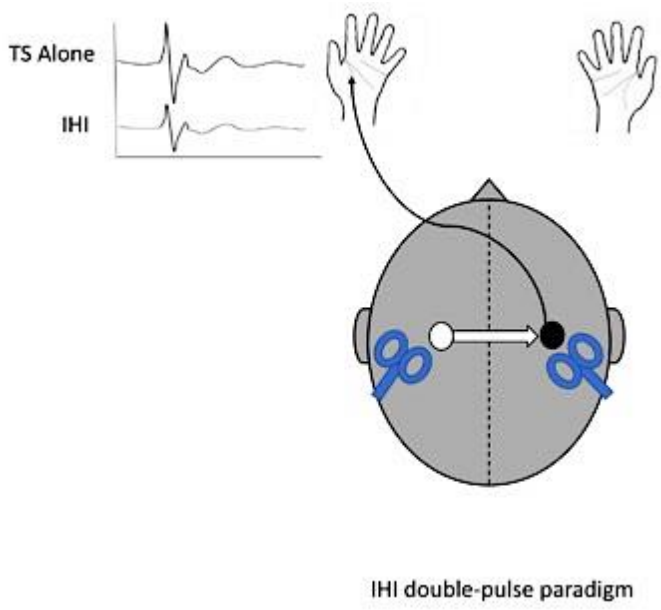

Figure 1.9. Pictorial representation of the double-pulse IHI paradigm. The conditioning stimulus (CS) over the left hemisphere activates excitatory neurons (white circle) resulting in an unconditioned MEP response. This unconditioned response is inhibited by a test stimulus (TS) that activates inhibitory neurons (black circle) resulting in an inhibited MEP (IHI).

Factors affecting the paired-pulse paradigm

There are several known factors that are important in the assessment of IHI when using the paired-pulse paradigm. These include interstimulus intervals (ISIs), the current direction induced by TMS coil orientation and the conditioning stimulus intensity (Chen et al., 2003; Ni et al., 2009).

The effect of ISI on IHI

Interstimulus intervals ranging from 8 – 50 ms are demonstrated to affect the level of IHI. As explained earlier, there are two distinct phases of IHI, short and long latency IHI. Short latency IHI occurs between 6 – 15 ms ISIs and has been predominantly found to occur at 10 ms, whereas LIHI occurs between 40 - 50 ms ISIs (Chen et al., 2003; Ferbert et al., 1992; Ni et al., 2009). Interestingly, the range of ISIs that can be investigated between M1s negates findings

of animal studies that suggested limited callosal connections exist between motor areas (Perez & Cohen, 2009). Nonetheless, these two phases are distinct as they demonstrate the deepest level of inhibition i.e., the maximum amount of IHI identified, at the given ISI's (Ferbert et al., 1992; Gerloff et al., 1998). For example, when eliciting IHI in upper limb muscles, the maximum amount of IHI is demonstrated at 10 ms ISI (Harris-Love et al., 2007). This is due to the different neuronal populations or physiological origins of SIHI and LIHI. This has been demonstrated by Chen et al. (2003) by examining the differences in IHI between 8 and 40 ms ISI's. They showed IHI at 8 ms was reduced with target muscle activation but 40 ms showed little change. Moreover, IHI at 40 ms was correlated to the ipsilateral silent period duration (another measure of inhibition that will be detailed below in section 1.4.1.3), whereas 8 ms was not. This suggests similar mechanisms may mediate IHI at 40 ms and the ipsilateral silent period. Taken together, SIHI and LIHI have different physiological origins mediated by different mechanisms and both affect the amount of IHI.

The effect of current direction on IHI

A key study by Chen et al. (2003) was one of the first to investigate the effect of current direction of the CS coil on IHI. This was conducted in 10 healthy participants during two conditions: i) at rest while muscles in both hands were relaxed; and ii) during an active condition requiring voluntary contraction of a right-hand muscle. The induced current directions tested in the right M1 were anterior medial (AM), posterior medial (PM), posterior lateral (PL) and anterior lateral (AL). The authors demonstrated the effect of current direction on IHI was not significant. That is, IHI was elicited at all current directions but the direction of the current in the brain did not affect the depth of IHI at 8 or 40 ms ISI when at rest and during the active condition. Similarly, Ni et al. (2009) demonstrated that CS current direction does not affect IHI at short or long latencies. Interestingly, this is in contrast to single-pulse TMS studies of ipsilateral or contralateral MEPs which show that the population of cortical neurons

activated by TMS depends on the induced current direction (Di Lazzaro et al., 2001; Di Lazzaro et al., 1999; Sakai et al., 1997; Werhahn et al., 1994; Wilson et al., 1996). For example, single-pulse TMS that induces current in a medial and lateral direction produces shorter latency MEPs or earlier latency responses in the contralateral hand muscles compared with anterior or posterior directed current (Sakai et al., 1997; Werhahn et al., 1994). A likely explanation is that corticomotor excitability (i.e., single-pulse TMS) and IHI reflect different neuronal populations (Boroojerdi et al., 1996; Le Pera et al., 2001; Svensson et al., 2003). Hence, the effect of TMS on corticospinal excitability does not necessarily result in a change in the IHI pathway due to the separate cortical neuron populations mediating each pathway. Thus, it is possible that the neuronal population mediating corticospinal activity of the corticospinal tract has lower thresholds than the neuronal population mediating IHI, making them more sensitive to current direction.

The effect of conditioning stimulus intensity on IHI

The effect of conditioning stimulus intensity has been demonstrated to be important in eliciting IHI. Chen et al. (2003) investigated conditioning stimulus intensities of 45 to 90% of stimulator output at rest and during muscle activation for SIHI and LIHI at 8 and 40 ms ISI, respectively. Interhemispheric inhibition increased at both rest and active conditions with stimulus intensities from 45% to 75% of stimulator output but showed no significant difference between 75% and 90% stimulator output. That is, stimulus intensity of the CS affects the depth of inhibition, with increasing stimulus intensity resulting in increasing inhibition. Ni et al. (2009) also demonstrated the effects of different CS intensities on SIHI and LIHI between M1s. Eight conditioning stimulus intensities from 60 - 200% of active motor threshold (AMT) were tested in increments of 20% at 10 and 50 ms ISI. The findings demonstrated inhibition increased with higher CS intensities for both SIHI and LIHI. However, LIHI showed inhibition over a wider range of CS intensities (120 - 200% of AMT) compared to SIHI, which required higher CS

intensities (from 160 - 200% of AMT). The findings further demonstrated for SIHI, CS location i.e., the cortical area chosen, is important regarding the effect produced by CS intensity. This suggests that for SIHI the effect of CS intensity depends on the CS location. However, this effect is not observed for LIHI. The differences in the intensities required to elicit SIHI and LIHI and that the CS location impacts each latency differently, suggests that SIHI and LIHI are mediated by different neuronal populations (Section 1.3.4). Specifically, LIHI is mediated by neurons with a lower firing threshold compared to SIHI.

1.4.1.3 Ipsilateral silent period technique (iSP)

The second method of IHI assessment investigated by Ferbert et al. (1992) is the ipsilateral silent period (iSP). This method involves the application of a single suprathreshold TMS pulse to the hemisphere ipsilateral to a voluntary contraction, which suppresses voluntary EMG activity giving an ipsilateral silent period (Figure 1.10) (Ferbert et al., 1992; Meyer et al., 1995; Triggs et al., 1993). Ferbert et al. (1992) demonstrated inhibition occurred 30 – 35 ms after the CS and lasted approximately 35 ms. The iSP uses onset latency, depth, and duration to assess IHI. The iSP measures the inhibition of volitional motor activity, making it a technique more suited than paired-pulse IHI to examine the control of voluntary movement (Beaule et al., 2012).

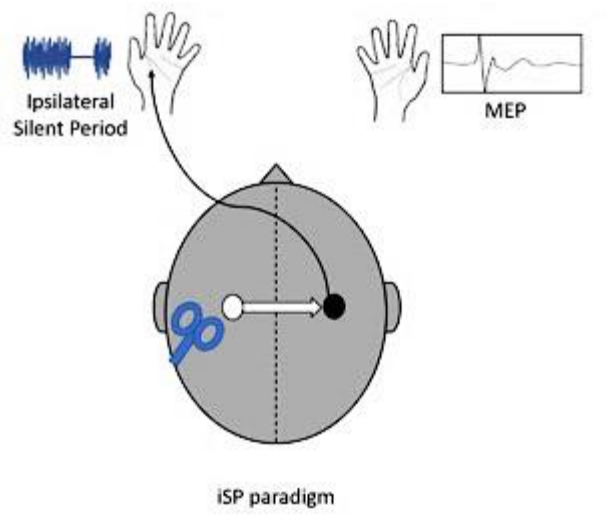

Figure 1.10. Pictorial representation of the ipsilateral silent period paradigm. A TMS coil is applied ipsilateral to the hand sustaining a contraction causing an interruption of EMG activity i.e., an ipsilateral silent period.

Similar to the paired-pulse paradigm, the iSP outcome can also be influenced by methodological factors. The duration of the iSP can be modulated by the intensity of the CS stimulation. As the CS intensity increases, the duration of the silent period increases (Chin et al., 2012). In addition, the current direction influences iSP and has been shown to increase iSP duration (Chen et al., 2003).

The reliability of the iSP measure has also been investigated. Intersession reliability of the iSP latency, duration, and depth was investigated by Fleming and Newham (2017) in young and older adults for the left and right first dorsal interosseous (FDI) muscles. Participants were instructed to activate the FDI muscle at approximately 75% of their maximum voluntary contraction (MVC). Their findings demonstrated moderate to good reliability for iSP duration for both groups (All ICC values > 0.6). Moderate to good reliability was demonstrated for iSP latency for the younger group but only for the left FDI of the older group (ICC, 0.69–0.91). In contrast, iSP depth was less reliable indicating poor reproducibility (ICC, < 0.4). However, the results also demonstrated inter-individual variation in some participants, but no pattern in the

variability was observed. This suggests the variability observed, which may affect the reproducibility of iSP, could be due to: i) inconsistent amount of voluntary muscle activity between sessions; ii) variation in TMS coil placement and orientation, as the orientation of coil placement and hence current direction has been shown to influence the iSP and, iii) the stimulation intensity used. Fleming and Newham (2017) used a fixed stimulation of 80% of stimulator output which could result in a variable amount of stimulation received and thus, variability in outcome if resting motor threshold (RMT) is variable across participants. Whereas, stimulating at a percentage of RMT ensures consistency in stimulation across participants (Groppa et al., 2012). It can be concluded that iSP duration is a reliable marker of IHI, but that a large change in iSP duration is required to be clinically meaningful. However, this is contrary to a review by Perez and Cohen (2009) that demonstrated inter-individual variability of the iSP in proximal arm muscles is higher when measured by iSP than with the paired-pulse protocol, which presents a disadvantage for this method.

The iSP reflects inhibition at the cortical level. The mechanism of iSP involves activation of $GABA_B$ receptors exciting inhibitory neurons and thus, decreasing corticospinal neuron firing and representing a measure of corticomotor disinhibition (Chin et al., 2012; Cracco et al., 1989). Studies investigating neurological patients have provided evidence that the iSP is mediated by fibres of the corpus callosum. For example, in patients with agenesis or cortical lesions of the corpus callosum, a delayed or absent iSP was demonstrated (Meyer et al., 1995; Meyer et al., 1998). However, no effect on iSP was observed where subcortical lesions affected the corticospinal tract and not the corpus callosum (Boroojerdi et al., 1996). Further, in children where complete myelination of the corpus callosum was yet to develop, iSP was either not detectable or significantly shorter than in adults (Heinen et al., 1998). It has also been suggested the neural mechanism underlying iSP may be similar to LIHI as both are mediated by $GABA_B$ receptors, while it differs from SIHI (Chen et al., 2003). Nonetheless, the iSP has proven to be

a good tool to investigate voluntary cortical motor output. Motor output to the contralateral hand is restricted, increasing IHI and inhibiting mirror movements (Beaule et al., 2012). This suggests that the mechanism underlying the iSP has an important role in supressing unwanted mirror movements.

1.4.1.4 Strengths and limitations of the paired-pulse and iSP paradigms

The current literature presents advantages and disadvantages for both the paired-pulse and iSP paradigms. It is well established that CS intensity influences the time course of IHI (Chen et al., 2003; Ni et al., 2009). When the CS intensity is increased for the paired-pulse technique the duration of inhibition increases, whereas it remains stable for the iSP. Though, the paired-pulse method is not affected by different current directions (Chen et al., 2003). Thus, when applying the TMS coil to deliver the CS, it can be positioned in any direction, usually 90 degrees to the vertex/midline to avoid overlapping. Coil overlap is recognised as a limitation of the paired-pulse technique, although it is commonly overcome by using a coil of smaller diameter to deliver the CS (Harris-Love et al., 2007; Hinder et al., 2010; Singer et al., 2013; Vercauteren et al., 2008). An undesirable consequence of this, however, is that the stimulation delivered to the brain is more focal than when using larger coils and may compromise the detection of the motor hotspot. Coil overlap is not an issue for iSP as only one coil is required for this technique. The magnitude of voluntary contraction for the iSP method has been employed over a wide variety of levels from 15 to 100% of MVC. It has been demonstrated that the amount of IHI does not differ across muscle contraction levels of 30%, 50% and 100% of MVC for iSP duration or normalised iSP but iSP area produces large variability (Kuo et al., 2017). However, this is not an issue for the paired-pulse method as MVC is not employed in this method.

Moderate to good reliability has been demonstrated for iSP duration in healthy individuals (Fleming & Newham, 2017). A single study has demonstrated significant test-retest reliability of paired-pulse IHI measurements at 12 ms for the left hemisphere and 10 ms for the right hemisphere at a group level in healthy individuals (De Gennaro et al., 2003). Due to high within and between-subject variability the findings did not support high reproducibility of the paired-pulse paradigm. However, for proximal arm muscles, inter-individual variability in IHI is higher with the iSP technique than the paired-pulse protocol (Perez & Cohen, 2009). In stroke patients, paired-pulse IHI has demonstrated moderate to excellent reliability from the contralateral to ipsilateral hemisphere (Cassidy et al., 2016).

In summary, there are advantages and disadvantages for both the paired-pulse and iSP techniques for measuring IHI. The current literature suggests that iSP or paired-pulse technique selection is best governed by the intended participant population, muscle tested, muscles relaxed or in voluntary contraction, the number of sessions, ISI tested and current direction. However, it has been suggested that iSP technique provides complementary but not identical information on IHI compared to the paired-pulse method (Perez & Cohen, 2009). Therefore, taking the latter information into consideration, for the purpose of this thesis it was deemed appropriate to use the paired-pulse method at short and long latencies to investigate IHI. Nonetheless, further studies that compare paired-pulse and iSP protocols to determine their reliability and reproducibility appear warranted.

1.4.2 Assessment of IHI between primary sensory cortices

1.4.2.1 The primary sensory cortex

The primary sensory cortex (S1) is part of the somatosensory cortex and is located in the postcentral gyrus of the cerebral cortex of each hemisphere. It comprises four cytoarchitectonic sub-divisions labelled Broadman's areas 1, 2, 3A and 3B (Figure 1.11). The role of the somatosensory system is to process sensory information. This includes tactile sensation such as pressure and vibration, proprioception i.e., head and body position and movement, and modalities of sensation such as pain and temperature (Jacobs, 2011). The sensory distribution of each body part is mapped on the sensory homunculus. Certain areas of the body have larger representations due to greater sensory innervation density. For example, the hand representation within S1 is much larger in comparison to other body parts (Penfield & Boldrey, 1937).

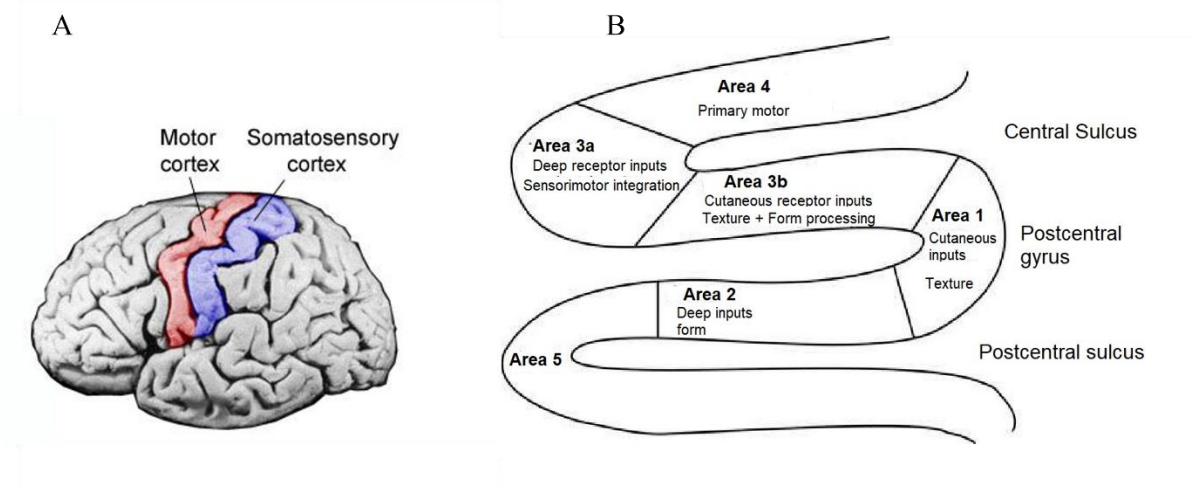

Figure 1.11. The primary sensorimotor cortex. (A) Image of the primary sensory cortex and primary motor cortex in the brain. Source: https://www.pinterest.com.au/pin/375909900120380546/ (B): Cytoarchitectonic sub-divisions of the primary sensory cortex. Area 3a, 3b 1, and 2 make up the primary sensory cortex. Modified from "The neural basis of haptic object processing" by James et al., 2007, Canadian Journal of Experimental Psychology, 61(3), p.220.

1.4.2.2 Sensory Evoked Amplitude

To investigate somatosensory cortex activity, sensory evoked potentials (SEPs) are recorded. The SEP measures presynaptic and postsynaptic electrical activity of the somatosensory cortex in response to sensory input such as peripheral or cutaneous stimulation at the skin surface, targeting the receptive area of a pre-selected nerve. In many research studies, the median and ulnar nerves in the upper limb are commonly stimulated as they produce large and reliable SEPs (Allison et al., 1991; Bergamaschi et al., 1993; Cruccu et al., 2008; Mauguière et al., 1999; Salerno et al., 1999). The radial nerve has also been assessed in studies of induced muscle pain (De Martino et al., 2018). However, radial nerve stimulation is studied less frequently as it is thought that the median nerve is sufficient in representing the whole body (Treede & Kunde, 1995). In the lower limb, the tibial nerve is a common stimulation site (Cruccu et al., 2008; Mauguière et al., 1999).

Sensory evoked potentials reflect cerebral action potentials of the hemisphere contralateral to noxious or non-noxious peripheral nerve stimulation, recorded over the scalp via EEG (Dawson, 1947; Passmore et al., 2014). The electrical activity recorded generates positive and negative deflections, resulting in a waveform. Multiple waveforms are recorded then averaged for analysis. The waveform is analysed for the different components identified by peaks and troughs (Figure 1.12). The latency of SEP components following the initial stimulation and the peak to peak amplitude can be used to interpret changes in neural activity and excitability of the cortex (Diers et al., 2007; Mauguiere, 2005; Passmore et al., 2014; Schabrun et al., 2015b; Schabrun et al., 2013). For example, suppressed SEP peak-to-peak amplitudes reflect inhibition whereas increased SEP amplitudes reflect facilitation, while prolonged latency can indicate slowing down of conduction of the peripheral nerve pathway due to disease, injury, or other factors such as age. Neural activity and excitability are typically measured in contralateral S1 but can also be measured between S1s to investigate interactions between the cortical regions.

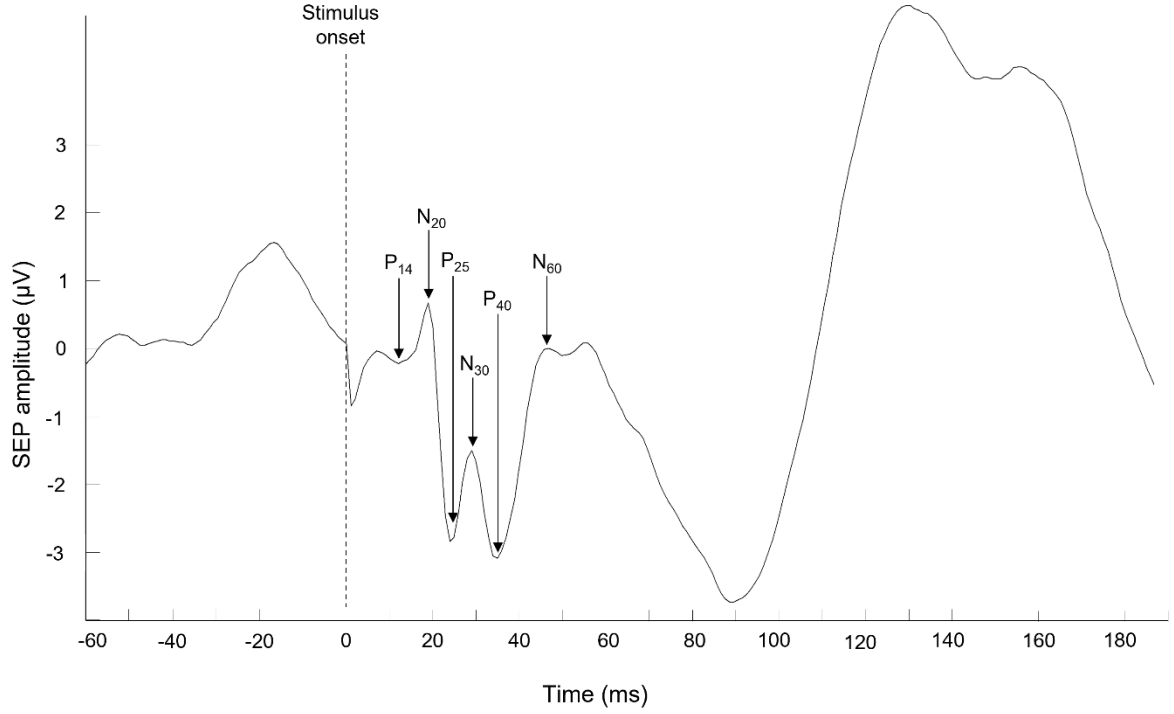

Figure 1.12. An example image of a sensory evoked potential (SEP). SEPs are recorded in response to non-noxious electrical stimuli at the median nerve in a healthy participant with different SEP components extracted. The components presented are the P14, N20, P25, N30, P40, N60 which represent the latency of the SEP component following the initial stimulation and whether the peak SEP component is a negative (N) or positive (P) peak or trough. Image extracted from Chapter 3, Study 2.

1.4.2.3 Techniques used to record S1 IHI

To measure IHI, SEPs are recorded in response to bilateral peripheral nerve stimulation at varying interstimulus intervals. These SEPs are typically recorded via EEG (Mauguiere, 2005; Passmore et al., 2014). Electroencephalography records electrical currents measured from the scalp surface allowing for the recording of activity across multiple brain regions and can be performed using widely available neuroscience recording equipment (Gevins & Smith, 2006). Hence, EEG is the predominant neurophysiological technique used in S1 IHI studies. A variety of techniques can be used to measure SEPs via EEG. This includes a whole-head EEG system or a single gold-cup electrode.

Whole-head EEG involves placing a cap on the participants head with electrodes spaced around the scalp comprising as few as 35 and up to 64 channels to record electrical activity from the brain. This configuration of electrodes also allows for the monitoring of signal artefacts and streamlining filtering and data analysis (Lau et al., 2012; Tong & Thakor, 2009). Advantages of whole-head EEG include reliability of EEG to record brain activity, ability to place more recording electrodes on the scalp, high temporal resolution, and is tolerable by participants. However, disadvantages of whole-head EEG include increased sensitivity of the signal-to-noise ratio from eye and scalp movement, low spatial resolution, and lengthy set-up time as electrodes need to be precisely placed on the scalp (Reis et al., 2014; Srinivasan, 1999).

Gold-cup EEG involves placing a silver/silver chloride electrode on the scalp at the desired cortical region for assessment and a reference electrode (OSET, 1999; Toleikis, 2005). Advantages of this method include that it is established as a reliable method to record brain activity (Rossini et al., 1990), uses significantly less recording electrodes and thus, has less set-up time, is tolerable by participants, and is a cost-effective and functionally feasible method. Disadvantages of gold-cup EEG include the recording of movement artefacts (e.g. from the

eyes or scalp) that will be observed in the EEG signal (Tallgren et al., 2005) and reduced accuracy and reliability due to inconsistent electrode placement. Consistency in the placement of EEG recording electrodes is required to produce reliable findings (Teplan, 2002; Toleikis, 2005). To improve consistency in electrode placement, standard placement protocols exist. Electrodes should be placed on the scalp according to the International 10 - 20 system, which is an internationally recognised method that allows for the standardised placement of EEG electrodes (Homan et al., 1987; Jasper, 1958).

1.4.2.4 Paired median nerve somatosensory evoked potential (PMNSEP) protocol

To measure interhemispheric interactions between somatosensory cortices, a paired median nerve somatosensory evoked potential (PMNSEP) protocol is employed (Brodie et al., 2014; Ragert et al., 2011). A conditioning stimulus at a suprathreshold intensity is delivered to the target nerve, such as the median or ulnar nerve over the wrist, prior to a suprathreshold test stimulus delivered to the target nerve in the opposite wrist at ISIs ranging from 5 – 35 ms (Brodie et al., 2014; Ragert et al., 2011; Hoffken et al., 2013). To our knowledge, this protocol has not been performed over the radial nerves. The range of ISIs from 5 – 35 ms allows for the investigation of the time window that interhemispheric interactions occur between S1s. For example, to measure IHI from the left to the right S1, a conditioning stimulus would be delivered to the right median nerve preceding a test stimulus to the left median nerve at a chosen ISI. A control condition is also applied whereby a single-pulse test stimulus is delivered to the target nerve over one wrist. However, a limitation of the single-pulse test stimulus is directed attention to the hand being stimulated which has shown to alter sensory processes and influence SEP amplitudes (Garcia-Larrea et al., 1999). To address this, a synchronous stimulation condition where electrical stimulation is applied to the right and left nerve simultaneously (i.e., 0 ms ISI) can be used to control for directed attention by equally dividing attention between the two hands (Brodie et al., 2014). It has been demonstrated that no differences in SEP

component amplitudes exist when the single-pulse test stimulus is used as the control condition compared to the synchronous 0 ms ISI condition (Brodie et al., 2014). Therefore, it appears appropriate to consider using a paired 0 ms ISI as a control condition as previous studies do suggest attention to electrical stimulation and not the task administered could influence SEP results (Eimer & Forster, 2003; García-Larrea et al., 1995; Rossi et al., 1998; Schubert et al., 2008).

1.4.2.5 SEP components

In response to peripheral stimulation, SEP waveforms are produced that originate from cortical and subcortical origins. The peak-to-peak amplitudes and latencies of the SEP response following stimulus onset are analysed as a proportion of the control condition (conditioned SEP / unconditioned SEP) for each SEP component. The ratio score is then interpreted to determine whether there is interhemispheric inhibition or facilitation between the S1's (Ferbert et al., 1992; Ragert et al., 2011). A ratio score < 1 denotes interhemispheric inhibition and a ratio score > 1 denotes interhemispheric facilitation i.e., disinhibition (Ferbert et al., 1992; Nelson et al., 2009; Sattler et al., 2012).

In humans, five SEP components have been analysed in response to IHI between somatosensory cortices. These are P_{14}/N_{20}, N_{20}/P_{25}, P_{25}/N_{30}, N_{30}/P_{40}, P_{40}/N_{60}. The P_{14}/N_{20} component comprises a subcortical and cortical component (Desmedt, 1985; Lee & Seyal, 1998; Noël et al., 1996; Passmore et al., 2014). The P_{14} component is a subcortical component that is generated at the caudal medial lemniscus at the level of the medulla of the brainstem (Desmedt, 1985; Lee & Seyal, 1998; Noël et al., 1996). The N_{20} component reflects cortical activity, representing area 3b of the primary sensory cortex (Passmore et al., 2014). The N_{20} /P_{25} SEP component is generated in areas 3b, 1 and 2 of the somatosensory cortex (Namiki et al., 1996). The N_{30}/P_{40} reflects the parietal cortex of the somatosensory area (P_{40}) and the pre-

central cortical region that is the site of M1 (N_{30}) (Passmore et al., 2014). However, it is also thought that the origin of the N_{30} involves a more complex cortical and subcortical connection linking the basal ganglia, thalamus, pre-motor areas and M1 (Kanovsky et al., 2003). The N60 component is thought to reflect activation in area 1 of the somatosensory cortex (Allison et al., 1992).

It can be noted from the origins of the SEP components above that communication between S1s can be mediated by other regions of the brain, such as the M1 and subcortical regions, which show the interconnectedness of the brain. Therefore, assessment of SEPs generated in S1 will provide important information regarding the specific areas in S1 or mediating regions that contribute to IHI between S1s.

The previous sections introduced IHI and reviewed the literature that suggests IHI is of cortical origin. The methods used to investigate IHI in M1 and S1 of humans were then reviewed. This included the paired-pulse and iSP paradigms that investigate IHI between M1s and the paired median nerve stimulation paradigm that investigates IHI between S1s. The following section reviews the literature that has investigated IHI in the healthy nervous system. This includes a review of unilateral and bilateral movement coordination in M1 and S1.

1.5 The functional role of interhemispheric inhibition in humans

Interhemispheric inhibition has a significant functional role in voluntary motor control and movement in humans. Interhemispheric inhibition has been implicated in unilateral and bilateral coordination, playing a crucial role in suppressing unwanted mirror movements (Beaule et al., 2012; Reis et al., 2008). Mirror movements occur when voluntary movements of one side of the body are mirrored involuntarily by the opposite side of the body due to excitatory information crossing the corpus callosum (Beaule et al., 2012).

Maturation of the corpus callosum and pathological circumstances affect the effectiveness of IHI in the control of unwanted mirror movements. Diffusor tensor imaging (DTI), a type of MRI technique, and TMS studies reveal mirror movements occur in young children under 10 years of age. This occurs due to the incomplete myelination of the corpus callosum rendering the IHI mechanism weak or absent. However, as the corpus callosum and IHI mechanism develop and mature with ageing, mirror movements decrease (Heinen et al., 1998; Koerte et al., 2009; Kwon et al., 2014; Müller et al., 1997). In adults, mirror movements are deemed a pathological phenomenon such as in conditions of stroke and writer's cramp (Duque et al., 2005; Merello et al., 2006; Murase et al., 2004). However, in some circumstances, normally developing children and older adults may develop mirror movements to various degrees when a motor task is fatiguing, demanding and cognitive distractions occur (Beaule et al., 2012).

The amount of IHI is shown to be increased or decreased depending on the task. An increase in IHI is associated with greater inhibition of motor activity of the opposite hemisphere and suppressed mirror movements. For example, an individual writing or performing a sport with their right hand requires increased IHI, whereby the excitatory neurons from the corresponding left hemisphere travel via the transcallosal fibres of the corpus callosum and synapse on inhibitory neurons on the homotopic area of the right hemisphere (Berlucchi, 1990; Daskalakis

et al., 2002; Ferbert et al., 1992; Perez & Cohen, 2008; Somogyi et al., 1998). Thus, the corpus callosum increases lateralisation of the left hemisphere, restricting motor output and suppressing mirror movements of the left hand. Conversely, decreased IHI may be required for a bimanual task such as playing a musical instrument requiring precise control of both hands. Table 1.8 summarises studies that have investigated IHI in unimanual and bimanual tasks.

In humans, IHI between M1s is involved in both the control of unimanual and bimanual coordination. The primary motor cortex is commonly investigated in IHI studies, and the functional role of IHI between M1s is discussed below.

1.5.1 Primary motor cortex

The primary motor cortex is located in the precentral gyrus within the frontal lobe and is involved in the planning, control, and execution of motor functions (Donoghue & Sanes, 1994). Initial research investigating the M1 hypothesised a somatotopic organisation of body parts including the face, arms, and legs, so that distinct regions of M1 control particular parts of the body. This somatotopic organisation was presented as the motor homunculus (Figure 1.13). However, research has increasingly shown that M1 representations of body parts overlap each other extensively (Donoghue & Sanes, 1994; Penfield & Boldrey, 1937). The ability of M1 to change structure, function and organisation is referred to as ‘neuroplasticity’ (Sanes & Donoghue, 2000). This is a lifelong process that can be adaptive or maladaptive. Investigations into M1 plasticity further clarify the role of IHI between M1s in unilateral and bilateral motor function.

