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The role of the brain in the transition from acute to chronic musculoskeletal pain: an investigation of neuroplastic mechanisms and novel treatments

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A thesis submitted for the degree of Doctor of Philosophy at

Western Sydney University

School of Science and Health

August 2018

Acknowledgements

I would like to start by thanking my primary supervisor Dr Siobhan Schabrun and co-supervisors A/Prof James McAuley and Dr Matthew Liston for providing me with the opportunity to join their research teams at Western Sydney University and Neuroscience Research Australia (NeuRA).

Dr Schabrun, thank you for giving me the opportunity to pursue my research interests four years ago. Your expertise in neuroscience and guidance throughout my candidature have been invaluable. Your passion for research and success have inspired me to pursue a research career. Dr Liston, thank you for your advice on a wide range of topics from research ideas, statistics and academic writing to coffee, tea and food. Your encouragement has helped me overcome numerous challenges in the last four years. A/Prof McAuley, thank you for all the enlightening and thought-provoking conversations. Your help with my first publication and the support for thesis writing and personal issues are greatly appreciated.

I wish to acknowledge Western Sydney University and NeuRA for supporting my research, the National Health & Medical Research Council for funding my candidature, the participants who sacrificed their time, and the co-authors of my publications and the journal reviewers and editors, whose feedback and comments have assured that my papers were of the highest possible standard.

To Valentina and Luke, thank you for all the help and hard work in UPWARD trial, and putting up with my occasional frustrations. Thapa, Simon, Rocco, Ghufran, Maxine, Bernie, Dan and Jane at Western Sydney University, I want to thank you for all your help and advice during my candidature. The staff of Physiotherapy and School of Science and Health, I would like to thank you for your encouragement and support during my time at Western Sydney University. I also want to thank Matt, Aidan, Edel, Pauline and Anika at NeuRA for giving me new insights into conducting a clinical trial. You have made my time at NeuRA enjoyable.

I would like to express my gratitude to my colleagues at Macarthur Physiotherapy for their support, especially Gaven Williams, who is not only an outstanding Musculoskeletal and Sports Physiotherapist but also a great mentor in my clinical career.

I want to thank my friends in the Sydney Chamber Choir and Taipei Male Choir for giving me the opportunities to continue enjoying choral singing in the last four years. The two CD recordings, and more than a dozen concerts and numerous rehearsals have indeed enriched my life through the beauty of music and the sense of achievement. Miguel, thank you for encouraging me to pursue PhD study several years ago and proof reading the Introduction of this thesis. To Seb, Richard, Lindy and Tom, I am deeply grateful for your advice, help, support and amazing friendship when I was in trouble. To Stephen, I want to thank you for your emotional support in the last few months.

To my family in Taiwan, I would like to express my great gratitude for giving me enduring support and encouragement, despite my long absence from your lives. I hope my completion of this thesis will make you proud. Finally, I want to thank my family in Australia, Ian. I could not have completed this thesis without your unconditional and loving support and care.

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

Wei-Ju Chang

Publications, abstracts and presentations arising from this thesis

Peer-reviewed journal articles

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.* 19:341-359, 2018

Chang WJ, Bennell KL, Hodges PW, Hinman RS, Young CL, Buscemi V, Liston MB, Schabrun SM. Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: A pilot randomised controlled trial. *PLoS One.* 12:e0180328, 2017

Chang WJ, O'Connell NE, Burns E, Chipchase LS, Liston MB, Schabrun SM. Organisation and function of the primary motor cortex in chronic pain: protocol for a systematic review and meta-analysis. *BMJ open.* 5:e008540, 2015

Chang WJ, Bennell KL, Hodges PW, Hinman RS, Liston MB, Schabrun SM. Combined exercise and transcranial direct current stimulation intervention for knee osteoarthritis: protocol for a pilot randomised controlled trial. *BMJ open.* 5:e008482, 2015

Conference presentations

Chang WJ, Buscemi V, Liston MB, Hodges PW, Schabrun SM (2018). Reduced primary motor and sensory cortex excitability in acute low back pain. Australian Pain Society 38th and New Zealand Pain Society Conjoint Annual Scientific Meeting. Sydney, Australia April 9-11th.

Chang WJ, Bennell KL, Hodges PW, Hinman RS, Liston MB, Schabrun SM (2017). Addition of transcranial direct current stimulation to quadriceps strengthening

exercise in knee osteoarthritis: a pilot randomised controlled trial. Australia Physiotherapy Association Conference MOMENTUM 2017. Sydney, Australia October 19-21th.

Chang WJ, O'Connell NE, Beckenkamp PR, Alhassani G, Liston MB, Schabrun SM (2017). Organisation and function of the primary motor cortex in chronic pain: a systematic review and meta-analysis. 10th Congress of the European Pain Federation EFIC. Copenhagen, Denmark Sept 6-9th.

Chang WJ, Bennell KL, Hodges PW, Hinman RS, Liston MB, Schabrun SM (2016). A combined exercise and transcranial direct current stimulation intervention for knee osteoarthritis: a pilot randomised controlled trial. International Association for the Study of Pain (IASP) World Congress on Pain, Yokohama, Japan Sept 26-30th.

Other related publications

Peer-reviewed journal articles

Ouellette AL, Liston MB, **Chang WJ**, Walton DM, Wand BM, Schabrun SM. Safety and feasibility of transcranial direct current stimulation (tDCS) combined with sensorimotor retraining in chronic low back pain: a protocol for a pilot randomised controlled trial. *BMJ open.* 7, 2017

Buscemi V, **Chang WJ**, Liston MB, McAuley JH, Schabrun S. The role of psychosocial stress in the development of chronic musculoskeletal pain disorders: protocol for a systematic review and meta-analysis. *Systematic reviews.* 6:224, 2017

Authors note

This thesis comprises four studies. Study 1 and 4 (Chapter 2 and 5) have been published. The content of these two publications has been preserved. Minimal editorial changes have been made to maintain consistent formatting throughout this document. A copy of these two publications in original format is provided in the Appendices (Appendix A and C). Study 2 and 3 (Chapter 3 and 4) have been submitted to the Journal of Pain and Pain Medicine respectively and are under review. References are presented at the end of the thesis to minimise repetition.

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Abbreviations

ACC	anterior cingulate cortex
ACR	American College of Rheumatology
aMT	active motor threshold
ANCOVA	analyses of covariance
ANOVA	analyses of variance
AT+EX	active transcranial direct current stimulation + exercise
BOLD	blood-oxygen-level-dependent
CI	confidence interval
CoG	centre of gravity
CPM	conditioned pain modulation
CPS	cortical silent period
CR	coefficient of repeatability
Cr	creatine
CRPS	complex regional pain syndrome
CS	conditioned stimulation
DASS 21	Depression Anxiety Stress Scale-21
DKI	diffusion kurtosis imaging
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EEG	electroencephalography
EMG	electromyography

fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GM	grey matter
HPTs	heat pain thresholds
ICC	intraclass coefficient
ICF	intracortical facilitation
LBP	low back pain
LICI	long-interval intracortical inhibition
M1	primary motor cortex
MEG	magnetoencephalography
MEP	motor evoked potential
MeSH	medical subject headings
ml	myo-inositol
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NA	not available
NFR	nociceptive flexor withdraw reflex
NRS	numerical rating scale
OA	osteoarthritis
PET	positron emission tomography
PCS	pain catastrophising scale
PPTs	pressure pain thresholds

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QST	quantitative sensory testing
rCBF	regional cerebral blood flow
RCT	randomised controlled trial
RMDQ	Roland Morris Disability Questionnaire
rMT	resting motor threshold
S1	primary sensory cortex
S2	secondary sensory cortex
SEM	standard error of the mean
SEP	sensory evoked potential
SICF	short-interval intracortical facilitation
SICI	short-interval intracortical inhibition
ST+EX	sham transcranial direct current stimulation + exercise
SVM	support vector machines
tDCS	transcranial direct current stimulation
TMD	temporomandibular disorder
TMS	transcranial magnetic stimulation
TS	test stimulation
VAS	visual analogue scale
VBM	voxel based morphometry
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Abstract

Musculoskeletal pain is a leading health problem globally. Its prevalence and associated socioeconomic costs have increased exponentially and this trend is expected to continue in the coming decades. While all stages of musculoskeletal pain contribute to the burden of disease, the costs attributed to chronic pain (pain lasting > 3 months) are most significant. Effective treatment would substantially reduce the impact of chronic musculoskeletal pain at both the individual and societal level. Yet, the effects of current treatments are, at best, moderate for pain and function. One explanation for the limited success of current treatments is an inadequate understanding of the neurophysiological mechanisms that underpin musculoskeletal pain. Addressing the evidence gap surrounding our mechanistic understanding of musculoskeletal pain is essential to guide the development of effective treatments.

Maladaptive neuroplasticity, manifesting as altered sensorimotor cortex organisation and impaired central pain processing, is the prevailing theory used to explain the development and maintenance of chronic musculoskeletal pain. Cross-sectional evidence derived from individual studies suggests maladaptive neuroplasticity in the primary motor cortex (M1) is present in chronic musculoskeletal pain and is associated with symptoms of pain and movement dysfunction. Yet, a systematic evaluation of the evidence for altered M1 plasticity in chronic pain is absent. Further, no study has characterised neuroplasticity in the acute stage of clinical musculoskeletal pain. This information is critical to better understand the time course of neuroplasticity in musculoskeletal pain. Finally, few

treatments exist that specifically target altered neuroplasticity in chronic musculoskeletal pain conditions. Thus, the overarching aim of this thesis was to investigate and target specific mechanisms of neuroplasticity (sensorimotor cortex organisation and central pain processing) in musculoskeletal pain.

This aim was achieved through four studies. First, a systematic review was conducted to examine the evidence for M1 functional, structural and organisational changes in a clearly defined chronic pain population from a comprehensive range of neurophysiological measures (Study 1). Database searches were performed, and the methodological quality of included studies was assessed. Meta-analyses, including pre-planned subgroup analyses based on pain condition were performed where possible. Sixty-seven studies (2290 participants) were included. Meta-analyses provided evidence of increased M1 long-interval intra-cortical inhibition in chronic pain. However, for most neurophysiological measures, evidence for altered M1 plasticity in chronic pain was inconclusive. In the absence of sufficient data to definitively conclude whether maladaptive M1 plasticity is present in the chronic stage of pain, Study 2 and 3 sought to further explore this question through the evaluation of neuroplasticity in the acute stage of clinical musculoskeletal pain.

Study 2 was the first to examine sensory, cingulate and motor cortex excitability, and M1 organisation, in acute clinical low back pain (LBP). Sensory and cingulate cortex excitability were assessed using sensory evoked potentials (SEPs), and M1 excitability and organisation using transcranial magnetic stimulation. Thirty-six individuals with acute, non-specific, clinical LBP and 36 age- and sex-matched, pain-free controls

participated. The results demonstrated that overall processing of non-noxious sensory inputs was lower (smaller area of the N_{80}-N_{150}-P_{260} SEP complex) in individuals with acute LBP than pain-free controls ($F_{1,70}$=45.28, p<0.01). Examination of specific SEP components revealed lower excitability of the secondary sensory (S2) and anterior cingulate (ACC) cortices (smaller area of the N_{150} and P_{260} SEP components respectively) in acute LBP, although inter-individual variability was high. Motor cortical map volume was lower in acute LBP ($F_{1,70}$=5.61, p=0.02), although measures of the map centre of gravity and number of discrete peaks were not different, suggesting that corticomotor excitability, but not organisation, is different between individuals with acute LBP and pain-free controls. At the group level, these data suggest that acute clinical LBP is characterised by lower sensorimotor and ACC excitability. However, post hoc analysis revealed two distinct patterns of S2 and ACC excitability (high vs. low) amongst individuals with acute LBP. This unique finding suggests that the cortical strategy adopted in response to acute pain might differ between individuals.

Study 3 compared central pain processing between 11 individuals experiencing their first episode of acute LBP, 11 individuals experiencing recurrent acute LBP, and 11 age- and sex-matched pain-free controls. Central sensitisation was assessed using pressure and heat pain thresholds (PPTs and HPTs) and the nociceptive flexor withdraw reflex (NFR), and descending inhibitory pain control was assessed using the conditioned pain modulation (CPM) paradigm. It was hypothesised that (1) individuals experiencing acute LBP, with or without a previous history of LBP, would have altered central pain processing, and (2) individuals with recurrent acute LBP

would demonstrate greater changes in central pain processing than those experiencing their first episode of acute LBP. The results revealed a shorter NFR latency in individuals experiencing their first episode of acute LBP when compared with pain-free controls (p=0.01) and descending inhibitory pain control was less efficient in both acute LBP groups when compared with pain-free controls. HPTs and PPTs did not differ between people with and without acute LBP. There were no differences between the two LBP groups for any outcome measure. These data provide evidence that descending inhibitory pain control is altered in acute clinical LBP. However, individuals with recurrent acute LBP did not demonstrate a greater degree of impairment than those experiencing their first episode of acute LBP, suggesting that LBP recurrence may not be related to altered central pain processing in the acute stage of pain.

To provide a clinical context for the results from Studies 1-3, Study 4 aimed to investigate the effect of a novel treatment combining transcranial direct current stimulation (tDCS) and strengthening exercise to target neuroplasticity (specifically altered central pain processing) in chronic pain. This was achieved through a pilot randomised, assessor- and participant-blind, sham-controlled trial in knee osteoarthritis. Participants were randomised to receive active tDCS and exercise or sham tDCS and exercise twice weekly for 8 weeks whilst completing home exercises twice per week. Outcome measures including pain, function and pain mechanisms were assessed before and after treatment. Thirty individuals entered randomisation and 25 (84%) completed the trial. The key finding from this pilot trial was that the addition of tDCS to exercise is safe, feasible and well tolerated. Analysis of secondary

outcomes revealed a trend towards greater improvements in pain, function and central pain processing in individuals who received active tDCS and exercise when compared with those who received sham tDCS and exercise. These data suggest that adding tDCS to strengthening exercise may improve pain, function and pain mechanisms beyond that which can be achieved with exercise alone in people with knee OA, providing the foundation for a fully powered clinical trial in future.

This thesis provides original and novel insight into our understanding of neuroplasticity in musculoskeletal pain and provides a foundation for the development and testing of novel interventions to reduce pain and disability. Specifically, this thesis demonstrates that: (1) evidence for M1 structural, organisational and functional changes in chronic pain conditions is inconsistent, (2) neuroplasticity in acute LBP is characterised by lower sensorimotor and cingulate cortex excitability and impaired descending inhibitory pain control when compared with pain-free individuals, although inter-individual variability is high and (3) adding tDCS to strengthening exercise may improve pain, function and pain mechanisms in knee osteoarthritis beyond that of exercise applied alone. Notably, subgroups distinguished by high or low S2 and ACC excitability may represent individual adaptation of different cortical strategies that relate to the processing of non-noxious input in acute clinical LBP and could be relevant for pain outcome. However, subgroups determined by a prior history of LBP do not differ in central pain processing in acute LBP. Future studies with larger sample sizes are needed to determine whether altered M1 plasticity is present in chronic musculoskeletal pain and to confirm findings of decreased sensorimotor cortex excitability and altered

central pain processing in acute pain. Finally, a fully powered randomised controlled trial is necessary to determine the effectiveness of adding tDCS to strengthening exercise for knee osteoarthritis.

Chapter 1

General Introduction

This chapter provides an overview of the literature on musculoskeletal pain, including the neurophysiological mechanisms hypothesised to underpin acute and chronic pain and the effectiveness of current treatments. As this thesis has a particular focus on sensorimotor cortical changes and altered central pain processing in musculoskeletal pain, literature pertaining to these mechanisms will be reviewed in detail. Subsequently, novel treatments with the potential to target these mechanisms will be identified and discussed. A critical review of literature relevant to each specific study is provided in the Introduction and Discussion sections of Chapters 2 to 5.

Chapter 1. General Introduction

Musculoskeletal pain is a highly prevalent and costly health problem with few effective treatments (Costa et al., 2018; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). A limited understanding of the neurophysiological mechanisms involved in musculoskeletal pain, particularly when pain persists beyond normal tissue healing times, is a key contributor to the lack of effective treatments. One important neurophysiological mechanism is the changes in brain function and structure. Maladaptive neuroplasticity that manifests as altered sensorimotor cortical organisation and upregulated central pain processing, is suggested to underpin the development of chronic (pain lasting more than 3 months) musculoskeletal pain. Although some evidence exists to support this hypothesis in cross-sectional studies of chronic pain, when these neurophysiological changes occur in the transition to chronicity is unclear. Relevant research in the acute stage of pain is scarce. This information is critical in order to comprehend the time course of these changes in musculoskeletal pain. In addition, few therapies exist that are specifically designed to target these neurophysiological mechanisms in musculoskeletal pain.