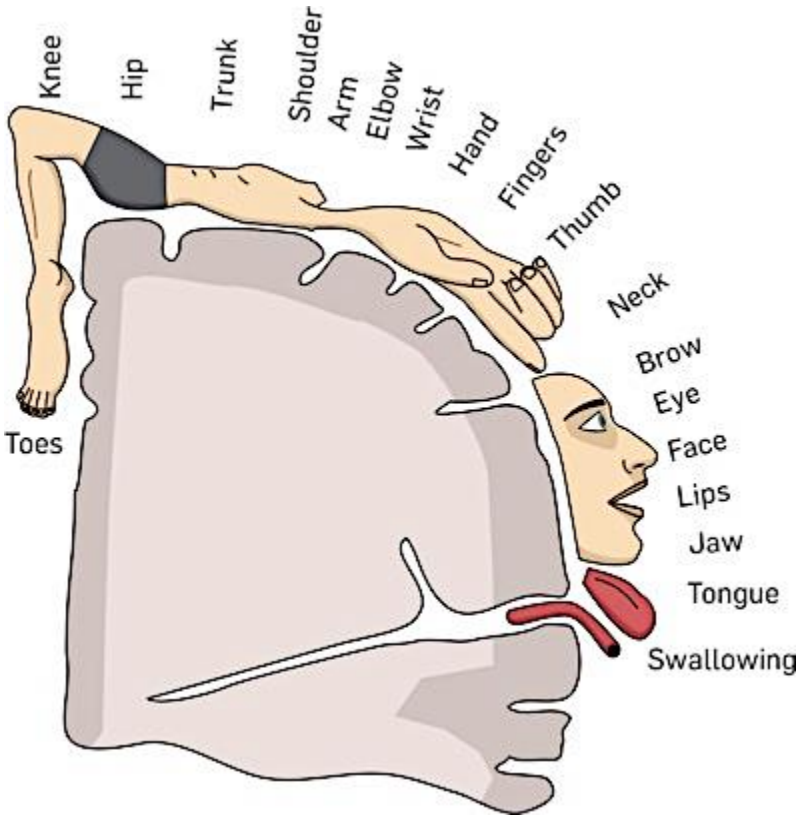

Figure 1.13. The motor homunculus. Source https://brainmapper.org/science/

IHI in M1 during unilateral movement coordination

Interhemispheric inhibition plays an important role in the execution of skilled motor functions, particularly in unilateral movement where it is involved in suppressing unwanted mirror movements (Beaule et al., 2012). During a unilateral muscle contraction, IHI is shown to be increased from the active M1 (corresponding to the active muscle) to the M1 at rest (Ferbert et al., 1992; Hinder et al., 2010; Morishita et al., 2012; Perez & Cohen, 2008; K. Uehara et al., 2013; Vercauteren et al., 2008). For example, Perez and Cohen (2008) investigated the influence of unimanual force on IHI in 10 healthy right-handed participants. They demonstrated that contraction of the right forearm muscles at 10% and 70% maximal wrist extension force resulted in increased IHI from the M1 contralateral to the active forearm to the ipsilateral M1 contralateral to the limb at rest. However, when the size of the conditioned MEP was matched across conditions, although there was IHI, the magnitude of IHI decreased from

contralateral to ipsilateral M1 with increasing force levels. This finding is consistent with those of other studies where readjusting the conditioned MEP resulted in decreased IHI from contralateral to ipsilateral M1 in response to a unimanual contraction (Chen et al., 2003; Chiou et al., 2013; Perez & Cohen, 2008; Vercauteren et al., 2008). Interestingly, these findings may conflict with our understanding that IHI would increase during a unimanual task.

There are several reasons why a decrease in IHI may be observed during a unimanual contraction or other unimanual tasks. First, a decrease in IHI to ipsilateral M1 during a forceful isometric contraction may occur to partially support the corticomotor output of the contralateral M1 (Perez & Cohen, 2008). Second, decreased IHI may suggest that the unimanual task is complex or fatiguing, resulting in increased motor output to compensate and may consequently result in unwanted mirror movements in the hand at rest (Beaule et al., 2012). Last, intracortical mechanisms such as SICI and LICI interact with IHI. Investigations have found that IHI influences the magnitude of SICI and SICI is decreased in response to a unilateral muscle contraction of the upper limb, thought to be due to changes in IHI (Chiou et al., 2013; Perez & Cohen, 2008). Further, it has been shown that both SICI and LICI reduced short and long latency IHI (Lee et al., 2007). Taken together, these findings suggest that there is a more complex mechanism involving multiple circuits in unilateral movement that should be considered. Many of these studies investigate the effect of unilateral contractions on short latency IHI at 10 ms ISI only. It remains to be understood how adjustments of the CS may affect LIHI during a unimanual contraction and whether the behaviour of LIHI would differ to SIHI.

Performing a complex unimanual motor task elicits different responses in SIHI and LIHI. Increased SIHI has been demonstrated from the active to the resting M1 during a complex unimanual task (Morishita et al., 2012) and during a simple unimanual task (Ferbert et al., 1992; Hinder et al., 2010; Perez & Cohen, 2008; K. Uehara et al., 2013; Vercauteren et al.,

2008). Morishita et al. (2014) explored the differences between SIHI and LIHI from the active to resting M1 during a complex unimanual task and confirmed an increase in SIHI, but demonstrated decreased LIHI. Similarly, Nelson et al. (2009) reported findings demonstrating decreased LIHI in response to isometric contraction of the index finger. This suggests the two phases of IHI could differ functionally and be elicited depending on the task complexity. Indeed, SIHI has been postulated to increase with increased muscle force output of limb movement (Perez & Cohen, 2008; K Uehara et al., 2013), whereas there is less evidence to suggest LIHI is related to unilateral task performance. While it seems that LIHI and SIHI have different functional roles and processes, further research is needed to provide a greater understanding of the functional differences of LIHI and SIHI during tasks with different complexities.

Whilst IHI is modulated during the execution of a unilateral task, the inconsistent findings of IHI in response to a unilateral movement task may be explained by the following methodological factors. First, the amount of IHI exerted between homologous areas of muscles may differ. For example, in animal studies, callosal connections are stronger in the midline and for proximal muscle representations than distal muscle representations (Iwamura, 2000; Iwamura et al., 2001). In humans, it has also been shown that the degree of IHI differs in representations of intrinsic hand muscles, thought to be due to a proximal-distal gradient (Sohn et al., 2003). In contrast, however, some studies suggest it is due to the role of the muscles in a functional movement synergy (Harris-Love et al., 2007). Second, task complexity such as complex vs simple tasks, or weak vs strong muscle contractions, could influence the degree of IHI. For example, studies demonstrate IHI was decreased bi-directionally (from active to resting M1 and vice versa) during muscle contraction of the hand muscle at 20% maximum voluntary contraction (MVC) (Nelson et al., 2009) compared to 5% of MVC, where an increase in IHI was demonstrated from active to resting M1 (Vercauteren et al., 2008).

Further, a complex unilateral motor task where participants completed a fine motor manipulation task found IHI markedly increased from the active to resting M1 (Morishita et al., 2014; Morishita et al., 2012), compared to unilateral simple motor tasks where IHI was slightly increased (Ferbert et al., 1992; Morishita et al., 2012), or decreased (Perez & Cohen, 2008). Last, the CS intensity setting, that is with or without adjusting CS intensity, may influence IHI. Readjusting CS intensity to the MEP amplitude when the muscle is at rest normalises the MEP amplitude to the increased corticospinal output caused by voluntary contraction. This results in smaller MEPs and maximum inhibition (Perez & Cohen, 2008; Sattler et al., 2012). The alternate method, where CS intensity is not adjusted, could result in larger MEP amplitudes due to voluntary contraction. However, it is argued that not adjusting CS intensity is a more accurate reflection of the amount of IHI from the contralateral to ipsilateral hemisphere (Perez & Cohen, 2008). Due to these methodological factors and reasons, the evidence to date remains inconclusive regarding findings of IHI in response to a unilateral movement task.

Investigations of IHI in movement execution demonstrate the role of IHI during different stages of movement. Prior to movement onset, increased IHI from the M1 contralateral to the hand in movement preparation is produced. As movement onset approaches, the amount of IHI decreases and turns into facilitation to allow movement to occur. In the opposite direction, the maximum amount of IHI contralateral to the hand at rest remains throughout the movement preparation phase to prevent unwanted mirror movements (Duque et al., 2005; Murase et al., 2004). Duque et al. (2007) investigated unilateral voluntary index finger movement in response to a GO signal of a reaction time paradigm in healthy individuals. This work revealed that IHI was exhibited at rest in both directions (from active to inactive M1 and vice versa), but during the finger movement task, IHI shifted predominately towards the ipsilateral M1 corresponding to the hand at rest. Meanwhile, IHI from the inactive to active M1 corresponding to the moving

finger was increased closer to movement onset and changed to facilitation with movement onset. The modulation of IHI during movement and the coordination between hands suggests the importance of IHI for the accurate control of unilateral and bimanual movement coordination (Duque et al., 2007; Murase et al., 2004).

IHI between M1s during bimanual movement coordination

Interhemispheric inhibition also plays an important role in bimanual movement coordination. Despite numerous studies investigating IHI between M1s in unilateral tasks, the functional relevance of IHI in bimanual movement necessitates further examination. In bimanual movement coordination studies, two types of movements are investigated: i) in-phase, where bilateral homologous muscles activate synchronously e.g. clapping hands; and ii) anti-phase, where bilateral homologous muscle groups contract in an alternating fashion e.g. playing the piano (Liuzzi et al., 2011). It has been demonstrated that decreased IHI between M1s promotes simple bimanual movements that allow synchronous control of both hands (Liuzzi et al., 2011; Wahl et al., 2016), whereas increased IHI is related to poorer performance on a bimanual force production task (Fling et al., 2013). In older adults, the execution of bimanual tasks becomes slower and less accurate, believed to be related to the integrity of the fibres in the corpus callosum and increased IHI (Fling et al., 2013; Gooijers & Swinnen, 2014). A recent study by Morishita et al. (2022) investigated the role of IHI in an anti-phase bimanual movement task in healthy young and older adults. Interestingly, they found no differences in IHI between the groups, but the performance of bimanual movement and mirror movements differed between the groups. Notably, they demonstrated the behavioural relevance of SIHI on bimanual movement. Greater SIHI was associated with less amount of mirror activity in young adults and better performance of the anti-phase task, contributing to efficient bimanual movement coordination. Based on previous studies, bimanual coordination is dependent on IHI and

disinhibition, and changes depending on the type of movement coordination e.g., in-phase and anti-phase.

The functional role of IHI between M1s is demonstrated to be important in the precision of unilateral tasks, to suppress unwanted mirror movements, and for bimanual control. However, there exist other cortical regions that are important in the transmission of IHI. One such region is the primary sensory cortex.

Table 1.8. A summary of studies examining IHI between M1s in response to motor movement in healthy individuals.

Author (year)	N	IHI Protocol	Task Protocol	Outcome Measure	Findings
Nelson et al. (2009)	15	Paired-pulse paradigm at 6, 8, 10, 12, 30, 40, 50 ms ISI from contralateral to ipsilateral M1 and vice versa	Unimanual isometric contraction of FDI muscle	MEP amplitude	Reduced IHI at all ISIs bi-directionally during isometric contraction
Vercauteren et al. (2008)	13	Paired-pulse paradigm at 10 ms ISI	Unilateral voluntary contraction of forearm muscles at 5% MVC	MEP amplitude	Increased IHI from active to resting M1 during muscle activation (decreased IHI when CS intensity matched)
Duque et al. (2007)	13	Paired-pulse paradigm at 10 ms ISI	Index finger movements in response to a RT paradigm	MEP amplitude	Increased IHI at movement preparation; Decreased IHI closer to movement onset
Perez and Cohen (2008)	10	Paired-pulse paradigm at 10 ms ISI	Wrist flexion at 10, 30, 70% force	MEP amplitude	IHI decreased at 30% and 70% force in the active hand; IHI increased in the rest hand
Chiou et al. (2013)	15	Paired-pulse paradigm at 10 ms ISI	Unilateral isometric contraction of the target muscle at 75% of MVC	MEP amplitude	Decreased IHI during the task ipsilateral to the moving limb compared to rest
Morishita et al. (2014)	13	Paired-pulse paradigm at 10 and 50 ms ISI from contralateral to ipsilateral M1	Fine-motor manipulation task and complex task	MEP amplitude	Increased SIHI and decreased LIHI during fine motor task

Gueugneau et al. (2013)	12	iSP paradigm from the left to right M1	Unilateral actual or mental actions with increasing complexity with the right hand	iSP duration; iSP area;	IHI increased with increasing complexity; iSP duration and area increased during actual and mental movements
Gerloff and Andres (2002)	18	Electroencephalography	Bimanual and unimanual finger tapping tasks	Task related relative coherence (TRCoh)	Interhemispheric TRCoh increased at early-stage bimanual coordination learning and decreased after 100% performance level was reached
Perez et al. (2014)	22	iSP paradigm from dominant to non-dominant M1	Unilateral and bilateral isometric voluntary contractions of biceps and triceps muscles	iSP onset, duration, depth, area	iSP depth and area increased during bilateral contractions of homologous agonist muscles but decreased with bilateral contraction of non-homologous muscles
Tazoe et al. (2013)	11	iSP paradigm of left M1 on muscle activity of the ipsilateral hand	Bimanual or unimanual force task of thumb abduction	Latency, duration, MEP amplitude, baseline EMG	IHI was unchanged with unimanual force compared to bimanual force

Note: N, sample size; CS, Conditioning Stimulus; FDI, First Dorsal Interosseous; MVC, Maximum Voluntary Contraction; MEP, Motor Evoked Potential; ISI, Interstimulus Interval; iSP, Ipsilateral Silent Period; IHI, Interhemispheric Inhibition; RT, Reaction Time; SIHI, Short Interhemispheric Inhibition; LIHI, Long Interhemispheric Inhibition; EMG, Electromyography; M1, Primary Motor Cortex; ms, millisecond.

1.5.2 The primary sensory cortex

The primary sensory cortex is part of the somatosensory system located in the parietal lobe that receives information such as pressure, vibration, movement, temperature, and the sensory-discriminative aspect of pain (Raju & Tadi, 2021; Schnitzler & Ploner, 2000). This information is projected to the opposite S1 via transcallosal connections allowing for interhemispheric interactions between cortices (Hlushchuk & Hari, 2006; Lipton et al., 2006).

Callosal connections between S1s were first demonstrated in animal studies of primates. Early studies showed that S1 callosal connections were limited to the representation of the midline including the trunk, face and head (Manzoni et al., 1980; Manzoni et al., 1989). Studies extending these findings showed that callosal connections are not restricted to the midline and include the extremities. Activation of bilateral receptive fields of the finger, forearm, foot and leg regions in the caudal end of S1 in monkeys confirmed this (Iwamura, 2000; Iwamura et al., 2001).

The density of callosal connections between cytoarchitectonic regions of S1 varies and determines the strength of connection between S1 regions (Killackey et al., 1983). In monkeys, area 2 of S1 has the densest connections compared to area 1, which has less connections, and area 3b has the least callosal connections (Killackey et al., 1983). It has also been demonstrated that callosal connections for representations of body regions differ. For example, the face and trunk representations have denser callosal connections than the hand and foot (Iwamura, 2000; Iwamura et al., 2001; Killackey et al., 1983). This information is of importance when trying to understand the transfer and integration of information from body regions and in understanding unimanual and bimanual coordination. Despite this valuable information, these findings are derived from research based on 4 - 6 monkeys only, which pose limitation issues such as reproducibility and skewing of the results. Although the translation of animal study findings to

humans can be limited, the findings provide a platform for exploring concepts in human studies. Several human studies support the findings from primate studies that demonstrate bilateral connectivity between S1s.

Interhemispheric inhibition between S1s

Interhemispheric inhibition in humans occurs between area 3b of S1 via transcallosal fibres (Brodie et al., 2014; Fling et al., 2013; Ragert et al., 2011). Despite research suggesting that transcallosal connections from area 3b of S1 are few, they are effective in the IHI mechanism (Iwamura et al., 2001). Studies investigating the involvement of interneurons in the S1 IHI pathway suggest the involvement of $GABA_B$ receptors. Palmer et al. (2012) demonstrated in rats the application of the $GABA_B$ receptor agonist to the S1 decreased IHI following electrical stimulation from the ipsilateral to the contralateral hind paw. The effect of the $GABA_B$ agonist strongly suggests IHI is mediated by $GABA_B$ receptors. Similarly, Kokinovic and Medini (2018) also demonstrated $GABA_B$ mediated IHI in a stroke model in mice. Under normal conditions, one S1 inhibited the opposite S1 via activation of $GABA_B$ receptors. However, following stroke in S1, $GABA_B$ mediated IHI was not detectable. Taken together, these studies suggest IHI between S1s is mediated by $GABA_B$ receptors. More recently, EEG studies in healthy humans have aimed to characterise interhemispheric interactions between S1s in response to a paired median nerve sensory evoked potential paradigm (Brodie et al., 2014; Ragert et al., 2011). These studies demonstrate IHI between S1s and are discussed below.

Interhemispheric inhibition between S1s using the PMNSEP protocol

Interhemispheric inhibitory interactions between S1s have been investigated in healthy humans. Two pioneering studies in this field were published by Ragert et al. (2011) and Brodie et al. (2014) that investigated whether interhemispheric interactions between S1s were inhibitory or excitatory. These studies also aimed to determine the time window of the transfer

of sensory information between S1s. Using the PMNSEP protocol in healthy participants while at rest, Ragert et al. (2011) investigated interhemispheric interactions from the right to the left S1 at ISIs of 5 - 30 ms and compared the ISIs to a test stimulus (TS) alone control condition. Their findings showed that interhemispheric interactions between S1s are inhibitory. Further, they demonstrated that when a conditioning stimulus (CS) is applied to the median nerve 20 - 25 ms preceding a test stimulus, the N_{20} component is inhibited relative to a test stimulus alone control condition. As the N_{20} component is of cortical origin and reflects early processing in S1, this shows that IHI occurs at an early stage of cortical processing in S1. These findings demonstrate that in a healthy cohort, IHI occurs from the right to left S1 at 20 - 25 ms ISIs.

Brodie et al. (2014) extended the research of Ragert et al. (2011) on IHI between S1s. They sought to confirm the robustness of the PMNSEP protocol by examining IHI in the opposite direction i.e., from the left to the right S1, in healthy participants at rest. Their findings demonstrated that a CS applied to the right median nerve preceding the TS at the left median nerve inhibited the P_{14}/N_{20} component at shorter ISIs (15, 20 ms) and inhibited the N_{20}/P_{25} component at both long and short ISI intervals (15, 20, 25, 30, 35 ms). No changes were found at longer latency SEP components. These results demonstrate that IHI occurring from the left to right S1 occurs at a cortical origin but may also be mediated by the thalamus, as indicated by inhibition of the P_{14} component.

Brodie et al. (2014) confirmed the PMNSEP protocol is a robust method to investigate interhemispheric interactions between S1s. Their findings extended that of Ragert et al. (2011) by demonstrating IHI between S1s in the opposite direction (from left to right S1) while also finding inhibition of the N_{20}/P_{25} component between 15 – 35 ms ISIs. This extension of findings may be attributed to slight methodology differences between studies. First, despite both studies using the PMNSEP protocol, Brodie et al. (2014) used a 0 ms ISI control condition whereby electrical stimuli were applied to the right and left median nerves simultaneously, as

opposed to using a TS alone condition. This condition was included to control for differences in directed attention to electrical stimulation, which has been shown to alter sensory processing by equally dividing attention between the two hands (García-Larrea et al., 1991). Additionally, both studies increased electrical stimulation to produce a thumb twitch, however Brodie et al. (2014) controlled this twitch by increasing the intensity to ~ 1 mV and adjusted the intensity throughout the experiment to maintain muscle twitch. As individuals may habituate to the stimulus during the experiment, this method ensures that a muscle twitch is present, and the intensity of electrical stimulation is adjusted to account for habituation. A further difference between studies is the range of ISIs investigated. Ragert et al. (2011) included earlier ISIs of 5 and 10 ms, whereas Brodie et al. (2014) included a later ISI of 35 ms in which the P_{14}/N_{20} component was inhibited. If longer ISIs were included in both studies, inhibition of long-latency SEPs may have been observed. Finally, both studies investigated IHI between S1s in different directions. Research shows that IHI is stronger from the dominant to non-dominant hemisphere (Netz et al., 1995). As Brodie et al. (2014) investigated IHI from dominant to non-dominant S1, this may further explain why they demonstrated inhibition of two SEP components as opposed to one by Ragert et al. (2011). In summary, the PMNSEP protocol provides an avenue to assess IHI between S1s via EEG in healthy individuals (Brodie et al., 2014; Ragert et al., 2011). These interhemispheric connections are important in processing sensory input for efficient motor processes.

S1 IHI in unilateral and bilateral motor execution

Unimanual and bimanual hand coordination is a skill that involves the functional coupling between sensorimotor areas. Neuroimaging and electrophysiological studies in monkeys (Lipton et al., 2006) and in humans (Brodie et al., 2014; Hlushchuk & Hari, 2006; Ragert et al., 2011) demonstrate, similarly to the M1 system, that unilateral peripheral hand stimulation (tactile, electrical) increases activation in contralateral S1 and suppresses ipsilateral S1,

characterised by decreased cortical activation or inhibited SEPs. For example, Hlushchuk and Hari (2006) demonstrated in healthy human participants that the contralateral as well as ipsilateral S1 was activated in response to unilateral tactile stimulation. Specifically, the ipsilateral S1 were deactivated to allow for better processing of sensory information such as texture and touch recognition. The mechanism underlying the transfer of sensory information is suggested to be IHI (Brodie et al., 2014; Ragert et al., 2011). This suppression of ipsilateral S1 has been demonstrated to correlate with an increased threshold of stimulus perception of the opposite unstimulated hand, reflecting functionally effective inhibition (Kastrup et al., 2008).

Interhemispheric interactions between S1s have been implicated in the precise timing and execution of bimanual movements. Andres et al. (1999) investigated functional coupling of S1s in asynchronous bimanual coordinated movements via EEG in healthy subjects. The authors demonstrated increased interhemispheric coherence between sensorimotor areas in the early phase of bimanual learning, but this reduced when bimanual performance stabilised. This is thought to be important in the early phase of bimanual integration and learning a new bimanual task. When learning new bimanual tasks or skills, the role of IHI suppresses mirror movements and pre-existing bimanual coordination tendencies to allow for the development of new bimanual coordination tasks. Once the new bimanual task is established, the level of IHI decreases while still maintaining bimanual coordination. It is evident that transcallosal signals not only convey motor information, but also sensory information to control asynchronous bimanual movements, as well as for simple unimanual movements (Geffen et al., 1994).

The role of ipsilateral S1 in sensory gating

For smooth execution of motor tasks in humans, the somatosensory system inhibits or reduces sensory input from the contralateral side of the body through a process called 'sensory gating'. This is a dynamic process between sensory input and motor output that requires inhibitory processes at the level of the somatosensory system (Borich et al., 2015). Sensory gating involves regulating the amount of sensory input to the brain by filtering irrelevant sensory signals or information that are not contributing to the task at hand (Freedman et al., 1987). First, sensory information activates sensory pathways in the peripheral nervous system (Seki & Fetz, 2012). The sensory information is then gated in the afferent pathway before it reaches the somatosensory cortex. When the filtered sensory information is sent to the somatosensory system, the motor output or execution of a movement task will be performed smoothly as only relevant information to the task at hand is processed (Borich et al., 2015; Perruchoud et al., 2014; Seki & Fetz, 2012).

Research suggests that sensory gating occurs in the hemisphere contralateral to the side of the body executing the movement (Borich et al., 2015). However, more recent research identifies that the ipsilateral S1 also has an important role in gating somatosensory information and that IHI mediates the process of gating (Borich et al., 2015; Lei & Perez, 2017; Perez & Cohen, 2008; Ragert et al., 2011). For example, Lei and Perez (2017) demonstrated during a unilateral voluntary activity performed by the right hand in healthy participants, the P_{25}/N_{33} component decreased from the left to right S1 (i.e., inhibition in ipsilateral S1) compared to the resting condition. The authors suggested that dense callosal connections mediated inhibition between S1s with IHI likely playing a key role. This highlights the importance of both somatosensory cortices in executing a motor task, whereby the ipsilateral S1 inhibits somatosensory information to the opposite limb, suppressing mirror movements of the hand at rest.

Methodological considerations in the functional role of S1 IHI

The functional role of S1 IHI described above provides valuable insight into the importance of IHI and ipsilateral S1 suppression in bimanual and unimanual movement, and sensory gating. However, several methodological limitations impact the integrity of the findings of these studies. First, many of the studies investigating S1 IHI have small sample sizes with no a priori power calculations of the primary hypothesis provided (Andres et al., 1999; Hlushchuk & Hari, 2006; Lei & Perez, 2017). Sample size calculations determine the smallest scientifically and meaningful effect size (Jones et al., 2003). Studies that do not provide sample size calculations may not be powered to detect differences in outcomes or in contrast may detect differences that are not present (type 1 error), thus affecting the validity of reported significance (Bacchetti, 2010; Button et al., 2013). Further, the motor tasks employed in these studies differ in difficulty, which may produce differential activation of cortical regions and activation of different sets of sensory fibres, making comparisons between findings difficult. For example, difficult cognitive-motor tasks require increased neural effort, demonstrated by increased activation and networking in motor planning and sensory areas (Rietschel et al., 2012), compared to relatively easier tasks. In other studies, long latency IHI is decreased during a complex unimanual task compared to a simple unimanual task (Morishita et al., 2014; Nelson et al., 2009). Despite these limitations, the combined findings provide important information of the functional role of IHI in normal sensorimotor control in healthy participants.

In summary, this section has reviewed the literature on the functional role of IHI in primary motor and sensory cortices. The functional role of IHI in unimanual and bimanual motor tasks in healthy humans has been identified. However, comparatively there is relatively little known about IHI between the M1s and S1s in individuals with pathology and those experiencing pain. The following section synthesises and reviews the literature on IHI in individuals with pathology.

1.6 Interhemispheric inhibition in pathological conditions

The previous section highlighted a multitude of studies exploring IHI in the healthy human brain. Fewer, though an important number of studies have investigated IHI between M1s in pathological conditions. These studies have examined participants with a range of conditions including focal hand dystonia, stroke and CRPS. Findings suggest impaired IHI may be implicated in the pathophysiology of these conditions and contribute to bilateral sensorimotor impairment. The following sections explore M1 and S1 IHI in pathological conditions.

1.6.1. M1 IHI in pathological conditions

Mirror dystonia is a clinical phenomenon that occurs in some individuals with focal hand dystonia (FHD), a condition characterised by excessive, involuntary muscle contractions in the fingers, hand, forearm, and sometimes shoulder. Mirror dystonia is a movement disorder that impairs control of the homologous muscles of the affected hand during specific tasks performed by the unaffected hand such as writing (Albanese et al., 2013; Fahn et al., 1998; Sitburana & Jankovic, 2008). Research suggests that the M1 contralateral to the dystonia affected hand exhibits reduced cortical inhibition and that GABA concentrations in the sensorimotor cortex are reduced (Berardelli et al., 1998; Levy & Hallett, 2002; Niehaus et al., 2001). However, IHI has also been suggested to play a role in the pathophysiology of FHD (Baumer et al., 2016; Beck et al., 2009; Nelson et al., 2010; Niehaus et al., 2001; Sattler et al., 2014).

Several investigations have examined M1 IHI in dystonia and elicited varying findings. A summary of these studies and findings are presented in Table 1.9. Beck et al. (2009) investigated IHI using the paired-pulse paradigm at a 10 ms ISI from the unaffected to affected M1 in 13 individuals with FHD (mean ± SD history of FHD 13 ± 10 years). The participant sample comprised 7 individuals with mirror dystonia and 6 individuals without mirror dystonia who were assessed while performing a motor task of the right index finger. The findings

showed in those individuals with FHD that have mirror dystonia, IHI was reduced from the unaffected to affected hemisphere, contralateral to the homologous muscles of the right index finger, in the pre-motor phase 50 ms before EMG onset. The authors concluded that IHI is impaired in individuals with FHD that have mirror dystonia, but IHI may not play a major role in the general pathophysiology of FHD as abnormal IHI was not found in FHD individuals without mirror dystonia.

Impaired IHI in FHD has also been demonstrated in the opposite direction i.e., from the affected to unaffected hemisphere. Sattler et al. (2014) investigated SIHI and LIHI at 10 and 40 ms respectively in individuals with FHD that had and did not have mirror dystonia (mean ± SD, history of symptoms 18 ± 16 years) and compared them to healthy controls. Interhemispheric inhibition was measured in both directions (from the hemisphere contralateral to the affected hand to the opposite hemisphere and vice versa). Their findings demonstrated that SIHI and LIHI were reduced in both directions when at rest, and during isometric muscle contraction, in individuals with FHD that had mirror dystonia. In contrast, no change in IHI was observed in individuals with FHD without mirror dystonia and healthy controls. This finding has also been demonstrated in individuals with writer's cramp when IHI was investigated using the iSP method. The duration of the iSP for the uninvolved muscles was found to be prolonged, suggesting decreased inhibition (Niehaus et al., 2001). These findings contrast with Nelson et al. (2010) who demonstrated no change in IHI in the unaffected hand, while demonstrating reduced SIHI and LIHI in the dystonia affected hand (from right to left M1) at rest, but not while holding a pen at 20% maximum voluntary contraction. This contrast in findings of IHI from the affected to unaffected M1 could be largely due to whether participants displayed mirror dystonia. Thus, the differences observed in results are likely due to differences in the populations examined. Sattler et al. (2014) recruited individuals with FHD that did and did not demonstrate mirror dystonia and demonstrated differences in IHI only in individuals that had

mirror dystonia, whereas Nelson et al. (2010) recruited individuals with FHD that did not have mirror dystonia. Other methodological discrepancies such as a larger sample size, longer symptom duration in years, higher symptom severity on the Writer's Cramp Rating Scale in the Sattler et al. (2014) study and different muscles assessed compared to Nelson et al. (2010) likely contribute to the contrasting findings between these studies.

Interestingly, Baumer et al. (2016) investigated whether a family history of dystonia could be a genetic marker for developing dystonia and if it is associated with reduced IHI. Among other factors, they found that a family history of dystonia significantly affected the degree of IHI, but dystonia per se did not influence IHI. This may be because the individuals with dystonia in this study did not have mirror movements, whereas in the previous studies mentioned above, IHI was altered in individuals who had FHD with mirror movements. Further, a case study of writer's cramp by Merello et al. (2006) demonstrated bilateral activation of motor areas contralateral to the hand with mirror movements, also suggesting that mirror movements are mediated by altered IHI. When combined, these findings support the theory that impaired IHI plays a role in the pathophysiology of focal hand dystonia when accompanied with mirror movements. In summary, both SIHI and LIHI have been found to be decreased in both directions from the affected hemisphere to the unaffected hemisphere, and vice versa. Reduced IHI at the unaffected side of the body in patients with mirror dystonia could suggest that IHI mediates the development of bilateral sensorimotor dysfunction.

Table 1.9. A summary of investigations and findings from examination of IHI between M1s in pathological conditions.

Study (year)	N	Diagnosis	Test protocol	Outcome measure	Finding
Butefisch et al. (2003)	13†	Stroke	Paired-pulse TMS from the stroke affected to the non-affected hemisphere	MEP amplitude	↓ IHI, facilitation of the non-affected M1
Murase et al. (2004)	9 *	Stroke	Paired-pulse IHI from the healthy hemisphere to the stroke affected hemisphere at rest and preceding unilateral finger movement	MEP amplitude	↓ IHI preceding finger movement
Duque et al. (2005)	8 †	Stroke	Paired-pulse IHI from the healthy to stroke affected hemisphere and vice versa	MEP amplitude	Abnormally ↑ IHI from healthy to stroke affected hemisphere pre-movement of finger task. IHI in the opposite direction was comparable to healthy controls.
Takechi et al. (2014)	24†	Stroke	Ipsilateral silent period induced by TMS from the un-affected to stroke affected hemisphere and vice versa	Silent period EMG duration	Abnormally ↑ IHI from unaffected to stroke affected hemisphere; inconclusive IHI result from in the opposite direction
Beck et al. (2009)	7;6†	FHD +; FHD -	Paired-pulse TMS from the non-affected to the dystonia affected hemisphere	MEP amplitude	↓ IHI in the premotor phase in FDI and APB muscles
Sattler et al. (2014)	9; 7†	FHD +; FHD -	Paired-pulse TMS, SIHI and LIHI from the dystonia affected hemisphere to non-affected hemisphere at rest and holding a pen	MEP amplitude	↓ SIHI and LIHI in both directions at rest and during holding a pen
Nelson et al. (2010)	7†	FHD -	Paired-pulse TMS, SIHI and LIHI in both directions at rest and holding a pen	MEP amplitude	↓ IHI was reduced in the dystonia affected hand (IHI from the right to the left) at SIHI and LIHI compared to the unaffected hand.
Baumer et al. (2016)	21; 15 *	Musicians Hand Dystonia; Sporadic WC	Paired-pulse paradigm from right to left M1 and vice versa at 6, 7, 8, 9, and 10 ms ISI at rest	MEP amplitude	Family history of dystonia is a factor on modulating IHI. IHI significantly differed between sporadic musicians hand dystonia with reduced IHI and healthy first-degree family members
Niehaus et al. (2001)	11;14 *	Simple WC; dystonic WC	iSP with coil over the left hand representation area ipsilateral to the left FDI muscle contraction	Latency (ms)	Latency of transcallosal inhibition was longer compared to healthy controls

Note: * denotes age and gender matched healthy controls; †denotes age matched; FHD +, focal hand dystonia with mirror movements; FHD -, focal hand dystonia with no mirror movements; WC, writer's cramp; TMS, transcranial magnetic stimulation; IHI, interhemispheric inhibition; SIHI, short-latency interhemispheric inhibition; LIHI, long-latency interhemispheric inhibition; M1, primary motor cortex; MEP, motor evoked amplitude; FDI, first dorsal interosseous; APB, abductor pollicis brevis; ms, millisecond; ↓ = reduced; ↑ = increased;

Stroke, including chronic, subcortical, and acute forms is another pathological condition in which IHI has been investigated (Duque et al., 2005; Liepert et al., 2000; Murase et al., 2004; Shimizu et al., 2002; Takechi et al., 2014; Traversa et al., 1998). Stroke occurs when blood supply to part of the brain is disrupted and can lead to long term disability with significant loss of function known as paresis (National Health Service, 2019). Following stroke, cortical reorganisation and plasticity occur in regions immediate and distant to the stroke site in the same and opposite hemisphere (Dancause et al., 2005; Frost et al., 2003). Studies investigating individuals with stroke have shown that movements of the paretic hand involve widespread changes in brain activation in the affected and unaffected hemisphere compared to controls performing the same motor task (Krakauer, 2005). Hence, the presence of increased activity in the healthy hemisphere suggests an imbalance of IHI between the two cortical hemispheres (Liepert et al., 2000; Niehaus et al., 2003; Shimizu et al., 2002).

Consistent findings among studies of IHI in stroke suggest IHI is impaired and negatively affects rehabilitation of the paretic arm (Duque et al., 2005; Murase et al., 2007; Takeuchi et al., 2010). For example, Murase et al. (2004) investigated IHI from the healthy hemisphere to the stroke affected hemisphere in nine participants with chronic stroke (mean ± SD stroke history 4.8 ± 3.3 years) and eight age-and gender matched healthy controls. The authors evaluated IHI at 10 ms ISI at the onset of voluntary movement in the paretic hand of patients and the matched hand of controls. The results showed IHI was comparable at rest between the two groups, but where IHI turned to facilitation in the healthy control group, IHI did not change preceding movement in the stroke group. This finding demonstrates excessive IHI from the healthy hemisphere to the stroke affected hemisphere, which correlated with the magnitude of motor deficits of the paretic hand of the stroke group. These deficits included lower performance on the movement task and low scores on a muscle strength scale.

Similar impairments in IHI in chronic stroke were observed by Duque et al. (2005). They studied IHI in movements of the paretic and non-paretic hands in response to a movement task in eight individuals with stroke (mean ± SD history of stroke 3 ± 2.1 years) and eight aged matched healthy controls. The results revealed that the paretic hand of the patient group was slower during the movement task compared to the unaffected hand and compared to controls. The authors also reported abnormally increased IHI from the healthy hemisphere to the stroke affected hemisphere in the movement of the paretic hand compared to the healthy hand. When combined, the results of these studies suggest that excessive IHI from the healthy to stroke affected hemisphere contributes to the motor deficits of the paretic hand in individuals with stroke, which is consistent with other studies (Grefkes et al., 2008; Takeuchi et al., 2010).

A meta-analysis by McDonnell and Stinear (2017) suggests that there is no clear evidence in stroke for IHI imbalance and do not support the theory of excessive IHI from the healthy hemisphere to stroke affected hemisphere. However, they deemed only seven studies on IHI in stroke to be eligible for inclusion in the analysis. Despite applying robust inclusion criteria, their study was confounded by heterogeneity issues between studies. This was primarily due to the use of two different techniques in measuring IHI, where four studies measured the iSP duration and three studies used a paired-pulse technique. Further, the stage of stroke investigated differed among studies with both acute or chronic stage of stroke participants investigated, and the mostly small sample sizes were not comparable. To date, a lack of studies and poor heterogeneity of research design limits the undertaking of quality meta-analysis of IHI in pathological conditions. Despite this, the current literature investigating IHI in stroke suggests there may be some modulation in IHI, with further studies required to empirically confirm this.

1.6.2. S1 IHI in pathological populations

Studies investigating IHI in healthy humans is available in M1 and some studies are available in pathological conditions. In contrast, there is less information on IHI between S1s in healthy individuals and relatively little data in people with a pathological condition. A few studies, however, demonstrate bilateral S1 modulation and suggest that IHI may have a role to play in the pathophysiology of these conditions.

Complex regional pain syndrome (CRPS) is associated with autonomic, sensory and perceptual problems, but the main characteristic is pain (Moseley et al., 2012). Studies in CRPS have consistently reported that the S1 representation of the CRPS-affected hand is smaller than the S1 representation of the unaffected hand, as identified in the systematic review by Di Pietro et al. (2013). However, subsequent research by Di Pietro et al. (2015) demonstrated that the S1 representation of the unaffected hand is larger than that of the corresponding S1 hand representation of healthy controls, suggesting that the representation of the CRPS-affected hand is not smaller, but rather, is larger. This suggests that the ipsilateral S1 is involved and modulated in CRPS, similarly to poor recovery in stroke due to maladaptive reorganisation of the unaffected hemisphere mediated by IHI (Murase et al., 2004). Di Pietro et al. (2016) conducted a further study to examine if the enlargement of the S1 representation of the unaffected hand was associated with the severity of functional impairment of the CRPS affected hand and pain duration. Participants completed self-reported questionnaires about use of the CRPS-affected hand and overall function. The authors found no associations between the unaffected hand and interactions between the affected hand and overall function or pain duration. They suggested that rather than the enlargement of S1 of the unaffected hand being a compensatory mechanism, interhemispheric differences may exist before the CRPS condition is developed. However, EMG recordings of the limb contralateral to the CRPS-affected side oppose the theory of disinhibition of muscles of the contralateral limb. Bank et al. (2014)

investigated mirror movements of the limb contralateral to the side with CRPS and demonstrated no disinhibition of contralateral motor activity of homologous muscles during unimanual movement. They suggest that central mechanisms, rather than interhemispheric mechanisms, are involved in CRPS of the affected hand. However, heterogeneity in the research methodologies of the CRPS studies make it difficult to draw a conclusion on S1 IHI in pathological conditions.

Summary

Although there are relatively few studies examining IHI between M1s and S1s in pathological conditions, a number of conclusions can be drawn. Despite small sample sizes and heterogeneity between some studies, there are consistent reports of impaired IHI between M1s in pathological conditions. When combined, the studies discussed above also suggest that impaired IHI could be associated with the development of somatosensory symptoms of the unaffected side of the body. Further, several investigations suggest that bilateral S1 is affected in unilateral chronic pain conditions, and this may be related to impaired IHI. This impairment could be associated with mirror movements of the unaffected hand. Therefore, IHI is a plausible mechanism that may explain bilateral sensorimotor dysfunction in these pathological conditions.

As bilateral sensorimotor symptoms are also observed in LE, it is possible that a similar maladaptive IHI response occurs to that observed in stroke, FHD and CRPS. That is, impaired IHI between M1s and S1s may underpin the development of bilateral sensorimotor dysfunction in unilateral LE and other musculoskeletal conditions. However, this hypothesis is yet to be investigated. A thorough search of the literature has found that to date, no study has examined how IHI may influence the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal conditions.

1.7 Interhemispheric inhibition and musculoskeletal pain

As discussed in section 1.6, IHI may potentially be implicated in the development of bilateral motor control deficits of the pathological conditions discussed. However, it is unclear what role IHI has in the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions. It is understood that intracortical neuroplastic changes occur in chronic musculoskeletal conditions such as increased LICI (Chang et al., 2018), so it may be possible that interhemispheric changes also occur. The following section discusses impaired IHI in musculoskeletal pain conditions and explores the potential role of IHI in such conditions.

1.7.1 Altered IHI between M1s during sustained musculoskeletal pain

Following an extensive review of the literature, only one study has explored IHI between M1s in musculoskeletal pain. Schabrun et al. (2016) investigated IHI between M1s in response to experimentally induced sustained pain. The authors injected nerve growth factor into the right ECRB muscle at day 0 and 2 to induce muscle soreness over multiple days. Neurophysiological measures including short and long latency IHI from the left M1 (corresponding to the painful muscle) to the right M1 (corresponding to the non-painful muscle) were assessed. Quantitative sensory and motor testing including pressure pain thresholds over the painful and non-painful muscles were assessed prior to the injection at day 0 and then on days 2, 4, and 14. The findings demonstrated that pressure pain sensitivity increased in the painful muscle at days 2 and 4 compared to day 0, and interestingly, in the non-painful muscle at day 4 compared with day 0. Short and long latency IHI was reduced from the left to the right M1 at day 4. This reduction in IHI was associated with reduced PPTs in the left (non-painful) muscle across all time-points. When IHI was assessed in the opposite direction (from right to left M1), no change in IHI was observed. These findings provide evidence that IHI may be altered in response to musculoskeletal pain and that this may explain the development of bilateral sensorimotor dysfunction in unilateral conditions. The study by Schabrun et al. (2016) provides insight into

IHI during sustained pain, however there are no studies investigating IHI in the acute or chronic phases of musculoskeletal pain. It is important that all these stages of pain are assessed to fully understand if and when IHI is modulated, and whether it occurs immediately following an injury or in the transition to sustained pain. Further, due to the absence of empirical investigation, it is currently not known whether IHI continues to change as pain becomes chronic or returns to normal function.

1.8 Summary of literature review

In summary, this literature review presented and discussed musculoskeletal pain and IHI. Musculoskeletal pain was discussed as a pertinent issue in the general population with some individuals that have unilateral musculoskeletal pain presenting with bilateral sensorimotor dysfunction. Lateral epicondylalgia was identified as a type of musculoskeletal condition presenting with this phenomenon and the pathophysiology of three interrelated components associated with LE was discussed. However, this review identified that there is currently little clarity around the underlying mechanism that leads to the development of bilateral sensorimotor dysfunction, but there are preliminary suggestions that the CNS may be involved. It was suggested that investigation of interactions and connectivity between cortical hemispheres may provide an explanation to the development of bilateral sensorimotor dysfunction. Specifically, IHI may be a relevant neurophysiological mechanism that could mediate the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions.

Further, the review discussed the anatomical and physiological components of the IHI mechanism and the role of the corpus callosum in IHI by reviewing early studies of animals and humans. It was demonstrated through callosotomy studies, the importance of the corpus callosum in interhemispheric facilitation and inhibition of information to the opposite

hemisphere to allow unilateral and bilateral processing of information. This was followed by a review of more modern methodological techniques of assessing IHI in humans using TMS and EEG. It was determined the paired-pulse paradigm is the more appropriate method of assessment for investigating IHI between the M1s using TMS compared to the iSP method.

The functional role of IHI in M1 and S1 was discussed and identified that IHI is important in the execution of unimanual and bimanual motor tasks as well as suppression of mirror movements. Lastly, the literature review demonstrated IHI is modulated in pathological conditions such as stroke, FHD and CRPS, and this is related to mirror movements and bilateral deficits. However, critical evidence is lacking regarding the effect of IHI in musculoskeletal pain conditions, specifically, why bilateral sensorimotor dysfunction develops in unilateral musculoskeletal conditions. As bilateral symptoms are observed in individuals with chronic musculoskeletal pain such as LE, similar to clinical presentations of pathological conditions, it is possible that IHI is impaired in musculoskeletal pain. Hence, three studies were conducted in this thesis to investigate the knowledge gaps identified in the literature review. The following aims for each study are presented in the next section.

1.9 Thesis aims and study rationales

The overarching aim of this thesis was to investigate the role of IHI in the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal conditions. We aimed to determine whether: i) IHI is altered in response to unilateral musculoskeletal pain; and ii) a relationship exists between altered IHI (if any) and the development of bilateral sensorimotor dysfunction. This was achieved via a series of studies using an experimental pain model to investigate IHI in M1 and S1, and a clinical population with chronic musculoskeletal pain.

1.9.1 Study one

Most studies investigating IHI in M1 have been in healthy individuals (Section 1.5) or in neurological populations (Section 1.6). Only one study has investigated IHI between M1s in response to musculoskeletal pain, with this study using an experimentally induced sustained muscle pain model (Section 1.7). Ideally, studies investigating IHI would assess participants pre-injury and pain to allow post-pain comparison and examination of the effect of injury and pain on IHI. However, because individuals are only identified once injury and pain is experienced, it is difficult to obtain this data in a clinical pain population. Experimental pain models provide a solution to this problem allowing the assessment of pain on cortical measures. Therefore, the aim of Study one (Chapter two) was to: i) investigate whether IHI between M1s is altered in response to experimentally induced unilateral acute muscle pain; and ii) determine the relationship between altered IHI and bilateral sensorimotor development. This was achieved by conducting a cross-sectional study on healthy individuals where hypertonic saline was injected to induce acute muscle pain. IHI was measured from the affected to the unaffected M1 before pain, immediately after pain resolution, and 30 mins following pain resolution. To further explore IHI during acute muscle pain, participants completed a questionnaire on the pain intensity and quality of the pain. Muscle sensitivity was assessed by pressure pain thresholds before pain induction and 30 mins after pain resolution.

1.9.2 Study two

The role of the primary sensory cortex has been explored in pain research. Changes between hemispheres have been recognised in conditions such as CRPS where the S1 cortical representation hemisphere of the unaffected limb is larger than the S1 cortical representation of the CRPS-affected limb with sensory dysfunction present in both the affected and unaffected limb (Di Pietro et al., 2015). However, it remains to be understood how IHI between S1s responds to tactile and sensory information in musculoskeletal pain. Therefore, Study two (Chapter three) aimed to: i) investigate whether IHI between S1s is altered in response to experimentally induced acute unilateral muscle pain in healthy individuals; and ii) investigate the relationship between altered IHI and bilateral sensorimotor dysfunction. This was achieved using EEG to measure sensory evoked potentials in response to acute muscle pain induced by injection of hypertonic saline. Sensory evoked potentials were recorded before pain, immediately after pain resolution, and 30 mins following pain resolution. Pain intensity and mechanical sensitivity were recorded to determine if a relationship existed between altered IHI (if found) and the pain profile of participants.

1.9.3 Study three

Previous research has demonstrated that primary motor cortex structural and functional organisation is altered in chronic musculoskeletal pain. Intracortical mechanisms have been thoroughly investigated demonstrating reduced intracortical inhibition within a single cortical hemisphere. However, inhibitory interactions between hemispheres have not been explored with no study having explored IHI between M1s in chronic musculoskeletal pain. Therefore, Study three (Chapter four) aimed to investigate whether IHI between M1s is altered in individuals with chronic lateral epicondylalgia compared to pain-free healthy controls. A TMS double-pulse paradigm was used to assess IHI at different conditioning intensities in individuals with chronic lateral epicondylalgia and pain free healthy controls.

CHAPTER 1 Introduction and Literature review

CHAPTER 2 IHI between primary motor cortices in response to acute muscle pain

CHAPTER 3 IHI between primary sensory cortices in response to acute muscle pain

CHAPTER 4 IHI between primary motor cortices in individuals with lateral epicondylalgia

CHAPTER 5 Discussion and Conclusion

CHAPTER 2

IHI BETWEEN PRIMARY MOTOR CORTICES IN RESPONSE TO ACUTE MUSCLE PAIN

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The full text version of the article presented in the journal's formatting style is presented in Appendix A.

G.A and S.S. conceptualised and designed the study. G.A. collected and analysed the data, interpreted the results and drafted the manuscript with input from M.L., and S.S. All authors discussed the results, commented on the manuscript and approved the final version.

2.1 Abstract

Bilateral deficits in sensorimotor function have been observed in unilateral musculoskeletal pain conditions. Evidence suggests a reduction in interhemispheric inhibition (IHI) from the 'affected' (contralateral to the side of pain) to the 'unaffected' primary motor cortex could contribute. However, the effect of short-lasting acute muscle pain on IHI, and whether any changes are related to early sensorimotor changes in the unaffected limb is unknown. Using a cross-sectional study design, IHI was investigated in 20 healthy individuals before, immediately after the resolution of pain and 30 minutes after the induction of acute muscle pain in the right first dorsal interosseous (FDI) muscle via bolus injection of hypertonic saline. Transcranial magnetic stimulation was used to assess corticomotor excitability and short- and long-latency IHI. Pain intensity and quality were recorded using an 11-point numerical rating scale and the McGill Pain Questionnaire. Pressure pain thresholds (PPTs) were assessed in the affected and unaffected FDI and both Tibialis Anterior muscles. Participants reported an average pain intensity of 4.8 (1.3) points. Compared with baseline, corticomotor excitability was reduced at all time points in the affected but not the unaffected primary motor cortex. IHI was reduced at all time points from the affected to the unaffected primary motor cortex. PPTs were reduced over both FDI muscles at 30 minutes follow-up. These findings suggest a reduction in IHI from the affected to the unaffected primary motor cortex that occurs rapidly following the onset of acute pain and could contribute to the development of bilateral symptoms.

Perspective: The affected primary motor cortex (contralateral to the side of pain) releases inhibition over the unaffected primary motor cortex within minutes following the onset of acute muscle pain. This finding could have relevance for the development of bilateral sensorimotor symptoms in unilateral pain conditions.

2.2 Introduction

Musculoskeletal pain is known to alter sensorimotor function of the affected body part. For example, individuals with chronic lateral elbow pain (chronic lateral epicondylalgia or 'Tennis Elbow') display increased sensitivity to mechanical stimuli (Jespersen et al., 2013), decreased maximal wrist extensor force and reduced grip force (Bisset et al., 2006b; Slater et al., 2005) on the painful side. Interestingly, bilateral deficits in sensorimotor function are also observed in these individuals, despite the presence of pain in only one limb (Bisset et al., 2006b; Coombes et al., 2012b; Fernández-Carnero et al., 2008). For example, a recent systematic review demonstrated flexed wrist postures, increased upper-limb reaction times, reduced speed of movement, and reduced pressure and thermal pain thresholds in the *unaffected* limb of people with chronic lateral elbow pain (Bisset et al., 2006b; Heales et al., 2014; Pienimaki et al., 1997). This observation suggests involvement of the central nervous system in the development of bilateral sensorimotor dysfunction, yet the mechanisms that mediate this effect are unknown.

Interhemispheric inhibition (IHI) is a neurophysiological mechanism where the primary motor cortex (M1) of one hemisphere inhibits the M1 of the opposite hemisphere via projections in the corpus callosum. IHI is involved in the control of skilled movements, as well as in the acquisition and transfer of motor skills (Reis et al., 2008). Normal modulation of IHI enables individuals to perform unimanual tasks without co-activation of contralateral muscles. However, in childhood, pathological conditions such as mirror dystonia and the elderly, mirror movements can be observed in the opposite limb when a task is complex or fatiguing, and this movement overflow is negatively correlated with the degree of IHI exerted over the inactive limb (Beaule et al., 2012). Further, there is evidence of a relationship between altered IHI and impaired motor recovery in stroke survivors. Specifically, the unaffected M1 has been shown to exert 'too much' inhibitory control over the stroke-affected M1, interfering with adaptive

neuroplasticity in the lesioned area and motor recovery of the paretic limb (Alia et al., 2017; Duque et al., 2005; Murase et al., 2004). The relationship between IHI and sensorimotor function observed in previous studies could also be relevant to the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions.

Only one study has examined IHI in musculoskeletal pain. That study reported a reduction in IHI from the affected M1 (corresponding to the painful muscle) to the unaffected M1 four days after repeated injection of nerve growth factor into the elbow extensor muscles to induce progressively developing, sustained muscle pain. The reduction in IHI was associated with the development of sensorimotor dysfunction (increased sensitivity to mechanical stimuli) in the unaffected limb (Schabrun et al., 2016). These data suggest a relationship between IHI and the development of bilateral sensorimotor dysfunction after several days of musculoskeletal pain. However, it is unknown how soon after pain onset IHI is altered and whether this is related to early sensorimotor changes in the unaffected limb.

Here we aimed to investigate: i) whether IHI is altered in response to rapid onset, short-lasting acute muscle pain; and ii) the relationship between altered IHI and changes in sensorimotor function in the unaffected limb. Based on previous work (Schabrun et al., 2016), we hypothesized that IHI would be reduced from the affected to the unaffected M1 in response to acute muscle pain and this would be associated with increased sensitivity to mechanical stimuli in the unaffected limb.

2.3 Methods

Twenty healthy individuals (8 males, 12 females; mean ± standard deviation [SD] age 26 ± 7 years) participated. Participants were recruited through the University and social media from May 2017 to September 2017. All participants were right handed according to the Edinburgh handedness inventory (Oldfield, 1971) and had no history of upper limb pain or injury, no neurological, respiratory, orthopaedic or circulatory disorders and no contraindications to transcranial magnetic stimulation (Keel et al., 2001). All procedures were approved by the institutional human research ethics committee (H11873). Participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

The sample size calculation was based on effect sizes from the only study to have examined IHI in musculoskeletal pain (Schabrun et al., 2016). Based on these data (difference in means between days 0 and 4 of 0.91 mV, SD of 0.90), a sample size of 10 participants was required to observe a statistically significant difference (80% power, alpha 0.05) should one exist. However, as these effects have not been examined in acute pain and the size of the effect is therefore unclear, we conservatively doubled the sample size, ensuring sufficient power to allow detection of a smaller effect size if needed.

2.3.1 Experimental protocol

Participants were seated with their head and neck supported and both arms resting in a supinated position on a pillow. Pressure pain thresholds were recorded bilaterally from the first dorsal interosseous (FDI) and tibialis anterior muscles at baseline and at 30 minutes follow up. Fifteen motor evoked potentials to single-pulse transcranial magnetic stimulation were elicited from the affected and unaffected M1 (order randomized between participants), followed by assessment of IHI, at 3 time-points: i) before pain; ii) immediately following the resolution of pain (once pain had returned to zero on an 11-point numerical rating scale); and iii) 30 minutes

after the resolution of pain. Muscle pain was induced by intramuscular injection of hypertonic saline into the right FDI muscle. The FDI muscle was chosen as the cortical representation has shown strong overlap with the extensor carpi radialis muscle (Devanne et al., 2006) and no previous studies have assessed IHI in hand muscles. Pain was rated on an 11-point numerical rating scale anchored with 'no pain' at zero and 'worst pain imaginable' at 10, every 30s immediately following hypertonic saline injection until each participant reported a pain score of zero. At the conclusion of the experiment, participants rated the intensity, location and quality of muscle pain using the short-form McGill Pain Questionnaire (Melzack, 1987) and a body chart. The experimental protocol is outlined in Figure 2.1.

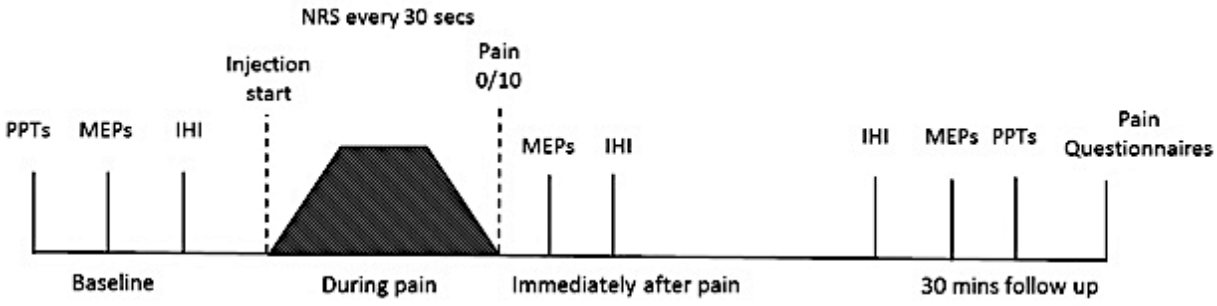

Figure 2.1: Experimental protocol. Measures of corticomotor output (MEP) and interhemispheric inhibition (IHI) were made at: i) baseline; ii) immediately after pain; and iii) 30 mins follow up. Pressure pain threshold (PPT) measurements were taken at baseline and at 30 minutes follow up. Pain was induced by injection of hypertonic saline into the right first dorsal interosseous (FDI) muscle and pain intensity monitored every 30 seconds on the numerical rating scale (NRS). The McGill pain questionnaire was completed at the conclusion of the experiment.

2.3.2 Pressure pain thresholds

Pressure pain thresholds were assessed at baseline and at 30 minutes follow up. Participants rested their arms on a steady surface and a hand-held pressure algometer (Wagner Instrument,

Greenwich, USA) was applied perpendicular to the skin at a rate of 1 kg/sec. Participants were instructed to vocalize the moment the sensation of pressure first turned to pain. Pressure pain thresholds were assessed in random order at four sites: 1) affected FDI; 2) unaffected FDI; 3) right Tibialis Anterior; and 4) left Tibialis Anterior. For each site the muscle belly was located and marked to ensure consistent positioning of the algometer over time. Pressure pain thresholds for the first dorsal interosseous muscle have been demonstrated to be reliable when using the average of three trials (Chesterton et al., 2007). The average of the three trials at each site, with 1-minute rest between each trial, was used for statistical analysis.

2.3.3 Electromyography

Electromyographic activity was recorded from the affected and unaffected FDI muscles. Disposable dual silver/silver chloride surface electrodes (Noraxon USA Inc, Arizona, USA) were positioned over each muscle belly. Ground electrodes were positioned over the right and left olecranon's. Data were amplified 1000 x, filtered between 20 to 1000 Hz and sampled at 2000 Hz using Signal software and a Micro 1401 data acquisition system (Cambridge Electronic Design, Cambridge UK).

2.3.4 Transcranial magnetic stimulation

Corticomotor excitability

Single-pulse transcranial magnetic stimulation stimuli were delivered to the M1 hand areas using a figure of 8 coil connected to a Magstim 200 stimulator (Magstim Co. Ltd, Dyfed, UK). Transcranial magnetic stimulation was performed over both the affected and unaffected M1 in all participants. The coil was oriented at a 45° angle to produce a posterior to anterior current flow and positioned over the optimal cortical site to evoke a response in each FDI muscle. The optimal cortical site to elicit motor evoked potentials in the affected and unaffected FDI muscles was determined as the site where the lowest stimulus intensity evoked the largest

response. These sites were marked with a pen to ensure accurate coil placement for the duration of the experiment. Resting motor threshold was defined as the lowest intensity of stimulation required to evoke a motor evoked potential >50 μV peak-to-peak amplitude in at least three of five consecutive trials (Rossi et al., 2009). Fifteen motor evoked potentials (rate of 1 every 6 s) were recorded from the affected and unaffected FDI at 120% of resting motor threshold. The hemisphere recording order was randomised between participants. The average peak-to-peak motor evoked potential amplitude (mV) was calculated at each time-point for the affected and unaffected M1 and this value used for analysis.

Interhemispheric Inhibition

IHI was probed using a conditioning-test paradigm. A conditioning pulse applied to the affected M1 preceded a test stimulus applied to the unaffected M1. To investigate short and long latency IHI, 10 and 40 ms interstimulus intervals were selected, respectively (Ferbert et al., 1992; Sattler et al., 2014; Sattler et al., 2012). In pseudorandom order, 10 trials were recorded at each interstimulus interval and a further 10 trials were recorded using the test stimulus alone (30 trials in total) with 5 seconds between each trial. Transcranial magnetic stimulation was delivered using two Magstim 200 magnetic stimulators (Magstim Co. Ltd, Dyfed, UK), each connected to a figure-of-eight coil with external wing diameters of 70 mm (unaffected M1) and 50 mm (affected M1). The coil delivering the test stimulus was positioned tangentially over the scalp perpendicular to the midsagittal line with the coil handle pointing backwards at a 45° angle inducing a posterior to anterior current direction. The conditioning stimulus coil was oriented 90 degrees relative to the midsagittal line to avoid overlapping the coils (Chen et al., 2003; Ni et al., 2009). It has been previously reported that the current direction of the conditioning stimulus does not affect the degree of IHI (Chen et al., 2003; Ni et al., 2009). To investigate our hypothesis, IHI was recorded from affected to unaffected M1 The test stimulus intensity was adjusted to produce a peak-to-peak motor evoked potential

amplitude of 1-1.5 mV (Morishita et al., 2014) in relaxed FDI and the conditioning stimulus intensity was set at 120% of resting motor threshold and adjusted if required, to elicit inhibition of ~ 50% at baseline in each participant (Gueugneau et al., 2017; Morishita et al., 2014; Perez & Cohen, 2008). Motor evoked potential responses were measured as peak-to-peak amplitudes and conditioned responses expressed as a proportion of the unconditioned test response for analysis.

2.3.5 Experimental muscle pain

An outcome assessor with experience performing injections performed the procedure. The FDI muscle was located by palpation and a single bolus of 0.5 mL of hypertonic saline (5.8%) was injected into the muscle belly of the right FDI after the skin was cleaned with alcohol. Injections were performed using a 0.5-mL syringe with a disposable needle (31G). There were no adverse effects reported from the injection.

2.3.6 Statistical Analysis

Statistical analysis was conducted in SPSS (version 25). Pressure pain thresholds were compared using a 2-way repeated measures ANOVA with factors ‘time’ (baseline, 30-min follow-up) and ‘side’ (affected, unaffected) for the FDI and Tibialis Anterior muscles, respectively. Cohen’s d effect sizes were calculated and are presented in the text.

Corticomotor excitability for each hemisphere and short- and long-latency IHI were assessed for normality and sphericity. Corticomotor excitability was compared between time points (baseline, immediately after pain, 30-min follow-up) using a one-way repeated measures ANOVA. To account for any influence of sex on IHI, short- and long-latency IHI were compared between time points (baseline, immediately after pain, 30-min follow-up) and sex (male, female) using a two-way repeated measures ANOVA. Pearson’s correlation coefficients were calculated to assess the relationship between the change in short- and long-latency IHI

over time (baseline to 30 min follow-up) and peak pain, pain duration and the change in pressure pain thresholds over time from affected and unaffected FDI. Where appropriate, post-hoc analyses were performed using Holm-Sidak tests corrected for multiple comparisons. Statistical significance was set at $p < 0.05$. Data in text are presented as mean ± standard deviation.

2.4 Results

2.4.1 Pain characteristics

Injection of hypertonic saline produced a peak pain intensity of 7.9 ± 1.8 points on the numerical rating scale and an average pain intensity over time of 4.8 ± 1.3 points. The average pain duration was 9.9 ± 3.4 minutes. The most frequent words used to describe the pain were sharp (90%), aching (85%) and throbbing (80%). Most participants reported pain localised to the injection site on the dorsal surface of the hand. Six participants reported pain that radiated toward the palmar surface of the hand, five participants reported pain that extended into the proximal forearm and one participant reported pain extending into the upper arm.

2.4.2 Neurophysiological measures

Group data (mean ± standard deviation) for pressure pain sensitivity, corticomotor excitability, short- and long-latency IHI and stimulator output at each time point are presented in Table 2.1.

2.4.3 Pressure pain sensitivity

Relative to baseline, pressure pain thresholds were reduced ($F_{1,19} = 22.56$, $p < 0.001$) in both the affected ($p < 0.001$, Cohen's d= 0.57; Figure 2.2A) and unaffected ($p = 0.005$, Cohen's d = 0.46; Figure 2.2B) FDI muscles 30 minutes after the induction of acute muscle pain. There were no differences between sides ($F_{1,19} = 0.31$ $p = 0.86$). Pressure pain thresholds recorded from the bilateral Tibialis Anterior muscles were unchanged over time ($F_{1,19} = 0.002$, $p = 0.96$).

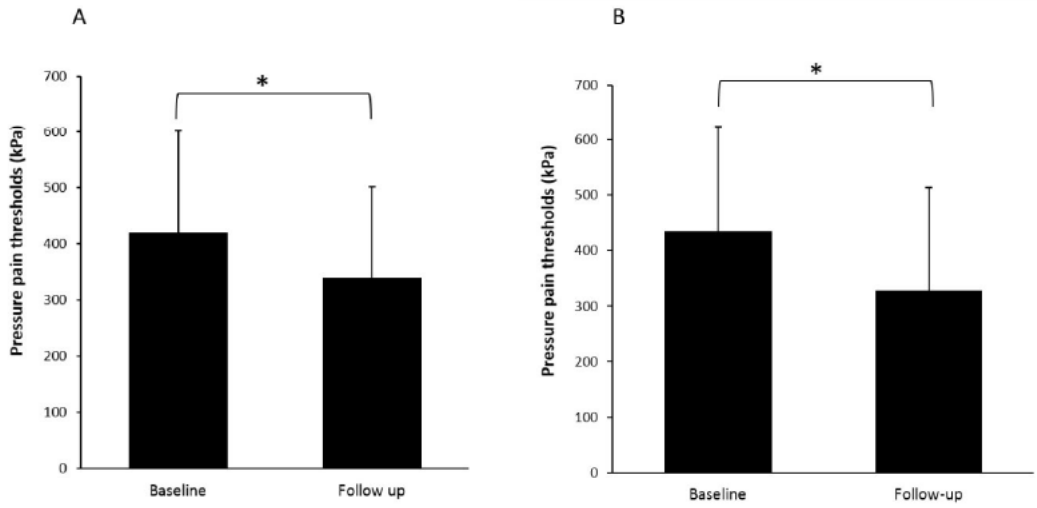

Figure 2.2. Group data (mean ± SD, N=20) for PPTs at right (A) and left FDI (B) at each time point (baseline and follow-up). The asterisk denotes a significant (P <0.05) difference from baseline. PPTs were reduced at follow-up in the right (injected) FDI and in the left (uninjected) FDI.