The overarching aim of this thesis was to investigate and target specific neurophysiological mechanisms (sensorimotor cortex plasticity and central pain processing) in musculoskeletal pain. This was achieved first, through a systematic review examining the evidence for functional, structural and organisational changes in the primary motor cortex (M1) in chronic musculoskeletal pain (Study 1), followed by investigation of sensorimotor and cingulate cortex excitability (Study 2) and

central pain processing (Study 3) in acute low back pain (LBP). Finally, Study 4 used a novel therapeutic approach (non-invasive brain stimulation in conjunction with exercise) to target altered central pain processing in knee osteoarthritis. The purpose of this introductory chapter is to provide a background for these studies.

1.1 Musculoskeletal pain is a major health problem

Musculoskeletal pain originates from muscles, tendons, ligaments, joints and the surrounding tissues and is defined as *chronic* when symptoms last for more than three months (van Tulder et al., 2003). Importantly, pain is a symptom, not a disease (Hancock et al., 2011). When pain is short-lasting ('acute' pain), it is considered a normal biological response to noxious stimuli that serves as an adaptive and protective strategy to promote healing after injury. However, when pain continues beyond the normal timeframe for tissue healing, it is considered maladaptive and is thought to be driven by pathological changes in the central nervous system.

Musculoskeletal pain is a pervasive problem worldwide, affecting 1.3 billion people in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Low back pain (LBP) and osteoarthritis (OA) are the leading musculoskeletal causes of disability, both ranking amongst the highest causes of global disease burden for years lived with disability (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). The prevalence of LBP has increased by more than 50% since 1990 and is predicted to continue to increase in the future (Vos et al., 2015). Similarly, the prevalence of OA has increased by 30% in the last decade, largely as the result of the aging global population (GBD 2016 Disease and Injury Incidence and Prevalence

Collaborators 2017). Although OA is a major cause of disability in older populations, other musculoskeletal pain conditions affect all age groups. For example, the prevalence of LBP increases with age, reaching its peak between 40-69 years of age (Hoy et al., 2012; Rosenfeld et al., 2018). Alarmingly, more than one third of children and adolescents experienced LBP and these individuals have a greater risk of developing chronic LBP in adulthood if symptoms persist longer than three months (Calvo-Munoz et al., 2013).

Musculoskeletal pain has become a major health and socioeconomic issue in developing and developed countries alike (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). In Australia, 30% of the population (6.9 million people) were affected by musculoskeletal pain in 2014-15, with back pain (3.7 million people) and osteoarthritis (2.1 million people) the leading contributors to the total burden of disease in this year (AIHW 2017). Following a global trend, the number of cases in Australia is expected to rise, with an estimation of 30.2% of the population (8.7 million people) affected by 2032 (Arthritis and Osteoporosis Victoria 2013). While all stages of musculoskeletal pain contribute to the burden of disease, the costs attributed to chronic pain are most significant. In 2012, the total cost of chronic musculoskeletal pain conditions, including direct health care expenditure and indirect costs associated with a loss of productivity, equalled $55.1 billion Australian Dollars (Arthritis and Osteoporosis Victoria 2013). These costs are expected to surge as the prevalence of these conditions increases (Arthritis and Osteoporosis Victoria 2013).

Although musculoskeletal pain is a major health issue, there are few effective treatments. For example, exercise therapy has been recommended by clinical guidelines for treating chronic LBP and knee OA, yet, the effect sizes are at best, moderate (Fransen et al., 2015; Maher et al., 2017; Megale et al., 2018; Silva Guerrero et al., 2018). The lack of effective treatments has a substantial impact on the quality of life in individuals with chronic musculoskeletal pain. For example, amongst people with chronic back pain, 17 % report 'severe' or 'very severe' pain, 7% report very high psychological distress, and for those with a comorbid disability, a substantial proportion report restrictions in mobility, self-care, employment and social participation (AIHW 2016).

One explanation for the limited success of current treatments is an inadequate understanding of the neurophysiological mechanisms that underpin musculoskeletal pain. Pain is widely acknowledged as biopsychosocial in nature. Therefore, the physiological, psychological and social elements of pain and their interactions should be considered in clinical practice and research (Gatchel and Okifuji 2006; O'Sullivan 2012; Waddell 1992). However, the contribution of physiological mechanisms to musculoskeletal pain has been overlooked in clinical practice and research (Gifford and Butler 1997; Hancock et al., 2011). Indeed, addressing the evidence gap surrounding our mechanistic understanding of musculoskeletal pain is a recommended research priority (Buchbinder et al., 2018).

1.2 Evidence for the role of the primary motor cortex in musculoskeletal pain

Maladaptive neuroplasticity in the primary motor cortex is hypothesised to contribute to the development and maintenance of chronic musculoskeletal pain. The following sections review the available evidence for this mechanism.

1.2.1 Movement dysfunction in musculoskeletal pain

Movement dysfunction is a key feature of musculoskeletal pain. Although it is widely accepted that people move differently when in pain, the underlying neurophysiological mechanisms are poorly understood. Traditional theories suggest that motor function changes homogeneously in response to pain (increased vs. decreased muscle activity) (Lund et al., 1991; Roland 1986). More recently however, these theories have been challenged by conflicting experimental and clinical data, leading to the contemporary view that motor adaptation in pain is dynamic, complex and inconsistent between individuals (Hodges and Tucker 2011; Peck et al., 2008). Motor adaptation in acute pain involves redistributing activity within the painful muscle and amongst the synergistic muscles, changing load distribution, and increasing stiffness (Hodges and Tucker 2011). This redistribution of muscle activity results in altered mechanical behaviour. For example, changes in active motor units within the quadriceps muscle during experimentally-induced acute knee pain alter the direction of knee extension force (Tucker and Hodges 2010). Evidence from acute experimental pain models suggests that individuals adopt various motor strategies according to the anatomical and functional complexity of the body segment involved (Bank et al., 2013; Hodges et al., 2013; Palsson et al., 2015; Peck et al., 2008; van den Hoorn et al., 2015). For example, the variability of movement increases while performing a complex, multi-joint task but reduces during a simple, single-joint task

(Bergin et al., 2014; van den Hoorn et al., 2015). Taken together, these data suggest that motor adaption in response to acute pain is an 'adaptive' strategy that aims to prevent symptom aggravation and further injury and ensure functional performance is unaffected (Bank et al., 2013; Hodges and Tucker 2011).

Although findings from acute experimental pain models provide insight into motor adaptation in pain, research investigating acute, *clinical* pain is scarce. Studies have shown motor abnormalities during trunk forward bending in acute LBP (<3 months) (Shojaei et al., 2017a; Shojaei et al., 2017b), and altered gait during walking in acute ankle sprain (4 weeks post-injury) and anterior knee pain (<3 months) (Fox et al., 2018; Punt et al., 2015). However, the definition of acute pain used in these studies is conflicting and does not always align with the clinical definition (<6 weeks) (van Tulder et al., 2003), hence these findings may not fully reflect how motor function changes in acute clinical pain. Although motor function returns to normal once acute experimental pain subsides (van den Hoorn et al., 2015), it is possible that motor changes may persist in some individuals with acute clinical pain. Unresolved motor changes in acute clinical pain are hypothesised to adversely impact tissue health and contribute to pain recurrence and chronicity (Hodges et al., 2013; MacDonald et al., 2009).

Movement dysfunction is present in chronic pain conditions (Allison et al., 2016; Bennell et al., 2013; Falla et al., 2014; Heales et al., 2016; Hodges 2001; Sjodahl et al., 2016; Tsao et al., 2008). Similar to acute experimental pain models, evidence shows inconsistent motor responses in chronic pain. For example, trunk muscle activity is

increased, decreased or unaffected in individuals with chronic LBP when compared with pain-free controls (van Dieën et al., 2003). It has been postulated that between-individual variability of motor adaptation in pain could explain why some people develop chronic pain while others do not (van den Hoorn et al., 2015). Although the physiological basis of movement dysfunction in musculoskeletal pain is uncertain, evidence suggests that altered central nervous system function may play a critical role (Bank et al., 2013; Coderre et al., 1993; Hodges and Tucker 2011; Maihofner et al., 2003; Mansour et al., 2014; Pelletier et al., 2015; Schabrun et al., 2016). As the primary motor cortex (M1) has an essential role in voluntary movement control and motor learning, functional, structural and organisational changes in M1 (termed 'neuroplasticity') may contribute to movement dysfunction.

1.2.2 Neuroplasticity in the primary motor cortex

The central nervous system changes continuously throughout life. This ability to change structure, function and organisation in the brain is known as neuroplasticity, a property that underpins the ability of neuronal networks to promptly adapt to the environment. In M1, neuroplasticity has been attributed to (1) an intracortical substrate of horizontal neuronal connections that mediate motor representations of body segments, and (2) synaptic modification driven by activity-dependent mechanisms (synaptic strength is increased by long-term potentiation and decreased by long-term depression of synaptic efficacy) (Jones 1993; Sanes and Donoghue 2000). Neuroplasticity is regulated by several neuromodulatory processes (Nahum et al., 2013). For example, when the brain engages in behaviours that involve sustained attention such as learning, the release of acetylcholine results in disinhibition to

facilitate plastic change (Nahum et al., 2013; Sarter et al., 2006; Sarter et al., 2001). If any unexpected events or conditions need attention, plasticity is enhanced by the release of noradrenaline, and controlled by dopamine for goal achievement and reward (Nahum et al., 2013).

Changes in motor output and altered peripheral sensory input induce M1 neuroplasticity. For example, learning a new motor skill induces enlarged M1 representation of the muscles involved in the task (Pascual-Leone et al., 1995). Sensory deafferentation such as amputation (Chen et al., 1998; Cohen et al., 1991; Kew et al., 1994), peripheral nerve lesion (Rijntjes et al., 1997), or ischaemic nerve block (Brasil-Neto et al., 1993; Ridding and Rothwell 1997) leads to a reduction in M1 representation of the affected limb and an expansion in representations adjacent to the affected limb. It has been shown that M1 neuroplasticity is modulated by gamma-aminobutyric acid (GABA)-mediated inhibition (Chen et al., 1998; Jones 1993; 2000; Sanes and Donoghue 2000; Zanette et al., 2004; Ziemann et al., 1998b; Ziemann et al., 1998c). Reduced GABAergic inhibition in M1 is thought to unmask latent excitatory neuronal connections that increase corticomotor excitability and induce M1 reorganisation in amputation and pain conditions (Chen et al., 1998; Schabrun et al., 2017b; Schabrun and Hodges 2012). Given the capacity of M1 to undergo neuroplasticity associated with motor function and learning, and the influence of peripheral sensory input on this plasticity, it has been widely hypothesised that maladaptive M1 neuroplasticity contributes to movement dysfunction in musculoskeletal pain (Berth et al., 2009; Masse-Alarie and Schneider 2016; Parker et

al., 2017; Schabrun et al., 2015c; Shanahan et al., 2015; Strutton et al., 2005; Tsao et al., 2008).

1.2.3 M1 neuroplasticity in musculoskeletal pain

Several neurophysiological methods have been used to investigate M1 neuroplasticity in musculoskeletal pain. For example, transcranial magnetic stimulation (TMS) has been used to examine M1 organisation (motor cortical representation) and function (corticospinal excitability and intracortical network activity) in chronic musculoskeletal pain, and magnetic resonance imaging (MRI) techniques have been used to assess M1 function and structure in acute or chronic pain. Table 1.1 provides a summary of the neurophysiological methods used to investigate M1 neuroplasticity.

Table 1.1 Summary of neurophysiological methods in M1 neuroplasticity research.

(Davis and Moayedi 2013; Jacobs et al., 2010; Kirveskari et al., 2010; Sharma et al., 2012; Sharma et al., 2011; Shiraishi et al., 2006; Ziemann et al., 2015)

Neurophysiological Methods	Measures
MRI (voxel-based morphometry)	Grey matter volume and cortical thickness in resting state
MRI (diffusion tensor imaging)	White matter connectivity in resting state
Functional MRI (blood-oxygen-level-dependent [BOLD] contrast to detect any increased neuronal synchronisation in an inter-regional network)	Functional connectivity between specific brain areas and in networks in resting state; brain responses (activation) to noxious stimuli or pain experience
Functional MRI (arterial spin labelling technique to detect increased regional cerebral blood flow (rCBF) within a specific region of interest)	Functional connectivity between specific brain areas and in networks in resting state; neuronal activity in response to noxious stimuli or pain experience
TMS (single-pulse paradigm to map the motor representation of target muscle)	Map volume, centre of gravity, number of discrete peaks of the motor map
TMS (single-pulse paradigm to measure M1 corticospinal excitability)	Rest and active motor threshold (glutamate mediated), motor evoked potential (MEP) amplitude and MEP latency (glutamate, GABA, noradrenaline and serotonin mediated), cortical silent period ($GABA_A$ and $GABA_B$ receptor mediated)

TMS (paired-pulse paradigm to measure M1 intracortical facilitatory and inhibitory network activity)	Short-interval intracortical inhibition ($GABA_A$ receptor mediated), long-interval intracortical inhibition ($GABA_B$ receptor mediated), intracortical facilitation (glutamate mediated), short-interval intracortical facilitation (glutamate mediated)
EEG	Bereitschaftspotential (a pre-movement EEG potential representing cortical motor physiology related to movement preparation), alpha event-related desynchronization (movement-related cortical activation)
MEG (20-Hz cortical rhythm reflects M1 functional state)	20-Hz rhythm suppression amplitude and peak (M1 excitation or disinhibition), 20-Hz rhythm rebound duration, amplitude and peak (increased M1 inhibition)
MRS (measure neurochemicals)	Concentration of biomarkers of neuronal function (N-acetylaspartate), glia function (myo-inositol), cell membrane integrity (choline) and neuronal-glial neurotransmission system (glutamate/glutamine)
PET	Glucose metabolism

MRI = magnetic resonance imaging; TMS = transcranial magnetic stimulation; EEG = electroencephalography; MEG = magnetoencephalography; MRS = magnetic resonance spectroscopy; PET = positron emission tomography.

1.2.3.1 M1 neuroplasticity in acute musculoskeletal pain

Using acute experimental pain models (pain lasting minutes to hours), there is strong evidence for reduced corticospinal excitability during and after pain cessation, in both painful and pain-free muscles of the same body segment (Burns et al., 2016b; c). M1 intracortical network activity is altered (reduced facilitation and increased inhibition) in response to acute muscle pain, although, intracortical inhibition is altered for networks mediated via $GABA_A$ and not $GABA_B$ receptors (Burns et al., 2016c; Schabrun and Hodges 2012). Overall, current systematic review evidence demonstrates altered M1 function in acute muscle pain that is characterised by reduced corticomotor excitability (Burns et al., 2016b; c). These data are in both chronic LBP and chronic lateral elbow pain (Schabrun et al., 2017b; Schabrun et al., 2015c), while slower activation of the transversus abdominis (TrA) muscle is associated with a posterolaterally shifted M1 representation of TrA in chronic LBP (Tsao et al., 2008). Altered M1 organisation in chronic musculoskeletal pain will be discussed in greater detail in section 1.3.1.2. However, it is unclear whether M1 reorganisation is present in other chronic pain conditions or when in the transition to chronic pain such changes develop.

A systematic review reported disinhibition of the M1 corticospinal pathway ($GABA_B$ receptor mediated) and intracortical network ($GABA_A$ receptor mediated) in chronic pain populations, but that study was restricted to data obtained using only a single neurophysiological measure (Parker et al., 2016). Further, although that review concluded M1 disinhibition is present in chronic pain, it is uncertain whether this alteration occurred exclusively in musculoskeletal conditions as data from migraine

studies were included in the meta-analyses. Indeed, it has been suggested that M1 disinhibition may occur in chronic neuropathic but not chronic nociceptive pain (Schwenkreis et al., 2010). Thus, despite the commonly held view that maladaptive neuroplasticity contributes to chronic pain, definitive evidence remains elusive. In particular, no systematic review has synthesised and critically appraised data on M1 neuroplasticity arising from a range of different neurophysiological methods in chronic musculoskeletal pain.

1.2.4 Study 1 rationale

Although two existing reviews provide some evidence for M1 neuroplasticity in chronic pain, these studies were restricted to a specific pain condition (Di Pietro et al., 2013a) or by the neurophysiological method used to assess changes occurring in M1 (Parker et al., 2016). A review that provides integrated and comprehensive information on M1 structure, organisation and function across i) a range of neuropathic and non-neuropathic chronic musculoskeletal pain conditions, and ii) using a range of complementary neurophysiological techniques is needed to determine the evidence of M1 maladaptive neuroplasticity in chronic pain.