Table 2.10. Group data (mean ± SD, N=20) for corticomotor excitability, interhemispheric inhibition and pressure pain threshold measures at baseline, immediately after pain and at 30 minutes follow-up.

	Baseline	**Immediately after pain**	**30 minutes follow-up**
Corticomotor excitability (mV)			
Affected M1	0.93±0.83	0.68±0.86*	0.66±0.64*
Unaffected M1	0.97±0.81	1.04±0.72	1.10±0.72
IHI for Affected to Unaffected M1 (mV)			
Unconditioned test response	1.30±0.37	1.23±0.23	1.24±0.35
IHI 10ms (proportion of test)	0.69±0.22	1.07±0.38*	1.05±0.41*
IHI 40ms (proportion of test)	0.61±0.22	1.03±0.49*	1.06±0.35*
Stimulator output (%)	56±11	56±9	55±12
Pressure pain thresholds (kPa)			
Affected FDI	435±190	-	329±185*
Unaffected FDI	420±181	-	339±162*
Right Tibialis Anterior	878±468	-	857±522
Left Tibialis Anterior	897±656	-	835±553

Note: IHI, interhemispheric inhibition; FDI, first dorsal interosseous; M1, primary motor cortex, *p<0.05 from baseline

2.4.4 Corticomotor excitability

The induction of pain in the right FDI led to suppression of motor evoked potentials from the affected M1 ($F_{2,38}$ = 6.60, p = 0.003). Corticomotor excitability was reduced immediately following the resolution of pain (p = 0.007) and at 30-min follow-up (p = 0.01; Figure 2.3A), relative to baseline. Motor evoked potentials from the unaffected M1 were unchanged over time ($F_{2,38}$ = 0.25, p = 0.77; Figure 2.3B).

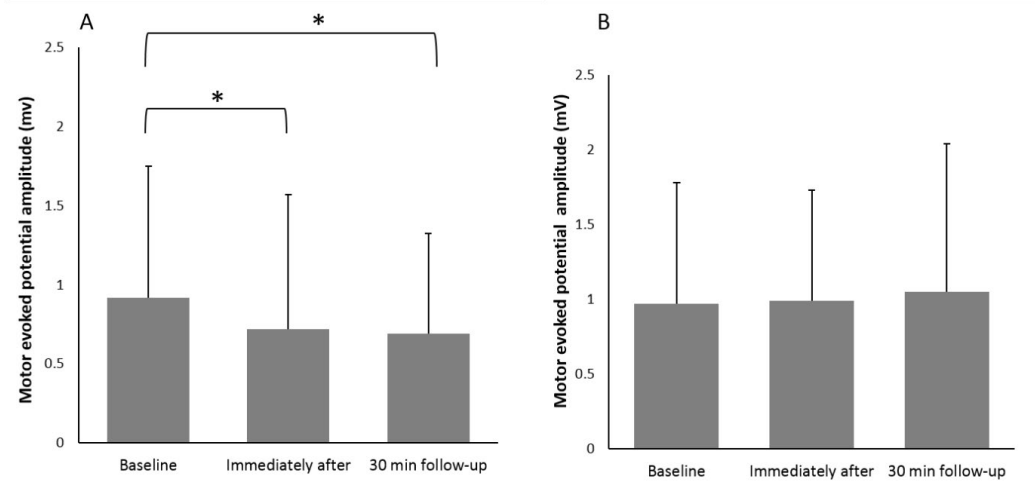

Figure 2.3. Group data (mean ± SD) of corticomotor excitability recorded from the left (A) and right (B) M1, before and after the resolution of pain. MEP amplitude was reduced at both time-points following the resolution of pain in left M1 (P < 0.05) but was unchanged over time in right M1.

2.4.5 Interhemispheric inhibition

Unconditioned motor evoked potential test amplitudes were stable over time ($F_{2,38}$ = 0.58, p = 0.56; Figure 2.4A). The induction of acute muscle pain affected the degree of IHI from the affected to the unaffected M1 at both short ($F_{2,36}$ = 9.07, p <0 .001; Figure 2.4B) and long latencies, ($F_{2,36}$ = 12.83 p <0.001; Figure 2.4C). Relative to baseline, short- and long-latency IHI were reduced immediately following the resolution of pain (short: t = 3.72, p = 0.002; long: t = 4.48, p<0.001) and remained reduced at 30-min follow-up (short: t = 3.65, p = 0.002; long:

t = 4.28 p < 0.001). Sex did not influence the IHI response (short: $F_{1,36}$ = 3.5, p = 0.078; long: $F_{1,36}$ = 0.42, p = 0.52).

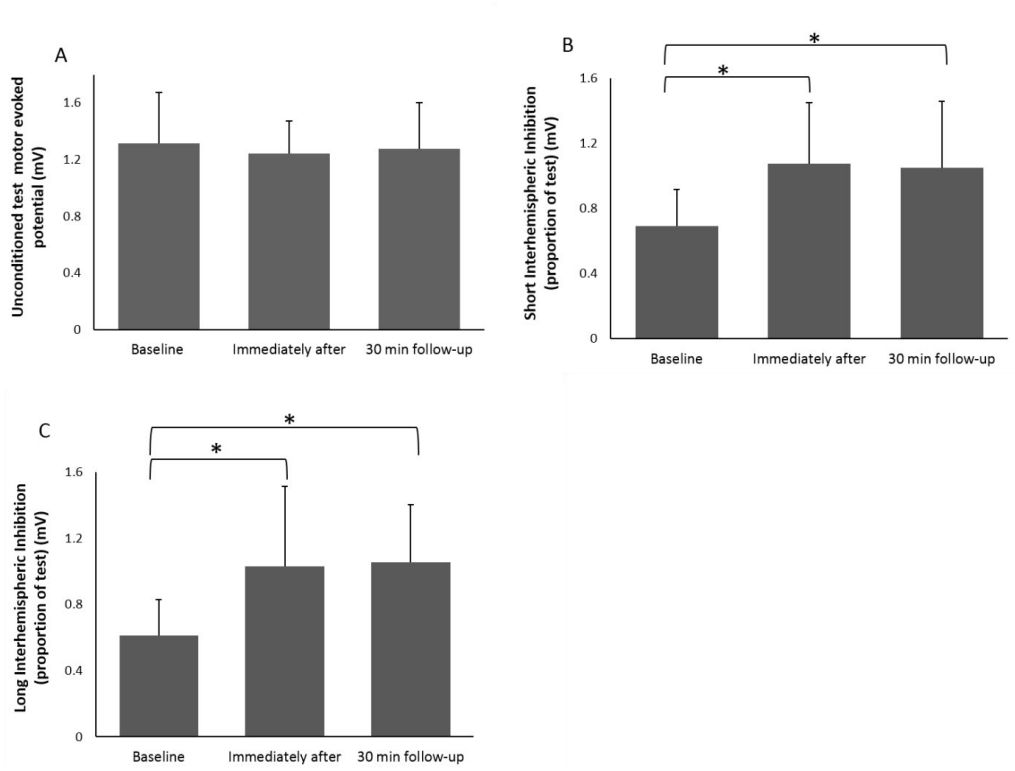

Figure 2.4. Group data (mean ± standard deviation) for the unconditioned (test) response (A), short interhemispheric inhibition (SIHI; B) and long interhemispheric inhibition (LIHI; C) obtained at each time point. There was no difference in the amplitude of the unconditioned MEP over time. SIHI and LIHI were reduced at both time points following the resolution of pain. A reduction in SIHI and LIHI is denoted by an increased proportion of the test response. Asterisks denote a significant (p < 0.05) difference from baseline.

A greater reduction in short- (r = -0.51, p = 0.02) and long-latency (r = -0.60, p= 0.005) IHI at 30-min follow-up was associated with a greater reduction in pressure pain thresholds in the affected FDI. There was no relationship between the change in IHI over time at either short (r = -0.19, p = 0.94) or long (r = 0.06, p = 0.80) latency and pressure pain thresholds in the unaffected FDI. There was no relationship between short- and long-latency IHI and peak pain or pain duration.

2.5 Discussion

This study is the first to investigate interhemispheric inhibition in response to acute onset muscle pain. The key finding was a reduction in IHI from the affected to the unaffected M1 at both short and long latencies that was present immediately after pain resolved and persisted at 30 mins follow-up. A unique observation was an increase in sensitivity to mechanical stimuli in the unaffected hand, despite the absence of pain on that side. These findings suggest a release of IHI over the unaffected M1 that occurs rapidly in response to pain that could relate to the development of sensorimotor symptoms in the unaffected hand.

A large body of evidence has shown reduced corticomotor excitability in the hemisphere contralateral to the painful side in response to acute muscle pain, an effect that persists in the immediate post-pain period and is not influenced by resumption of normal motor activity (Burns et al., 2016b; Schabrun et al., 2017b). The present data support these findings. The effect of pain on the contralateral M1 has been further characterised by studies demonstrating increased intracortical inhibition, reduced intracortical facilitation, and reduced integration of sensory information with motor output in response to acute pain (Burns et al., 2016c; Schabrun & Hodges, 2012). Taken together, these data have been interpreted as evidence of a protective strategy that serves to limit movement of the painful part and reduce the risk of further tissue damage (Hodges & Tucker, 2011). However, despite evidence of changes occurring in the contralateral M1, interaction between the two M1 hand areas in acute pain has not been investigated.

Interhemispheric inhibition can be assessed in humans using paired-pulse transcranial magnetic stimulation with a stimulating coil positioned over each M1, and pulses delivered at interstimulus intervals in the range of 6 – 50 ms (Di Lazzaro et al., 1999; Ferbert et al., 1992; Ni et al., 2009). Application of a conditioning stimulus in one hemisphere activates excitatory

transcallosal projections that synapse with inhibitory interneuronal networks in the opposite hemisphere, altering the excitability of pyramidal output neurons (Di Lazzaro et al., 1999; Ferbert et al., 1992; Hanajima et al., 2001). Indeed, primate studies demonstrate the existence of transcallosal projections between the two M1 hand areas (Jenny, 1979) and further animal and human work has shown these projections convey information between the two motor cortices (Chowdhury & Matsunami, 2002; Hanajima et al., 2001). Evidence from patient studies demonstrates that IHI is mediated via these transcallosal pathways (Boroojerdi et al., 1996; Meyer et al., 1995; Meyer et al., 1998) and both short- and long-latency IHI are thought to be dependent on $GABA_B$ mediated neurotransmission (Daskalakis et al., 2002; Irlbacher et al., 2007; Kukaswadia et al., 2005). These data, in conjunction with previous studies demonstrating no inhibition of the H-reflex during IHI recording, suggest IHI is of cortical origin (Ferbert et al., 1992; Gerloff et al., 1998; Harris-Love et al., 2007).

Only one previous study has examined IHI in musculoskeletal pain. Using a clinically-relevant model of progressively developing sustained muscle pain, that study showed a reduction in IHI from the affected to the unaffected M1 four days after the onset of pain that was associated with an increase in mechanical sensitivity in the unaffected arm (Schabrun et al., 2016). The present data extend these findings and show that IHI is reduced in response to rapid onset, short-lasting pain of high intensity (peak pain intensity of 7.9 ± 1.8 points). Although we were unable to measure IHI during pain due to its short-lasting nature, a reduction in IHI was observed in the immediate post-pain period and this effect persisted for at least 30 mins following pain resolution. Consistent with data from the sustained pain model, and patients with chronic lateral elbow pain, mechanical sensitivity was increased in the unaffected hand (Bisset et al., 2018; Coombes et al., 2012b; Schabrun et al., 2016). However, in contrast to previous studies, we did not find a linear correlation between the degree of IHI and mechanical sensitivity in the unaffected hand. This discrepancy could be explained by the different pain

durations (minutes vs. days), pain intensities or differences in the presence of pain at the time of testing across studies. For instance, in the sustained pain model, IHI was tested when participants were experiencing pain whereas in the current study, IHI was tested only once pain had resolved. Alternatively, a non-linear relationship may exist between these parameters in the acute stage of pain. Longitudinal studies that encompass both the early (pain lasting minutes to hours) and later (pain lasting days to weeks) acute stages of pain are required to further elucidate the temporal profile of altered IHI and how this relates to the development of sensorimotor dysfunction in the unaffected hand.

The precise mechanism through which reduced IHI could influence sensorimotor function on the unaffected side is unknown. In the current study, corticomotor excitability in the ipsilateral M1 was unaltered. However, as corticomotor excitability and IHI are known to reflect different neuronal populations this finding is unsurprising (Boroojerdi et al., 1996; Le Pera et al., 2001; Svensson et al., 2003). One possibility is that a release of inhibition over the unaffected M1 led to reduced inhibition of thalamic neurons that in turn, influenced mechanical sensitivity on the unaffected side. Evidence for this hypothesis is drawn from studies demonstrating a reduction in pain with M1 stimulation. This is thought to be mediated by corticothalamic projections that suppress sensory information being relayed in the spinothalamic tract (Lefaucheur et al., 2006; Lucas et al., 2011). Further, imaging studies suggest effects of M1 stimulation on other pain-processing regions including the anterior cingulate cortex, orbitofrontal cortex, insula, secondary sensory cortex, and periaqueductal gray matter (Garcia-Larrea & Peyron, 2007; Garcia-Larrea et al., 1999; Peyron et al., 2007). A release of IHI over the unaffected M1 could therefore reduce downstream inhibition of thalamic neurons, the periaqueductal gray, and/or other pain-processing regions, increasing sensitivity to pressure stimuli. Alternatively, IHI is known to play a key role in interlimb transfer of motor skills and ‘cross-education’ of the uninvolved limb following strength training. For example, repeated unimanual practice of a

motor task results in transfer of implicit knowledge, as well as speed and accuracy, to the untrained hand and the degree of transfer is associated with the magnitude of the reduction in IHI from the 'active' to the 'inactive' M1 (Camus et al., 2009; Perez et al., 2007). Similarly, studies have shown interhemispheric 'transfer' of sensory stimuli such that proprioceptive input to a hand muscle reduces corticomotor excitability and increases IHI from the affected to unaffected hemisphere of the contralateral homologous muscle (Swayne et al., 2006). A salient stimulus such as pain could similarly result in information transfer to the unaffected M1. Interestingly, the direction of change in IHI differed in the presence of non-noxious proprioceptive stimuli (increased IHI) compared with the pain stimulus (decreased IHI) provided here. This discrepancy likely reflects the salience and processing of non-noxious vs. noxious stimuli in the cortex. However, further research is needed to compare the effects of different types of sensory, motor and pain stimuli on IHI.

Although altered IHI in the acute stage of pain is likely to be a protective strategy that resolves with time, a disturbance in the inhibitory balance between the affected and the unaffected hemispheres that persists when pain fails to resolve could contribute to the development of bilateral symptoms and provide a target for therapeutic modulation. Indeed, a number of studies have sought to target the imbalance in IHI in stroke patients in order to improve functional recovery (Fregni et al., 2005; Hummel et al., 2005; Vines et al., 2008; Williams et al., 2010). For example, bilateral application of transcranial direct current stimulation has been used to downregulate activity in the unaffected M1, and upregulate activity in the affected M1, and has been shown to improve function in the paretic limb (Morishita & Inoue, 2016). Although studies have applied non-invasive brain stimulation techniques over a single hemisphere in pain conditions (Antal et al., 2010; Fenton et al., 2009; Fregni et al., 2006; Passard et al., 2007), no study has attempted to target the imbalance in IHI through bilateral hemispheric stimulation.

Several limitations should be considered. Based on previous studies in pain, IHI was assessed only in one direction, from the affected to the unaffected hemisphere, and it was not possible to assess IHI during pain due to the short-lasting nature of the pain model. Future studies should assess IHI in both directions, consider longer-lasting pain models, such as infusion of hypertonic saline, and use a longer follow-up in the post-pain period, to further elucidate the temporal profile of altered IHI in response to acute pain. An isotonic saline control condition was not utilised in this study. Although our findings argue against temporal effects on our measures (pressure pain thresholds and corticomotor excitability were stable over time in the tibialis muscles and unaffected M1, respectively), future work should seek to determine the reliability of the IHI response within an individual over time in the absence of pain. Outcome assessors in this preliminary study were not blinded. To minimise the risk of bias, future studies in this area should employ stringent blinding procedures. Finally, future studies should include more comprehensive assessment of sensorimotor function to determine which aspects may be related to altered IHI in the presence of pain and investigate IHI in chronic pain conditions.

2.6 Conclusion

This study is the first to demonstrate reduced IHI from the affected to the unaffected hemisphere following acute muscle pain. This information may have relevance for the investigation of bilateral symptoms in unilateral pain conditions and potentially, for the development of therapeutic protocols that aim to restore the inhibitory imbalance in musculoskeletal pain.

CHAPTER 1 Introduction and Literature review

CHAPTER 2 IHI between primary motor cortices in response to acute muscle pain

CHAPTER 3 IHI between primary sensory cortices in response to acute muscle pain

CHAPTER 4 IHI between primary motor cortices in individuals with lateral epicondylalgia

CHAPTER 5 Discussion and Conclusion

CHAPTER 3

IHI BETWEEN PRIMARY SENSORY CORTICES IN RESPONSE TO ACUTE MUSCLE PAIN

The work presented within this chapter has been published in The Journal of Pain as per the following reference:

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The supplementary material of the article is presented in Appendix B.

G.A and S.S. conceptualised and designed the study. G.A. collected and analysed the data, interpreted the results and drafted the manuscript with input from P.C., M.L., and S.S. All authors discussed the results, commented on the manuscript and approved the final version.

3.1 Abstract

Bilateral deficits in sensorimotor function have been observed in unilateral musculoskeletal pain conditions. Altered interhemispheric inhibition (IHI) between primary sensory cortices (S1s) is one mechanism that could explain this phenomenon. However, IHI between S1s in response to acute muscle pain, and the relationship between IHI and pressure pain sensitivity in the unaffected limb have not been examined. In 21 healthy individuals, IHI was assessed using somatosensory evoked potentials in response to paired median nerve electrical stimulation at: i) baseline; ii) immediately following pain resolution; and iii) at 30-minutes follow-up. Acute muscle pain was induced by injection of hypertonic saline into the right abductor pollicis brevis (APB) muscle. Pressure pain thresholds were assessed at the right and left APB muscles before and 30-minutes after pain resolution. Compared to baseline, IHI from the affected to unaffected S1 was unaltered in response to acute muscle pain immediately following pain resolution, or at 30-minutes follow-up. Pressure pain thresholds were reduced over the right ($p = 0.001$) and left ($p = 0.001$) APB muscles at 30-minutes follow-up. These findings suggest IHI between S1s is unaffected by acute, short-lasting muscle pain, despite the development of increased sensitivity to pressure in the unaffected APB muscle.

Perspective: IHI from the affected S1 (contralateral to the side of pain) to unaffected S1 is unaltered following the resolution of acute muscle pain. This finding suggests that IHI between S1s may not be relevant in the development of bilateral sensorimotor symptoms in unilateral pain conditions.

3.2 Introduction

In some individuals with unilateral musculoskeletal pain conditions, sensorimotor function is altered bilaterally (Bisset et al., 2006b; Heales et al., 2014). For example, in acute and chronic complex regional pain syndrome, reduced thermal sensory function and heat hyperalgesia are present in both the affected and unaffected limb (Huge et al., 2008). Similarly, in unilateral carpal tunnel syndrome, thermal hyperalgesia and widespread pressure hypersensitivity have been observed in the unaffected hand and wrist (de la Llave-Rincon et al., 2009; Fernández-de-las-Peñas et al., 2009) Altered interhemispheric inhibition (IHI) is one mechanism that could underpin this phenomenon.

Interhemispheric inhibition is a neurophysiological mechanism where one cortical hemisphere inhibits activity in the opposite hemisphere via transcallosal fibres (Meyer et al., 1995). During unilateral processing, IHI inhibits the transfer of tactile and sensory information to the opposite cortical hemisphere, preventing contralateral mirroring effects (Beaule et al., 2012). For example, unilateral sensory input (i.e., from touch or electrical stimulation) has been shown to increase excitability of the contralateral primary sensory cortex (S1) while decreasing excitability of the ipsilateral S1, an effect thought to be mediated by IHI (Hlushchuk & Hari, 2006; Nihashi et al., 2005).

Previous studies have shown a reduction in IHI between the primary motor cortices (M1s) in response to acute and prolonged musculoskeletal pain. Specifically, IHI was reduced from the affected M1 (corresponding to the painful muscle) to the unaffected M1 when pain lasted minutes (Alhassani et al., 2019) to days (Schabrun et al., 2016). Notably, when pain persisted for several days, the reduction in IHI was associated with increased pressure sensitivity in the unaffected limb (Schabrun et al., 2016). These findings suggest a possible relationship between

IHI and the development of bilateral symptoms in unilateral pain conditions. However, it is unclear whether IHI is altered between S1s in response to acute muscle pain.

This study aimed to examine IHI between S1s in response to short-lasting acute muscle pain and investigate the relationship (if any) between S1 IHI and bilateral deficits in sensorimotor function. Based on previous studies in M1 (Alhassani et al., 2019) (Schabrun et al., 2016), we hypothesized that IHI would be reduced from the affected to the unaffected S1 in response to acute muscle pain and that this would be associated with increased pressure sensitivity in the unaffected limb.

3.3 Method

3.3.1 Participants

Twenty-one healthy individuals (8 males, 13 females, mean ± SD age 27 ± 7 years) participated. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Potential participants were excluded if they: had major neurological, orthopaedic, psychiatric or circulatory disorders, were pregnant, were taking central nervous system acting medication, had a personal or family history of epilepsy, or had other contraindications to transcranial magnetic stimulation (Keel et al., 2001). Participants had no history of upper limb pain, injury or peripheral neuropathy resulting in sensory loss. Data collection occurred between November 2017 and January 2018. Individuals participating in this study were not involved in study 1. All procedures were approved by the institutional human research ethics committee (University of Western Sydney: H11873). Participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

As IHI between S1s has not been previously examined in musculoskeletal pain, the sample size was based on a previous study by Brodie and colleagues (Brodie et al., 2014) of IHI in healthy individuals that used an identical method to that reported here. Using a difference in means between the paired 0 ms interstimulus interval (ISI) condition and the paired 25 ms ISI condition of 1.1 uV (SD = 1.46), a sample size of 16 participants would be required to detect a statistically significant change (80 % power, alpha 0.05) in IHI from baseline to follow-up should one exist. However, as these effects have not been examined in acute muscle pain and the size of the effect is unclear, as well as accounting for the restriction of time, the sample size in the current study was increased to 21 to provide greater statistical power.

3.3.2 General experimental protocol

The experimental protocol is outlined in Figure 3.1. Participants were seated with their head and torso supported and elbows flexed at a 90° angle such that their forearms were resting in a supinated position on a pillow. Consistent with the protocol described by Brodie et al. (2014), IHI was assessed using somatosensory evoked potentials (SEPs) recorded from the right S1 in response to a paired median nerve electrical stimulation protocol with 25 ms ISI. Two control conditions (paired median nerve stimulation with 0 ms ISI, right median nerve stimulation alone) were also included. Two blocks of 300 SEPs were recorded for each condition at: i) baseline; ii) immediately following pain resolution (when pain reached 0/10); and iii) 30-min follow-up. It was not possible to record SEPs during pain due to the short-lasting nature of hypertonic saline-induced pain. Participants were instructed to keep their eyes closed and jaw relaxed during SEP recordings. Muscle pain was induced by intramuscular injection of hypertonic saline into the right abductor pollicis brevis (APB) muscle. Following injection, participants rated their pain every 30 s on an 11-point numerical rating scale anchored with '0' as no pain and '10' as worst pain imaginable from the time of injection until pain had ceased. Pressure pain thresholds were recorded from the right and left APB muscles and the right and left tibialis anterior muscles at baseline and 30-min follow-up. The Tibialis Anterior muscles were included to examine the muscle specificity of any increase in mechanical sensitivity in response to pain. At the conclusion of the experiment, participants rated the intensity, location, and quality of muscle pain using the short-form McGill Pain Questionnaire and a body chart.

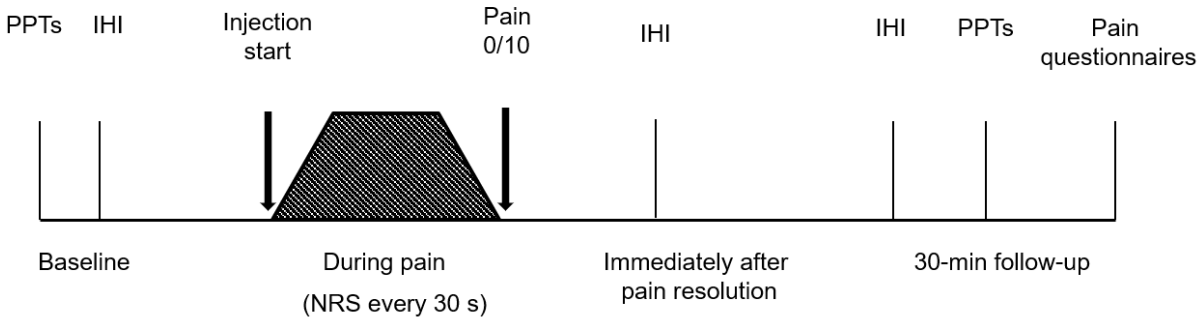

Figure 3.1. Experimental protocol. Pressure pain thresholds (PPTs) were assessed at baseline and 30-minutes follow-up. Measures of interhemispheric inhibition (IHI) were made at: i) baseline ii); immediately after pain resolution; and at iii) 30- minutes follow-up. Pain was induced by injection of hypertonic saline into the right abductor pollicis brevis muscle and pain intensity monitored every 30 seconds on a numerical rating scale (NRS) until pain reached 0/10. The Short-form McGill pain questionnaire (SF-MPQ) and body chart were completed at the conclusion of the experiment.

3.3.3 Assessment of IHI

Somatosensory evoked potentials

Using electroencephalography (EEG), SEPs were recorded from the right S1 hand area. Two blocks of 300 SEPs were recorded for each condition (25 ms ISI, 0 ms ISI and CS alone) at each time point with a 1-min rest interval applied between each SEP block. The recording time for one SEP block was 15 minutes with a total recording time of 30 minutes for each time-point. Gold plated cup electrodes were positioned over C4 (3 cm lateral, 2 cm posterior to Cz) and referenced to Fz (Homan et al., 1987). The skin electrode impedance was kept below 5 Ω. EEG signals were amplified 50000 x, bandpass filtered 5 - 500 Hz and sampled at 1000 Hz using Signal software and a Micro 1401 data acquisition system (Cambridge Electronic Design, Cambridge UK).

Electrical stimulation protocols

Disposable silver/silver chloride surface electrodes (3M, Red Dot) were placed over the right and left median nerves aligned with the wrist crease. An additional electrode positioned 2 cm proximal to the wrist crease on each forearm acted as the cathode. Electrical pulses (square wave, monophasic, 0.1 ms duration, rate of 2 Hz) were delivered to the median nerves using two DS7AH constant current stimulators (Digitimer Ltd, UK) triggered by Signal software (Version 5.08, Cambridge Electronic Design Ltd, Cambridge, UK). To check that stimulation intensity was sufficient, electromyography (disposable dual silver/silver chloride surface electrodes [Noraxon USA Inc, Arizona, USA]) were placed on each APB muscle belly and stimulation intensity set to produce a muscle twitch of ~ 1 mV peak to peak amplitude (baseline: mean ± SD = 1.08 ± 0.13 mV right hand, 1.09 ± 0.14 mV left hand; immediately after pain: 1.05 ± 0.10 mV right hand, 1.09 ± 0.11 mV left hand; 30-min follow-up: 1.08 ± 0.08 mV right hand, 1.10 ± 0.11 mV left hand). Signals were grounded to the olecranon, amplified 1000 x, filtered 20 to 1000 Hz, and sampled at 1000 Hz. Electromyography activity was visually monitored throughout the experiment to ensure consistent twitch amplitudes. Small adjustments in stimulation intensities (± 1 - 2 mA) were made to maintain consistent twitch amplitudes if needed.

Three electrical stimulation protocols were used for the assessment of IHI: i) paired median nerve stimulation with a 25 ms ISI; ii) paired median nerve stimulation with a 0 ms ISI; and iii) right median nerve stimulation alone (Brodie et al., 2014; Ragert et al., 2011). In the 25 ms ISI condition, a conditioning stimulus (CS) was delivered to the right median nerve 25 ms prior to a test stimulus (TS) delivered to the left median nerve (Figure 3.2). This protocol was selected as it has been shown to elicit IHI between S1s in previous studies (Brodie et al., 2014; Ragert et al., 2011) In the 0 ms ISI condition, electrical stimuli were simultaneously applied to the right and left median nerves. This condition was included to control for differences in

directed attention to electrical stimulation, which has been shown to alter sensory processing by equally dividing attention between the two hands (García-Larrea et al., 1991). Finally, a right median nerve stimulation alone condition was included to eliminate any potential influence of an ipsilateral component generated from the conditioning stimulus (right median nerve stimulation) on the response to the test stimulus (left median nerve stimulation) in the 25 ms ISI condition (Brodie et al., 2014). The order of the three conditions was pseudorandomized during the experiment. No participant reported discomfort or fatigue during the experimental session.

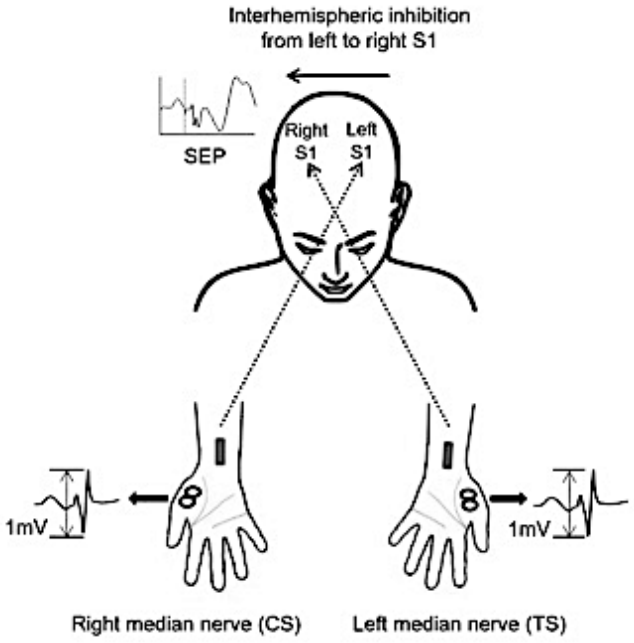

Figure 3.2. Interhemispheric inhibition was assessed by recording somatosensory evoked potentials (SEPs) from the left primary sensory cortex (S1) to the right S1 in response to three median nerve electrical stimulation protocols: i) 25 ms interstimulus interval (ISI) condition - a conditioning stimulus (CS) was delivered to the right median nerve 25 ms prior to a test stimulus (TS) delivered to the left median nerve; ii) 0 ms ISI condition - electrical stimuli were applied to the right and left median nerve simultaneously; and iii) right median nerve stimulation alone condition - a single electrical pulse was delivered to the right median nerve. Median nerve stimulation was set to produce a muscle twitch of 1 mV peak-to-peak in each abductor pollicis brevis (APB) muscle. Stimulating electrodes are denoted by the grey bars and electromyographic recording electrodes by the open circles.

Individual SEP traces were carefully visually inspected. Several criteria were used to identify traces with significant noise or artefact. Traces considered to contain electrical noise (determined by the presence of sinusoidal waves) or a stimulus artefact of a duration sufficient to mask the onset of the SEP were identified and discarded. Traces with biological noise such as muscle artefact (determined by the presence of high frequency activity) were identified and discarded. Less than 5 % of SEP traces were discarded. Following the procedure described by Ragert et al. (2011), the remaining traces from the two blocks of 300 SEPs were averaged for each condition. The average raw ipsilateral SEP response from the right median nerve stimulation alone condition was subtracted from the average raw SEP response for the paired 25 ms ISI and 0 ms ISI conditions. Peak to peak amplitudes for five SEP components (P_{14}/N_{20}, N_{20}/P_{25}, P_{25}/N_{30}, N_{30}/P_{40}, P_{40}/N_{60}) were identified and manually extracted from the subtracted data, for each individual, for the 25 ms ISI and 0 ms ISI conditions (Figure 3.3) (Ragert et al., 2011).

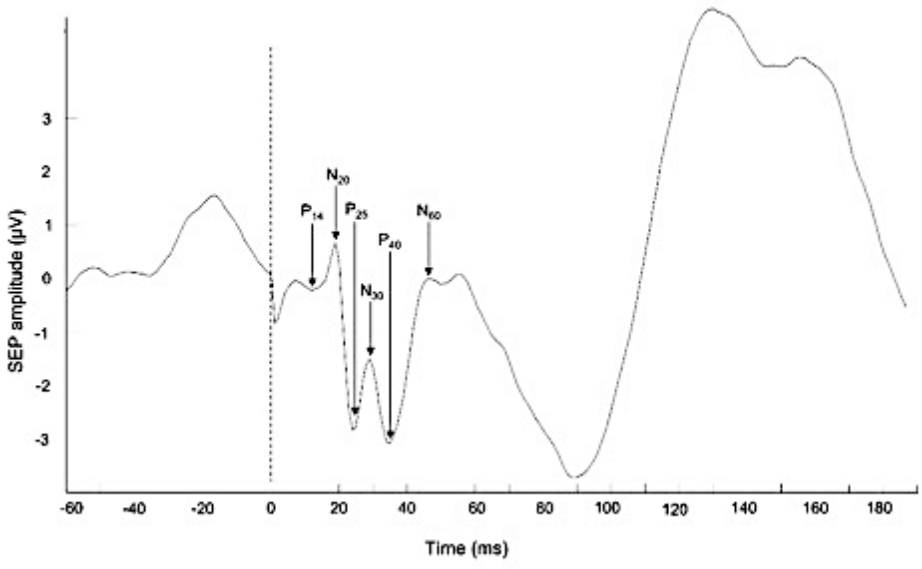

Figure 3.3. An example 0 ms ISI raw SEP trace from a single participant. Five components were subtracted and used for analysis – P_{14}/N_{20}, N_{20}/P_{25}, P_{25}/N_{30}, N_{30}/P_{40}, P_{40}/N_{60}. The dotted line indicates the conditioning and test stimulus onset for the paired 0 ms ISI condition.

3.3.4 Experimental muscle pain

Prior to injection the skin was cleaned with Nuprep gel and chlorhexidine solution. Sterile solutions of 5.8% hypertonic saline were prepared and a bolus of 0.5 mL was injected into the middle of the right APB muscle belly. Injections were performed using a 0.5 mL syringe with a disposable needle (BD Ultra Fine short needle, 31 G 8mm) (Schabrun et al., 2017b). There were no adverse effects reported from the injection.

3.3.5 Pressure pain thresholds

Pressure pain thresholds were assessed using a hand-held pressure algometer (SOMEDIC electronics, Algometer type II, Solna, Sweden). Pressure was applied perpendicular to the skin at a rate of 30 kpa/s. Participants were instructed to vocalize the moment the sensation of pressure first turned to pain. Pressure pain thresholds were assessed at four sites in pseudorandom order: 1) right APB; 2) left APB; 3) right Tibialis Anterior; and 4) left Tibialis Anterior. Sites 1 and 2 were located slightly medial of the distal 1/4 of the 1st ossa metacarpalia. The tibialis anterior measurement site was identified as one-third of the distance from the inferior border of the patella to the midpoint of the transverse crease of the ankle and 2.5 cm lateral to the tibial tuberosity. Each site was marked to ensure consistent positioning of the algometer over time. The mean of three recordings made at each site, at 1-minute intervals, was used for statistical analysis. A single rater conducted all testing and analysis to ensure consistency.

3.3.6 Statistical Analysis

Statistical analyses were performed with SPSS software (version 25). Data for the five extracted SEP components from the 25 ms ISI and 0 ms ISI conditions were assessed for sphericity using Mauchly's test of sphericity and Greenhouse-Geisser corrections for non-sphericity were applied where appropriate. Two separate analyses were performed to answer

two research questions. First, one-way repeated measures ANOVAs were performed for each SEP component with factor condition (paired 25 ms ISI, paired 0 ms ISI) as the independent variable and SEP component amplitude as the dependent variable using only data from the baseline timepoint. This analysis was conducted to ensure that the median nerve stimulation protocol was capable of inducing IHI between S1s in the absence of pain. Second, the ratio score for each SEP component was compared between time points (baseline, immediately after pain, 30-min follow-up) using a one-way repeated measures ANOVA to determine the effect of pain on IHI. Ratio scores were necessary to allow determination of interhemispheric inhibition or facilitation by expressing the SEP response from the 25 ms ISI condition as a proportion of the SEP response from the 0 ms ISI control condition (25 ms ISI condition / 0 ms ISI condition) for each SEP component. A ratio score < 1 denotes interhemispheric inhibition and a ratio score > 1 denotes interhemispheric facilitation. This approach has been used previously to assess IHI occurring between the left and right S1 (Brodie et al., 2014; Ragert et al., 2011). Holm-Sidak tests were used to correct for multiple comparisons.

Pressure pain thresholds were compared using a two-way repeated measures ANOVA with factors ‘time’ (baseline, 30-min follow-up) and ‘side’ (right, left) for the APB and Tibialis anterior muscles respectively. Pearson’s correlation coefficients were calculated to assess the relationship between the change in IHI over time (baseline to 30-min follow-up) for each SEP component and the change in pressure pain thresholds over time for right and left APB muscles.

Effect sizes were calculated using Partial eta squared. Partial eta squared is interpreted as 0.01 indicating a small effect size, 0.06 indicating a medium effect size, and 0.14 indicating a large effect size (Cohen, 2013). Data in text is presented as mean ± standard deviation (SD) unless stated otherwise. Statistical significance was set at $p < 0.05$.

3.4 Results

3.4.1 Pain characteristics

Injection of hypertonic saline produced on average, a peak pain intensity (i.e., average of the highest pain score reported by each participant) of 7.7 ± 1.6 points out of 10 on the numerical rating scale. The average pain intensity reported over time was 4.3 ± 1.4 points. The average pain duration was 7.3 ± 2.1 min. The most frequent words selected from the short-form McGill pain questionnaire to describe the pain were sharp (81%), aching (67%), throbbing (62%) and tender (62%). The majority of participants reported pain localised to the site of the injection on the palmer surface of the hand. Two participants reported pain that extended into the proximal forearm and two participants reported pain on the posterior side of the hand.

3.4.2 Presence of interhemispheric inhibition at baseline

Prior to the induction of pain, the mean peak-to-peak amplitude of the P_{14}/N_{20} ($F_{1,20} = 8.2$, $p = 0.009$, $\eta^2 = 0.29$), N_{20}/P_{25} ($F_{1,20} = 28.6$, $p < 0.001$, $\eta^2 = 0.59$) and N_{30}/P_{40} ($F_{1,20} = 10.2$, $p = 0.005$, $\eta^2 = 0.34$) SEP components were inhibited relative to the 0 ms ISI condition (Figure 3.4), confirming IHI was elicited by the paired median nerve stimulation protocol for these components. The mean peak-to-peak amplitude of the P_{25}/N_{30} ($F_{1,20} = 1.03$, $p = 0.32$, $\eta^2 = 0.05$) and P_{40}/N_{60} ($F_{1,20} = 2.1$, $p = 0.16$, $\eta^2 = 0.09$) SEP components were unchanged relative to the 0 ms ISI condition (Table 3.1).

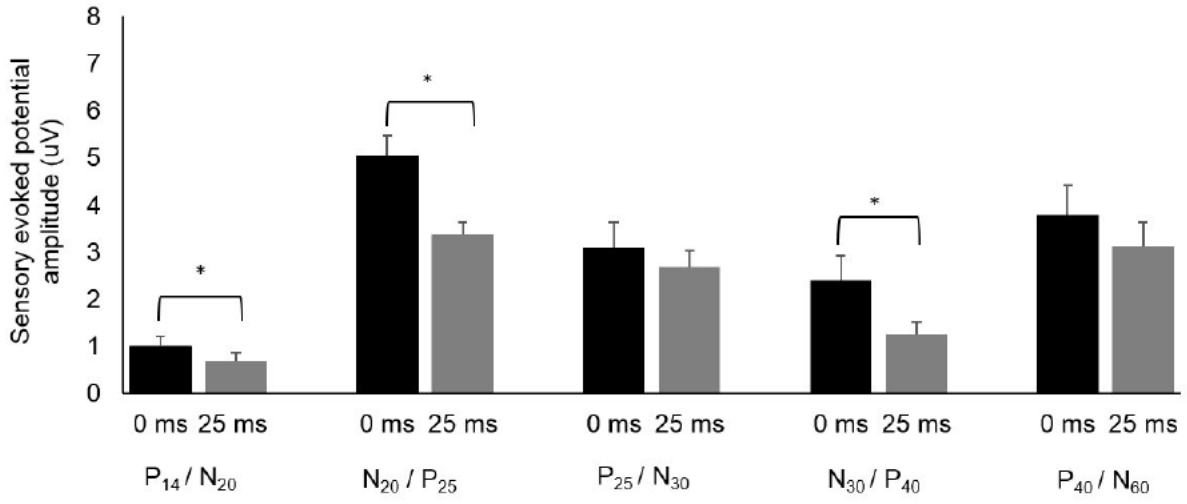

Figure 3.4. Group data (mean ± standard deviation) peak-to-peak raw amplitudes for each somatosensory evoked potential (SEP) component for the 0 ms ISI and 25 ms ISI conditions at baseline. Relative to the 0 ms ISI control condition, the P_{14}/N_{20}, N_{20} P_{25} and N_{30}/P_{40} SEP components were inhibited in response to the 25 ms ISI condition. *$p < 0.05$.

Table 3.1. Group data (mean ± SD, N = 21) for peak-to-peak amplitudes (raw values) for each SEP component at baseline, immediately after pain and at 30-min follow-up.

Component	**Baseline**		**Immediately after pain**		**30-min follow-up**	
	0 ms	25 ms	0 ms	25 ms	0 ms	25 ms
P_{14}/N_{20}	1.0 ± 1.1	0.7 ± 0.8	1.4 ± 1.6	0.8 ± 0.9*	1.6 ± 2.0	1.2 ± 1.5
N_{20}/P_{25}	5.0 ± 2.0	3.4 ± 1.1	5.3 ± 3.0	3.6 ± 1.6*	5.0 ± 2.9	3.1 ± 1.3*
P_{25}/N_{30}	3.1 ± 2.5	2.7 ± 1.6	3.3 ± 2.6	2.7 ± 1.6	3.4 ± 2.2	3.0 ± 1.7
N_{30}/P_{40}	2.4 ± 2.5	1.3 ± 1.2	2.7 ± 2.7	1.5 ± 1.6*	2.3 ± 2.0	1.3 ± 1.3*
P_{40}/N_{60}	3.8 ± 2.9	3.1 ± 2.3	4.0 ± 3.1	3.1 ± 2.8*	3.4 ± 2.7	3.0 ± 2.6

Note: SEP values are in µV. SEP, sensory evoked potential; *p <0.05 inhibited from baseline

3.4.3 Interhemispheric inhibition in response to acute muscle pain

When expressed as a proportion of the 0 ms ISI condition, the SEP response elicited by the 25 ms ISI condition was not altered in response to acute muscle pain for any component P_{14}/N_{20}: $F_{2,40} = 0.27$, $p = 0.77$, $\eta^2 = 0.01$; N_{20}/P_{25}: $F_{2,40} = 0.70$, $p = 0.47$, $\eta^2 = 0.03$; P_{25}/N_{30}: $F_{2,40} = 0.87$, $p = 0.40$, $\eta^2 = 0.04$; N_{30}/P_{40}: $F_{2,40} = 0.13$, $p = 0.83$, $\eta^2 = 0.006$; and P_{40}/N_{60}: $F_{2,40} = 2.4$, $p = 0.12$, $\eta^2 = 0.11$; Fig. 5; Appendix B, supplementary Figure 1).

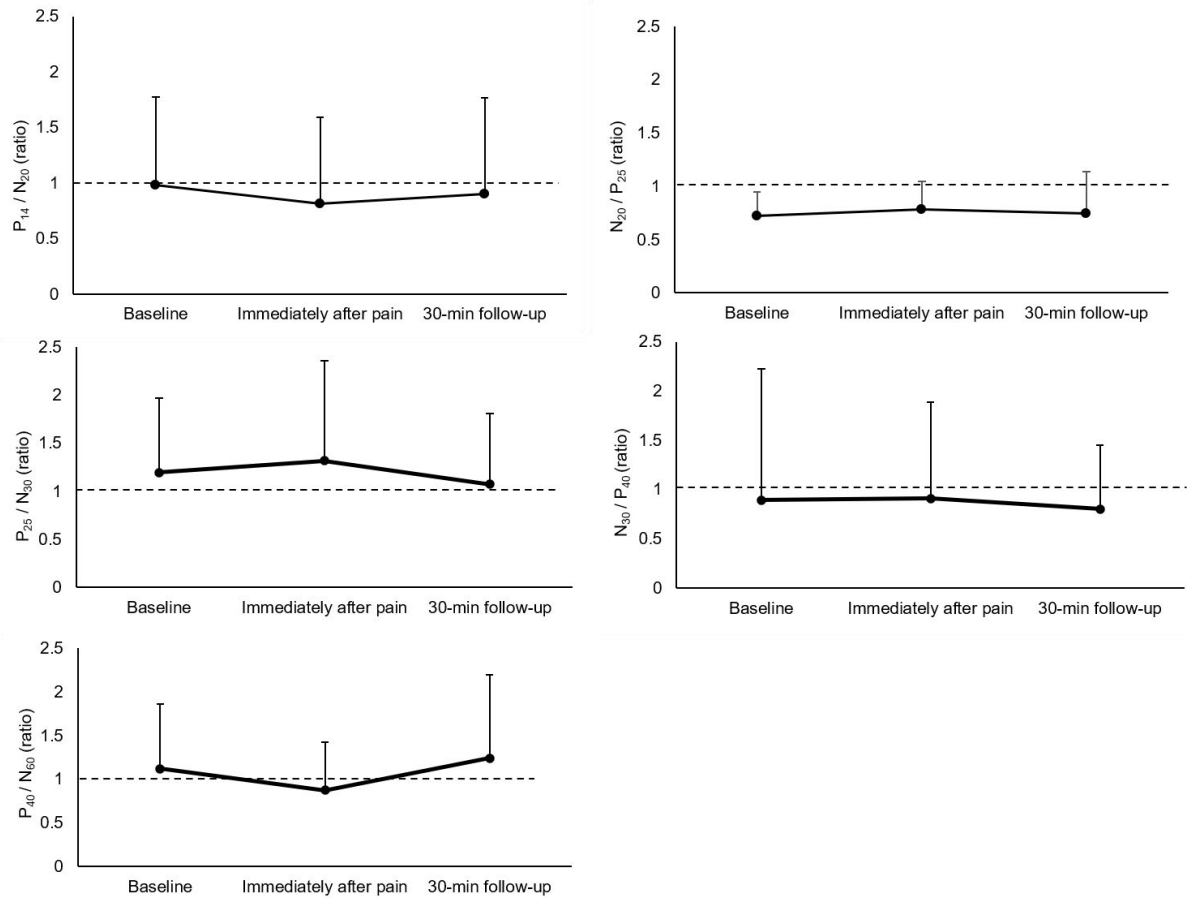

Figure. 3.5. Group data (mean ± standard deviation) for each SEP component (25 ms ISI condition expressed as a proportion of the 0 ms ISI control condition) at baseline, immediately after pain resolution and 30-min follow-up. There was no change for any SEP component over time.

3.4.4 Pressure pain sensitivity

Relative to baseline, pressure pain thresholds were reduced (main effect: $F_{1,20} = 16.1$, $p = 0.001$, $\eta^2 = 0.45$) in both the right ($p < 0.001$; Figure 3.6A) and left ($p = < 0.001$; Figure 3.6B) APB muscles 30-min after the resolution of muscle pain. There was no difference between sides ($F_{1,20} = 0.44$, $p = 0.51$, $\eta^2 = 0.02$) and no interaction between time and side ($F_{1,20} = 0.75$, $p = 0.40$, $\eta^2 = 0.04$). Pressure pain thresholds recorded from the Tibialis Anterior muscles were unchanged over time ($F_{1,20} = 0.20$, $p = 0.64$, $\eta^2 = 0.01$). There was no relationship between the change in IHI over time and pressure pain thresholds in the right or left APB muscles for any SEP component.

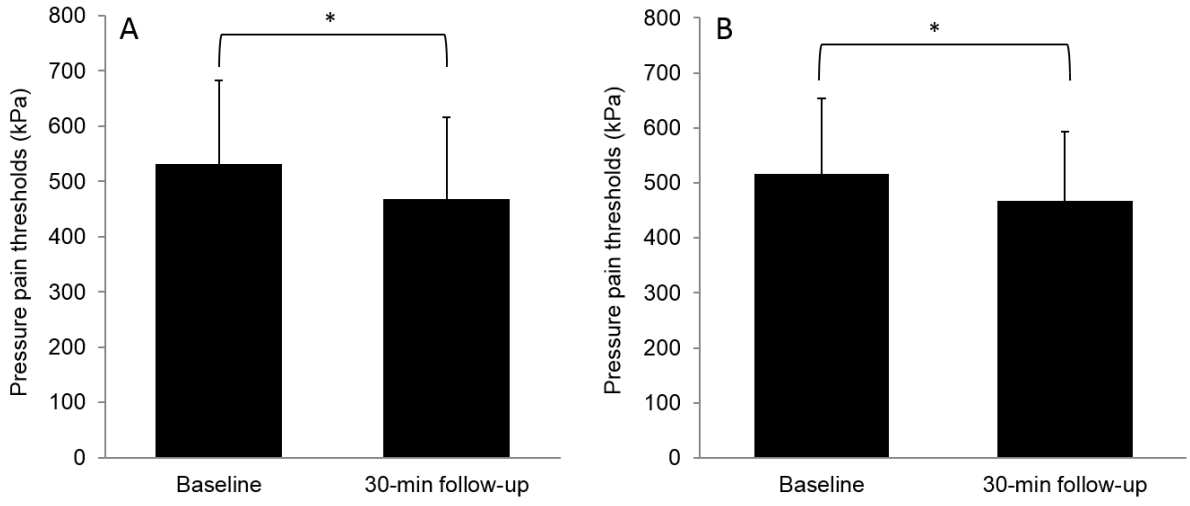

Figure 3.6. Group data (mean ± standard deviation) for pressure pain thresholds in the right (A) and left (B) APB muscles at baseline and 30-min follow-up. Pressure pain thresholds were reduced at 30-min follow-up in both APB muscles. *$p < 0.05$.

3.5 Discussion

This study investigated IHI between S1s in response to acute muscle pain. The induction of pain did not influence IHI when assessed from the left S1 (corresponding to the injected hand) to the right S1 (corresponding to the non-injected hand) immediately following pain resolution or at 30-min follow-up. However, an increase in sensitivity to pressure in the non-injected hand was observed at 30-min follow-up, despite the absence of pain on that side. There were no differences in pressure pain sensitivity between sides. This effect is in line with findings of previous literature in chronic unilateral pain and unilateral experimental muscle pain (Alhassani et al., 2019) that demonstrate similar levels of increased sensitivity to pressure on the unaffected as well as the affected side. These findings suggest that IHI between S1s may not contribute to the development of pressure sensitivity in the unaffected hand.

Interhemispheric inhibition between S1s can be assessed in humans using a paired median nerve electrical stimulation protocol. Sensory information from an electrical conditioning stimulus applied to one median nerve is transmitted to the contralateral S1 before traveling across the corpus callosum to synapse with inhibitory interneuronal networks in the ipsilateral S1 (Brodie et al., 2014; Ragert et al., 2011). Using this method, previous studies have shown inhibition of short-latency SEP components in the ipsilateral S1 at interstimulus intervals ranging from 15-30 ms (Brodie et al., 2014; Ragert et al., 2011). This finding was replicated in the current study with the P_{14}/N_{20}, and N_{20}/P_{25} SEP components in the ipsilateral S1 displaying inhibition at baseline (pre-pain) using a 25 ms ISI. Interestingly, we also demonstrated inhibition of the N_{30}/P_{40} SEP component which was not observed in previous studies. Although the reason for this discrepancy is unclear, one explanation is that our larger sample size (N=21) provided greater statistical power with which to detect this effect compared to previous studies (N=10 and N=12) (Brodie et al., 2014; Ragert et al., 2011). Regardless, our findings confirm

the paired median nerve stimulation protocol used in the present study is capable of eliciting IHI between S1s for short-latency SEP components.

To our knowledge, this is the first study to investigate IHI between S1s in response to pain. The data demonstrate no influence of acute, experimentally induced muscle pain on IHI between S1s, despite an increase in pressure sensitivity in the unaffected hand. This finding is in contrast to studies investigating IHI between the primary motor cortices where the presence of both acute and sustained pain reduces IHI from the pain-affected to the unaffected primary motor cortex, and the magnitude of the reduction in IHI is associated with the increase in pressure sensitivity (Alhassani et al., 2019; Schabrun et al., 2016). Why acute muscle pain influences interhemispheric interactions between primary motor, but not primary sensory cortices is unclear.

One explanation is that somatosensory IHI does not occur directly between S1s but rather, is transmitted indirectly via well-defined transcallosal M1 connections along an S1-M1-M1-S1 pathway (Brodie et al., 2014; Zapallow et al., 2013). Indeed, studies in non-human primates have identified relatively few direct transcallosal connections between S1s (Killackey et al., 1983; Krubitzer et al., 1998). An alternate possibility is that somatosensory IHI is transmitted between the secondary sensory cortices (S2) or via an indirect S1-S2-S2-S1 pathway (Brodie et al., 2014). Dense transcallosal connections and larger and more complex neuronal receptive fields are reported between homologous S2s when compared with homologous S1s (Fabri et al., 2005; Fabri et al., 2001; Hoechstetter et al., 2001; Iwamura, 2000; Jones & Powell, 1969; Manzoni et al., 1989). Similarly, dense intracortical connections are known to exist between area 3B of S1 and S2 (Kaas, 1993; Manzoni et al., 1986). Further evidence in support of this hypothesis is drawn from studies demonstrating interhemispheric transfer of tactile information between homologous S2s (Frot & Mauguière, 1999; Stancak et al., 2002) that underpins

bilateral activation of S2 in response to unilateral stimulation (Picard et al., 1990) and suppression of the ipsilateral S2 during bimanual tasks (Jung et al., 2012).

Another possibility is that the development of bilateral symptoms in unilateral pain conditions is mediated by other brain regions such as the dorsolateral prefrontal cortex (DLPFC) (Sevel et al., 2016). The DLPFC is implicated in endogenous pain modulation through a range of cognitive and emotional processes and recent studies have shown that interhemispheric DLPFC connectivity influences pain tolerance. For example, one study using dynamic causal modelling for fMRI demonstrated a relationship between individual differences in thermal pain sensitivity and connectivity between the contralateral and ipsilateral DLPFC. Specifically, greater connectivity, consistent with IHI, was associated with lower thermal pain sensitivity (Sevel et al., 2016). Further research is needed to elucidate the pathways underpinning interhemispheric transfer of somatosensory information in the human brain and to determine the role of somatosensory IHI (if any) in the development of bilateral symptoms in unilateral pain conditions.

Finally, spinal mechanisms could explain bilateral increases in pressure sensitivity. The spinothalamic tract, which is probed with PPTs, could mediate bilateral pressure sensitivity via wide dynamic range neurons that exhibit bilateral receptive fields ascending ipsilaterally (Coghill, 2020; Dum et al., 2009; Giesler et al., 1981). Indeed, previous studies have shown increased sensitivity to PPTs at sites adjacent to injury and/or pain in clinical (Arendt-Nielsen et al., 2011; Hidalgo-Lozano et al., 2010), and experimental studies (Gibson et al., 2006), suggesting a potential role for spinal mechanisms. Future studies should investigate PPTs adjacent to the painful area to explore the contribution of spinal mechanisms to bilateral increases in pressure sensitivity.

There are some limitations associated with the current study that should be addressed in future research. First, we used a short-lasting human pain model administered to healthy participants. Whether similar findings exist in sustained pain models or in those with chronic clinical pain conditions is unknown. Further, we were unable to record SEPs during pain due to the short-lasting nature of hypertonic saline induced pain. The use of longer lasting pain models in future studies would allow recording of IHI during pain. Second, bilateral changes in sensorimotor function were examined as pressure pain sensitivity only. Future studies should include a more comprehensive examination of sensorimotor function (including muscle strength, reaction time, thermal pain sensitivity, etc.) at a greater number of timepoints during and after the resolution of pain to more clearly characterise these changes in response to acute muscle pain. Third, the SF-MPQ was administered 60 minutes after the resolution of pain. The time delay between administering the SF-MPQ and the resolution of pain required participants to complete the questionnaire based on recall rather than the actual experience of pain and this may have affected the accuracy of responses recorded by participants. Fourth, the effect of sex on IHI was not assessed in this study. As sex differences have been shown to influence IHI (Davatzikos & Resnick, 1998; De Gennaro et al., 2003; Hausmann et al., 2006; Weis & Hausmann, 2010; Weis et al., 2008), future studies should include investigation of this factor. Finally, investigation of transfer of information between S1 and other brain regions such as S2, M1, and DLPFC, as well as concurrent investigation of S1 and M1 interhemispheric and intracortical mechanisms, are needed to contextualise these results within the distributed brain network that is known to underpin pain processing.

3.6 Conclusion

This study examined the effect of acute muscle pain on IHI between S1s in healthy individuals. The findings suggest IHI from the left to the right S1 is not affected by acute muscle pain, despite increased sensitivity to pressure in the pain free hand. Altered IHI between S1s may not contribute to the development of bilateral sensorimotor changes in acute muscle pain. This finding requires confirmation in studies using longer lasting pain models and clinical populations.

CHAPTER 1 Introduction and Literature review

CHAPTER 2 IHI between primary motor cortices in response to acute muscle pain

CHAPTER 3 IHI between primary sensory cortices in response to acute muscle pain

CHAPTER 4 IHI between primary motor cortices in individuals with lateral epicondylalgia

CHAPTER 5 Discussion and Conclusion

CHAPTER 4

IHI BETWEEN PRIMARY MOTOR CORTICES IN INDIVIDUALS WITH LATERAL EPICONDYLALGIA

The work presented within this chapter has been submitted and is under review in The Journal of Pain with the following title:

Interhemispheric inhibition between primary motor cortices is not altered in individuals with chronic lateral epicondylalgia.

G.A and S.S. conceptualised and designed the study. G.A. collected and analysed the data, interpreted the results and drafted the manuscript with input from P.C., M.L., and S.S. All authors discussed the results, commented on the manuscript and approved the final version.

4.1 Abstract

Lateral epicondylalgia, commonly referred to as tennis elbow, is a musculoskeletal condition characterised by pain and sensorimotor dysfunction. In some individuals with chronic unilateral LE, sensorimotor symptoms develop on the unaffected side despite no evidence of tissue damage. Altered interhemispheric inhibition (IHI) is one mechanism that could underpin this phenomenon. The aim of this cross-sectional study was to examine IHI between the primary motor cortices (M1) in individuals with chronic LE and healthy controls. In 20 individuals with chronic LE and 20 healthy participants, transcranial magnetic stimulation was used to assess: i) short and long latency IHI from the affected (corresponding to the injured side) to the unaffected M1; and ii) corticomotor excitability of the affected and unaffected M1. Sensorimotor function was evaluated bilaterally at the extensor carpi radialis brevis muscle using pressure pain threshold, grip strength, two-point discrimination and temporal summation tests. Short- and long-latency IHI from the affected to the unaffected M1, and corticomotor excitability of the affected and unaffected M1, were not altered in individuals with LE compared with healthy participants. No differences in sensorimotor function were observed for the affected or unaffected ECRB muscles when individuals with LE were compared with healthy participants. IHI is not altered in individuals with chronic LE who did not display significant sensorimotor dysfunction. Further studies are required to determine the mechanisms that underpin the development of bilateral sensorimotor symptoms in unilateral LE.

Perspective: IHI is unaltered from the affected M1 (corresponding to the painful muscle) to unaffected M1 in individuals with LE compared to healthy controls. The absence of bilateral sensorimotor dysfunction and low pain severity in this cohort of individuals with LE may explain this finding.

4.2 Introduction

Lateral epicondylalgia (LE), commonly known as tennis elbow, is a musculoskeletal condition affecting 1-3% of the general population (Shiri et al., 2006). Characterised by structural changes of the extensor carpi radialis brevis (ECRB) tendon (e.g. thickening and tears of the tendon) and pain over the lateral epicondyle (Coombes et al., 2009b; Skinner & Curwin, 2007; Vaquero-Picado et al., 2016), LE is commonly triggered by repetitive forceful contraction of the wrist extensor muscles (Fan et al., 2009; Shiri et al., 2006). In some individuals with unilateral LE, sensorimotor symptoms develop on the unaffected side (Bisset et al., 2006b). These individuals exhibit reductions in grip force, increased upper limb reaction times and reduced speed of movement in both affected and unaffected limbs, and adopt a wrist posture that is 11 degrees less extended bilaterally than healthy controls (Bisset et al., 2006b; Heales et al., 2014; Pienimaki et al., 1997). Studies investigating peripheral mechanisms that may explain sensorimotor symptom development on the unaffected side suggest that the underlying pathophysiology is more complex than can be explained by peripheral mechanisms alone (Coombes et al., 2009b; Heales et al., 2014). This suggests the development of sensorimotor symptoms on the unaffected side may be mediated by the central nervous system, yet the mechanism remains unknown.

Altered interhemispheric inhibition (IHI) between the primary motor cortices (M1's) is one mechanism that could underpin bilateral symptom development in chronic unilateral LE. Interhemispheric inhibition is a neurophysiological mechanism mediated by transcallosal pathways where one hemisphere inhibits activity in the opposite hemisphere (Boroojerdi et al., 1996). This allows individuals to perform unilateral movements while preventing unwanted mirror movements of the opposite side (Beaule et al., 2012). Previous research has suggested a relationship between altered IHI and sensorimotor dysfunction of the unaffected side in unilateral musculoskeletal pain conditions. For example, experimental pain studies have

demonstrated reduced IHI from the affected M1 (corresponding to the painful side) to the unaffected M1 (corresponding to the non-painful side) in otherwise healthy participants (Alhassani et al., 2019; Schabrun et al., 2016). Specifically, in response to acute muscle pain induced by hypertonic saline injection into the ECRB muscle, IHI was reduced immediately after pain resolution and at 30 minutes follow-up (Alhassani et al., 2019). Similarly, following repeated intramuscular injection of nerve growth factor into the ECRB muscle to induce progressively developing sustained muscle pain, IHI was reduced four days after pain onset (Schabrun et al., 2016). In both studies, increased sensitivity to mechanical stimuli was observed in the unaffected (non-injected) muscle. However, a greater reduction in IHI was associated with a greater increase in sensitivity of the non-injected side only in the sustained pain model. This finding could suggest a relationship between IHI and sensorimotor dysfunction of the unaffected side that emerges as pain persists. Although evidence exists examining IHI in response to acute and sustained muscle pain, no study has investigated whether IHI is altered between M1s in chronic musculoskeletal pain conditions, such as LE.

Therefore, this preliminary study aimed to compare IHI between M1s in individuals with chronic LE and healthy controls. Based on previous work (Alhassani et al., 2019; Schabrun et al., 2016), we hypothesised that IHI would be reduced from the ‘affected’ to the ‘unaffected’ M1 in individuals with LE.

4.3 Methods

4.3.1 Participants

Twenty individuals (11 males, 9 females, mean ± SD age 45 ± 9 years) with LE, and 20 age- and sex-matched healthy controls (age matched ± 5yrs; 46 ± 10 years) participated. As IHI is yet to be examined in LE, the sample size was based on a previous study that examined IHI in response to experimental pain induced in the ECRB muscle (Schabrun et al., 2016). Based on these findings, mean difference in IHI between days 0 (baseline) and 4 (follow-up) of 0.73 mV and 1.4 mV respectively, standard deviation 0.64 mV, a sample size of 16 participants in each group was required to observe a statistically significant difference in IHI between groups (80% power, alpha 0.05) should one exist. However, as these effects have not been examined in chronic musculoskeletal pain and the size of the effect is unclear, 20 participants were recruited in each group.

Individuals with LE were included if they had experienced pain over one or both humeral lateral epicondyles for greater than 6 weeks that was aggravated by palpation, gripping, resisted wrist and/or middle finger extension (Linaker et al., 1999). For individuals with pain over both humeral lateral epicondyles, the side that developed first was considered the affected side. Exclusion criteria included: i) the use of oral or topical pain-relief medication 48 hrs prior to the study; ii) concomitant neck or arm pain that prevented participation in usual work or recreational activities; iii) corticosteroid injections in the last 6 months; and iv) evidence of self-reported sensory disturbances associated with neuropathic lesions, history of fractures, elbow surgery, arthritic or inflammatory disorders or pain localized to the radiohumeral joint (Coombes et al., 2009b). Age- and sex-matched healthy participants who had no current pain condition and no history of LE served as the control group. All potential participants completed the transcranial magnetic stimulation safety questionnaire and were excluded if they had major neurological, orthopaedic, psychiatric or circulatory disorders, were pregnant, were taking

central nervous system acting medication or had a personal or family history of epilepsy (Keel et al., 2001). Data collection occurred between October 2018 and June 2019. All procedures were approved by the institutional human research ethics committee (Western Sydney University: H11873) and all participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

4.3.2 Experimental protocol

The experimental protocol is outlined in Figure 4.1. All experimental procedures were completed in a single test session. The protocol was performed in the following order: 1) self-reported outcomes of pain and disability; 2) tests of sensorimotor function; 3) assessment of corticomotor excitability; 4) assessment of IHI at four conditioning stimulus intensities: 120%, 130%, 140% and 150% of resting motor threshold (RMT). Conditioning stimulus intensity order was randomised between participants. Rest intervals of at least two minutes were provided between each IHI conditioning stimulus intensity block.