The aim of study 1 (Chapter 2) was to evaluate the evidence of altered M1 structure, organisation and function in chronic musculoskeletal pain of neuropathic and non-neuropathic origin. This was achieved via a systematic review and meta-analysis of TMS studies examining M1 corticomotor excitability in chronic musculoskeletal pain conditions. Due to limited data, a narrative synthesis was performed to evaluate the evidence from studies that investigated M1 structure, organisation and function in

chronic pain using a range of other neurophysiological methods (e.g. fMRI, EEG). The integration of information from a range of complementary neurophysiological techniques in this review provides the first comprehensive evaluation of the neurophysiological evidence for M1 neuroplasticity in chronic musculoskeletal pain.

1.3 Evidence of altered sensorimotor and cingulate cortex excitability in musculoskeletal pain

It is widely accepted that sensory and motor function are altered in response to pain. Pain is a multifaceted experience encompassing (1) a sensory-discriminative component for localising and determining the source of pain, (2) an affective-motivational component for engaging the emotional and cognitive processes of pain (i.e. threat detection), and (3) a motor output component that facilitates a protective, aversive behaviour (Casey 1982; Davis and Moayedi 2013). As the primary motor, sensory and cingulate cortices are involved in these aspects of pain processing, neuroplasticity in these cortical regions is likely to play an important role in musculoskeletal pain (Diers et al., 2007; Peyron et al., 2000; Schabrun et al., 2015a). The following sections review the current evidence for altered motor, sensory and cingulate cortex excitability in musculoskeletal pain.

1.3.1 The primary motor cortex (M1) in musculoskeletal pain

There is a growing body of evidence that demonstrates altered M1 function (corticospinal pathway excitability, intracortical network activity, and M1 representation) in musculoskeletal pain (Bradnam et al., 2016; Burns et al., 2016a; Caumo et al., 2016; Masse-Alarie et al., 2016; 2017a; Morgante et al., 2017; Parker

et al., 2016; Parker et al., 2017; Rio et al., 2016; Schabrun et al., 2016; Schabrun et al., 2017b; Schabrun et al., 2015c; Shanahan et al., 2015; Tarrago Mda et al., 2016; Te et al., 2017; Tsao et al., 2011; Tsao et al., 2008). Primary motor cortex function can be investigated in humans using various transcranial magnetic stimulation (TMS) methods.

1.3.1.1 Transcranial magnetic stimulation

TMS is a non-invasive, safe and pain-free technique. It has been widely used to investigate M1 neurophysiology such as corticospinal pathway excitability and M1 representation of the target muscle (via single-pulse paradigms), and intracortical facilitatory and inhibitory mechanisms (via paired-pulse paradigms) (Barker et al., 1985; Claus et al., 1992; Kujirai et al., 1993; Valls-Sole et al., 1992; Wassermann et al., 1992). When a single-pulse TMS is applied to the scalp over M1, a corticomotor response, known as a motor evoked potential (MEP, measured over the target muscles by electromyography), is induced by an electromagnetic current in the underlying neural tissues (Barker et al., 1985). Several factors related to the methodology (e.g. stimulation intensity, the type of coil, muscle activity), or the inherent neurological status (the excitability of the cortical, spinal and peripheral neurons of the corticomotor pathways) are known to influence the amplitude of the MEP (Di Lazzaro et al., 2004; Di Lazzaro et al., 1998; Groppa et al., 2012). A TMS methodological checklist has been developed to enhance the consistency and soundness in reporting and controlling the relevant factors in TMS studies (Chipchase et al., 2012a). As TMS mapping was used in this thesis to examine the topographical

representation of back muscles in M1 (Study 2), this section will focus on the relevant literature of the mapping method.

TMS mapping protocols are used to produce a topographical map representing the excitability and organisation of corticospinal neurons projecting to the target muscle. Single-pulse TMS is delivered via a coil to the M1 contralateral to the target muscle. The locations of stimuli are guided by a grid that is drawn on a swim cap worn by the participant, or by a neuronavigation system. The scalp sites from which MEPs in the target muscle can be evoked and the amplitude of the MEPs at each location, are subsequently determined (Uy et al., 2002b; Wilson et al., 1993). A map of the MEP amplitudes of the target muscle is then produced by superimposing the MEPs over respective scalp sites (Figure1.1). M1 representational changes can be induced by interventions (e.g. motor learning, peripheral electrical stimulation) or pathological conditions (e.g. amputation, peripheral nerve lesion, pain) (Kew et al., 1994; Pascual-Leone et al., 1995; Rijntjes et al., 1997; Schabrun et al., 2014a). Three map parameters (map volume, centre of gravity and the number of discrete peaks) are used to quantify M1 representational changes:

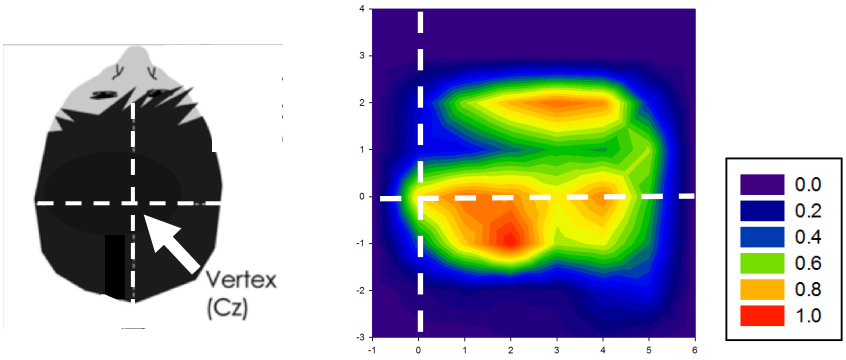

Figure 1.1 Transcranial magnetic stimulation (TMS) mapping of corticomotor excitability and representation of a target muscle. *Single-pulse TMS is used to create a visual representation of the excitability and organisation of corticospinal neurons projecting to a target muscle. The average amplitude of MEPs induced at each scalp site is used to compose a map of the representation of the target muscle. The example provided here was constructed from MEP responses recorded from the left erector spinae muscle of a pain-free individual. The data used to generate this map has been normalised to maximal MEP amplitude (1mV). The colour scale indicates increments of 0.2 mV. Warmer colours indicate higher corticomotor excitability. Maps are orientated to the vertex.*

(i) Map volume, defined as the sum of the averaged MEP amplitudes at all scalp sites where corticomotor responses are evoked, is a measure of the total excitability of the M1 representation (Tsao et al., 2008; Uy et al., 2002b; Wassermann et al., 1992). Changes in map volume reflect changes in corticomotor excitability or the territory of the M1 neuronal network projecting to the target muscle (Te et al., 2017; Tsao et al., 2011; Tsao et al., 2008). For example, in the early stage of motor learning, increased M1 excitability is observed as an enlargement in the representations of the

muscles involved in the task. Conversely, once the new motor skill is acquired, map representations diminish, indicating decreased M1 excitability (Pascual-Leone et al., 1994; Pascual-Leone et al., 1995).

(ii) Centre of gravity (CoG), expressed by a latitude/longitude based coordinated system, provides the amplitude-weighted centre of a M1 representation (Tsao et al., 2008; Uy et al., 2002b; Wassermann et al., 1992; Wilson et al., 1993). The CoG is a reliable and repeatable measure (Boroojerdi et al., 1999; Uy et al., 2002b). Using the CoG, shifts in the location of the M1 representation of a target muscle can be measured and the extent of the overlap (or smudging) between M1 representations of adjacent muscles can be quantified (Masse-Alarie et al., 2017b; Schabrun et al., 2017b; Schabrun et al., 2015c; Tsao et al., 2011; Tsao et al., 2008).

(iii) The number of discrete peaks, representing the areas of greatest excitability within a M1 representation, is a novel measure used to quantify M1 organisational changes. A visual inspection is used to identify the discrete peaks on the map according to pre-defined selection criteria (Schabrun et al., 2016; Schabrun et al., 2015c; Schabrun et al., 2014a). Discrete map peaks have been reported in studies measuring M1 representations of the back, forearm and quadriceps muscles (Masse-Alarie et al., 2017b; Schabrun et al., 2016; Schabrun et al., 2015c; Schabrun et al., 2014a; Te et al., 2017). It has been hypothesised that multiple discrete peaks of activity in a M1 map reflect multiple control centres for a single muscle that allow the inter-muscle coordination essential for most motor functions (Schabrun et al., 2015c). For example, recent research mapped the M1 representations of four forearm

muscles during three motor tasks in pain-free individuals (Masse-Alarie et al., 2017b). The results show that specific and independent discrete map peaks are observed for a single muscle during different motor tasks, and M1 maps of synergist muscles share more discrete peak sites (greater overlap) than those of antagonist muscles.

1.3.1.2 Altered M1 excitability and organisation in musculoskeletal pain

As noted previously, TMS mapping data have provided evidence of altered M1 excitability (map volume) and organisation (CoG location and the number of discrete peaks) in musculoskeletal pain. In chronic pain, M1 excitability measured by map volume varies between pain conditions and individual studies. When compared with pain-free controls, map volume is greater in individuals with lateral epicondylalgia and chronic LBP (transversus abdominis), less in those with chronic patellofemoral pain, but inconsistent in the erector spinae muscles in those with chronic LBP (no change or less) (Elgueta-Cancino et al., 2018; Schabrun et al., 2017b; Schabrun et al., 2015c; Te et al., 2017; Tsao et al., 2011; Tsao et al., 2008). Altered map volume represents changes in corticomotor excitability that are thought to be mediated by GABAergic disinhibition (Schabrun et al., 2015c). There is evidence of M1 reorganisation in chronic LBP showing shifted CoG locations (posteriorly for transversus abdominis and opposite directions for erector spinae muscles) and greater overlap of M1 representations of trunk muscles (Elgueta-Cancino et al., 2018; Schabrun et al., 2017b; Tsao et al., 2011; Tsao et al., 2008). Inconsistent findings in chronic LBP are likely due to methodological differences. For example, surface electrodes have a broader detection area for electromyography (EMG) signal

whereas intramuscular fine-wire electrodes obtain discrete EMG recording from individual muscle fascicles. Greater overlap of M1 representations of the forearm muscles and quadriceps muscles have also been shown in chronic lateral epicondylalgia and patellofemoral pain respectively (Schabrun et al., 2015c; Te et al., 2017). When compared with pain-free controls, a reduction in the number of discrete peaks of M1 representations has been consistently reported in chronic musculoskeletal pain conditions (Elgueta-Cancino et al., 2018; Schabrun et al., 2017a; Schabrun et al., 2017b; Schabrun et al., 2015c; Te et al., 2017; Tsao et al., 2011; Tsao et al., 2008).

Altered M1 excitability and organisation are associated with pain characteristics or impaired motor control. For example, a smaller map volume is associated with higher pain intensity in individuals with upper LBP and a reduction in the number of discrete peaks of erector spinae is observed only in individuals with moderate-severe chronic LBP (Schabrun et al., 2017b). Individuals with chronic LBP who have a greater number of discrete peaks in the erector spinae muscle perform better on a thoracolumbar movement dissociation test (Elgueta-Cancino et al., 2018). Similarly, a larger map volume and more posterolaterally shifted CoG location is associated with a delay in transversus abdominis activation during an arm lifting task in chronic LBP (Tsao et al., 2008). These findings suggest that M1 neuroplasticity reflects maladaptive motor strategies and may underpin movement dysfunction in chronic musculoskeletal pain. However, the causal relationship between altered M1 representation and motor control impairments requires confirmation in future research using longitudinal study designs. Although there is evidence of altered M1 excitability in acute

musculoskeletal pain (see Section 1.2.3.1), data pertaining to M1 representations are lacking. Currently, no study has examined M1 representations in acute pain, either in response to experimentally-induced pain or in response to acute clinical pain.

1.3.2 Sensory and cingulate cortex excitability in musculoskeletal pain

The sensory and cingulate cortices play a significant role in pain processing. Functionally, the primary (S1) and secondary (S2) sensory cortices are involved in the sensory-discriminative aspect of pain that identifies the locations and characteristics of sensory afferent inputs (Bromm and Lorenz 1998; Casey 1982; Diers et al., 2007; Maihöfner et al., 2006). S2 and the anterior cingulate cortex (ACC) are involved in the affective-motivational aspect of pain with roles in pain perception and the integration and processing of nociceptive and non-nociceptive inputs (Apkarian et al., 2005; Casey et al., 2001; Frot et al., 2001; Fulbright et al., 2001; Treede et al., 2000). It has been postulated that neuroplasticity in these cortical regions is an important physiological mechanism underpinning musculoskeletal pain (Apkarian et al., 2005).

1.3.2.1 Neuroplasticity in the sensory and cingulate cortex

Altered sensory input can induce neuroplasticity in S1. For example, an enlarged S1 representation of the index finger in blind individuals is associated with increased sensory input resulting from reading Braille (Pascualleone and Torres 1993). Conversely, following amputation, the S1 representation of the missing hand is reduced and invaded by the adjacent S1 representation of the lips. In addition, the S1 representation of the missing hand becomes responsive to stimuli from the once adjacent S1 representation (such as the face and lips) (Flor et al., 1995;

Ramachandran and Altschuler 2009). These findings led to the hypothesis that phantom limb pain is caused by maladaptive neuroplasticity, and based on this, it was predicted that amputees who exhibited a greater reduction in the S1 representation of the missing limb would experience greater phantom limb pain (Flor et al., 1995). However, this hypothesis was contradicted by recent research demonstrating that greater phantom limb pain is associated with greater S1 representation of the missing hand (Makin et al., 2013). These findings suggest that while sensory deafferentation initially induces S1 reorganisation characterised by a reduced representation of the amputated limb, persistent phantom pain arises from neuroplasticity that drives the expansion of cortical representations. These data suggest a role for sensory cortex neuroplasticity in the development and maintenance of chronic pain.

Indeed, organisational and structural changes in the sensory cortex are present in chronic musculoskeletal pain. For example, the S1 representation of the back in chronic LBP is shifted medially, and in complex regional pain syndrome (CRPS), a systematic review reported that the S1 representation of the affected hand is smaller when compared with that of pain-free controls (Di Pietro et al., 2013b; Flor et al., 1997; Maihofner et al., 2003). Notably, these plastic changes appear to be specific to the type of pain condition (Apkarian et al., 2011) and are associated with pain characteristics (e.g. intensity or duration of pain) (Baliki et al., 2011; Flor et al., 1997; Schmidt-Wilcke et al., 2006) and psychological factors (e.g. exaggerated illness behaviour) (Lloyd et al., 2008). For example, individuals with chronic neuropathic pain demonstrate altered organisation and structure in S1 whereas those with non-neuropathic pain do not (Gustin et al., 2012). Greater S1 reorganisation is associated

with longer symptom duration in chronic LBP (Flor et al., 1997). Further, a network meta-analysis indicates an increase in S1 grey matter in chronic musculoskeletal pain with high variability between different pain conditions (Cauda et al., 2014). Indeed, the reductions in S1 and S2 grey matter volume are more comparable in chronic LBP and osteoarthritis than CRPS, and the change is only observed in individuals with a long duration of pain (> 5 years) (Baliki et al., 2011). While these findings support the presence of organisational and structural changes of the sensory cortex in chronic musculoskeletal pain, evidence in the acute stage of pain is limited. One study using magnetoencephalography has shown that experimental muscle pain induces rapid (within minutes) S1 reorganisation characterised by a reduction and shift in the representation of the painful hand (Soros et al., 2001). For altered excitability in the sensory and cingulate cortices, there has been preliminary research in both the chronic and acute musculoskeletal pain. The relevant literature is discussed in the following section.

1.3.2.2 Altered sensory and cingulate cortex excitability in musculoskeletal pain

Electroencephalography (EEG) is a non-invasive, neurophysiological method that provides reliable information about brain functioning. EEG has been used to examine brain neuroelectrical activity that reflects cortical processing during rest, sensory stimulation or cognitive tasks (de Vries et al., 2013; Flor et al., 2004; Pinheiro et al., 2016; Rossi et al., 1998). Sensory evoked potentials (SEPs) are an EEG measure that has been used to quantify the processing of noxious and non-noxious sensory input at the cortical level in acute and chronic musculoskeletal pain (Diers et al., 2007; Schabrun et al., 2013). SEP components contain a series of negative and positive

deflections (Figure 1.2). The peak amplitude or the area under the curve of the individual SEP components are calculated to measure the excitability of the sensory and cingulate cortices when individuals receive noxious or non-noxious stimuli (Diers et al., 2007; Schabrun et al., 2015a; Schabrun et al., 2013).

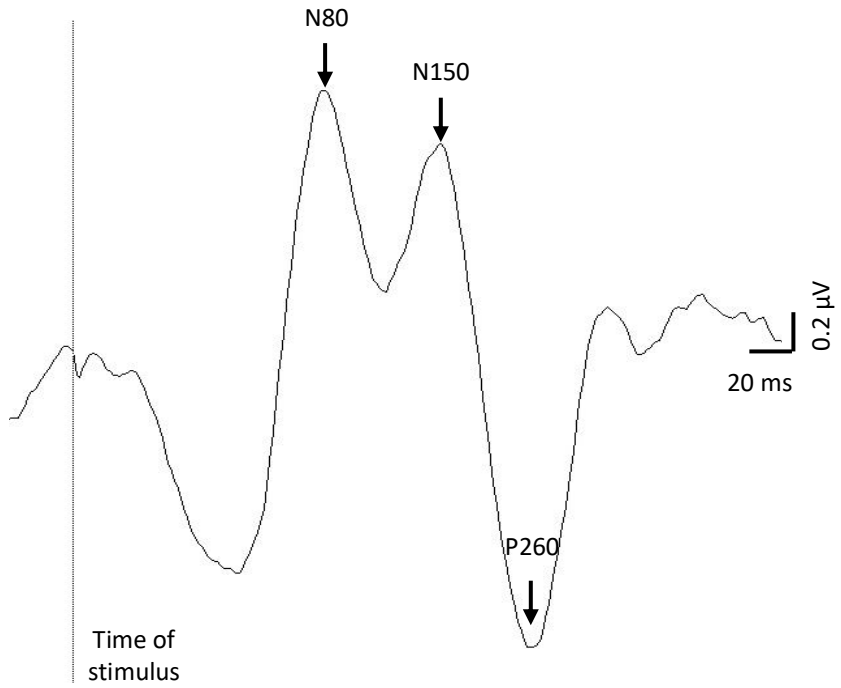

Figure 1.2 Sensory evoked potential (SEP) recorded in response to non-noxious electrical stimuli at the low back of a pain-free individual. *Electroencephalography was recorded using a gold plated cup electrode positioned over the primary sensory cortex on the side contralateral to the site of electrical stimuli and referenced to Fz using the International 10/20 System. The first major negative peak is N_{80}, followed by the second negative peak, N_{150}, and immediately followed by a major positive peak, P_{260}. The N_{80} component peaks approximately 80 ms after the onset of stimulus, the N_{150} component peaks around 120 ms after the onset of stimulus and the P_{260} component peaks around 150 ms after the onset of stimulus. This trace is the averaged waveform of 500 stimuli.*

The early latency component of the SEP, N_{80} is thought to originate from S1 and is thought to reflect the sensory-discriminative aspect of pain (Bromm 2001; Bushnell et al., 1999). Individuals with chronic LBP demonstrate greater excitability of the N_{80} SEP component in response to noxious stimuli when compared with pain-free controls, indicating heightened S1 excitability (Diers et al., 2007). The N_{150} and P_{260} SEP components are thought to originate from the S2 and ACC respectively, reflecting the affective-motivational aspect of pain (Treede et al., 2000; Treede et al., 1999). Unlike S1 where studies consistently demonstrate increased excitability in response to chronic LBP, evidence for altered S2 excitability in chronic LBP is conflicting. While SEP data show no change in the N_{150} SEP component, fMRI findings show greater S2 excitability (Diers et al., 2007; Flor et al., 2004; Ladouceur et al., 2018). Similarly, findings for ACC excitability are mixed in chronic LBP with one study reporting lower amplitude of the P_{260} SEP component (Diers et al., 2007) and two reporting no difference (Flor et al., 2004; Ladouceur et al., 2018), likely due to different methodology used in the studies. Yet, magnetoencephalography (Flor et al., 1997) and functional MRI (Baliki et al., 2006; Giesecke et al., 2004; Kregel et al., 2015) provide evidence that individuals with chronic LBP have greater excitability of the sensory and cingulate cortices when compared with pain-free controls. Taken together, current evidence suggests that chronic musculoskeletal pain is characterised by increased S1 excitability, but data for S2 and ACC excitability are conflicting between studies.

In the acute stage of pain, a recent meta-analysis of SEP data provided strong evidence of a reduction in S1 excitability during acute experimentally-induced pain

and a moderate reduction after pain has resolved (Burns et al., 2016b). In line with SEP data, functional MRI studies also demonstrate reduced S1 excitability in response to acute experimental pain (Zhang et al., 2014; Zhang et al., 2017). Less clear, is how S2 and ACC excitability changes in acute pain, as relevant SEP data are absent and functional MRI report conflicting findings (increased or decreased excitability) in ACC (Zhang et al., 2014; Zhang et al., 2017). Overall, the direction of altered S1 excitability appears to be opposite in the acute (decreased) and chronic (increased) stage of musculoskeletal pain (Figure 1.3). Importantly, whether and how the sensory and cingulate cortex excitability changes in individuals with acute, *clinical* musculoskeletal pain has not been investigated.

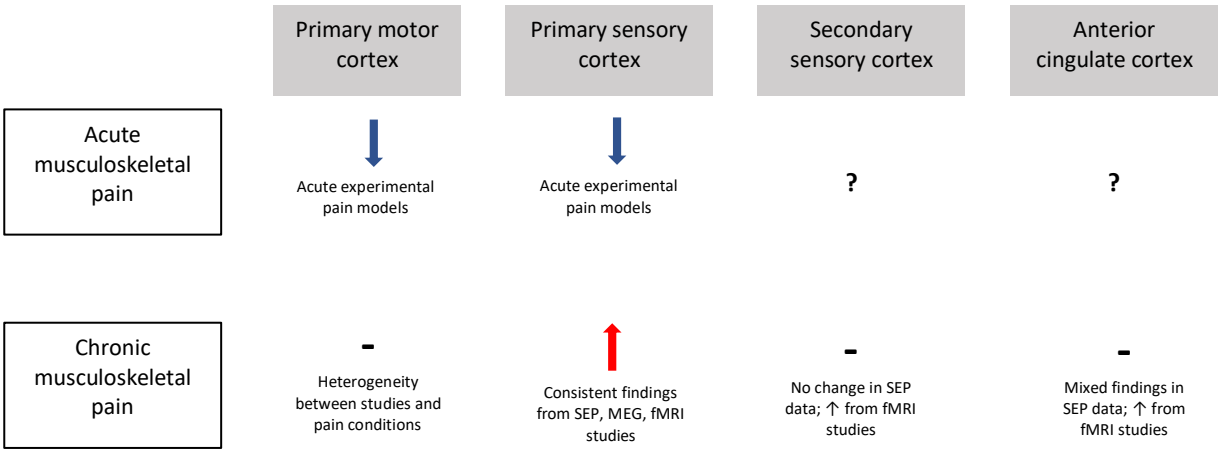

Figure 1.3 Overview of current evidence for sensorimotor and cingulate cortex excitability in musculoskeletal pain. *In acute musculoskeletal pain, there is evidence of decreased excitability in the primary motor and sensory cortex but evidence for the secondary sensory and anterior cingulate cortices is absent. These data are derived exclusively from acute experimental pain models and there are no data available from any acute clinical musculoskeletal pain population. In chronic musculoskeletal pain, there is consistent evidence of increased excitability in the primary sensory cortex, however, evidence for the primary motor, secondary sensory and anterior cingulate cortices is conflicting. Note: '↓' = decreased excitability; '↑' = increased excitability; '?' = no evidence available; '–' = inconclusive evidence.*

1.3.3 Study 2 rationale

Although sensorimotor excitability decreases in response to acute experimentally-induced musculoskeletal pain (pain of rapid onset, lasting minutes to hours) (Burns et al., 2016b), it remains unclear whether sensory, cingulate and motor cortex excitability is altered in acute, *clinical* pain (pain lasting up to six weeks), and if so, whether the direction of change resembles that observed in acute experimental pain (reduced excitability) or that observed in chronic pain (greater excitability).

Furthermore, whether M1 reorganisation is present in acute clinical pain has not been investigated.

The aim of Study 2 (Chapter 3) was to compare (1) the excitability of the sensory and cingulate cortices and (2) the excitability and organisation of M1 between individuals with acute, clinical, non-specific LBP and pain-free controls. This was achieved using EEG to measure SEPs in response to non-noxious stimuli, and TMS mapping to examine M1 excitability and the M1 representation of the erector spinae muscles in both groups. Based on findings from acute experimental pain models, it was hypothesised that the excitability of the motor, sensory and cingulate cortices would be lower in individuals with acute, clinical LBP than pain-free controls. Using non-invasive neurophysiological methods, this study provides the first evidence of motor, sensory and cingulate cortex excitability and M1 organisation in acute clinical musculoskeletal pain.

1.4 Evidence of altered central pain processing in musculoskeletal pain

Central pain processing plays an important role in shaping an individual's pain perception (Fields 2004; Heinricher et al., 2009; Nir et al., 2012). Pain facilitation through *central sensitisation* leads to hyperalgesia (increased pain sensitivity) in response to an injury and is thought to promote tissue healing (Staud 2012; Sterling 2010; Woolf 2011). Conversely, *descending inhibitory pain control* downregulates peripheral nociceptive input, produces endogenous analgesia and is thought to enable escape from potentially dangerous situations (Heinricher et al., 2009; Millan 2002; Staud 2012). Central sensitisation and impaired descending inhibitory pain

control, mechanisms indicative of altered central pain processing, are present in musculoskeletal pain (Staud 2012; Vuilleumier et al., 2017; Woolf and Salter 2000). The following sections review the current evidence for these mechanisms in musculoskeletal pain.

1.4.1 Central pain processing

1.4.1.1 Measures of central sensitisation

Central sensitisation, driven by increased synaptic efficacy and decreased inhibition of somatosensory pathways, is defined as 'an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity' (e.g. hyperalgesia or allodynia) (Woolf 2011; Woolf and Salter 2000). Ongoing nociceptive input from peripheral structures can induce neuronal plasticity in the central nervous system (Banic et al., 2004; Latremoliere and Woolf 2009). Subsequently, altered tissue sensitivity can occur not only the injured area, but also in remote body regions (known as widespread hyperalgesia) (Curatolo et al., 2006). Central sensitisation manifests as increased spinal excitability and widespread hyperalgesia and can be evaluated using the nociceptive flexor withdraw reflex (NFR) and quantitative sensory testing (QST) methods (Desmeules et al., 2003; Lim et al., 2012; Staud 2012; Woolf 2011).

The NFR is a polysynaptic spinal reflex elicited by electrical stimulation of the sural nerve and recorded over the biceps femoris muscle by electromyography (Chan and Dallaire 1989; Rhudy and France 2007; Skljarevski and Ramadan 2002) (Figure 1.4). As the NFR bypasses the peripheral nociceptors to directly stimulate spinal pathways,

it is used to quantify the excitability of spinal neurons in research of central sensitisation (Desmeules et al., 2003). The lowest stimulator intensity required to elicit a NFR response (termed the NFR threshold) is associated with the subjective pain threshold, and the NFR amplitude is related to perceived pain intensity (Chan and Dallaire 1989; Sandrini et al., 2005; Skljarevski and Ramadan 2002; Willer et al., 1987). A reduction in the threshold, an increase in the amplitude, or a reduction in the latency of the NFR indicate increased spinal excitability (Courtney et al., 2011; Lim et al., 2011). Although the NFR is reliable, it can be influenced by age, sex and psychological states (such as stress and emotion) (Biurrun Manresa et al., 2011; 2013; Rhudy and France 2011; Rhudy et al., 2005; Sandrini et al., 2005).

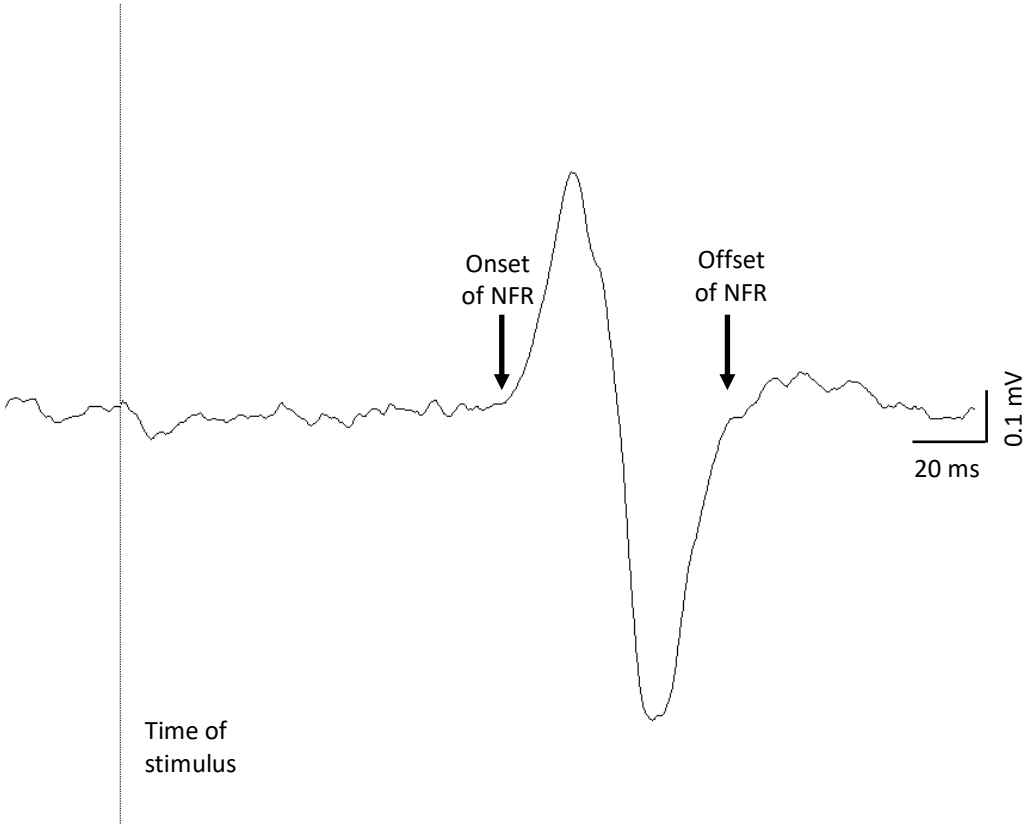

Figure 1.4 Nociceptive flexor withdraw reflex (NFR) recorded in response to electrical stimuli at the sural nerve of a pain-free individual. *Electromyography was recorded using a surface electrode positioned over the biceps femoris muscle. The latency of the NFR is the interval between the time of the stimulus and the onset of the NFR response. The onset of the NFR is typically within 90-150 ms following the time of the stimulus. The area under the curve between the onset and offset of the NFR (root mean square) is calculated to represent the magnitude of the NFR response.*

QST includes different forms of psychophysical testing that quantify the function of somatosensory pathways (Pavlakovic and Petzke 2010; Uddin and MacDermid 2016). As pain mechanisms are recommended to be considered in the diagnosis and treatment of musculoskeletal pain (Pavlakovic and Petzke 2010; Woolf et al., 1998), QST has been widely used to evaluate physiological mechanisms, sensory function and pain sensitivity in various pain conditions (Backonja et al., 2009; Pfau et al., 2014;

Rolke et al., 2006a; Rolke et al., 2006b). Pain threshold detection methods via different modalities (e.g. thermal or mechanical stimuli) are commonly used to examine allodynia or hyperalgesia (Arendt-Nielsen and Yarnitsky 2009; Backonja et al., 2013). These methods involve administering a ramp stimulus of gradually increasing intensity until the individual reports that the sensation has first changed to one of pain (termed the pain threshold). Although QST is valid and reliable, it assesses an individual's subjective response to a quantified stimulus, and therefore, can be influenced by an individual's attention, motivation and cognition (Backonja et al., 2013; Marcuzzi et al., 2017). Research suggests that individuals' sex and comorbidity should also be controlled when using QST, as the relationship between pain threshold detection and disability is mediated by these factors (Uddin et al., 2016; Uddin et al., 2014).

1.4.1.2 Measures of descending inhibitory pain control

Descending inhibitory pain control is assessed in humans using a conditioned pain modulation (CPM) paradigm. This QST method is based on the 'pain-inhibits-pain' phenomenon where a heterotopic, tonic conditioning stimulus causes a decrease in pain perception evoked by another noxious stimulus (test stimulus) applied elsewhere in the body (Arendt-Nielsen and Yarnitsky 2009; Yarnitsky et al., 2010) (Figure 1.5). Descending inhibitory pain control involves periaqueductal grey, rostral ventromedial medulla and other supraspinal regions (e.g. ACC, prefrontal and orbitofrontal cortex) (Knudsen et al., 2018; Pud et al., 2009). The CPM paradigm therefore provides information on the net balance between endogenous facilitatory and inhibitory mechanisms, and is reliable in assessing the strength of pain inhibition

(Arendt-Nielsen 2017; Kennedy et al., 2016; Yarnitsky et al., 2010).