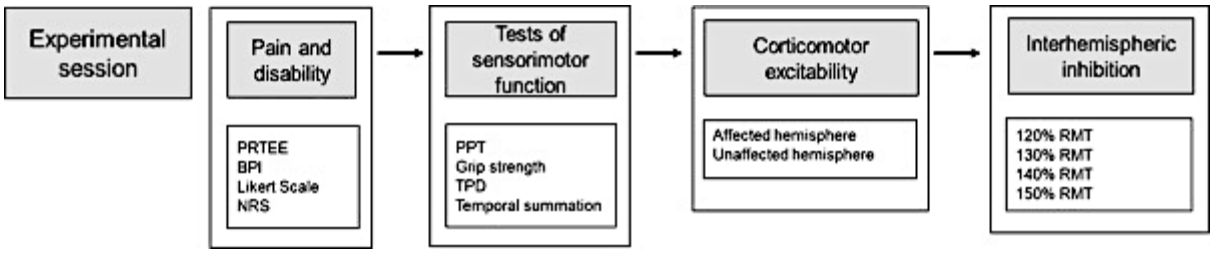

Figure 4.1. Experimental protocol. Participants attended a single experimental session performed in the following order: At the beginning of the session, self-reported pain and disability outcomes (LE individuals only) were collected followed by tests of sensorimotor function. Neurophysiological measures of corticomotor excitability and IHI were then assessed. PRTEE, pain rated tennis elbow evaluation; BPI, brief pain inventory; NRS, numerical rating scale; PPT, pressure pain threshold; TPD, two-point discrimination; resting motor threshold, RMT.

4.3.3 Self-reported outcomes of pain and disability

The Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire was used to assess pain and disability for all LE participants for the week preceding testing. Scores for pain (sum of five items out of 50) and function (sum of 10 items, divided by 2, out of 50) were combined to give a total score ranging from '0' (no pain and no functional impairment) to '100' (worst pain imaginable with significant functional impairment). The Brief Pain Inventory short form (BPI-sf) was used to assess pain and disability in the 24 hours preceding testing. Pain severity was scored as a mean of the four items relating to severity, and pain interference was scored as a mean of the seven items relating to interference (Cleeland & Ryan, 1994; Tan et al., 2004). Participants completed a modified Likert scale of muscle soreness for the upper limb with '0' indicating a complete absence of soreness and '6' indicating a severe muscle soreness (Slater et al., 2003). Healthy controls verbally confirmed they did not have pain or muscle soreness on the day of testing. Pain intensity at the time of testing was recorded using an 11-point numerical rating scale (NRS) anchored with '0' as no pain and '10' as worst pain imaginable.

4.3.4 Tests of sensorimotor function

Pressure pain thresholds

Pressure pain thresholds were assessed using a hand-held pressure algometer (SOMEDIC electronics, Algometer type II, Solna, Sweden). Pressure was applied perpendicular to the skin at a rate of 30 kpa/s. Participants were instructed to vocalise the moment the sensation of pressure first turned to pain. Pressure pain thresholds were assessed at four sites in pseudorandom order: 1) affected ECRB (or matched ECRB for healthy controls); 2) unaffected ECRB (or matched ECRB for healthy controls); 3) right Tibialis Anterior; and 4) left Tibialis Anterior. Sites 1 and 2 were determined by identifying a position 1 cm lateral to a point that was 5 cm distal to the lateral epicondyle (Bergin et al., 2015). The ECRB muscle belly was chosen as evidence suggests pain and sensitivity radiate from the lateral humeral epicondyle

distally into the forearm affecting muscle tissue of ECRB (Bisset et al., 2015; Bisset et al., 2018). The tibialis anterior measurement sites were identified as one-third of the distance from the inferior border of the patella to the midpoint of the transverse crease of the ankle and 2.5 cm lateral to the tibial tuberosity. The Tibialis Anterior muscles were included to examine the muscle specificity of any increase in mechanical sensitivity in response to pain. Each site was marked to ensure consistent positioning of the algometer over time. The mean of three recordings made at each site, at 1-minute intervals, was used for statistical analysis. A single rater with training in pressure pain threshold assessment conducted all testing and analysis to ensure consistency. Pressure pain thresholds of the extensor carpi radialis muscle has demonstrated moderate to excellent intra and inter-rater reliability in healthy and musculoskeletal populations (Middlebrook et al., 2020).

Pain-free grip strength and maximum grip strength

Pain-free and maximum grip strength were assessed using a hand-held dynamometer (Hydraulic Hand Dynamometer, Saehan Corporation, Korea) based on the protocol by Slater et al., 2005. Participants assumed a seated position and were assisted in placing their arm in 90° flexion, shoulder in a neutral position, forearm pronated, and elbow extended. To measure pain-free grip strength, participants with LE were instructed to squeeze the dynamometer with the hand on their affected side, with increasing force and immediately cease squeezing at the onset of pain. As the presence of existing pain is required for this test, healthy controls did not complete this assessment. To assess maximal grip strength, all participants were instructed to squeeze the dynamometer as hard as possible, regardless of pain (Bisset et al., 2006b). Pain-free, and maximal grip strength (kg) of each arm was determined based on the average of three consecutive trials at a rate of one trial every 30 s.

Two-point discrimination

Two-point discrimination (TPD) was assessed at the belly of the ECRB muscle starting with the unaffected side (matched side in healthy controls) with a stainless steel TPD prong with straight tips (Bailey Instruments Ltd., Manchester, UK). Two-point discrimination was measured according to an established protocol (Luomajoki & Moseley, 2011; Moseley, 2008). Testing commenced with 0 mm between the two points of the prong, gradually increasing the distance by 5 mm increments until the subject was able to perceive two points from one. The participant was instructed to say 'one' when the distance between the probes felt like one point and 'two' when distance between the probes felt like two points. Catch trials were included randomly by using only one point or the widest possible distance to make sure the participants were not guessing according to the pattern of stimuli presented. The distance between points at which the participant reported feeling two points was measured in millimetres. The mean of three recordings taken consecutively at each site, at 1 min intervals, was used for analysis.

Temporal summation

Temporal summation was assessed over both ECRB muscles and the right tibialis anterior muscle according to an established protocol (Hayashi et al., 2013). Using a pressure algometer, 10 sequential pressure stimulations (one second duration), with a two second interval were applied at the previously calculated pressure pain threshold for each site. Each participant scored their pain intensity for each of the 10 stimuli during the sequential stimulation on an 11-point NRS anchored with '0' as no pain and '10' as worst pain imaginable. A total of 10 NRS scores were recorded for each site. For analysis, the 10 NRS scores for each site were first normalised by subtraction of the first stimulus score. The average NRS scores from pressure stimulations 2 – 4 (NRS 1), 5 – 7 (NRS 2) and 8 – 10 (NRS 3) were calculated and used for analysis.

4.3.5 Neurophysiological measures

Electromyography

Prior to electromyographic recording, the skin was shaved and cleaned with Nuprep skin prep gel (Weaver and Company, Aurora, CO, USA) and chlorhexidine solution (Livingstone International, NSW, Australia). Electromyography was recorded from both ECRB muscles using disposable dual silver/silver chloride surface electrodes (Noraxon USA Inc, Arizona, USA). Electrodes were positioned over the muscle belly, determined as 1 cm lateral to a point that was 5 cm distal to the lateral epicondyle (Bergin et al., 2015). Ground electrodes were positioned over the right and left olecranon. Electromyography signals were amplified 1000 x, filtered between 20 to 1000 Hz and sampled at 2000 Hz using Signal software and a Micro 1401 data acquisition system (Cambridge Electronic Design, Cambridge UK).

Corticomotor excitability

Transcranial magnetic stimulation was performed over both M1s in all participants. Single-pulse stimuli were delivered to the M1 representation of the ECRB muscles using a figure-of-eight coil connected to a Magstim 200 stimulator (Magstim Co Ltd., Dyfed, UK). The coil was oriented at a 45° angle to produce a posterior to anterior current flow and positioned over the optimal cortical site to evoke an EMG response in each ECRB muscle. The optimal cortical site to elicit motor evoked potentials in the affected and unaffected ECRB muscles, and the matched sides in healthy controls, was determined as the site where the lowest stimulus intensity evoked the largest response. These sites were marked with a pen to ensure accurate coil placement throughout testing. Resting motor threshold (RMT) was defined as the lowest intensity of stimulation required to evoke a motor evoked potential > 50 μV peak-to-peak amplitude in at least three of five consecutive trials (Rossi et al., 2009). Fifteen motor evoked potentials (rate of 1 every 6 s) were recorded from each M1 at 120% of resting motor threshold. The hemisphere test order was randomised between participants. The average peak-to-peak

motor evoked potential amplitude (mV) was calculated at each time-point for each M1 and this value used for analysis.

Interhemispheric Inhibition

Interhemispheric inhibition was probed using a conditioning-test paradigm. A conditioning pulse applied to the M1 corresponding to the affected side (or matched side for healthy controls) preceded a test stimulus applied to the 'unaffected' M1. Transcranial magnetic stimulation was delivered using two Magstim 200 magnetic stimulators (Magstim Co. Ltd., Dyfed, UK), each connected to a figure-of-eight coil with external wing diameters of 70 mm (M1 corresponding to the unaffected side, matched side in healthy controls) and 50 mm (M1 corresponding to the affected side, matched side in healthy controls). The coil delivering the test stimulus to the affected side was positioned tangentially over the scalp, perpendicular to the midsagittal line, with the coil handle pointing backwards at a 45° angle to induce a posterior to anterior current direction. The conditioning stimulus coil was oriented 90° relative to the midsagittal line to avoid overlapping the coils (Chen et al., 2003; Ni et al., 2009). It has been previously reported that the current direction of the conditioning stimulus does not affect the degree of IHI (Chen et al., 2003; Ni et al., 2009). To investigate short and long latency IHI, 10 and 40 ms interstimulus intervals were selected, respectively. These interstimulus intervals were selected as they demonstrate the maximum amount of inhibition identified (Ferbert et al., 1992; Sattler et al., 2012). Short and long latency IHI were recorded from the affected M1 to the unaffected M1. The test stimulus intensity was adjusted to produce a peak-to-peak motor evoked potential amplitude of 0.3 - 0.4 mV in relaxed ECRB and the conditioning stimulus intensity was set at 120%, 130%, 140% and 150% of RMT. These intensities were selected as they have been shown to elicit reliable levels of IHI in forearm muscles of healthy individuals (Ibey et al., 2015). In pseudorandom order, 10 trials were recorded at each interstimulus interval and a further 10 trials were recorded using the test stimulus alone (30 trials in total)

with 5 seconds between each trial for each conditioning intensity. Motor evoked potential responses were measured as peak-to-peak amplitudes and conditioned responses were expressed as a proportion of the unconditioned test response for analysis. A ratio score of <1 denotes interhemispheric inhibition and a ratio score of >1 denotes interhemispheric facilitation.

4.3.6 Statistical analysis

Statistical analyses were performed with SPSS software (version 25, IBM Corp, Armonk, NY, USA). Prior to performing 3-way mixed ANOVA analysis or repeated measures ANOVA analysis, data were assessed using Mauchly's test for sphericity. Greenhouse-Geisser corrections for non-sphericity were applied where appropriate. Prior to performing one-way ANOVA analysis, data were assessed for homogeneity using Levene's test, where this was violated the Welch t test was applied. Where appropriate, Holm-Sidak corrections were applied to account for multiple comparisons. Data in text are presented as mean ± standard deviation unless otherwise stated. Statistical significance was accepted at $p \leq 0.05$.

4.3.6.1 Tests of sensorimotor function

Pressure pain thresholds

Pressure pain thresholds were compared using a 3-way mixed ANOVA with a between-subject factor 'group' (LE vs healthy control) and within subject factors 'side' (affected, unaffected) and 'muscle' (ECRB vs tibialis Anterior).

Maximum and pain free grip strength

Maximum grip strength was compared between the LE and healthy control groups for each side using separate one-way ANOVAs. As only individuals with LE completed the test of pain free grip strength, pain-free grip strength at the affected side was compared to maximum grip

strength at the affected side only within the LE group using a one-way repeated measures ANOVA.

Two-point discrimination

Two-point discrimination was compared between LE and healthy control groups for each side using separate one-way ANOVAs.

Temporal summation

Temporal summation was compared between LE and healthy control groups with factor 'NRS score' (NRS 1, NRS 2, NRS 3) for the ECRB of the affected and unaffected (or matched) side and the right tibialis anterior muscle using separate one-way repeated measures ANOVA.

4.3.6.2 Neurophysiological measures

Corticomotor excitability was compared between groups (LE vs healthy control) for each hemisphere using separate one-way ANOVAs. Short and long latency IHI were compared between groups (LE vs healthy controls) for each conditioning intensity (120% 130%, 140% and 150%) using separate one-way ANOVAs.

4.4 Results

4.4.1 Self-reported outcomes of pain and disability

Participant characteristics are summarised in table 4.1. The average duration of LE was 26 ± 52 months. For the PRTEE questionnaire the total score for the week preceding testing (combined pain and function subscale) was 38.5 ± 14.7 out of 100. For the BPI-sf the average score for pain severity and pain interference in the 24 hours preceding testing were 3.2 ± 1.4 and 3.1 ± 2.1 out of 10 respectively. The average current pain intensity in individuals with LE reported on the day of testing was 3 ± 1.8 points out of 10 on the NRS. On the modified muscle soreness Likert scale the average score reported was 3.2 ± 1.2, equivalent to a light muscle soreness when lifting objects or carrying objects (Slater et al., 2003).

4.4.2 Tests of sensorimotor function

There were no differences in pressure pain thresholds between individuals with LE and healthy controls ($F_{1,38}$ = 2.39, p = 0.13, Table 4.3) and no differences between the affected and unaffected (or matched) sides ($F_{1,38}$ = 0.28, p = 0.59).

Maximum grip strength was lower on the affected side in individuals with LE compared with the matched side of healthy controls ($F_{1,32.97}$ = 4.01, p = 0.05; Table 4.3). No difference in maximum grip strength was observed for the unaffected side in individuals with LE compared with the matched side for healthy controls ($F_{1,38}$ = 3.22; p = 0.8). Within the LE group, pain free grip strength was lower than maximum grip strength on the affected side (Max Grip strength 27.3 ± 11.5 kg; Pain free Grip strength 22.5 ± 10.2 kg; $F_{1,19}$ = 18.44, p < 0.001).

Two-point discrimination did not differ between individuals with LE and healthy controls for either the affected ($F_{1,38}$ = 1.39, p = 0.24) or unaffected ($F_{1,38}$ = 0.01, p = 0.89) sides (Table 4.3).

No difference in temporal summation was observed between individuals with LE and healthy controls for the ECRB of the affected side ($F_{2,76} = 0.25$, $p = 0.63$), unaffected side ($F_{2,76} = 1.53$, $p = 0.22$) or the right tibialis anterior muscle ($F_{2,76} = 0.03$, $p = 0.91$).

4.4.3 Neurophysiological measures

There was no difference in corticomotor excitability between individuals with LE and healthy controls for either hemisphere (affected: $F_{1,38} = 0.06$, $p = 0.81$; unaffected: $F_{1,38} = 0.6$, $p = 0.44$; Figure 4.2; Table 4.2). The magnitude of short- and long-latency IHI did not differ between individuals with LE and healthy controls at any conditioning intensity (short IHI: p all > 0.15; long IHI: all p > 0.07) (Figure 4.3; Table 4.2).

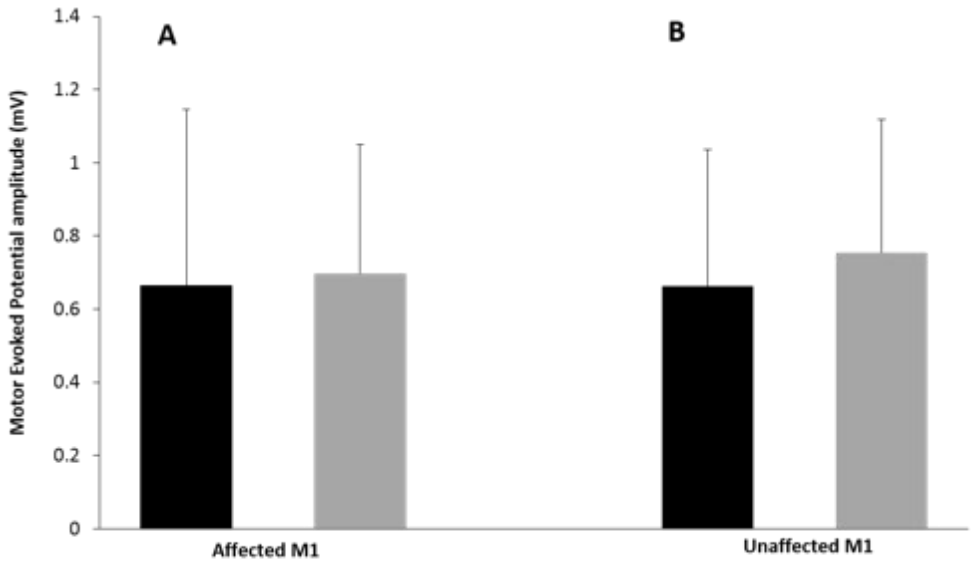

Figure 4.2. Group data (mean ± standard deviation) for corticomotor excitability for the LE (black bars) and healthy control (grey bars) groups recorded for the affected and unaffected M1 (or the matched hemispheres for healthy controls). Corticomotor excitability did not differ between groups. M1, primary motor cortex.

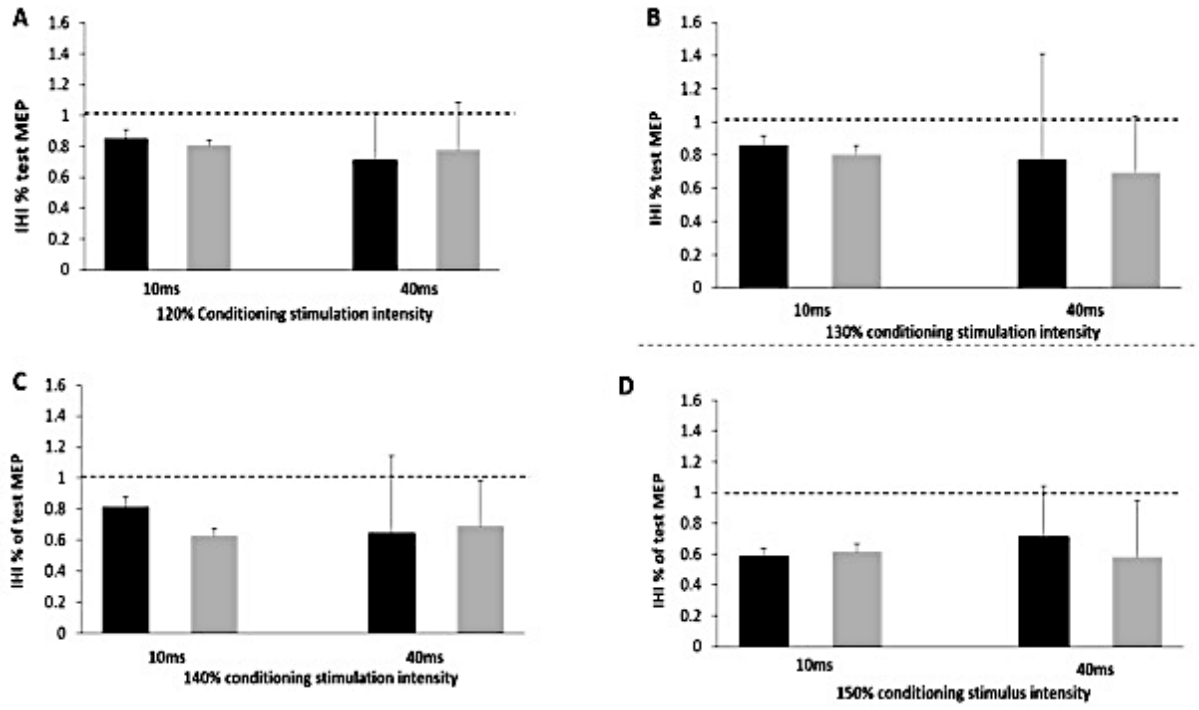

Figure 4.3. Group data (mean ± standard deviation) for IHI from the affected to the unaffected M1 for the LE group (black bars; n = 20) and the matched hemispheres of healthy controls (grey bars; n = 20). Four blocks of 30 trials were recorded at conditioning stimulus (CS) intensities of 120%, 130%, 140% and 150% of resting motor threshold. IHI was determined by expressing the conditioned MEP as a percentage of the unconditioned test MEP (percentage of test MEP). There was no difference in the magnitude of IHI between groups at conditioning stimulus intensities of 120% (A), 130% (B), 140% (C) or 150% (D). IHI, interhemispheric inhibition; LE, lateral epicondylalgia; MEP, motor evoked potential.

Table 4.1 Demographic and clinical characteristics for individuals with lateral epicondylalgia (n = 20)

Subject	Gender	Age (years)	Dominant arm	Affected arm(s)	Symptom duration (months)	NRS (/10)
1	M	36	R	R	48	2
2	M	59	R	R	2	2
3	M	55	R	R	240	1
4	F	48	R	R	36	4
5	F	36	R	R	2	0
6	F	40	R	R	2	7
7	F	37	R	R	36	0
8	F	55	R	R	5	3
9	M	37	R	R	12	4
10	M	39	R	L	2	3
11	M	47	R	R	2	2
12	F	49	L	L	7	3
13	M	61	R	R	12	4
14	F	33	R	R & L	6	3
15	F	47	R	R & L	6	3
16	M	51	R	R & L	7	5
17	F	45	R	R & L	36	3
18	M	33	R	L & R	24	1
19	M	62	R	R & L	12	4
20	M	41	R	R & L	18	6

Note: NRS, numerical rating scale; M, male; F, female; R, right; L, left

Table 4.2. Healthy control and LE group data for peak-to-peak amplitudes for corticomotor excitability (raw values) and interhemispheric inhibition (ratios).

	LE				**Healthy controls**			
Corticomotor excitability (mV)								
Affected M1	0.66 ± 0.48				0.70 ± 0.35			
Unaffected M1	0.66 ± 0.37				0.75 ± 0.37			
IHI for affected to unaffected M1 (mV)	120% CS	130% CS	140% CS	150% CS	120% CS	130% CS	140% CS	150% CS
Unconditioned test response	0.39 ± 0.05	0.36 ± 0.05	0.40 ± 0.06	0.40 ± 0.06	0.38 ± 0.03	0.38 ± 0.05	0.40 ± 0.05	0.39 ± 0.05
IHI 10 ms (proportion of test)	0.86 ± 0.31	0.84 ± 0.57	0.82 ± 0.49	0.58 ± 0.33	0.79 ± 0.27	0.81 ± 0.34	0.63 ± 0.29	0.62 ± 0.37
IHI 40 ms (proportion of test)	0.72 ± 0.34	0.77 ± 0.34	0.64 ± 0.30	0.71 ± 0.39	0.75 ± 0.27	0.70 ± 0.28	0.69 ± 0.18	0.58 ± 0.22

Values are mean ± standard deviation (LE: n = 20; Healthy controls: n = 20)
Note: IHI, interhemispheric inhibition; M1, primary motor cortex; CS, conditioning stimulus

Table 4.3. Sensorimotor outcomes for LE (n = 20) and healthy controls (n = 20)

	LE			Healthy controls		
Pressure pain thresholds (kPa)						
Affected ECRB	280.87 ± 135.28			369.59 ± 163.9		
Unaffected ECRB	318.4 ± 133.08			381.81 ± 163.59		
Affected Tibialis anterior	611.50 ± 268.87			751.91 ± 304.11		
Unaffected Tibialis anterior	649.60 ± 285.99			739.72 ± 259.31		
Maximum grip strength (kg)						
Affected ECRB	27.29 ± 11.54			33.49 ± 7.64		
Unaffected ECRB	26.30 ± 11.23			31.93 ± 8.37		
Pain-free grip strength (kg)						
Affected ECRB	22.53 ± 10.19			-		
Two-point discrimination (mm)						
Affected ECRB	37.49 ± 8.99			34.16 ± 8.82		
Unaffected ECRB	34.28 ± 7.77			34.70 ± 11.90		
Temporal summation (NRS)	NRS 1	NRS 2	NRS 3	NRS 1	NRS 2	NRS 3
Affected ECRB	5.42 ± 6.68	12.94 ± 11.84	17.51 ± 15.68	2.41 ± 5.10	7.86 ± 12.35	12.86 ± 18.48
Unaffected ECRB	1.85 ± 5.42	10.30 ± 13.07	16.03 ± 19.82	4.55 ± 10.83	8.78 ± 19.26	12.80 ± 23.03
Right Tibialis Anterior	1.98 ± 5.08	8.53 ± 12.65	11.46 ± 16.61	2.08 ± 4.28	7.84 ± 12.83	11.24 ± 14.21

Note: ECRB, extensor carpi radialis brevis; kPa, kilopascals; kg, kilogram; mm, millimetres; NRS, numerical rating scale

4.5 Discussion

The aim of this preliminary study was to investigate interhemispheric inhibition between the primary motor cortices in individuals with and without chronic LE. No difference was observed in the magnitude of IHI or in the level of corticomotor excitability between individuals with chronic LE and healthy controls. Contrary to our hypothesis, and previous work in LE, we did not observe impaired sensorimotor function in individuals with LE relative to healthy controls which could explain the lack of neurophysiological findings in this cohort.

Interhemispheric inhibition can be assessed using paired-pulse stimulation at ISI's between 6 - 50 ms (Ferbert et al., 1992). Occurring via transcallosal pathways of the corpus callosum, IHI is mediated by GABAergic neurotransmitters (Irlbacher et al., 2007). To our knowledge, this is the first study to investigate IHI in any clinical musculoskeletal pain condition. Our findings demonstrate no difference between individuals with chronic LE and healthy controls in short or long latency IHI at any conditioning stimulus intensity. In experimental pain studies, decreased IHI from the affected (corresponding to the painful muscle) to unaffected M1 has been demonstrated in response to acute and sustained muscle pain (Alhassani et al., 2019; Schabrun et al., 2016). Specifically, IHI decreased in response to pain lasting minutes (Alhassani et al., 2019) to days (Schabrun et al., 2016). Based on these previous studies, we hypothesised that IHI would be altered in chronic LE. However, our findings did not support this theory.

One explanation for our results is the relatively low pain severity experienced by our LE cohort that may have been insufficient to drive alterations in IHI. The LE participants in this study self-reported mild pain on the numerical rating scale on the day of testing of 3 ± 1.8 out of 10 and low interference of pain with daily function (BPI: 3.1 ± 2.1 out of 10). In addition, the absence of impaired sensorimotor function in our cohort may have explained the lack of change

in IHI. Indeed, studies have shown that individuals with higher pain and worse disability (severe LE; PRTEE score > 54) have significantly impaired sensorimotor function when compared to a healthy control group (Coombes et al., 2012b). Further, within that same study, pressure pain thresholds were lower in the severe LE sub-group compared to the mild LE sub-group. The finding of higher mechanical sensitivity in individuals with severe LE symptoms implies a greater contribution of central nervous system mechanisms including potential central disinhibition of nociceptive pathways (Huge et al., 2008). Thus, it is plausible that low pain severity (NRS score < 4) and preserved sensorimotor function in our LE cohort was associated with normal functioning of IHI. Future studies with sufficient power to examine a range of clinical presentations of LE are needed to definitively determine whether IHI is altered in chronic LE.

The current study does not provide sufficient evidence to associate altered IHI with the development of bilateral sensorimotor symptoms in LE. However, it is noteworthy that a strong body of evidence supports this relationship in neurological conditions such as stroke. For example, increased IHI is exerted from the unaffected to the affected M1 in stroke and this increase in inhibition is associated with impaired motor recovery of the paretic limb (Duque et al., 2005; Murase et al., 2007). More studies are needed to determine whether such an association is also observed in musculoskeletal disorders. Further, future studies should include sufficient power to compare IHI between individuals presenting with unilateral vs. bilateral symptoms and tighten the inclusion criteria for pain duration and current pain scores. Indeed, it is conceivable that IHI is only altered in those presenting with bilateral symptoms.

Finally, the relationship between pain, tissue damage, sensorimotor function and peripheral and/or central mechanisms may not be linear or causal in chronic musculoskeletal conditions such as LE. For example, in musculoskeletal pain conditions it is well documented that

individuals may suffer from severe and/or widespread pain in the absence of tissue pathology (Arendt-Nielsen & Graven-Nielsen, 2011). In LE, individuals report improvements in pain and function despite the presence of on-going sensorimotor deficits, suggesting sensorimotor function may not be closely related to pain and disability (Bisset et al., 2009). Thus, a non-linear relationship between LE severity, altered IHI, corticomotor excitability, and sensorimotor dysfunction may exist, and this could be explored in future studies.

In addition to the limitations discussed above, there are several other limitations associated with the current study that should be acknowledged. First, we did not assess IHI in the opposite direction i.e., from the unaffected to the affected hemisphere. As IHI is bi-directional in nature it is possible that impairments exist in the opposite direction. Future studies should investigate IHI bi-directionally to comprehensively understand the relationship between IHI and bilateral symptom development in chronic LE. Second, handedness may impact IHI, with more inhibition demonstrated from the dominant to non-dominant hemisphere (Bäumer et al., 2007; Netz et al., 1995). Studies involving a larger sample should control for this confounding variable. Third, IHI results may be impacted by analysis of two affected sides of some individuals where ANOVAs evaluated side (affected, unaffected). Care should be taken when interpreting the results. Fourth, although our sample was sufficiently powered to detect a group difference between individuals with LE and healthy controls, a larger sample would have allowed comparison between those with unilateral and bilateral LE and those with LE of varying severity and this should be considered in future. Finally, variability in IHI and corticomotor excitability at the affected side is observed in the data, particularly IHI at the 10 ms ISI. Whilst the degree of variability in IHI is consistent with previous literature (Schabrun et al., 2016; Alhassani et al., 2019; Sattler et al., 2012), future studies may seek to explore individual factors known to influence neuroplasticity and contribute to variability in TMS

measures such as age, caffeine consumption, exercise, time of day and disease specific factors such as symptom severity and duration".

4.6 Conclusion:

This study investigated IHI between the primary motor cortices of individuals with chronic LE and healthy controls. There was no difference in the degree of IHI between those with LE and those without. Future studies are needed to confirm the finding that IHI does not contribute to sensorimotor dysfunction in musculoskeletal disorders such as LE.

CHAPTER 1 Introduction and Literature review

CHAPTER 2 IHI between primary motor cortices in response to acute muscle pain

CHAPTER 3 IHI between primary sensory cortices in response to acute muscle pain

CHAPTER 4 IHI between primary motor cortices in individuals with lateral epicondylalgia

CHAPTER 5 Discussion and Conclusion

CHAPTER 5

DISCUSSION AND CONCLUSION

The overarching aim of this thesis was to determine whether: i) IHI is altered in response to unilateral musculoskeletal pain; and ii) a relationship exists between altered IHI (if any) and the development of bilateral sensorimotor dysfunction. To achieve this, three studies were conducted. These studies provided novel insight into IHI in experimentally induced acute muscle pain and chronic lateral elbow pain. This chapter synthesises the body of work forming this thesis, highlighting how these findings make a valued contribution to the current body of knowledge. Research implications, future research directions, and limitations are also discussed.

5.1 Contribution of the thesis to the body of knowledge

Bilateral sensorimotor deficits have been observed in some people with unilateral musculoskeletal conditions (Heales et al., 2014). One mechanism hypothesised to underpin the development of bilateral symptoms in unilateral musculoskeletal pain conditions is altered IHI. Interhemispheric inhibition has been investigated in neurological conditions such as stroke and focal hand dystonia (Beck et al., 2009; Duque et al., 2005; Murase et al., 2004; Nelson et al., 2010; Sattler et al., 2014; Takechi et al., 2014), but to date, only one study has examined IHI in musculoskeletal pain (Schabrun et al., 2016). Prior to the research undertaken in this thesis, no data were available on the effect of acute or chronic musculoskeletal pain on IHI between M1s and S1s. Obtaining such data is important in providing a better understanding of the relationship between IHI, pain duration and bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions. Hence, studies 1 and 2 (Chapters 2 - 3) of this thesis aimed to explore the effect of experimentally induced acute unilateral muscle pain on IHI between M1s and S1s, respectively. The relationship between altered IHI (if any) and changes in sensorimotor function at the unaffected side was examined in both studies. Study 3 (Chapter 4) compared IHI between M1s in individuals with chronic lateral epicondylalgia and healthy controls.