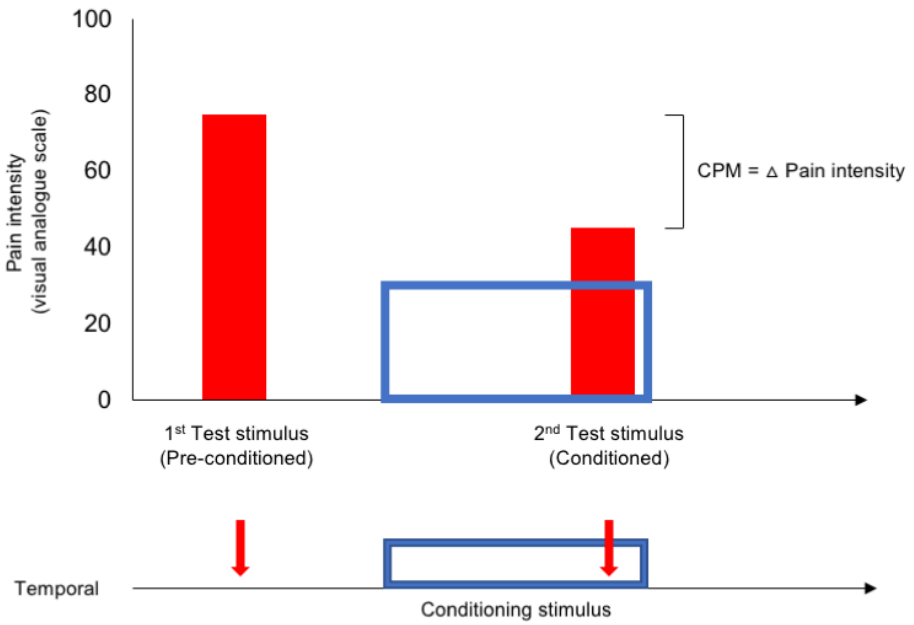

Figure 1.5 A schematic representation of the "pain-inhibits-pain" phenomenon. *The upper panel shows the "pain-inhibits-pain" phenomenon, a reduction in pain (measured on a 0-100 visual analogue scale) between the 1st and 2nd test stimulus is induced by administering a tonic, painful conditioning stimulus (the blue square) on a remote body area. The lower panel shows the temporal sequence of administering the 1st test stimulus (left downward arrow), the conditioning stimulus (the blue square) and the 2nd test stimulus (right downward arrow). The 2nd test stimulus is applied during the conditioning stimulus. Note. CPM = conditioned pain modulation (Adapted from (Arendt-Nielsen and Yarnitsky 2009).*

Modalities such as heat or cold, pressure, chemical irritation or an electrical stimulus can be used as the test stimulus, while cold or heat induced pain are commonly used as the conditioning stimulus (Goubert et al., 2015; Klyne et al., 2015). CPM is quantified by calculating either i) the change in pain threshold or ii) the change in the intensity of the test stimulus before and after the conditioning stimulus is applied (Figure 1.6). A reduction in pain in the first body region (increased pain threshold or

decreased pain intensity of the test stimulus) is thought to represent normal descending inhibitory pain control and is commonly reported in pain-free individuals (Kennedy et al., 2016).

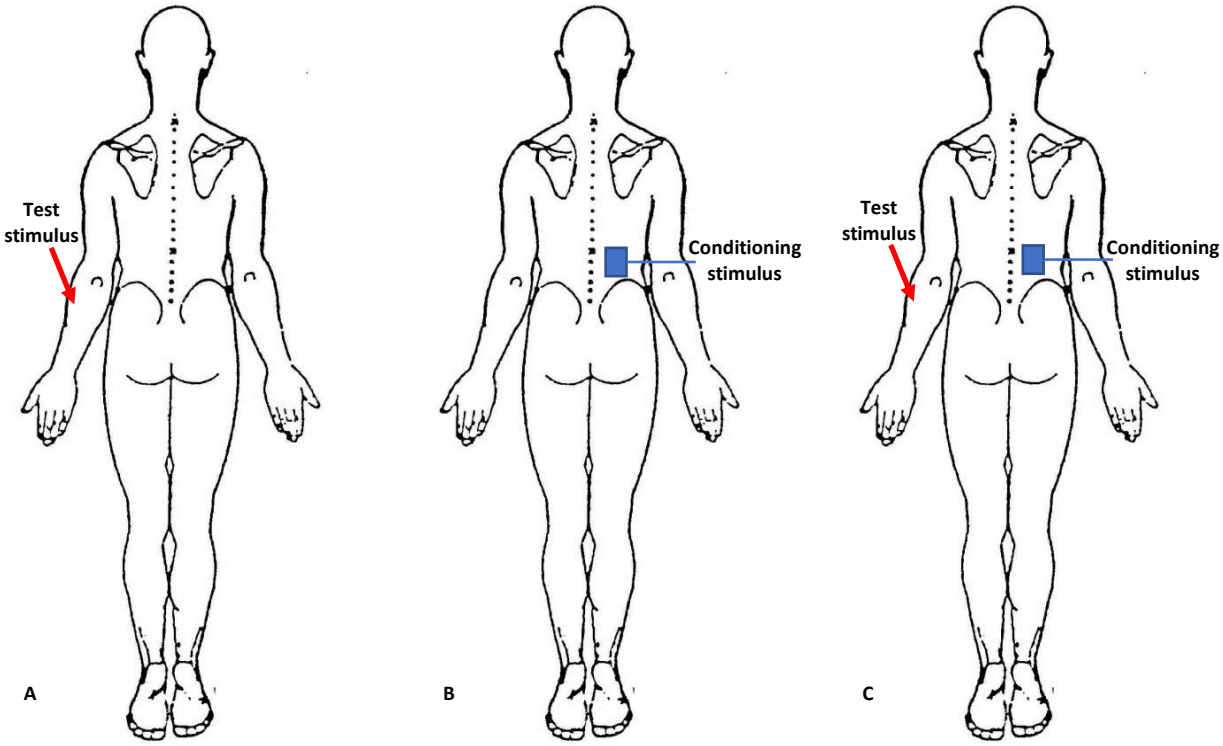

Figure 1.6 An example of a conditioned pain modulation protocol. *Pressure pain threshold (test stimulus) is measured on the left forearm (A). A tonic heat pain (conditioning stimulus) is then applied on the right lumbar region (B). When the heat pain on the right lumbar region reaches the pre-determined intensity (i.e. 50 on a 0-100 visual analogue scale), the pressure pain threshold is measured again on the left forearm (C). The function of the descending inhibitory pain control mechanism is quantified by calculating the difference between the two pressure pain threshold measures.*

Several factors should be considered in the design of the CPM paradigm. For example, the test and the conditioning stimuli should be applied over contralateral heterotopic sites (different body parts) for valid CPM responses (Klyne et al., 2015). Individuals' age and sex should be controlled as CPM decreases with age and is more efficient in

males than females (Edwards et al., 2003; Lewis et al., 2012b; Popescu et al., 2010; Pud et al., 2009; van Wijk and Veldhuijzen 2010). Evidence indicates that more efficient CPM responses are correlated with higher levels of anxiety and pain catastrophising but lower levels of depression in pain-free individuals (Nahman-Averbuch et al., 2016). Further, a systematic review shows that some analgesic medications and oral contraceptives reduce CPM efficiency (Goubert et al., 2015).

1.4.2 Evidence of altered central pain processing in musculoskeletal pain

1.4.2.1 Central pain processing in chronic musculoskeletal pain

There is a rich body of evidence suggesting altered central pain processing in chronic musculoskeletal pain. A meta-analysis provides evidence of increased spinal excitability (reduction in NFR threshold) in primary headache, fibromyalgia, chronic knee and whiplash-associated neck pain (Lim et al., 2011). Systematic reviews confirm the presence of widespread hyperalgesia in chronic shoulder and osteoarthritic pain (Fingleton et al., 2015; Noten et al., 2017; Suokas et al., 2012). A meta-analysis also provides strong evidence of impaired CPM in chronic pain (e.g. fibromyalgia, headache, arthritis) (Lewis et al., 2012b). However, this result should be interpreted with caution as the meta-analysis included studies investigating visceral (i.e. irritable bowel syndrome, pancreatitis) and neurological (e.g. stroke and Parkinson's disease) disorders.

Despite meta-analyses broadly demonstrating altered central pain processing in chronic musculoskeletal pain conditions when data are pooled, evidence for altered central pain processing in chronic LBP specifically, is equivocal. For example, there

are inconsistent findings for spinal excitability (increased or no change) (Biurrun Manresa et al., 2013; Peters et al., 1992), and conflicting findings for widespread hyperalgesia (present or absent) (Roussel et al., 2013; Sanzarello et al., 2016). Similarly, evidence for impaired CPM in chronic LBP is limited, with studies reporting an impaired (Correa et al., 2015; Rabey et al., 2015), unchanged (Owens et al., 2016; Peters et al., 1992), or partially impaired (unchanged CPM magnitude but reduced duration of the response) (Mlekusch et al., 2016) CPM response.

The conflicting findings for altered central pain processing in chronic LBP could reflect the presence of different subgroups of individuals within this population that are characterised by different pain mechanisms. For example, one recent study demonstrated that impaired CPM is present only in chronic widespread back pain and not chronic local back pain (Gerhardt et al., 2017). Studies in other chronic musculoskeletal pain conditions provide further support for this hypothesis. In knee osteoarthritis, only some subgroups of individuals demonstrate widespread hyperalgesia and impaired CPM and these individuals also report greater pain severity and physical dysfunction (Arendt-Nielsen et al., 2015; Egsgaard et al., 2015; Osgood et al., 2015). Similarly, while individuals with fibromyalgia display impaired CPM at the group level compared with pain-free controls, only a subgroup of individuals (42%) actually demonstrate an abnormal CPM response (Potvin and Marchand 2016). Taken together, these findings suggest that altered central pain processing may be a feature of chronic musculoskeletal pain for some individuals and not others.

1.4.2.2 Altered central pain processing in acute musculoskeletal pain

There is preliminary evidence of altered central pain processing in acute musculoskeletal pain. A meta-analysis provides evidence of central sensitisation (increased spinal excitability and widespread hyperalgesia) in acute whiplash-related neck pain, but not in acute idiopathic neck pain (Marcuzzi et al., 2015). As longitudinal data show that widespread hyperalgesia in acute whiplash injury is associated with poor prognosis (severe chronic pain and disability), central sensitisation has been suggested to contribute to the development of chronic whiplash-related neck pain (Kasch et al., 2005; Sterling et al., 2003; Sterling et al., 2005). However, evidence for impaired CPM in acute whiplash-related neck pain is limited, with one study reporting an impaired response (Daenen et al., 2014) while the other reported no change (De Kooning et al., 2015). In children with acute musculoskeletal pain, there is no evidence of impaired CPM (Lewandowski Holley et al., 2017).

Specific to acute LBP, current evidence for altered central pain processing is limited. While NFR data indicate increased spinal excitability in acute LBP (Biurrun Manresa et al., 2013), evidence for widespread hyperalgesia is conflicting, with one study showing mechanical hyperalgesia in remote body regions (Vuilleumier et al., 2017), and one study showing no change (O'Neill et al., 2011). Similarly, evidence for impaired CPM is mixed, with three studies demonstrating no change and one demonstrating partially impaired CPM (Klyne et al., 2018; Marcuzzi et al., 2018; Mlekusch et al., 2016; Vuilleumier et al., 2017) (Figure 1.7). Similar to chronic musculoskeletal pain, the discrepancies observed in studies of acute musculoskeletal

pain could be explained by the presence of different subgroups of individuals characterised by different mechanistic phenotypes.

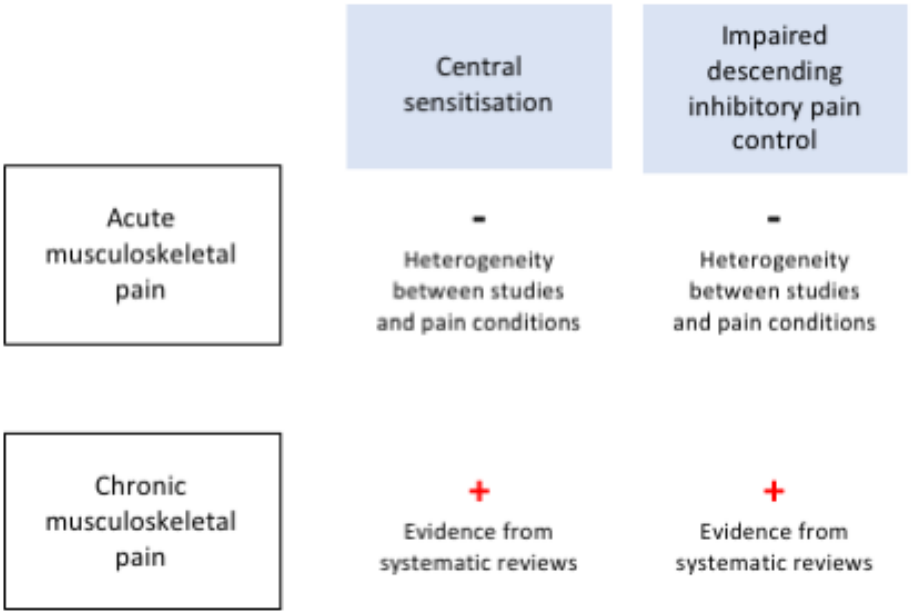

Figure 1.7 Overview of current evidence for central pain processing in musculoskeletal pain. *In acute musculoskeletal pain, there is limited evidence of altered central pain processing. There is heterogeneity between studies and musculoskeletal pain conditions. In chronic musculoskeletal pain, there is evidence of central sensitisation and impaired descending inhibitory pain control from several systematic reviews. However, evidence of altered central pain processing in chronic low back pain is conflicting. Note: ' + ' = supporting evidence; ' – ' = inconclusive evidence.*

Factors that contribute to the development of altered central pain processing in some individuals experiencing musculoskeletal pain but not others, remains unclear. One possible contributing factor could be an individual's past history of pain. Symptom recurrence in musculoskeletal pain is common. For example, one-third of individuals with an acute episode of LBP experience recurrent symptoms within 12 months (da

Silva et al., 2017). As mentioned previously, the literature shows conflicting findings for widespread hyperalgesia and CPM in acute LBP. It is plausible that the degree of central sensitisation and impaired descending pain inhibition in acute LBP is related to an individual's past history of pain with people who have previously experienced LBP presenting with greater sensitisation and greater impairment of descending pain inhibition. However, whether individuals with a prior history of LBP were included in previous study cohorts is not reported. Thus, it is unknown whether those with acute, recurrent LBP display greater central sensitisation and/or impaired descending pain control, than those experiencing a first episode of acute LBP. The influence of a past history of LBP on central pain processing in an acute episode of LBP remains elusive as relevant data are absent.

1.4.3 Study 3 rationale

Musculoskeletal pain demonstrates a variable course of symptomatic episodes and remission, and recurrence (Carroll et al., 2008; da et al., 2012; da Silva et al., 2017; Lda 2009; Vos et al., 2008). The physiological mechanisms of recurrent musculoskeletal pain are poorly understood, although researchers propose altered central pain processing as one possible mechanism (Graven-Nielsen and Arendt-Nielsen 2010; Hartvigsen et al., 2018; Nijs et al., 2016; Vierck 2006; Wand and O'Connell 2008). It is plausible that central pain processing differs between individuals experiencing a first ever episode of acute musculoskeletal pain (e.g. LBP) and those with a history of recurrent acute musculoskeletal pain. However, there has been no research examining central pain processing in acute, recurrent

musculoskeletal pain. Whether changes in central pain processing are consistent in people with acute musculoskeletal pain regardless of pain history remains unknown.

The aim of Study 3 (Chapter 4) was to compare central pain processing between individuals experiencing i) their first episode of acute non-specific LBP, ii) recurrent acute non-specific LBP, and iii) pain-free controls. This was achieved using measures of NFR and QST to evaluate central sensitisation and descending pain inhibitory control. It was hypothesised that: (1) individuals experiencing acute LBP, with or without a previous history of LBP, would have greater central sensitisation and impaired descending inhibitory pain control than pain-free controls, and (2) individuals with recurrent acute LBP would demonstrate greater central sensitisation and impaired descending inhibitory pain control than those experiencing their first episode of acute LBP. This study was the first to explore whether a previous history of LBP affects central pain processing in individuals with an acute episode of LBP.

1.5 Novel treatment for chronic musculoskeletal pain

The previous sections provide the current state of the evidence for sensorimotor plasticity and altered central pain processing, two mechanisms theorised to underpin the development of chronic musculoskeletal pain (see sections 1.2-1.4). However, few existing therapies are specifically designed to target these mechanisms. The addition of non-invasive brain stimulation technologies such as transcranial direct current stimulation (tDCS), to traditional therapy (such as exercise) is a novel, therapeutic approach with the potential to target the neurophysiological

mechanisms of chronic musculoskeletal pain. The following sections review the evidence for exercise and tDCS in chronic musculoskeletal pain.

1.5.1 Evidence for exercise for chronic musculoskeletal pain

Exercise can provide analgesic effects peripherally and centrally. For example, strengthening exercise can modulate peripheral sensory afferents by improving muscle control (i.e. muscle coordination and strength) and proprioception to enhance control of a painful joint, thus reducing nociceptive inputs and optimising normal sensory inputs (Beckwee et al., 2013; Hall et al., 2018; Runhaar et al., 2015). Centrally, exercise is known to induce an endogenous analgesic effect that reduces pain sensitivity in pain-free individuals (Hoffman et al., 2004; O'Leary et al., 2007). This effect is thought to stem from activation of opiodergic mechanisms and upregulation of descending pain control systems (Koltyn and Arbogast 1998; Koltyn et al., 2014; Millan 2002). A systematic review shows that isometric, aerobic and dynamic resistance exercises can reduce sensitivity to painful stimuli in pain-free individuals (Naugle et al., 2012). Similar exercise-induced analgesic effects have also been reported in chronic pain populations (e.g. LBP, rheumatoid arthritis and knee osteoarthritis) (Burrows et al., 2014; Fingleton et al., 2017; Kosek et al., 2013; Meeus et al., 2015).

There is a rich body of evidence examining exercise for the treatment of chronic musculoskeletal pain. A recent overview of 21 Cochrane Reviews shows that exercise has small to moderate effects on pain and physical function across a range of chronic pain conditions (e.g. LBP, osteoarthritis, mechanical neck pain, fibromyalgia) with few

adverse events (Geneen et al., 2017). For example, meta-analyses indicate that hand exercises (e.g. strengthening and flexibility exercises) have small effects on pain, function and joint stiffness for hand osteoarthritis (Østerås et al., 2017). Similarly, there is strong evidence that exercise has small effects on pain and function for chronic LBP (Hayden et al., 2005). However, no single type of exercise is better than another for chronic LBP (Saragiotto et al., 2016). In contrast, it has been shown that strengthening and endurance exercises for the cervico-scapulothoracic and shoulder regions reduce pain and improve function in individuals with chronic neck pain, cervicogenic headache and radiculopathy whereas stretching exercise provides no benefit (Gross et al., 2015a). As a result, exercise has been recommended in clinical guidelines internationally for conditions including LBP (O'Connell et al., 2016; Oliveira et al., 2018), osteoarthritis (Hochberg et al., 2012; McAlindon et al., 2014), and neck pain (Blanpied et al., 2017).

Although there is evidence to support beneficial effects of exercise in chronic musculoskeletal pain, the effects are at best, moderate (Fransen et al., 2015; Maher et al., 2017; Megale et al., 2018; Silva Guerrero et al., 2018). One possible contributing factor could be the presence of different subgroups of individuals within chronic musculoskeletal pain populations. For example, researchers propose that specific exercise targeting distinct subgroups within chronic LBP may provide better patient outcomes and to this end, have attempted to identify subgroups of individuals who might respond better to specific exercise therapy (Foster et al., 2011; Karayannis et al., 2012). However, there is a lack of evidence supporting this assertion. Although motor control exercise has been used to target the subgroup of chronic LBP

individuals with impaired trunk muscle control, research shows that such intervention does not provide additional benefits when compared with general exercise (Saner et al., 2015). Further, it is likely that current exercise programs alone may not adequately target sensorimotor plasticity and altered central pain processing mechanisms in chronic musculoskeletal pain. Novel treatments that enhance the benefits of exercise through synergistic mechanistic effects are one avenue that might better target these mechanisms and further improve clinical outcomes for chronic musculoskeletal pain.

1.5.2 Transcranial direct current stimulation (tDCS)

1.5.2.1 Overview of neurophysiological mechanisms of tDCS

tDCS is a non-invasive brain stimulation technique where weak and painless direct currents are applied to the brain via two scalp electrodes. During the application, tDCS evokes polarisation of the neural tissue under the electrodes and alters neuronal membrane potentials (Nitsche and Paulus 2001). This leads to an increase or decrease in spontaneous neuronal firing that manifests as increased or decreased cortical excitability, reminiscent of neuroplasticity (Miranda et al., 2006; Wagner et al., 2007). Although the physiological mechanisms are not fully understood, tDCS-induced neuroplasticity is thought to be the result of altered synaptic function through modulation of sodium and calcium channels and activation of N-methyl-D-aspartate receptors (Nitsche et al., 2003a; Nitsche et al., 2005a). Altered excitability occurs not only in the region below the electrode but in distant interconnected areas (Lang et al., 2005; Miranda et al., 2006; Wagner et al., 2007). Indeed, applying anodal

tDCS over dorsolateral prefrontal cortex (DLPFC) can increase M1 excitability through functional connections between these cortical regions (Vaseghi et al., 2015).

The direction of change in cortical excitability induced by tDCS is polarity dependent. Although inter-individual variability is high (Chew et al., 2015; Labruna et al., 2016; Strube et al., 2015), application of anodal tDCS over M1 typically results in depolarisation that increases M1 excitability, whereas cathodal tDCS typically results in hyperpolarisation that decreases M1 excitability (Nitsche et al., 2003b; Nitsche and Paulus 2000; 2001). Thus, tDCS electrode placement is subject to the desired neuromodulating effect. For example, to increase M1 excitability, the anodal is applied over the M1 contralateral to the target body region with the cathodal over an inactive site (e.g. the ipsilateral frontal lobe). The increase in cortical excitability induced by anodal tDCS may outlast the stimulation period and continue for up to 90 minutes (Nitsche and Paulus 2001). While altered M1 excitability during stimulation results from altered resting membrane potential, the after-effect involves increased M1 intracortical facilitation and decreased M1 intracortical inhibition (Nitsche et al., 2003b; Nitsche et al., 2005a).

Research shows that tDCS has an analgesic effect, thought to involve the modulation of pain processing in cortical and subcortical regions (e.g. M1, ACC, thalamus) and upper brainstem, upregulating descending inhibitory pain mechanisms, and inducing synaptic neuroplasticity in underlying brain regions (Fenton et al., 2009; Fregni et al., 2006a; Fregni et al., 2006b; Garcia-Larrea et al., 1999; Nitsche et al., 2005a; Strafella et al., 2004). Recent meta-analyses from a Cochrane Review demonstrate that tDCS

has a small effect on pain (17% reduction in pain intensity, a clinically important difference) and a moderate effect on quality of life in chronic pain populations (O'Connell et al., 2018). However, as the review includes studies investigating central pain from neurological disorders (i.e. stroke, spinal cord injury, multiple sclerosis) and viral infections, the evidence for musculoskeletal pain remains uncertain.

1.5.2.2 Factors to be considered in tDCS application

Current evidence indicates that the use of tDCS in humans is safe (Pinto et al., 2018). There are few, mild and transient adverse events (e.g. tingling, itchiness, skin redness, headaches, sleepiness and trouble concentrating) reported by individuals receiving active and sham stimulation (Nikolin et al., 2018; O'Connell et al., 2018). Indeed, the latest safety data show that tDCS protocols (stimulation duration $\leq$ 40 minutes, current intensity $\leq$ 4 mA) in human trials (over 33200 sessions and 1000 individuals with repeated sessions) have not caused any serious adverse events (Bikson et al., 2016). A systematic review indicates that repeated exposure to active tDCS is unlikely to increase risk of adverse events when compared with sham tDCS (Nikolin et al., 2018).

As tDCS protocols used in clinical trials comprise different parameters such as target brain area (mostly M1 or DLPFC), current intensity (1 or 2 mA), number of treatments (5-10 consecutive sessions) and stimulation duration (10-30 minutes), the optimal stimulation protocol for chronic pain remain unclear (O'Connell et al., 2018). Another important factor to be considered when determining the tDCS protocol for chronic pain is whether the effects of adding tDCS to other therapies differ from those of

using tDCS alone. Indeed, the use of tDCS as an adjunct intervention to traditional therapies has been proposed as a novel therapeutic approach to provide better clinical outcomes for chronic musculoskeletal pain (Schabrun and Chipchase 2012b). There is a growing body of research in the combined application of tDCS and conventional therapies. The following section will provide an overview of relevant literature in this area.

1.5.3 Addition of tDCS to exercise for chronic musculoskeletal pain

With the capacity to modulate cortical excitability, tDCS has the potential to enhance the effectiveness of conventional therapies such as exercise in chronic musculoskeletal pain. Specifically, as increased M1 excitability is associated with motor learning (Bagce et al., 2013; Hirano et al., 2015; Jensen et al., 2005; Ljubisavljevic 2006), applying anodal tDCS over M1 is thought to bolster the brain's responsiveness to the afferent input generated by subsequent treatment such as motor control training or exercise through a phenomenon known as '*priming'* (Hendy and Kidgell 2013; Reis and Fritsch 2011; Schabrun and Chipchase 2012b). In the neuroplasticity context, priming is defined as 'enhancing the sensitivity of the brain to therapy by using techniques that increase or decrease the excitability of the cortex' (Schabrun and Chipchase 2012b). Indeed, tDCS has been used as a priming device to augment the effects of conventional rehabilitation for neurological disorders (e.g. stroke, cerebral palsy, Parkinson's disease) (Duarte Nde et al., 2014; Geroin et al., 2011; Hesse et al., 2011; Kaski et al., 2014).

Applying anodal tDCS over M1 in addition to exercise therapy has the potential to bolster the mechanistic and clinical effects of exercise through two mechanisms. First, anodal tDCS can prime the brain to increase its responsiveness to the corticomotor benefits of exercise, including increased cortical excitability, greater voluntary muscle activation, strength gains, better muscle coordination and motor control (Koltyn and Arbogast 1998). Second, adding anodal tDCS to exercise may exert additive and complementary effects on pain modulation pathways already activated by exercise. Therefore, the combined application of tDCS and exercise may enhance mechanistic and clinical outcomes in musculoskeletal pain.

While tDCS has been used to enhance the effects of various therapies on pain and function in chronic pain populations, the results are mixed (Table 1.2). The inconsistent evidence is likely due to the heterogeneity of tDCS protocols and pain conditions and small study sample sizes. Furthermore, research investigating the effects of adding tDCS to an exercise program in individuals with chronic musculoskeletal pain is scarce. Only one study examines the effect of adding tDCS to exercise for chronic musculoskeletal pain (Mendonca et al., 2016). That study demonstrates greater decreases in pain intensity and anxiety in individuals with fibromyalgia when anodal tDCS over M1 is delivered during aerobic exercise than when tDCS or exercise are delivered alone. Another study combining tDCS and an exercise regime (including manual therapy) shows no additional effect on pain in individuals with temporomandibular disorder (Oliveira et al., 2015). The unfavourable result of that study is likely due to a lack of priming effect as tDCS was delivered *after* exercise. There has been no study investigating the effects of adding

tDCS to other forms of exercise (e.g. strengthening exercise) in chronic musculoskeletal pain.

Table 1.2 Studies using combined intervention of transcranial direct current stimulation and other therapies in chronic pain populations.

Study	Population (Sample size)	Study Design	Intensity (mA); Duration (minutes)	Anodal	Cathodal	Other therapy	Groups	No. of stimulation	Outcome measures	Results
(Boggio et al., 2009)	Stroke (3) and neuropathic pain (5)	Crossover	2; 30	M1 contralateral to pain	Supraorbital ipsilateral to pain	TENS	tDCS/TENS; tDCS/sham TENS; sham tDCS/sham TENS	1	Pain intensity (VAS)	Significant pain reduction as compared with baseline after tDCS/TENS and tDCS condition, but not after sham stimulation. tDCS/TENS induced greater pain reduction than tDCS.
(Soler et al., 2010)	Spinal cord injury (39)	RCT	2; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	Visual illusion (VI)	tDCS/VI; tDCS/sham VI; sham tDCS/VI; sham tDCS/sham VI	10 (daily for 2 weeks)	Pain intensity, Neuropathic Pain Symptom Inventory and Brief Pain Inventory	tDCS/VI reduced the intensity pain more than other interventions. tDCS/VI showed a improvement in all pain subtypes. At 12 weeks after treatment, only tDCS/VI still presented significant improvement on the overall pain intensity.

(Riberto et al., 2011)	Fibromyalgia (23)	RCT	2; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	Multidisciplinary rehabilitation	tDCS/rehab; sham tDCS/rehab	Weekly rehab (3x/week) and tDCS (once a week) for 4 months	Pain (VAS), quality of life with SF-36, fibromyalgia pain questionnaire and health assessment questionnaire	tDCS/rehab had a significantly greater reduction of SF-36 pain domain scores and as compared with sham tDCS/rehab treatment
(Kumru et al., 2013)	Spinal cord injury (52)	Parallel arm study	2; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	Visual illusion (VI)	tDCS/VI	10 (daily for 2 weeks)	Pain (numerical rating scale); heat pain thresholds	13 patients reported a mean decrease of 50% in pain after tDCS/VI and improved heat pain threshold
(Choi et al., 2014)	Myofascial pain syndrome (21)	Parallel arm study	2; 20	M1 or DLPFC contralateral to pain	Supraorbital ipsilateral to pain	Trigger point injection (TPI)	tDCS (M1)/TPI; tDCS (DLPFC)/TPI; sham tDCS/TPI	5 consecutive sessions	Pain (VAS)	The mean VAS values were decreased in all three groups after 5 days. There was a significant change between before and after stimulation only in the DLPFC group.
(Sakrajai et al., 2014)	Myofascial pain syndrome (31)	RCT	1; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	Standard care: stretching, ultrasound, hot packs, posture instruction	tDCS/standard care; sham tDCS/ standard care	5 consecutive sessions	Pain, passive range of motion, physical function	tDCS reported significantly more reductions in pain intensity and more improvement in shoulder adduction PROM that at 1-week follow-up than sham tDCS

(Schabrun et al., 2014a)	Chronic recurrent Low back pain (20)	Crossover	1; 30	M1 contralateral to pain	Supraorbital ipsilateral to pain	Peripheral electrical stimulation (PES)	tDCS/PES; tDCS/ sham PES; sham tDCS/ PES; sham tDCS/sham PES	1	Pain (VAS); M1 organisation; sensitisation and sensory function	tDCS/PES reduced pain and sensitization, normalised M1 organization and improved sensory function.
(Luedtke et al., 2015)	Chronic low back pain (135)	Parallel arm study	2; 20	Left M1	Right Supraorbital	Cognitive behavioural management (CBM)	tDCS/ CBM; sham tDCS/ CBM	5 consecutive sessions	Pain (VAS) and disability (Oswestry disability index)	tDCS was ineffective for pain and disability, and did not influence the outcome of CBM
(Oliveira et al., 2015)	Temporomandibular disorder (32)	RCT	2 (20)	M1 contralateral to pain	Supraorbital ipsilateral to pain	Myofascial release, exercise, joint mobilisation	Exercise/tDCS; exercise/sham tDCS	5 consecutive sessions	Pain (VAS)	Both groups showed a decrease in pain but there were no differences between groups
(Mendonca et al., 2016)	Fibromyalgia (45)	RCT	2; 20	Left M1	Right Supraorbital	Aerobic exercise (AE)	tDCS/AE; tDCS/control AE; sham tDCS/AE	5 consecutive sessions	Pain (VAS), level of anxiety, mood, M1 plasticity	tDCS/AE had a significant effect on pain, anxiety and mood.
(Hazime et al., 2017)	Chronic low back pain (92)	RCT	2; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	PES	tDCS/PES; tDCS/sham PES; Sham tDCS/PES; Sham tDCS/sham PES	12	Pain (VAS), disability and global perception	A 2-point pain reduction was achieved only by active tDCS/PES and PES alone. Global perception was improved at 4 weeks and maintained 3

										months after treatment only with active tDCS/PES. None of the treatments improved disability.
(Thibaut et al., 2017)	Chronic visceral pain (6)	Crossover	2; 20	Left M1	Right Supraorbital	Transcranial pulsed current stimulation (tPCS)	tDCS/tPCS; tPCS; tDCS; sham	1	Pain (VAS)	No effects on pain
(Lagueux et al., 2018)	Complex regional pain syndrome (22)	RCT	2; 20	M1 contralateral to pain	Supraorbital ipsilateral to pain	Graded motor imagery (GMI)	tDCS/GMI; sham tDCS/GMI	5 consecutive sessions in the first 2 weeks then 1x/week for 4 weeks	Pain (Brief Pain inventory)	No difference in pain.
(Schabrun et al., 2018)	Chronic low back pain (16)	Crossover	1; 30	M1 contralateral to pain	Supraorbital ipsilateral to pain	PES	tDCS/PES; tDCS/sham PES; sham tDCS/PES; sham tDCS/sham PES	1	Pain severity (11-point NRS), M1 excitability pain sensitization, Schober's test and two-point discrimination	Pain reduced in all 3 active interventions. tDCS/PES led to an increased range of motion of forward flexion and PPT increased at the site of pain. tDCS/PES increased M1 excitability in the LBP group but had no effect in controls.