Study 1 (Chapter 2) demonstrated that: i) IHI was reduced from the affected to the unaffected M1 following the resolution of acute unilateral muscle pain in a hand muscle; and ii) increased sensitivity to pressure developed on both the affected and unaffected sides. However, in contrast with previous studies, no linear correlation was found between the reduction in IHI and the increased sensitivity to pressure on the unaffected side. This discrepancy in findings may be explained by methodological differences between Study 1 and previous studies (described in Study 1, Chapter 2) such as the duration and intensity of induced muscle pain. Alternatively, a non-linear relationship may exist between IHI and sensorimotor function.

Regardless, the findings suggest that decreased IHI occurs rapidly in response to acute muscle pain and this mechanism could have a role (albeit non-linear) in the development of sensorimotor dysfunction in the unaffected hand.

Study 2 (Chapter 3) hypothesised that IHI would be altered between S1s in response to experimentally induced acute unilateral muscle pain and would be associated with the development of sensorimotor dysfunction on the unaffected side. Contrary to our hypothesis, Study 2 demonstrated no change in IHI between S1s following induction of acute unilateral muscle pain in a hand muscle. However, increased sensitivity to pressure was identified on both the affected and unaffected sides. This finding suggests that S1 IHI is not affected by acute muscle pain and is not associated with the increased sensitivity to pressure observed in the unaffected hand.

Study 3 (Chapter 4) compared IHI between M1s in individuals with chronic LE, and age and sex matched healthy pain-free individuals. Previous studies in pathological populations such as stroke and focal hand dystonia have shown a relationship between altered IHI and sensorimotor dysfunction. For example, in stroke, increased IHI from the unaffected to the stroke-affected hemisphere inhibits recovery of the lesioned hemisphere as well as motor recovery of the paretic limb. In focal hand dystonia, decreased IHI from the unaffected to affected hemisphere is associated with the development of mirror movements on the unaffected side (Baumer et al., 2016; Beck et al., 2009; Duque et al., 2005; Murase et al., 2004; Murase et al., 2007; Sattler et al., 2014). Based on these previous findings, it was hypothesised that IHI would be reduced from the affected (corresponding to the LE affected side) to the unaffected M1 in individuals with LE. However, the findings from Study 3 demonstrated no difference in IHI between M1s of individuals with LE compared to healthy controls. Furthermore, impaired sensorimotor function was not observed in individuals with chronic LE, relative to healthy

controls. Preserved sensorimotor function and the relatively low pain severity experienced by the recruited LE cohort (3 ± 1.8 out of 10 points on the numerical rating scale on the day of testing) may explain the normal functioning of IHI in this study.

Taken together, these studies provide an original contribution to the body of knowledge on IHI between human M1s and S1s in the presence of musculoskeletal pain. The studies provide novel evidence that: i) IHI is altered between M1s but not S1s in response to acute muscle pain; and ii) IHI between M1s is not altered in individuals with chronic LE when compared to healthy controls (Figure 5.1). The following sections present in depth interpretive discussion of the findings of altered IHI in M1 but not S1 in response to acute muscle pain, followed by a discussion of IHI in chronic musculoskeletal pain.

Thesis Aim:
Exploring interhemispheric inhibition in musculoskeletal pain

What is the role of IHI in experimentally induced acute unilateral muscle pain?	
IHI between primary motor cortices **Study 1 (Chapter 2):** ↓ IHI + increased bilateral sensitivity to pressure pain.	**IHI between primary sensory cortices** **Study 2 (Chapter 3):** No change in IHI + increased bilateral sensitivity to pressure pain.

What is the role of IHI in chronic musculoskeletal pain?
IHI between primary motor cortices in chronic lateral epicondylalgia **Study 3 (Chapter 4):** No change in IHI, and no change in sensorimotor function in the chronic LE group.

Figure 5.1. Schematic representation of the main findings from Studies 1 – 3. IHI, interhemispheric inhibition; ↓ = decreased; ↑ = increased.

5.2 Altered IHI between M1s but not S1s in response to acute muscle pain

The role of IHI in response to acute musculoskeletal pain had not been previously investigated. This thesis provides information that enhances our knowledge on the role of IHI between M1s and S1s in response to experimentally induced acute unilateral muscle pain and the possible mechanism underpinning the development of bilateral sensorimotor dysfunction. In support of our hypothesis, Study 1 demonstrated a reduction in IHI from the affected to unaffected M1. However, IHI between S1s was unchanged in Study 2. Bilateral sensorimotor changes characterised by increased sensitivity to pressure pain following the resolution of acute unilateral muscle pain were observed in both Studies 1 and 2. Yet, no relationship was observed between altered M1 IHI and increased sensitivity in the non-injected hand in Study 1. Studies 1 and 2 had separate sets of participants. As such, variability in the participant demographics and characteristics across the two studies may explain the differences in findings. However, a non-linear relationship may exist between IHI and sensorimotor function in Study 1, and it is plausible that decreased IHI between M1s following acute short-lasting pain reflects a protective strategy.

Altered IHI between M1s in response to acute muscle pain may occur to protect the body from further pain and / or injury, or the threat of further pain and / or injury. Adaptations to pain are complex and occur at multiple sites along the CNS pathway including the cortex (i.e., decreased cortical excitability, and increased intracortical inhibition) and the spinal cord (i.e., peripheral noxious input initiating central sensitisation) (Hodges & Tucker, 2011). Altered IHI may be part of this complex adaptation that occurs at the CNS. Whilst an association between reduced IHI and increased sensitivity to pressure was not observed in Study 1, an association between these two variables was observed by Schabrun et al. (2016), in response to sustained muscle pain. This discrepancy in findings may be due to differences in experimental pain models (hypertonic saline vs nerve growth factor) and the pain duration (minutes vs days). It is possible

that a longer duration of pain i.e., pain that persists over multiple days and sensitises the system, is required to observe an association between decreased IHI and sensorimotor dysfunction. Further, the observed decreased IHI may reflect a redistribution of activity to the unaffected hand that may serve to decrease pain severity and prevent ongoing sensitisation of the painful hand (Hodges & Tucker, 2011). This may also reflect the motor systems goal to employ alternate motor strategies to protect the painful part. Therefore, when pain is acute, a decrease in IHI between M1s could relate to the development of sensorimotor symptoms in the unaffected hand, thus providing a protective strategy by activating the unaffected muscles to anticipate future threat or pain. Whilst this hypothesis requires confirmation, this protective strategy could provide a beneficial short-term adaptation but lead to potential long-term consequences such as the development of bilateral sensorimotor dysfunction and chronic pain.

Whilst reduced IHI was demonstrated between M1s, this was not demonstrated between S1s in response to acute muscle pain. Possible explanations include: (i) S1 and M1 IHI circuits act independently; (ii) S1 and M1 IHI circuits are reciprocally connected; and (iii) IHI changes in response to acute muscle pain occur between S2s.

5.2.1 S1 and M1 IHI circuits act independently in response to pain

One potential explanation for why acute muscle pain influences IHI between M1s and not S1s is that S1 and M1 circuits receive and process acute muscle pain independent of each other. For example, Schabrun et al. (2013) investigated the sensory-motor interaction of the hemisphere corresponding to the painful muscle before, during and immediately after hypertonic saline induced acute muscle pain and found S1 excitability reduced during and after pain resolution. In contrast, M1 excitability was reduced only after pain resolution changes. Further, there were no correlations between changes in M1 and S1 excitability at any time point. Similarly, we showed in Study 1 that M1 IHI was reduced immediately after, and 30

mins following the resolution of acute muscle pain but IHI between S1s was unchanged at any time point in Study 2. The temporal dispersion of processing of the M1 and S1 IHI circuits suggests that they may be affected by pain independently of each other.

Neuroimaging study findings also suggest independent processing of M1 and S1 in response to pain. As M1 and S1 are in close proximity, it is possible that when one region is stimulated concomitant activation of the other region occurs. Rao et al. (2020) investigated whether continuous theta burst stimulation (cTBS) of S1 to increase pain thresholds is confounded by M1 excitability changes. They demonstrated that cTBS over S1 in healthy individuals increased pain thresholds of a hand muscle to electrical stimulation but did not influence M1 excitability. As cTBS over S1 did not modulate M1 excitability, this suggests independent processing of S1 and M1 in response to pain. Neuroimaging studies using Positron Emission Tomography (PET) however, are inconclusive regarding whether M1 is modulated independently or in conjunction with S1. These studies sought to better characterise cortical processing of noxious stimuli and demonstrated variable findings that show increased (Casey et al., 1996; Coghill et al., 1994; Talbot et al., 1991), decreased (Peyron et al., 1999) or unchanged M1 activity (Jones et al., 1991) in combination with S1 changes in pain. These inconsistent findings are likely attributed to methodological variations between studies such as the method of induced pain, pain intensity, duration, and the temporal resolution limitation of PET, that limit comparisons between studies and drawing conclusions. In Studies 1 and 2, methodologies were similar with pain induced via injection of hypertonic saline in the hand muscles. Further, both studies demonstrated comparable mean peak pain intensities on the day of testing (Study 1: 7.9 ± 1.8 on the NRS; Study 2: 7.7 ± 1.6 on the NRS), and average pain durations (Study 1: 9.9 ± 3.4 minutes; Study 2: 7.3 ± 2.1 minutes) yet resulted in contrasting IHI findings (Study 1: reduced IHI between M1s; Study 2: no change in IHI between S1s). It is therefore possible to speculate that independent S1 and M1 IHI processing may occur in response to acute short-lasting pain

with a significant reduction in M1 IHI following pain resolution. Future studies may seek to examine whether S1 IHI is affected in response to pain, and measure M1 IHI concurrently to better understand the interactions and relationship.

5.2.2 M1 and S1 IHI circuits are reciprocally connected

An alternate explanation for the differences in M1 and S1 IHI processing in response to pain is that M1 and S1 are reciprocally connected with a more complex interactive relationship. The primary sensory cortex has the ability to alter IHI between motor cortices contributing to altered motor output (Zapallow et al., 2013). Zapallow et al. (2013) demonstrated application of cTBS over the left S1 increased IHI from the left to right M1 (corresponding to the ipsilateral left hand) 45 – 60 minutes following cTBS. They suggest this occurs as S1 influences ipsilateral M1 excitatory transcallosal connections which strongly excite inhibitory interneurons of the opposite M1, decreasing corticospinal output of that hemisphere and altering motor output. Further, this finding supports the hypothesis that homologous S1 are indirectly connected through a transcallosal pathway from S1-M1-M1-S1 (Brodie et al., 2014; Zapallow et al., 2013). It is suggested that this indirect pathway has longer processing times between 36 - 80 ms (Ragert et al., 2011). Therefore, taking together the indirect transcallosal pathway processing time, and previous studies demonstrating M1 IHI changes 45 - 60 minutes following S1 stimulation, it is possible that in response to short-lasting muscle pain, disinhibition between S1s occurs: i) at an ISI later than 25 ms, reflecting a longer processing time that we did not capture; and / or ii) at a follow up time longer than 30 minutes. Hence, future studies may seek to investigate S1 IHI at ISI's longer than 25 ms and follow-up the effects of pain for longer than 30 minutes to determine whether, and how long after the resolution of acute muscle pain, S1 IHI changes occur.

Further, sequential activations of other cortical regions may be involved in the reduction of IHI in response to pain. It is understood that pain engages a widespread network such as the supplementary motor area, pre-motor area, the anterior cingulate cortex, S2, and the thalamus (Coghill, 2020; Coghill et al., 1999; Coghill et al., 1994; Peyron et al., 2000). A reduction in IHI may occur due to the concomitant activation and input of M1, S1, and other regions of the pain network that contribute to the transcallosal connection of cortical hemispheres. For example, inhibition of the N30 SEP component was observed pre-pain in Study 2. The N30 component represents a complex cortical and subcortical loop linking the basal ganglia, thalamus, pre-motor areas and M1 (Kanovsky et al., 2003; Passmore et al., 2014). Hence, inhibition of the N30 component may suggest activation of other cortical regions altering the neural circuitry that underpins IHI. Alternatively, reorganisation can occur at the spinal level first and project to the cortex (Jones, 2000). The thalamus receives nociceptive input projecting to S1 and M1. A reduction in inhibition of thalamic neurons in response to pain may occur prior to reaching the S1 and M1 regions (Kandić et al., 2021). Once the nociceptive information reaches the M1 and S1 regions, the information is transferred callosally, contributing to sensory components of pain. To this end, future studies may be required to examine the concomitant activation of other cortical regions in the modulation of IHI in response to pain.

In addition to the hypothesis that M1 and S1 IHI circuits are reciprocally connected, integration of sensory and motor information is required to successfully achieve a sensorimotor task, known as sensorimotor integration. Sensory afferent input arrives to S1 before it is conveyed to M1 (Umeda et al., 2019; Zagha et al., 2013) and synaptic inputs are shown to be stronger from S1 to M1 than inputs from M1 to S1 (Rocco-Donovan et al., 2011). Research has shown that sensory afferent input affects the excitability of motor projections to the muscles in the same arm and the excitability of projections to muscles in the opposite arm (Swayne et al., 2006; Werhahn et al., 2002a; Werhahn et al., 2002b). For example, vibrations applied to the

left first dorsal interosseous (FDI) muscle resulted in reduced MEP amplitudes and increased IHI of the right FDI muscle suggesting transcallosal fibres mediating this effect (Swayne et al., 2006). We can hypothesise that a similar mechanism of sensorimotor integration occurred in Studies 1 and 2 whereby the sensory information i.e., painful input, was transferred from the periphery, reached and was processed by the primary sensory cortex and conveyed to the motor cortices decreasing IHI. Furthermore, as S1 conveys information about somatosensation, proprioception and visuomotor changes to M1 (Edwards et al., 2019), and M1 integrates the sensory information provided by S1 to process, plan and predict movement (Avanzino et al., 2015), it is plausible that increased pressure sensitivity at the unaffected hand muscles demonstrated in Studies 1 and 2 occurred as a result of altered sensorimotor information.

5.2.3 IHI changes in response to acute muscle pain occur between S2s

Another possible explanation why reduced IHI occurred between M1s and not S1s is that a reduction in IHI in response to musculoskeletal pain may occur between S2 rather than S1. Indeed, the literature demonstrates interactions between ipsilateral and contralateral inputs to S2 with dense transcallosal connections and large receptive fields reported between homologous S2s compared to S1s (Hoechstetter et al., 2001; Iwamura, 2000; Picard et al., 1990). Bilateral activation of S2 has been demonstrated in response to tactile information that is unilateral, and suppression of ipsilateral S1 is observed in response to bilateral stimulation attributed to interhemispheric transfer of information between S2s (Frot & Mauguière, 1999; Picard et al., 1990; Stancak et al., 2002). Further, S2 is shown to have a role in the sensory-discriminative dimension of pain (Maihöfner et al., 2006) with bilateral activation of S2 demonstrated in response to pain (Fabri et al., 2005; Fabri et al., 2001; Fabri et al., 1999) and specifically when processing pain of high intensity. For example, using magnetoencephalography, Timmermann et al. (2001) demonstrated strong activation in S2 in response to pain of high intensity above threshold levels but weaker activations in S2 when

pain was of a threshold level. While there is some evidence demonstrating S1 activation is related to pain intensity (Antal et al., 2008; Coghill et al., 1994; Grundmann et al., 2011), other investigations do not show this relationship (Jones et al., 1991; Peyron et al., 2000; Schabrun et al., 2015b; Xu et al., 1997). As Study 2 used an acute muscle pain model that induced a sharp intense pain with a rapid decline in intensity (Peak pain: NRS 7.7 ± 1.6 out of 10), and S2 is known to process pain of high intensity, this could suggest that changes in S2 IHI may have occurred that we were unable to explore in this thesis. Further studies are required to investigate whether IHI between S2s is affected by acute muscle pain and whether a relationship exists with pain intensity.

When combined, the findings from Studies 1 and 2 demonstrate a reduction in IHI between M1s but not between S1s, providing novel insight into IHI at an acute stage of pain and expanding our understanding of the temporal profile of IHI in response to acute experimental muscle pain. As IHI between M1s has been demonstrated in response to acute experimental muscle pain (Study 1) and previously in response to sustained experimental muscle pain (Schabrun et al., 2016), we therefore investigated M1 IHI in chronic musculoskeletal pain to add to the knowledge of the temporal profile of IHI in response to musculoskeletal pain.

5.3 The influence of chronic musculoskeletal pain on IHI in M1

To our knowledge there are no previously published studies that investigate IHI between M1s in a chronic musculoskeletal population. To this end, Study 3 (Chapter 4) aimed to investigate IHI between M1s in individuals with chronic LE. Our findings did not show any change in IHI between M1s in individuals with chronic LE compared to healthy controls, nor were bilateral sensorimotor deficits identified in the LE group. Several possibilities could explain these findings.

One possibility is that low pain severity may not be a driver of altered IHI. In Study 1, IHI was found to be reduced in response to experimentally induced acute pain rated as a mean peak pain intensity of 7.9 ± 1.8 out of 10 on the NRS. However, in Study 3, mean pain intensity on the day of testing was reported as 3 ± 1.8 points out of 10 on the NRS and altered IHI was not observed. A recently published systematic review by Chowdhury et al. (2022) demonstrated that reduced corticomotor excitability is associated with higher pain intensity when pain lasts days to weeks, however, reduced excitability is associated with lower pain intensity when pain lasts minutes to hours. In chronic unilateral LE, cortical reorganisation changes such as increased cortical excitability of muscle representations, large overlapping of centre of gravity and reduced number of discrete peaks of muscle representations were associated with high pain severity (Schabrun et al., 2015a). Further, it is suggested that when pain intensity levels are perceived stable by an individual and no further changes in pain intensity are expected, altered motor cortex excitability returns to baseline (Farina et al., 2001; Nijs et al., 2012). For example, Farina et al. (2001) showed MEP amplitudes were significantly inhibited 20 - 30 minutes following the induction of pain and progressively returned to baseline values after 80 minutes when pain was perceived as stable. As cortical processing of pain is reflected differently along the motor pathway and in response to different pain durations, it is plausible that altered IHI may have progressively returned to normal levels once individuals in our chronic LE sample perceived their pain as stable and were not expecting further increases in pain severity. Further, individual differences in IHI in response to pain may relate to pain severity. For example, individuals that display corticomotor depression experience greater pain than those who display facilitation (Seminowicz et al., 2019). It is possible that a similar relationship occurs with IHI that we were unable to evaluate in this study. To investigate this hypothesis further, future studies may aim to characterise the relationship between individual differences in altered IHI and different levels of pain severity.

Another possibility for preserved IHI between M1s in chronic LE is that the degree of IHI varies for different muscles. In humans, it has been shown that the degree of IHI differs in representations of intrinsic hand muscles compared to proximal muscles such as the biceps brachii muscle, thought to be due to a proximal-distal gradient (Sohn et al., 2003). In contrast, however, some studies suggest it is due to the role of the muscles in a functional movement synergy (Harris-Love et al., 2007). Furthermore, previous work highlights corticomotor responsiveness can differ between muscles and tasks in response to pain with proximal and distal muscles adapting differently to comparable experimental muscle pain (Hodges & Tucker, 2011). It is possible that preserved IHI in the chronic LE group reflects the location and function of the ECRB muscle and its ability to adapt differently to pain. Taken together, we can speculate the response of IHI may vary based on the location and function of a given muscle.

Alternatively, smaller IHI changes of the ECRB muscle may have been detected with a combination of brain imaging techniques as opposed to a single modality. Across Studies 1 - 3 we used TMS and EEG individually. Indeed, these brain imaging techniques have advantages with TMS exhibiting moderate temporal and spatial resolution (Wagner et al., 2007), and EEG directly recording brain activity with high temporal resolution in milliseconds, allowing assessment of the brain's temporal processes such as sensory and motor processes (Schomer & Da Silva, 2012). However, limitations of these techniques also exist. For example, the temporal and spatial resolution of TMS is strongly affected by the thickness and size of the brain (Post & Keck, 2001) and the focality of stimulation is dependent on coil size and shape (Rossi et al., 2021; Rossi et al., 2009). Limitations of EEG include low spatial resolution (Schomer & Da Silva, 2012). TMS-EEG has emerged as a powerful tool that has been used increasingly to assess cortical excitability and connectivity (Tremblay et al., 2019). This combination has allowed for high temporal resolution with the ability to differentiate between inhibitory and

facilitatory cortical activations (Wagner et al., 2007) with a recent study showing combined TMS-EEG benefits from the spatial resolution of TMS (Passera et al., 2022).

Combining TMS-EEG would allow for effective evaluation of interhemispheric connectivity in the following ways. First, TMS-induced MEPs could be compared to the EEG signal to determine whether inhibition between M1s via TMS is correlated to inhibition of the EEG signal and determine if the same mechanisms and cortical areas mediate IHI (Barr et al., 2013). Second, combined TMS-EEG would allow the compartmentalisation of IHI recorded between M1s via TMS into its component frequencies (e.g. delta, theta, beta, alpha) via EEG to further characterise the physiology of IHI. For example, beta band oscillations are associated with motor movement (Pfurtscheller, 1997) and gamma oscillations are associated with the experience of pain (Barr et al., 2013). In chronic stroke, increased beta between hemispheres reflecting abnormal IHI has been demonstrated and associated with motor function impairment (Borich et al., 2016). This approach could be used in musculoskeletal pain as a neurophysiological marker of IHI to better understand the relationship between IHI and bilateral sensorimotor dysfunction. Some technical limitations exist with combining TMS-EEG such as the recording of auditory and visual artifacts (Bestmann et al., 2008; Paus, 2005; Wagner et al., 2007). However, combining brain imaging techniques can allow for higher temporal and spatial resolution that could detect smaller changes in IHI that a single brain stimulation technique used in isolation may not be able to. Therefore, combined TMS-EEG could optimise brain stimulation and provide a more detailed picture of the IHI mechanism in response to musculoskeletal pain than one brain imaging technique alone can provide.

Finally, a lack of bilateral sensorimotor deficits in the chronic LE group when compared to healthy controls may explain why IHI changes were not observed. The lack of bilateral deficits observed contrasts with the literature that identifies bilateral sensorimotor deficits in unilateral LE such as reduced grip force, increased upper limb reaction times and reduced speed of

movement (Heales et al., 2014). A larger sample size may have had increased power to detect changes in sensorimotor function in the chronic LE group. As no previous studies have investigated IHI in a chronic musculoskeletal population, we based our sample size on a study that investigated IHI in response to sustained muscle pain of the ECRB muscle (Schabrun et al., 2016). Our sample size of N = 20 reflects similar sample sizes of previous studies in chronic unilateral LE that have demonstrated bilateral sensorimotor dysfunction and as such, we estimated our sample to be sufficient to show an effect (Apaydin et al., 2020; Bisset et al., 2018; Chourasia et al., 2012). Further, studies investigating IHI in pathological conditions such as stroke and focal hand dystonia have recruited small samples (N < 13) and have identified statistically significant changes in IHI in those pathological populations (Beck et al., 2009; Duque et al., 2005; Murase et al., 2004; Nelson et al., 2010). Sample size calculations determine the smallest scientifically and meaningful effect size (Jones et al., 2003). Studies that do not provide sample size calculations may not be powered to detect differences in outcomes or in contrast may detect differences that are not present (type 1 error), thus affecting the validity of reported significance (Bacchetti, 2010; Button et al., 2013). However, in some cases sample size calculations are difficult to calculate where the study is a pilot or exploratory and no previous data is available to determine information including the mean, variability and error required for the calculation (Jones et al., 2003). Hence, some authors argue against sample size calculation (Bacchetti, 2002, 2010). To this end, future studies with larger samples may be needed to demonstrate bilateral sensorimotor symptom development and explore the relationship to IHI in these individuals.

5.4 Research implications

The findings of Studies 1 - 3 provide new insight into the role of IHI in response to musculoskeletal pain and how this may relate to the development of bilateral sensorimotor dysfunction. The findings suggest that IHI is altered between M1s at an acute stage of muscle

pain, and that sensorimotor dysfunction develops at the affected and unaffected side in the FDI muscle. The outcomes of this thesis provide the following implications for future research investigating IHI in musculoskeletal pain.

Findings from studies 1 and 2 demonstrate the development of bilateral sensorimotor dysfunction in response to acute unilateral muscle pain. Our findings demonstrate altered sensory function is mirrored in the non-painful muscle immediately following pain characterised by reduced PPTs. This may have implications for the recovery of the affected limb and risk of developing sensorimotor symptoms bilaterally. It is common that studies compare the painful limb to the unaffected limb (Dorf et al., 2007; Pienimäki et al., 2011; Pienimäki et al., 2002; Smidt et al., 2002). However, the unaffected side should not be used as a control in studies due to crossed effects from the affected to unaffected side and the potential that study findings will not accurately reflect the condition of the affected limb. Further, it is important to note that the development of bilateral symptoms following acute pain resolution may be part of a protective mechanism from further injury and produces altered movement strategies (Hodges & Tucker, 2011). Further research is required to confirm this to understand whether this process is indeed a beneficial short-term strategy.

Bilateral sensitivity to pressure was demonstrated in studies 1 and 2. This supports the notion that transfer of motor or sensory information can cross over from one side of the body to homologous muscles of the opposite side, a phenomenon known as cross-education (Zhou, 2000). The underlying mechanisms of cross-education are poorly understood, but cortical mechanisms via interhemispheric connections such as IHI is one proposed mechanism. Although our findings demonstrated a reduction in IHI, no association was found between reduced IHI and increased sensitivity to pressure bilaterally. This may suggest that a non-linear relationship exists between these two outcomes (as described above in section 5.2) or that a relationship may be observed when pain is sustained (Schabrun et al., 2016). Alternatively, IHI

may not be the mechanism mediating the increased sensitivity to pressure and another mechanism may be involved. Spinal mechanisms may instead mediate the transfer of sensory information to the unaffected side. Nociceptive input is transmitted from the spinal cord to the brain through multiple pathways (Coghill, 2020). One potential pathway is the spinothalamic tract. Nociceptive information is projected to the spinothalamic tract and this information is distributed bilaterally through wide dynamic range neurons that have bilateral receptive fields. Thus, nociceptive information ascending ipsilaterally could mediate the sensitivity to pressure of the unaffected hand (Coghill, 2020; Dum et al., 2009; Giesler et al., 1981). Indeed, the spinothalamic tract is assessed with pressure pain thresholds and research has demonstrated increased sensitivity to pressure pain thresholds at sites contralateral to the injury (Arendt-Nielsen et al., 2011; Gibson et al., 2006; Hansson et al., 2007). This hypothesis requires further investigation to determine the underlying mechanism mediating bilateral sensorimotor dysfunction.

5.5 Future directions

This thesis has presented findings that provide insight into the role of IHI in response to unilateral musculoskeletal pain. The discussion in each study chapter and above has highlighted areas of research that require further investigation to extend the findings from this thesis. The directions for future research are summarised below.

- When added to the current literature, the findings from this thesis suggest that in response to acute unilateral muscle pain, IHI between M1s is reduced and sensorimotor dysfunction develops bilaterally despite the absence of pain on the unaffected side. However, further research is required to determine the causal nature of the relationship between IHI and bilateral sensorimotor dysfunction in unilateral musculoskeletal pain. This research may follow up the effects of acute muscle pain for longer than 30 minutes to determine the

duration of the effects, and whether an association between reduced IHI and sensorimotor dysfunction is observed at a later time point following pain resolution.

- To further develop a comprehensive understanding of IHI in response to acute muscle pain, future studies could combine neuroimaging and brain stimulation techniques, such as TMS with EEG. Combining these techniques would allow for higher temporal and spatial resolution in the measurement of IHI between M1s and S1s that may detect smaller changes in IHI compared to a single brain stimulation technique.
- To further understand how IHI is modulated in response to musculoskeletal pain, future studies may consider sub-grouping individuals based on low, mid, or high pain severity. As previous studies show decreased corticomotor excitability is associated with low pain severity (Chowdhury et al., 2022), and increased cortical excitability is associated with higher pain severity (Schabrun et al., 2015a), IHI may be altered differently in response to different pain severities.
- While IHI has been investigated between M1s and S1s in response to pain, existing research suggests that S2 has an important role in pain processing. Therefore, further research is required to investigate IHI between S2s and determine if a relationship between the development of bilateral symptoms and IHI changes exists.

5.6 Limitations

The limitations of each individual study have been discussed in Chapters 2, 3 and 4. Therefore, the following section recognises limitations that may influence the overall interpretation of the findings from this thesis.

First, the work presented in this thesis was limited to investigating IHI in the direction from the affected to unaffected hemisphere. This approach was selected as a previous study by Schabrun et al. (2016) demonstrated that in sustained experimental muscle pain, IHI is

unchanged in the opposite direction i.e., from the unaffected to affected hemisphere. However, as IHI is bidirectional it is possible that impairments exist in the opposite direction that we did not examine. Future studies could extend the work presented in this thesis and investigate IHI in the opposite direction to examine the mechanism of IHI more comprehensively.

Second, although we suggest that IHI may underpin the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal conditions, causality cannot be inferred. The studies presented in this thesis are cross-sectional and additional longitudinal studies are warranted. Further Study 3 (Chapter 4) was a proof-of-concept study that did not demonstrate sensorimotor deficits in the LE group compared to healthy participants. To further examine the role of IHI in a chronic musculoskeletal population, a powered sample of participants with confirmed transfer of bilateral sensorimotor symptoms is required to determine the relationship between IHI and bilateral sensorimotor dysfunction development.

Third, this thesis explored IHI between M1s and S1s only. Other brain regions within the cortex as well as sub-cortical regions may be involved in the modulation of IHI. For example, the thalamus has been shown to mediate IHI to the sensory cortices (Castro-Alamancos, 2002; Pinault, 2004; Staines et al., 2002). Similarly, IHI between S2s has been demonstrated in animal and human studies, and the role of S2 has been implicated in pain (Fabri et al., 2005; Fabri et al., 2001; Fabri et al., 1999; Hamada et al., 2002; Hoechstetter et al., 2001). It is possible that altered IHI in other brain regions may have influenced the development of bilateral sensorimotor deficits in response to acute muscle pain in studies 1 and 2 (Chapters 2 and 3). Therefore, the role of IHI in other cortical and subcortical regions in response to musculoskeletal pain warrants further exploration.

Fourth, individuals with bilateral LE were included in this thesis. This may influence the interpretation regarding altered IHI in chronic unilateral LE. As such, care should be taken when interpreting these findings.

Finally, the investigator was not blind to data collection or analyses. Investigator blinding reduces the risk of bias and improves internal validity (Guyatt et al., 2011; Higgins et al., 2011). Investigator blinding is not consistently implemented in cross-sectional studies due to feasibility of some studies (Hulley et al., 2013). However, wherever feasible, to reduce bias and improve overall data accuracy, future studies should implement investigator blinding during data collection and analysis

5.7 Conclusion

The three studies in this thesis (Chapters 2 - 4) provide original contributions to our understanding of IHI in response to unilateral musculoskeletal pain when using experimental pain models and a chronic pain population. An observed reduction in IHI between M1s in response to experimentally induced acute unilateral muscle pain suggests that IHI may mediate bilateral sensitivity to pressure during an acute stage of musculoskeletal pain. However, IHI between S1s may be preserved in response to acute muscle pain. This thesis also found no changes in sensorimotor function bilaterally or changes in IHI between M1s in individuals with chronic LE compared to healthy controls. The absence of bilateral sensorimotor dysfunction likely explains why no change in IHI was observed in individuals with chronic LE. Therefore, we were unable to confirm or exclude altered IHI as a mechanism and / or mediator of bilateral symptom development. Further research is required, including longitudinal studies in clinical populations who transition from acute to chronic musculoskeletal pain, to empirically determine if an association exists between alterations in IHI and bilateral symptom development.

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APPENDIX A

Publication from Chapter 2, Study 1: Interhemispheric inhibition between primary motor cortices in response to acute muscle pain

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Original Reports

Interhemispheric Inhibition Is Reduced in Response to Acute Muscle Pain: A Cross-Sectional Study Using Transcranial Magnetic Stimulation

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Abstract: **Bilateral deficits in sensorimotor function have been observed in unilateral musculoskeletal pain conditions. Evidence suggests a reduction in interhemispheric inhibition (IHI) from the "affected" (contralateral to the side of pain) to the "unaffected" primary motor cortex (M1) could contribute. However, the effect of short-lasting acute muscle pain on IHI, and whether any changes are related to early sensorimotor changes in the unaffected limb, is unknown. Using a cross-sectional study design, IHI was investigated in 20 healthy individuals before, immediately after, and 30 minutes after the induction of acute muscle pain in the right first dorsal interosseous muscle via a bolus injection of hypertonic saline. Transcranial magnetic stimulation was used to assess corticomotor excitability and short and long latency IHI. Pain intensity and quality were recorded using an 11-point numerical rating scale and the McGill Pain Questionnaire. Pressure pain thresholds were assessed in the affected and unaffected first dorsal interosseous and both tibialis anterior muscles. Participants reported an average pain intensity of 4.8 points (standard deviation = 1.3 points). Compared with baseline, corticomotor excitability was decreased at all time points in the affected but not the unaffected M1. IHI was decreased at all time points from the affected to the unaffected M1. Pressure pain thresholds were decreased over both first dorsal interosseous muscles at 30 minutes of follow-up. These findings suggest a decrease in IHI from the affected to the unaffected M1 that occurs rapidly after the onset of acute pain and could contribute to the development of bilateral symptoms.**

Perspective: ***The affected M1 (contralateral to the side of pain) releases inhibition over the unaffected M1 within minutes after the onset of acute muscle pain. This finding could have relevance for the development of bilateral sensorimotor symptoms in unilateral pain conditions.***

Key words: *Interhemispheric inhibition, primary motor cortex, transcranial magnetic stimulation, hypertonic saline, musculoskeletal pain.*

Musculoskeletal pain is known to alter the sensorimotor function of the affected body part. For example, individuals with chronic lateral elbow pain (chronic lateral epicondylalgia or "tennis elbow") display increased sensitivity to mechanical stimuli,[32] decreased maximal wrist extensor force, and decreased grip force[6,57] on the painful side. Interestingly, bilateral deficits in sensorimotor function are also observed in these individuals, despite the presence of pain in only one limb.[6,12,18] For example, a recent systematic review demonstrated flexed wrist postures, increased upper limb reaction times, decreased speed of movement, and decreased pressure and thermal pain thresholds in the unaffected limb of people with chronic lateral elbow pain.[6,27,49] This observation suggests the involvement of the central nervous system in the

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development of bilateral sensorimotor dysfunction, yet the mechanisms that mediate this effect are unknown.