(Yoo et al., 2018)	Fibromyalgia (58)	Parallel arm study	2; 20 or 40	Left DLPFC	Right DLPFC	Occipital nerve stimulation (ONS)	Sham ONS; tDCS on the occipital nerve; tDCS on bilateral DLPFC before ONS	8	Fibromyalgia Impact Questionnaire, the Beck Depression Inventory and pain	Both groups improved in sham stimulation but the prefrontal added group had no additional effect on improving any of the tested measures.

DLPFC = dorsolateral prefrontal cortex; M1= the primary motor cortex; RCT = randomised controlled trial; tDCS = transcranial direct current stimulation; VAS = visual analogue scale.

1.5.4 Study 4 rationale

Knee osteoarthritis is a prevalent health problem causing significant pain, physical dysfunction and reduced quality of life (Vos et al., 2015). Strengthening exercise is the cornerstone of conservative treatment for knee osteoarthritis and is recommended in all clinical guidelines (Hochberg et al., 2012; McAlindon et al., 2014). While exercise is effective in knee osteoarthritis, meta-analyses indicate treatment benefits are at best, moderate, for pain and physical function, and small in quality of life (Fransen et al., 2015). As mentioned previously, adding anodal tDCS over M1 may bolster the mechanistic effects and therapeutic benefits of strengthening exercise for knee osteoarthritis and improve clinical outcomes. However, there has been no research investigating the effects of adding tDCS to strengthening exercise in individuals with osteoarthritic pain.

The aim of Study 4 (Chapter 5) was to: (1) determine the safety, feasibility and patient-perceived response of adding tDCS to an exercise program for knee osteoarthritis; and (2) provide data to inform a sample size calculation for a fully-powered trial based on trends of efficacy in pain, physical function and pain system function should these be observed. This was achieved by conducting a pilot randomised, assessor- and participant-blind, sham-controlled trial. Eligible individuals with knee osteoarthritis were randomly allocated to receive either *active tDCS + exercise*, or *sham tDCS + exercise*. Outcome measures of feasibility, safety, pain, function and pain system function were assessed immediately before and after the 8-week intervention. This pilot study was the first to examine the potential

therapeutic effects of adding tDCS to strengthening exercise for chronic musculoskeletal pain.

In the following chapters (Chapter 2 to 5) each study is described in detail.

Chapter 2

Altered Primary Motor Cortex Structure, Organisation and Function in Chronic Pain: A Systematic Review and Meta-Analysis

As discussed in detail in Chapter 1, maladaptive neuroplasticity in M1 is a prevailing theory underpinning the symptoms of pain and movement dysfunction in chronic musculoskeletal pain. The aim of this chapter is to systematically review and meta-analyse these data from a comprehensive range of neurophysiological measures in chronic pain. The content has been published in *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. 19:341-359, 2018*. A copy of this publication is provided in Appendix A. **Note**: the protocol of this study has been published in *Chang WJ, O'Connell NE, Burns E, Chipchase LS, Liston MB, Schabrun SM. Organisation and function of the primary motor cortex in chronic pain: protocol for a systematic review and meta-analysis. BMJ open. 5:e008540, 2015.* A copy of this publication is provided in Appendix B.

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2.1 Abstract

Chronic pain can be associated with movement abnormalities. The primary motor cortex (M1) has an essential role in the formulation and execution of movement. A number of changes in M1 function have been reported in studies of people with chronic pain. This review systematically evaluated the evidence for altered M1 structure, organisation and function in people with chronic pain of neuropathic and non-neuropathic origin. Database searches were conducted and a modified STROBE checklist was used to assess the methodological quality of included studies. Meta-analyses, including pre-planned subgroup analyses based on condition were performed where possible. Sixty-seven studies (2290 participants) using various neurophysiological measures were included. There is conflicting evidence of altered M1 structure, organisation and function for neuropathic and non-neuropathic pain conditions. Meta-analyses provided evidence of increased M1 long-interval intra-cortical inhibition in chronic pain populations. For most measures, the evidence of M1 changes in chronic pain populations is inconclusive.

Perspective: This review synthesises the evidence of altered M1 structure, organisation and function in chronic pain populations. For most measures, M1 changes are inconsistent between studies and more research with larger samples and rigorous methodology is required to elucidate M1 changes in chronic pain populations.

2.2 Introduction

Chronic pain conditions such as low back pain (LBP), neck pain and knee osteoarthritis (OA) are leading causes of disability globally (Vos et al., 2012) and are associated with significant and rising health-care and socio-economic costs (March et al., 2014). Despite this, effective treatment remains elusive.

People with chronic pain conditions commonly present with abnormalities of movement. For example, excessive finger flexion has been reported during grip release in chronic lateral elbow pain, greater hip adduction and internal rotation during stair climbing in lateral hip pain, and delayed onset of trunk muscle activation during arm elevation in recurrent LBP (Allison et al., 2016; Heales et al., 2016; Tsao et al., 2008). As a result, rehabilitation to target movement dysfunction is a treatment for musculoskeletal pain. However, treatment success with this approach is limited (Airaksinen et al., 2006; Qaseem et al., 2017) and there is debate regarding the type, quantity and timing of interventions needed to effectively target movement dysfunction in chronic musculoskeletal pain or indeed whether such an approach is warranted (Aladro-Gonzalvo et al., 2013; Gross et al., 2015b; Hayden et al., 2005).

The physiological basis of movement dysfunction in pain is poorly understood. The primary motor cortex (M1) has an essential role in the formulation and execution of movement and is likely to have a role in movement abnormalities. Indeed, a recent systematic review provided evidence of reduced M1 output (i.e. corticospinal excitability) in response to acute muscle pain that may represent an adaptive mechanism to protect against further pain or injury (Burns et al., 2016b). Similarly,

studies investigating M1 in experimental models of progressively developing, sustained muscle pain show altered M1 organisation (increased representations of painful muscles) and function (reduced M1 inhibition) four days after pain onset (Schabrun et al., 2016). Studies have reported that changes in M1 structure, organisation and function may also be present when pain becomes chronic. For example, associations have been reported between the severity of pain and/or the degree of movement dysfunction in chronic musculoskeletal disorders such as low back, elbow and patellofemoral pain and reorganisation of the M1 representation (i.e. greater representational overlap, reduced number of discrete peaks) of muscles in the region of pain (Schabrun et al., 2015b; Schabrun et al., 2015c; Te et al., 2017). However, it is unclear whether M1 reorganisation presents in other chronic pain conditions and whether it can be observed via different neurophysiological methods.

Previous reviews examining changes in M1 in chronic pain have been restricted to specific pain conditions or by the neurophysiological method used to assess M1. For instance, a systematic review revealed limited evidence for bilateral M1 disinhibition in complex regional pain syndrome (CRPS) of the upper limb (Di Pietro et al., 2013a). Whether similar alterations in M1 are present in other forms of chronic pain is unknown. Indeed, it has been suggested that M1 disinhibition may occur in chronic neuropathic but not chronic nociceptive pain (Schwenkreis et al., 2010). A second systematic review reported similar findings of disinhibition across a range of chronic pain conditions (including migraine) but was restricted to data obtained using transcranial magnetic stimulation (TMS) (Parker et al., 2016). The integration of information on M1 structure, organisation and function across i) a range of

neuropathic and non-neuropathic conditions, and ii) using a range of complementary neurophysiological techniques, is necessary to provide comprehensive information on whether M1 is altered in chronic pain. This information is timely given the range of treatment techniques being tested that target M1 in chronic pain (Chang et al., 2015a; Mendonca et al., 2016; Sakrajai et al., 2014; Schabrun et al., 2014a).

The aim of this review was to systematically evaluate the evidence of altered M1 structure, organisation and function in chronic pain conditions of neuropathic and non-neuropathic origin across a range of neurophysiological methods.

2.3 Methods

The protocol of this review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42015014823) and has been published elsewhere (Chang et al., 2015b) (Appendix B). This review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

2.3.1 Search Strategy

The search was conducted in five electronic databases (PubMed, MEDLINE, Embase, PsychINFO and CINAHL) from inception to February 2017, using key words and medical subject headings (MeSH) terms related to chronic pain and M1 organisation/function (Appendix A.1). The reference list of eligible studies and relevant reviews were manually searched for additional articles.

2.3.2 Eligibility criteria

Inclusion criteria were: (1) full text studies published in English, including in press or accepted studies, (2) adult (aged over 18 years) humans with non-neuropathic or neuropathic pain, (3) duration of pain greater than three months (Ostelo et al., 2005), (4) investigated and reported measures of the organisation and/or function of the primary motor cortex (regardless of the anatomical or functional definition used) using TMS, magnetic resonance imaging (MRI), electroencephalography (EEG) magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) (Table 2.1). Studies were excluded if: included participants presented chronic pain associated with neurological disorders, cancer or visceral pain, or the study did not include a healthy control group or used the unaffected limb or body side as a control. Cross-sectional or prospective studies, including case-control and randomised controlled trials that provided baseline data with information relevant to the review objective and that met the eligibility criteria, were included.

Table 2.1 Summary of M1 structural, organisational and functional constructs and their associated neurophysiological methods and outcome measures.

	M1 structure	**M1 organisation**	**M1 function**
Neurophysiological Methods and outcome measures	MRI- Cortical thickness (voxel-based morphometry); White matter structure (diffusion tensor imaging)	Functional MRI- Activation/connectivity (regional cerebral blood flow, blood-oxygen-level-dependent contrast) TMS- M1 representation (Map volume, centre of gravity of M1 representation)	TMS- Corticospinal excitability (rMT, aMT, MEP amplitude and latency, CSP); intra-cortical facilitation/inhibition EEG- Cerebrocortical motor activity MEG- 20-Hz cortical rhythm (rebound amplitude/duration, reactivity) MRS- Neurochemical metabolism PET- Glucose metabolism

MRI = magnetic resonance imaging; TMS = transcranial magnetic stimulation; EEG = electroencephalography; MEG = magnetoencephalography; MRS = magnetic resonance spectroscopy; PET = positron emission tomography; rMT = resting motor threshold; aMT = active motor threshold; MEP = motor evoked potential; CSP = cortical silent period.

2.3.3 Study selection

Search results were imported into Endnote X7. After removing duplicates, two reviewers independently screened titles and abstracts of all studies to remove those not relevant to the review objective. The full text of all remaining studies was retrieved and evaluated against the eligibility criteria. If there was uncertainty or disagreement, a third reviewer was consulted.

2.3.4 Data extraction

Two independent reviewers extracted the following data: pain condition, country of origin, study design and setting, inclusion/exclusion criteria, source of participants, sample size, participant demographics, duration and severity of chronic pain, neurophysiological methods, specifics of the investigative model, type and location of stimulation and outcomes (i.e., M1 excitability, representation, reactivity, neurochemical or glucose metabolism). Any disagreements were resolved in consensus with a third reviewer. If data were missing authors were contacted a maximum of three times, after which the data were considered irretrievable.

2.3.5 Quality and risk of bias assessment

Study quality and risk of bias were assessed by two independent reviewers using a modified version of the STROBE statement for cross-sectional and cohort studies (Parkitny et al., 2013; von Elm et al., 2007; 2014). Disagreements were resolved by consensus with a third reviewer. The modified STROBE statement looked at potential for bias in five domains: (1) source of participants, (2) participant selection, (3) methodology, (4) statistical analysis, and (5) funding (Appendix A.2). Each domain

would be allocated 1 point if the risk of bias was low and no point if the risk of bias was considered high. The maximum score possible was five points. For studies using TMS, an additional methodological quality assessment was undertaken using an adapted version of the TMS methodological checklist (Chipchase et al., 2012a). Two items that were not relevant for this review were removed from the checklist (Item 22 - time between days of testing and item 30 - size of the unconditioned MEP controlled). Each domain that was reported (r) and/or controlled (c) was allocated 1 point. In total, the maximum score possible for the reported and controlled items of the TMS methodological checklist were, respectively, 26 and 25 for single-pulse TMS, and 29 and 28 for paired-pulse TMS. The ratio of the summed score relative to the maximum score for the reported [r/(26 or 29)x100] and controlled [c/(25 or 28)x100] items was calculated. The median percentage for the reported and controlled items was then calculated. TMS studies received one point in the '*methodology*' category of the modified STROBE statement if the percentage of reported and controlled items were both above the median value.

2.3.6 Data synthesis

Meta-analyses were performed to aggregate the data from TMS studies. Due to increased heterogeneity in the methodology of included studies, a narrative synthesis was used to summarise the findings of studies using other neurophysiological methods (Shamseer et al., 2015). TMS outcome measures (resting and active motor threshold (rMT and aMT), motor evoked potential (MEP) amplitude and latency, cortical silent period (CSP), map volume, intra-cortical inhibition and facilitation) were pooled and separate meta-analyses were performed using Review

Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Cohen d effect sizes were used to analyse effect estimates (d ≤ 0.2 small; 0.5 moderate; ≥ 0.8 large) (Cohen 1998). Meta-analyses were performed using random-effects model when data from at least two studies addressing that outcome were accessible. Statistically significant heterogeneity was identified using the χ^2 test and was considered when χ^2 $P < 0.10$. The I^2 statistic was used to evaluate the degree of heterogeneity. Substantial heterogeneity was considered present when $I^2 > 50\%$ (Higgins and Green 2011). Meta-analysed data are presented as effect estimates (standardised mean difference with 95% confidence intervals).

2.3.7 Subgroup and sensitivity analysis

Pre-planned subgroup analyses were conducted according to the type of musculoskeletal condition where significant heterogeneity was identified. The median value of the modified STROBE statement score of the TMS studies was used as a cut-off point to divide studies into either low or high risk-of-bias groups. The influence of high risk-of-bias studies was examined by re-running the analysis with those studies excluded.

2.4 Results

The initial search identified 5028 records, from which 120 full text articles were retrieved to assess eligibility. Sixty-nine studies met the inclusion criteria in the review. The authors of 14 studies were contacted to request additional data pertaining to M1 function. Two studies were excluded as a result of unsuccessful attempts to acquire these data (Daligadu et al., 2013; Vidor et al., 2014). Thus, a total

of 67 studies were included in this review. The study flow chart can be seen in Figure 2.1.