Interhemispheric inhibition (IHI) is a neurophysiological mechanism where the primary motor cortex (M1) of one hemisphere inhibits the M1 of the opposite hemisphere via projections in the corpus callosum. IHI is involved in the control of skilled movements, as well as in the acquisition and transfer of motor skills.[50] Normal modulation of IHI enables individuals to perform unimanual tasks without the coactivation of contralateral muscles. However, in childhood, pathological conditions such as mirror dystonia, and in the elderly, mirror movements can be observed in the opposite limb when a task is complex or fatiguing, and this movement overflow is negatively correlated with the degree of IHI exerted over the inactive limb.[4] Further, there is evidence of a relationship between altered IHI and impaired motor recovery in stroke survivors. Specifically, the unaffected M1 has been shown to exert "too much" inhibitory control over the stroke-affected M1, interfering with adaptive neuroplasticity in the lesioned area and motor recovery of the paretic limb.[2,15,43] The relationship between IHI and sensorimotor function observed in previous studies could also be relevant to the development of bilateral sensorimotor dysfunction in unilateral musculoskeletal pain conditions.

Only one study has examined IHI in musculoskeletal pain. That study reported a decrease in IHI from the affected M1 (corresponding with the painful muscle) to the unaffected M1 4 days after repeated injection of nerve growth factor into the elbow extensor muscles to induce progressively developing, sustained muscle pain. The decrease in IHI was associated with the development of sensorimotor dysfunction (increased sensitivity to mechanical stimuli) in the unaffected limb.[54] These data suggest a relationship between IHI and the development of bilateral sensorimotor dysfunction after several days of musculoskeletal pain. However, it is unknown how soon after pain onset IHI is altered and whether this is related to early sensorimotor changes in the unaffected limb.

Here we aimed to investigate i) whether IHI is altered in response to rapid onset, short-lasting acute muscle pain and ii) the relationship between altered IHI and changes in sensorimotor function in the unaffected limb. Based on previous work,[54] we hypothesized that IHI would be decreased from the affected to the unaffected M1 in response to acute muscle pain and this would be associated with an increased sensitivity to mechanical stimuli in the unaffected limb.

Methods

Participants

Twenty healthy individuals (8 males, 12 females; mean ± standard deviation age = 26 ± 7 years) participated. Participants were recruited through the university and social media from May 2017 to September 2017. All participants were right handed according to the Edinburgh handedness inventory (Oldfield 1971) and had no history of upper limb pain or injury; no neurological, respiratory, orthopedic, or circulatory disorders; and no contraindications to transcranial magnetic stimulation.[33] All procedures were approved by the institutional human research ethics committee (H11873). Participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

The sample size calculation was based on effect sizes from the only study to have examined IHI in musculoskeletal pain.[54] Based on these data (difference in means between days 0 and 4 of .91 mV, standard deviation = .90), a sample size of 10 participants was required to observe a statistically significant difference (80% power; $\alpha = .05$) should one exist. However, because these effects have not been examined in acute pain and the size of the effect is therefore unclear, we conservatively doubled the sample size, ensuring sufficient power to the allow detection of a smaller effect size if needed.

Experimental Protocol

Participants were seated with their head and neck supported and both arms resting in a supinated position on a pillow. Pressure pain thresholds were recorded bilaterally from the first dorsal interosseous (FDI) and tibialis anterior muscles at baseline and at 30 minutes follow-up. Fifteen motor evoked potentials to single pulse transcranial magnetic stimulation were elicited from the affected and unaffected M1 (order randomized between participants), followed by an assessment of IHI, at 3 time-points: i) before pain, ii) immediately after the resolution of pain (once pain had returned to zero on an 11-point numerical rating scale), and iii) 30 minutes after the resolution of pain. Muscle pain was induced by intramuscular injection of hypertonic saline into the right FDI muscle. Pain was rated on an 11-point numerical rating scale anchored at 0 (no pain) and 10 (worst pain imaginable), every 30 seconds immediately after hypertonic saline injection until each participant reported a pain score of 0. At the conclusion of the experiment, participants rated the intensity, location, and quality of muscle pain using the short-form McGill Pain Questionnaire[38] and a body chart. The experimental protocol is outlined in Fig 1.

Pressure Pain Thresholds

Pressure pain thresholds were assessed at baseline and at 30 minutes follow-up. A hand-held pressure algometer (Wagner Instrument, Greenwich, Connecticut) was applied perpendicular to the skin at a rate of 1 kg/sec. Participants were instructed to vocalize the moment the sensation of pressure first turned to pain. Pressure pain thresholds were assessed at 4 sites: 1) affected FDI, 2) unaffected FDI, 3) right tibialis anterior, and 4) left tibialis anterior. For each site, the muscle belly was located and marked to ensure consistent positioning of the algometer over time. The average of the 3 trials at each site, with a 1-minute rest between each trial, was used for statistical analysis.

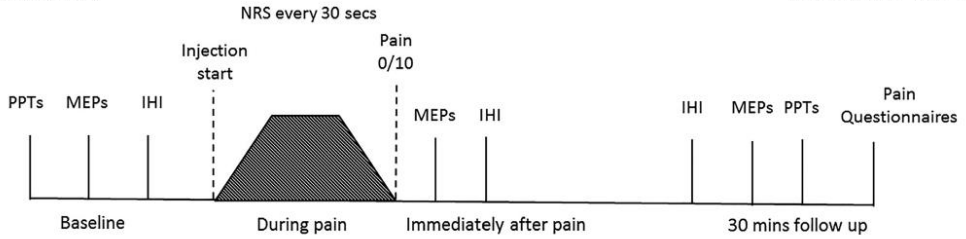

Figure 1. Experimental protocol. Measures of corticomotor excitability (motor evoked potential amplitude; MEP) and IHI were made at (i) baseline, (ii) immediately after pain, and (iii) 30 minutes follow-up. Pressure pain threshold (PPT) measurements were taken at baseline and at 30 minutes follow-up. Pain was induced by injection of hypertonic saline into the right FDI muscle and pain intensity monitored every 30 seconds on the numerical rating scale (NRS). The McGill Pain Questionnaire was completed at the conclusion of the experiment.

Electromyography

Electromyographic activity was recorded from the affected and unaffected FDI muscles. Disposable dual silver/silver chloride surface electrodes (Noraxon USA Inc, Scottsdale, Arizona) were positioned over each muscle belly. Ground electrodes were positioned over the right and left olecranons. Data were amplified 1,000×, filtered between 20 and 1000 Hz, and sampled at 2,000 Hz using Signal software and a Micro 1401 data acquisition system (Cambridge Electronic Design, Cambridge UK).

Transcranial Magnetic Stimulation

Corticomotor Excitability

Single-pulse transcranial magnetic stimulation stimuli were delivered to the M1 hand areas using a figure-of-8 coil connected to a Magstim 200 stimulator (Magstim Co. Ltd, Dyfed, UK). Transcranial magnetic stimulation was performed over both the affected and unaffected M1 in all participants. The coil was oriented at a 45° angle to produce a posterior to anterior current flow and positioned over the optimal cortical site to evoke a response in each FDI muscle. The optimal cortical site to elicit motor evoked potentials in the affected and unaffected FDI muscles was determined as the site where the lowest stimulus intensity evoked the largest response. These sites were marked with a pen to ensure accurate coil placement for the duration of the experiment. Resting motor threshold was defined as the lowest intensity of stimulation required to evoke a motor evoked potential of >50 μV peak-to-peak amplitude in ≥3 of 5 consecutive trials.[51] Fifteen motor evoked potentials (rate of 1 every 6 seconds) were recorded from the affected and unaffected FDI at 120% of resting motor threshold. The hemisphere recording order was randomized between participants. The average peak-to-peak motor evoked potential amplitude (mV) was calculated at each timepoint for the affected and unaffected M1 and this value used for analysis.

IHI

IHI was probed using a conditioning test paradigm. A conditioning pulse applied to the affected M1 preceded a test stimulus applied to the unaffected M1. To investigate short and long latency IHI, 10 and 40 ms interstimulus intervals were selected, respectively.[17,52,53] In pseudorandom order, 10 trials were recorded at each interstimulus interval and a further 10 trials were recorded using the test stimulus alone (30 trials in total) with 5 seconds between each trial. Transcranial magnetic stimulation was delivered using 2 Magstim 200 magnetic stimulators (Magstim Co. Ltd), each connected to a figure-of-eight coil with external wing diameters of 70 mm (unaffected M1) and 50 mm (affected M1). The coil delivering the test stimulus was positioned tangentially over the scalp perpendicular to the midsagittal line with the coil handle pointing backward at a 45° angle, inducing a posterior to anterior current direction. The conditioning stimulus coil was oriented 90° relative to the midsagittal line to avoid overlapping the coils.[11,44] It has been previously reported that the current direction of the conditioning stimulus does not affect the degree of IHI.[11,44] To investigate our hypothesis, IHI was recorded from affected to unaffected M1. The test stimulus intensity was adjusted to produce a peak-to-peak motor evoked potential amplitude of 1.0 to 1.5 mV[42] in relaxed FDI and the conditioning stimulus intensity was set at 120% of the resting motor threshold and adjusted if required, to elicit inhibition of approximately 50% at baseline in each participant.[24,42,46] Motor evoked potential responses were measured as peak-to-peak amplitudes and conditioned responses expressed as a proportion of the unconditioned test response for analysis.

Experimental Muscle Pain

A single bolus of .5 mL of hypertonic saline (5.8%) was injected into the muscle belly of the right FDI after the skin was cleaned with alcohol. Injections were performed using a .5-mL syringe with a disposable needle (31G).

Statistical Analysis

Pressure pain thresholds were compared using a 2-way repeated measures analysis of variance with the factors time (baseline, 30-minute follow-up) and side (affected, unaffected) for the FDI and tibialis anterior

muscles, respectively. Cohen's d effect sizes were calculated and are presented in the text.

Corticomotor excitability for each hemisphere and short and long latency IHI were assessed for normality and sphericity. Corticomotor excitability was compared between time points (baseline, immediately after pain, 30-minute follow-up) using a 1-way repeated measures analysis of variance. To account for any influence of sex on IHI, short and long latency IHI were compared between time points (baseline, immediately after pain, 30-minute follow-up) and sex (male, female) using a 2-way repeated measures analysis of variance. Pearson's correlation coefficients were calculated to assess the relationship between the change in short and long latency IHI over time (baseline to 30 minutes follow-up) and peak pain, pain duration, and the change in pressure pain thresholds over time from affected and unaffected FDI. Where appropriate, post hoc analyses were performed using Holm-Sidak tests corrected for multiple comparisons. Statistical significance was set at a P value of <.05. Data in text are presented as mean ± standard deviation.

Results

Pain Characteristics

Injection of hypertonic saline produced a peak pain intensity of 7.9 ± 1.8 points on the numerical rating scale and an average pain intensity over time of 4.8 ± 1.3 points. The average pain duration was 9.9 ± 3.4 minutes. The most frequent words used to describe the pain were sharp (90%), aching (85%), and throbbing (80%). The majority of participants reported pain localized to the site of the injection on the dorsal surface of the hand. Six participants reported pain that radiated toward the palmar surface of the hand, 5 participants reported pain that extended into the proximal forearm, and 1 participant reported pain extending into the upper arm.

Neurophysiological Measures

Group data (mean ± standard deviation) for pressure pain sensitivity, corticomotor excitability, short and long latency IHI and stimulator output at each time point are presented in Table 1.

Pressure Pain Sensitivity

Relative to baseline, pressure pain thresholds were decreased, ($F_{1,19}$ = 22.56, P < .001), in both the affected (P < .001; Cohen's d = .57; Fig 2A) and unaffected (P = .005; Cohen's d = .46; Fig 2B) FDI muscles 30 minutes after the induction of acute muscle pain. There were no differences between sides, ($F_{1,19}$ = .31, P = .86). Pressure pain thresholds recorded from the bilateral tibialis anterior muscles were unchanged over time, ($F_{1,19}$ = .002, P = .96).

Corticomotor Excitability

The induction of pain in the right FDI led to suppression of motor evoked potentials from the affected M1, ($F_{2,38}$ = 6.60, P = .003). Corticomotor excitability was reduced immediately after the resolution of pain (P = .007) and at 30-minutes follow-up (P = .01; Fig 3A) relative to baseline. Motor evoked potentials from the unaffected M1 were unchanged over time, ($F_{2,38}$ = .25, P = .77; Fig 3B).

IHI

Unconditioned motor evoked potential test amplitudes were stable over time, ($F_{2,38}$ = .58, P = .56; Fig 4A). The induction of acute muscle pain affected the degree of IHI from the affected to the unaffected M1 at both short, ($F_{2,36}$ = 9.07, P < .001; Fig 4B) and long latencies, ($F_{2,36}$ = 12.83, P < .001; Fig 4C). Relative to baseline, short and long latency IHI were reduced immediately after the resolution of pain (short: t = 3.72, P = .002; long: t = 4.48, P < .001) and remained reduced at 30-

Table 1. Group Data for Corticomotor Excitability, IHI and Pressure Pain Threshold Measures at Baseline, Immediately After Pain and at 30 Minutes Follow-Up

	Baseline	*Immediately After Pain*	*30 Minutes Follow-Up*
Corticomotor excitability (mV)			
Affected M1	.93 ± .83	.68 ± .86*	.66 ± .64*
Unaffected M1	.97 ± .81	1.04 ± .72	1.10 ± .72
IHI for affected to unaffected M1 (mV)			
Unconditioned test response	1.30 ± .37	1.23 ± .23	1.24 ± .35
IHI 10 ms (proportion of test)	.69 ± .22	1.07 ± .38*	1.05 ± .41*
IHI 40 ms (proportion of test)	.61 ± .22	1.03 ± .49*	1.06 ± .35*
Stimulator output (%)	56 ± 11	56 ± 9	55 ± 12
Pressure pain thresholds (kPa)			
Affected FDI	435 ± 190	—	329 ± 185*
Unaffected FDI	420 ± 181	—	339 ± 162*
Right tibialis anterior	878 ± 468	—	857 ± 522
Left tibialis anterior	897 ± 656	—	835 ± 553

Values are mean ± standard deviation (N = 20).
*P < .05 from baseline.

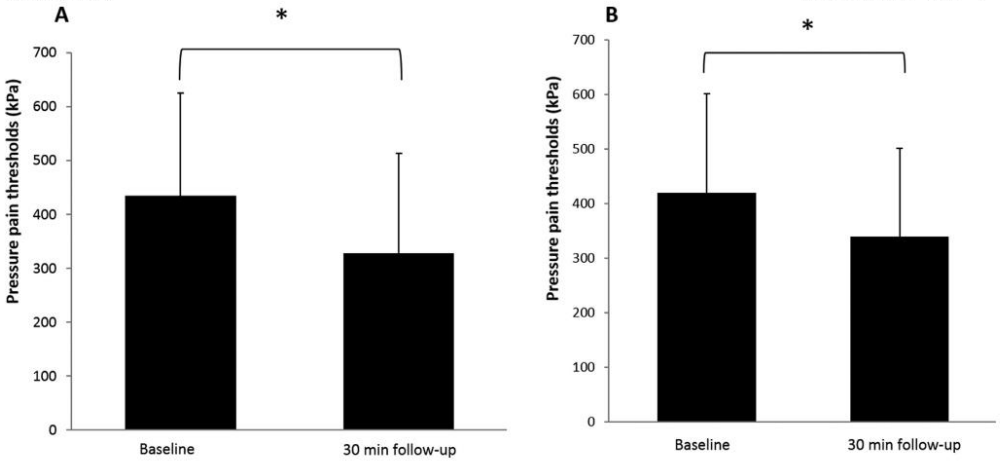

Figure 2. Group data (mean ± standard deviation) for pressure pain thresholds recorded from the affected (**A**) and unaffected FDI (**B**) at each time point (baseline and 30 min follow-up). The asterisk denotes a significant ($P < .05$) difference from baseline. Pressure pain thresholds were reduced at follow-up in both FDI muscles.

minute follow-up (short: t = 3.65, $P = .002$; long: t = 4.28, $P < .001$). Sex did not influence the IHI response, (short: $F_{1,36} = 3.5$, $P = .078$; long: $F_{1,36} = .42$, $P = .52$).

A greater reduction in short (r = -.51; $P = .02$) and long latency (r = -.60; $P = .005$) IHI at the 30-minute follow-up was associated with a greater reduction in pressure pain thresholds in the affected FDI. There was no relationship between the change in IHI over time at either short (r = -.19; $P = .94$) or long (r = .06; $P = .80$) latency and pressure pain thresholds in the unaffected FDI. There was no relationship between short and long latency IHI and peak pain or pain duration.

Discussion

This study is the first to investigate IHI in response to acute onset muscle pain. The key finding was a decrease in IHI from the affected to the unaffected M1 at both short and long latencies that was present immediately after pain resolved and persisted at 30 minutes follow-up. A unique observation was an increase in sensitivity to mechanical stimuli in the unaffected hand, despite the absence of pain on that side. These findings suggest a release of IHI over the unaffected M1 that occurs rapidly in response to pain and could relate to the development of sensorimotor symptoms in the unaffected hand.

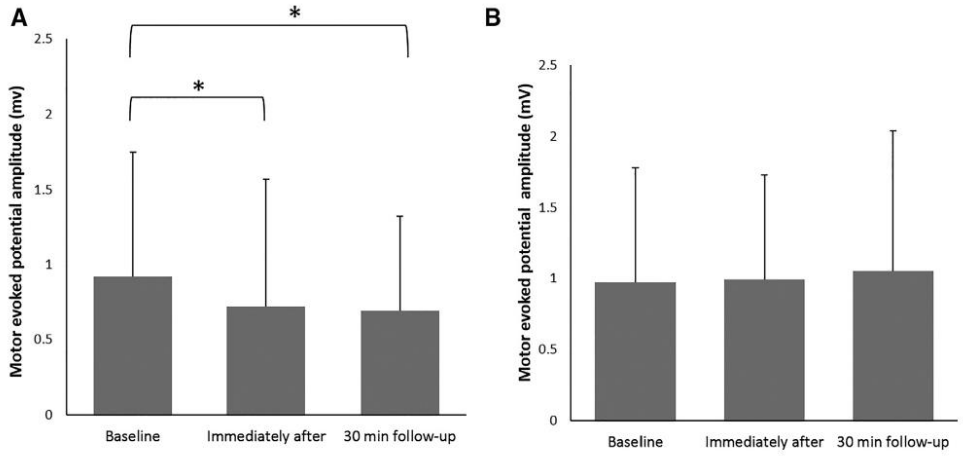

Figure 3. Group data (mean ± standard deviation) for corticomotor excitability recorded from the affected (**A**) and unaffected (**B**) M1, before and after the resolution of pain. Motor evoked potential amplitude was reduced at both time-points after the resolution of pain in the affected M1 ($P < .05$), but was unchanged over time in the unaffected M1.

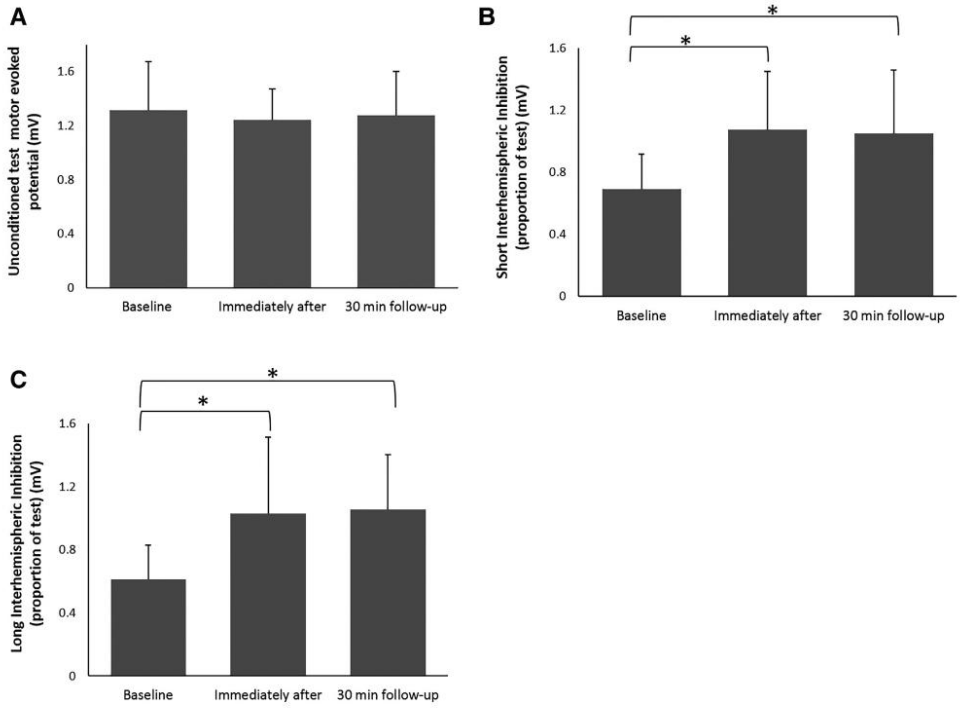

Figure 4. Group data (mean ± standard deviation) for the unconditioned (test) response (**A**), short IHI (**B**) and long IHI (**C**) obtained at each time point. There was no difference in the amplitude of the unconditioned test motor evoked potential over time. Short and long latency IHI were reduced at both time points after the resolution of pain. Asterisks denote a significant ($P < .05$) difference from baseline.

A large body of evidence has shown decreased corticomotor excitability in the hemisphere contralateral to the painful side in response to acute muscle pain, an effect that persists in the immediate postpain period and is not influenced by resumption of normal motor activity.[8,56] The present data support these findings. The effect of pain on the contralateral M1 has been further characterized by studies demonstrating increased intracortical inhibition, decreased intracortical facilitation, and a decreased integration of sensory information with motor output in response to acute pain.[9,55] Taken together, these data have been interpreted as evidence of a protective strategy that serves to limit the movement of the painful part and decrease the risk of further tissue damage.[28] However, despite evidence of changes occurring in the contralateral M1, interaction between the two M1 hand areas in acute pain has not been investigated.

IHI can be assessed in humans using paired pulse transcranial magnetic stimulation with a stimulating coil positioned over each M1, and pulses delivered at interstimulus intervals in the range of 6 to 50 ms.[14,17,44] The application of a conditioning stimulus in one hemisphere activates excitatory transcallosal projections that synapse with inhibitory interneuronal networks in the opposite hemisphere, altering the excitability of pyramidal output neurons.[14,17,25] Indeed, primate studies demonstrate the existence of transcallosal projections between the two M1 hand areas[31] and further animal and human work has shown these projections convey information between the two motor cortices.[1,25] Evidence from patient studies demonstrates that IHI is mediated via these transcallosal pathways[7,39,40] and both short and long latency IHI are thought to be dependent on gamma-amino-butyric acid type B-mediated neurotransmission.[13,30,34] These data, in conjunction with previous studies demonstrating no inhibition of the H-reflex during IHI recording, suggest IHI is of cortical origin.[17,23,26]

Only one previous study has examined IHI in musculoskeletal pain. Using a clinically relevant model of progressively developing sustained muscle pain, that study showed a decrease in IHI from the affected to the unaffected M1 4 days after the onset of pain that was associated with an increase in mechanical sensitivity in the unaffected arm.[54] The present data extend these findings and show that IHI is decreased in response to rapid onset, short-lasting pain of high intensity (peak pain intensity of 7.9 ± 1.8 points). Although we were unable to measure IHI during pain owing to its short-lasting nature, a decrease in IHI was observed in the immediate postpain period and this effect persisted for ≥30 minutes after pain resolution. Consistent with data

from the sustained pain model, and patients with chronic lateral elbow pain, mechanical sensitivity was increased in the unaffected hand.[5,12,54] However, in contrast with previous studies, we did not find a linear correlation between the degree of IHI and mechanical sensitivity in the unaffected hand. This discrepancy could be explained by the different pain durations (minutes vs days), pain intensities or differences in the presence of pain at the time of testing across studies. For instance, in the sustained pain model, IHI was tested when participants were experiencing pain, whereas in the current study, IHI was tested only once pain had resolved. Alternatively, a nonlinear relationship may exist between these parameters in the acute stage of pain. Longitudinal studies that encompass both the early (pain lasting minutes to hours) and later (pain lasting days to weeks) acute stages of pain are required to further elucidate the temporal profile of altered IHI and how this relates to the development of sensorimotor dysfunction in the unaffected hand.

The precise mechanism through which decreased IHI could influence sensorimotor function on the unaffected side is unknown. In the current study, corticomotor excitability in the ipsilateral M1 was unaltered. However, because corticomotor excitability and IHI are known to reflect different neuronal populations this finding is unsurprising.[7,35,58] One possibility is that a release of inhibition over the unaffected M1 led to reduced inhibition of thalamic neurons that, in turn, influenced mechanical sensitivity on the unaffected side. Evidence for this hypothesis is drawn from studies demonstrating a decrease in pain with M1 stimulation. This decrease is thought to be mediated by corticothalamic projections that suppress sensory information being relayed in the spinothalamic tract.[36,37] Further, imaging studies suggest effects of M1 stimulation on other pain-processing regions including the anterior cingulate cortex, orbitofrontal cortex, insula, secondary sensory cortex, and periaqueductal gray matter.[21,22,48] A release of IHI over the unaffected M1 could, therefore, decrease the downstream inhibition of thalamic neurons, the periaqueductal gray, and/or other pain-processing regions, increasing sensitivity to pressure stimuli. Alternatively, IHI is known to play a key role in interlimb transfer of motor skills and "cross-education" of the uninvolved limb after strength training. For example, repeated unimanual practice of a motor task results in transfer of implicit knowledge, as well as speed and accuracy, to the untrained hand and the degree of transfer is associated with the magnitude of the reduction in IHI from the "active" to the "inactive" M1.[10,47] Similarly, studies have shown interhemispheric transfer of sensory stimuli such that proprioceptive input to a hand muscle decreases corticomotor excitability and increases IHI from the affected to unaffected hemisphere of the contralateral homologous muscle.[59] A salient stimulus such as pain could similarly result in information transfer to the unaffected M1. Interestingly, the direction of change in IHI differed in the presence of non-noxious proprioceptive stimuli (increased IHI) compared with the pain stimulus (decreased IHI) provided here. This discrepancy likely reflects the salience and processing of non-noxious versus noxious stimuli in the cortex. However, further research is needed to compare the effects of different types of sensory, motor, and pain stimuli on IHI.

Although altered IHI in the acute stage of pain is likely to be a protective strategy that resolves with time, a disturbance in the inhibitory balance between the affected and the unaffected hemispheres that persists when pain fails to resolve could contribute to the development of bilateral symptoms and provide a target for therapeutic modulation. Indeed, a number of studies have sought to target the imbalance in IHI in stroke patients to improve functional recovery.[19,29,60,61] For example, bilateral application of transcranial direct current stimulation has been used to downregulate activity in the unaffected M1 and upregulate activity in the affected M1, and it has been shown to improve function in the paretic limb.[41] Although studies have applied noninvasive brain stimulation techniques over a single hemisphere in pain conditions (eg,[3,16,20,45]), no study has attempted to target the imbalance in IHI through bilateral hemispheric stimulation.

Several limitations should be considered. Based on previous studies in pain, IHI was assessed only in 1 direction, from the affected to the unaffected hemisphere, and it was not possible to assess IHI during pain owing to the short-lasting nature of the pain model. Future studies should assess IHI in both directions, consider longer lasting pain models such as infusion of hypertonic saline, and use a longer follow-up in the postpain period to further elucidate the temporal profile of altered IHI in response to acute pain. An isotonic saline control condition was not used in this study. Although our findings argue against temporal effects on our measures (pressure pain thresholds and corticomotor excitability were stable over time in the tibialis muscles and unaffected M1, respectively), future work should seek to determine the reliability of the IHI response within an individual over time in the absence of pain. Outcome assessors in this preliminary study were not blinded. To minimize the risk of bias, future studies in this area should use stringent blinding procedures. Finally, future studies should include a more comprehensive assessment of sensorimotor function to determine which aspects may be related to altered IHI in the presence of pain and investigate IHI in chronic pain conditions.

Conclusions

This study is the first to demonstrate decreased IHI from the affected to the unaffected hemisphere after acute muscle pain. This information may have relevance for the investigation of bilateral symptoms in unilateral pain conditions and potentially, for the development of therapeutic protocols that aim to restore the inhibitory imbalance in musculoskeletal pain.

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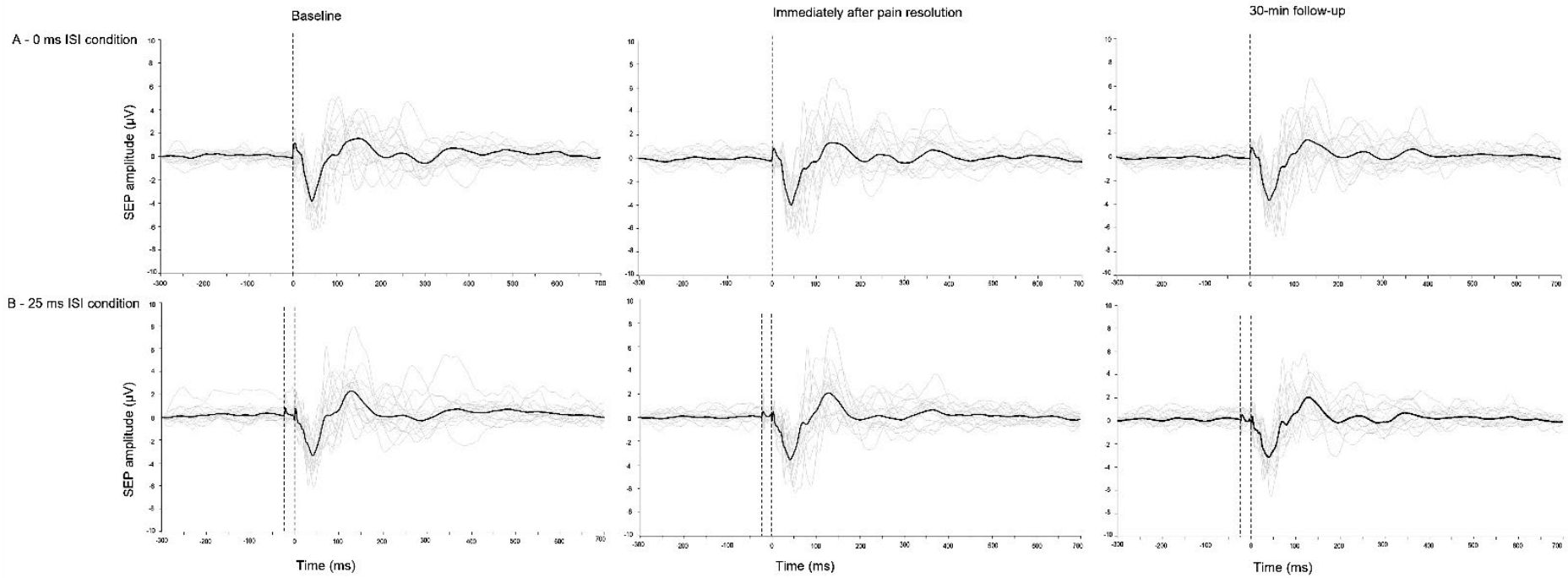
APPENDIX B

Supplementary Figure 1 for Study 2 (Chapter 3)



Supplementary Figure 1: Individual SEP raw traces with superimposed grand averages for the 0 ms ISI (top row) and 25 ms ISI (bottom row) stimulation conditions at i) baseline (left panels), ii) immediately after the resolution of pain (middle panels) and iii) 30-min after pain resolution (right panels). Traces have been offset to 0 μV from -300 ms to allow comparisons across time points. The dotted lines represent the time of stimulus onset.