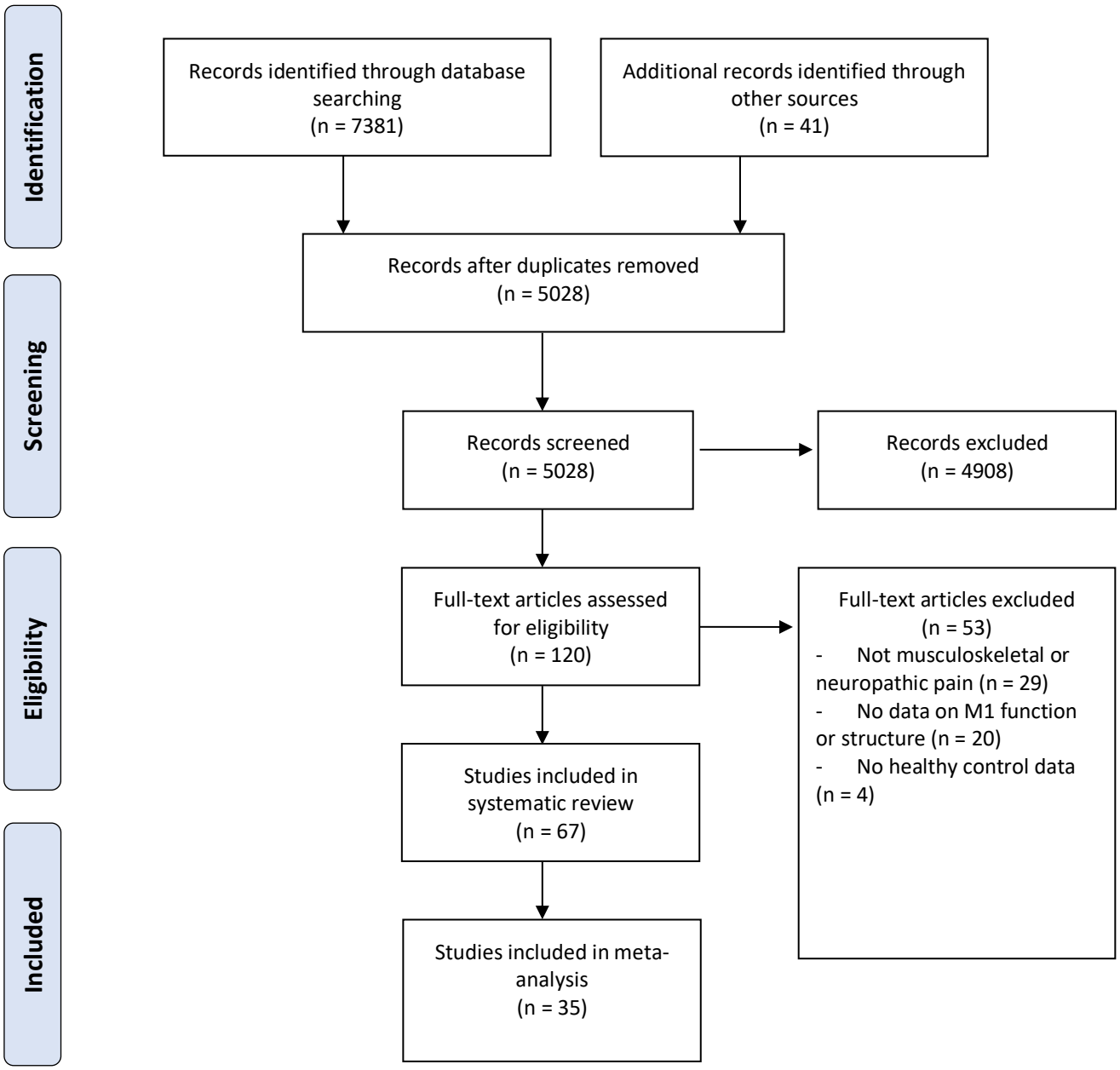

Figure 2.1 PRISMA flow diagram of the screening and inclusion of studies.

2.4.1 Study characteristics

The included studies encompassed seven neurophysiological methods: TMS (n=35 studies), fMRI (n=16 studies), MRI (n=6 studies), MEG (n=3 studies), MRS (n=3 studies), EEG (n=1 study), and PET (n=1 study). Two studies investigated both functional and structural MRI changes (Tian et al., 2016; van Velzen et al., 2015). In total, the included studies involved 1248 chronic pain (20 different pain conditions) and 1042 healthy participants. CRPS (n=16 studies) and LBP (n=16 studies) were the most frequently investigated conditions. Five studies investigated two or more chronic pain conditions (Caumo et al., 2016; Rio et al., 2016; Rittig-Rasmussen et al., 2014; Salerno et al., 2000; Schwenkreis et al., 2010). Participant sex (n=4 studies) and age (n=3 studies), pain intensity (n=22 studies), and the duration of the pain (n=7 studies) were not reported by some of the included studies. The characteristics of included studies are summarised in Table 2.2 and 2.3.

Table 2.2 Characteristics of included studies using transcranial magnetic stimulation (TMS).

Study (First author, Year)	Condition	Country	Chronic Pain Participants				Healthy Participants		Modality	Stimuli	Target Muscles	Outcome Measures
			Study Size (M/F)	Age	Pain Duration	Pain Intensity (0-10)	Study Size (M/F)	Age				
(Salerno et al., 2000)	Fibromyalgia Rheumatoid arthritis	France	13 (0/13) 5 (0/5)	50.1 ± 5.6 50.0 ± 5.1 (SEM)	NA	NA	13 (NA)	49.1 ± 5 (SEM)	Double cone coil on cortical representation of the target muscles	Single and paired pulses	First dorsal interosseous, Tibialis anterior	rMT, MEP amplitude, CSP, SICIC, ICF, LICI
(Schwenkreis et al., 2003)	CRPS I- Hand	Germany	25 (9/16)	49.1 ± 13.8	26.1 ± 47 months	NA	20 (10/10)	20-78 (95% CI)	Circular coil (14 cm) on vertex	Single and paired pulses Mono-phasic*	First dorsal interosseous	rMT, MEP amplitude, SICI, ICF
(Strutton et al., 2003)	Chronic sciatica	UK	9 (NA)	NA	NA	NA	7 (NA)	NA	Double cone coil on hotspot	Single pulse Mono-phasic*	Tibialis anterior, Lateral gastrocnemius	rMT, aMT
(On et al., 2004)	Patello-femoral pain	Turkey	13 (0/13)	25 ± 8.1 (SEM)	3.46 ± 1.9 years (SEM)	NA	13 (0/13)	25.1 ± 7.4 (SEM)	Circular coil (9 cm) on hotspot	Single pulse Mono-phasic	Vastus medialis obliques, Vastus lateralis, Extensor digitorum brevis	MEP amplitude,

(Eisenberg et al., 2005)	CRPS I- Hand	Israel	6 (4/2)	33 ± 12.7	31 ± 41 months	7.3 ± 3.1	14 (10/4)	30.9 ± 12.7	Figure of eight coil (9 cm) on Hotspot	Single and paired pulses Mono-phasic*	Abductor pollicis brevis	SICI
	CRPS I- Foot		6 (5/1)	32 ± 9	20 ± 21 months	6.7 ± 2.3						
(Krause et al., 2005)	CRPS I- Hand	Germany	12 (2/10)	55.9 ± 15.6	NA	NA	10 (NA)	42.4	Figure of eight coil (9 cm) on Hotspot	Single pulse Mono-phasic*	Long extensor muscle	rMT, MEP amplitude, CSP
(Strutton et al., 2005)	Low back pain	UK	24 (15/9)	39.1 ± 2.2	NA	NA	11 (7/4)	35.9 ± 3.2	Double cone coil on vertex	Single pulse Mono-phasic*	Erector spinae	aMT, MEP latency, CSP
(Krause et al., 2006)	CRPS- Hand	Germany	14 (4/10)	37 (17-72)	> 6 months	NA	10	38 (24-63)	Figure of eight coil (7 cm) on M1	Single pulse Mono-phasic*	Long extensor muscle	rMT, MEP amplitude, Map volume
(Turton et al., 2007)	CRPS I- Hand	UK	8 (1/7)	45 ± 13	6.6 ± 4.9 years	6.3 ± 1.4	8 (1/7)	45 ± 13	Figure of eight coil (9.5 m) on Hotspot	Single pulse Mono-phasic*	Abductor pollicis brevis	MEP amplitude

(Tsao et al., 2008)	Low back pain	Australia	11 (5/6)	24 ± 7	5.6 ± 4.2 years	5.5 ± 2	11 (4/7)	23 ± 3	Figure-of-eight coil (7cm) and Double cone coil (11cm) on hotspot and M1	Single pulse Mono-phasic	Transversus abdominus	rMT, aMT, Map volume
(Berth et al., 2009)	Rotator cuff tear	Germany	10 (10/0)	64.9 ± 4.6	> 6 months	NA	13 (10/3)	27.2 ± 8.1	Figure of eight coil on hotspot	Single pulse Mono-phasic*	Deltoid	MEP amplitude,
(Turgut and Altun 2009)	Diabetic neuropathic pain	Turkey	20 (5/15)	63.9 ± 7.3	12.4 ± 6.7 years	8.1 ± 1.3	30 (14/16)	58.3 ± 6.5	Circular coil (14 cm) on hotspot	Single pulse NA	First dorsal interosseous	rMT, MEP amplitude, MEP latency, CSP
(Mhalla et al., 2010)	Fibromyalgia	France	21 (0/21)	52.2 ± 10.4	14.1 ± 11.9 years	5.5 ± 1.3	21 (0/21)	46.7 ± 11.6	Figure of eight coil	Single and paired pulses NA	First dorsal interosseous	rMT, SICI, ICF
(Schwenkreis et al., 2010)	Neuralgia-Hand Osteoarthritis hand	Germany	26 (14/12) 20 (10/10)	50.9 ± 11.7 56.6 ± 10.2	39.3 ± 44.8 months 35.6 ± 42.9 months	4.7 ± 2.1 3.9 ± 2	14 (6/8)	58.8 ± 12.7	Circular coil (14 cm) on vertex	Single and paired pulses Mono-phasic	First dorsal interosseous	rMT, SICI, ICF

(Clark et al., 2011)	Low back pain	USA	10 (5/5)	23.7 ± 6.1	3.2 ± 3.1 years	2.6 ± 1.6	10 (5/5)	22.9 ± 1.9 (SEM)	Custom-modified 110-mm double cone coil on vertex	Single pulse NA	Erector spinae	MEP amplitude
(Schwenkreis et al., 2011)	Fibromyalgia	Germany	16 (2/14)	48.7 ±8.4	NA	NA	23 (7/16)	37.7 ± 11.5	Circular coil (14 cm) on vertex	Single and paired pulses Mono-phasic*	Forearm superficial flexor	rMT, MEP amplitude, CSP, SICI, ICF
(Tsao et al., 2011)	Low back pain	Australia	9 (4/5)	25 ± 3.4	3.6 ± 2.3 years	4.7 ± 1.1	11 (5/6)	24 ± 5	Figure of eight coil (7 cm) on M1	Single pulse Mono-phasic	Deep multifidus, erector spinae	Map volume
(Masse-Alarie et al., 2012)	Low back pain	Canada	13 (6/7)	53.7 ± 7.4	16 ± 10 years	2.9 ± 2.5	9 (4/5)	48.7 ± 6.8	Double cone coil (7 cm) on hotspot	Single and paired pulses Mono-phasic	Transversus abdominus, Internal oblique	MEP amplitude, SICI

(Vallence et al., 2013)	Chronic tension type headache	Australia	11 (5/6)	35 ± 13.2	3.5 ± 1.7	NA	18 (7/11)	28 ± 8 (unclear)	Figure of eight (9cm) on hotspot	Single pulse Mono-phasic*	Abductor pollicis brevis	rMT, MEP amplitude
(Kittelson et al., 2014)	Osteoarthritis knee	USA	17 (8/9)	63.9 ± 1.8 (SEM)	NA	NA	20 (10/10)	58.3 ± 2.5 (SEM)	Double cone coil on hotspot	Single and paired pulses Mono-phasic*	Vastus lateralis	rMT, MEP amplitude, SICI, ICF
(Marker et al., 2014)	Neck pain	USA	9 (2/7)	42.4 ± 11	> 12 months	1.7 ± 1.4	8 (4/4)	31.5 ± 14.5	Figure of eight coil (7 cm) on hotspot	Single and paired pulses Mono-phasic	Upper trapezius	rMT, aMT, MEP amplitude, SICI
(Rittig-Rasmussen et al., 2014)	Neck pain Knee pain	Denmark	20 (14/6) 15 (10/5)	29 ± 7 27 ± 6	> 3 months	1.7 ± 0.6 1.5 ± 0.6	15 (12/3)	25 ± 3.5	Figure of eight coil on hotspot	Single pulse Mono-phasic	Upper trapezius, Abductor pollicis brevis	aMT, MEP amplitude, MEP latency

(Bradnam et al., 2016)	Shoulder pain	Australia	8 (1/7)	64.9 (49-75)	> 12 months	4.4 ± 1.2	18 (9/8)	41.3 (20-68)	Figure of eight (7 cm) on hotspot	Single pulse Mono-phasic*	Infraspinatus	aMT, MEP amplitude, CSP
(Schabrun et al., 2015b)	Low back pain	Australia	27 (13/14)	30 ± 9	5.3 ± 4 years	4.6 ± 1.9	23 (12/11)	27 ± 5	Figure of eight coil on M1	Single pulse Mono-phasic	L3 and L5 erector spinae	Map volume
(Schabrun et al., 2015c)	Lateral epicondylalgia	Australia	11 (5/6)	44 ± 11	9 ± 6 months	2.7 ± 2	11 (5/6)	42 ± 11	Figure of eight coil (7 cm) on M1	Single pulse Mono-phasic*	Extensor carpi radialis brevis, Extensor digitorum	rMT, MEP amplitude, Map volume
(van Velzen et al., 2015)	CRPS I- Hand	Netherlands	12 (2/10)	51 ± 9.5	88 ± 26.9 months	6.7 ± 1.8	12 (1/11)	52 ± 13	Figure of 8 coil on hotspot	Single pulse Biphasic*	First dorsal interosseous	rMT, MEP amplitude
(Burns et al., 2016a)	Lateral epicondylalgia	Australia	14 (4/10)	41.5 ± 9.9	37.3 ± 74.8 months	3.5 ± 2.8	14 (4/10)	42.1 ± 11.1	Circular coil (9 cm) on hotspot	Single and paired pulses Mono-phasic*	Extensor carpi radialis brevis	rMT, aMT, MEP amplitude, SICI, ICF, LICI

(Caumo et al., 2016)	Myofascial pain	Brazil	54 (0/54)	46.1 ± 12.1	NA	7.2 ± 2.2	14 (0/14)	32.4 ± 10.8	Figure of eight coil on M1	Single and paired pulses	First dorsal interosseous	MEP amplitude, CSP, SICI, ICF
	Fibromyalgia		19 (0/19)	50.4 ± 8.8		7.9 ± 1.9						
	Osteoarthritis knee		27 (0/27)	64.4 ± 7.8		6.3 ± 2.2						
(Masse-Alarie et al., 2017a)	Low back pain	Canada	35 (20/15)	38 ± 14.6	65.8 ± 72.8 months	4.2 ± 2.1	13 (6/7)	37.6 ± 12.5	Double cone coil on hotspot	Single and paired pulses Mono-phasic	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
(Masse-Alarie et al., 2016)	Low back pain	Canada	11 (6/5)	33.8 ± 12.5	NA	2 ± 1.9	13 (6/7)	37.6 ± 12.5	Double cone coil (7 cm) on hotspot	Single and paired pulses Mono-phasic*	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
(Rio et al., 2016)	Patellar tendon pain	Australia	11 (10/1)	26 (18-37)	90 months (5-192)		8 (7/1)	26 (18-37) (median)	Double cone coil (110mm) on hotspot	Single pulse	Rectus femoris	aMT
	Anterior knee pain		10 (6/4)	26.5 (18-37)	9 months (12-264) (median)					Mono-phasic*		

(Tarrago Mda et al., 2016)	Osteoarthritis knee	Brazil	21 (0/21)	64.5 ± 7.72	6.73 ± 2.53 years	NA	10 (0/10)	34.1 ± 11.64	Figure of eight coil on hotspot	Single and paired pulses	First dorsal interosseous	rMT, MEP amplitude, CSP, SICI, ICF
(Morgante et al., 2017)	CRPS I- Hand	USA	10 (1/9)	48.2 ± 5.5 (SE)	11.3 ± 1.8 months (SE)	8.1 ± 0.73	10 (1/9)	48.3 ± 12.5 (SE)	Figure of eight coil on hotspot	Single and paired pulses Mono-phasic	Abductor pollicis brevis	rMT, aMT, CSP, SICI, ICF
(Parker et al., 2017)	Osteoarthritis hand	New Zealand	23 (6/17)	72 ± 6	13.5 ± 13.1 years	NA	20 (6/14)	71 ± 7	Figure of 8 coil on hotspot	Single and paired pulses Mono-phasic	First dorsal interosseous	rMT, MEP amplitude, CSP, SCIC, LICI, SICF
(Te et al., 2017)	Patello-femoral pain	Australia	11 (3/8)	21 ± 7	29 ± 6 months	2.3 ± 2.2	11 (3/8)	24 ± 6	Figure of eight coil on M1	Single pulse Mono-phasic	Rectus femoris, Vastus lateralis, Vastus medialis	aMT, Map volume

CRPS: complex regional pain syndrome; NA: not available; M1: primary motor cortex; rMT: resting motor threshold; aMT: active motor threshold; MEP: motor evoked potential;

CSP: cortical silent period; SICI: short-interval intracortical inhibition; LICI: long-interval intracortical inhibition; ICF: intracortical facilitation; SICF: short-interval intracortical

facilitation. *Information obtained from the stimulator manufacture's website. SEM: standard error of the mean; CI: confidence interval. Values are mean ± standard deviation unless otherwise stated.

Table 2.3 Characteristics of included studies using other neurophysiological methods.

Study (First author, Year)	Condition	Country	Chronic Pain Participants				Healthy Participants		Modality	Stimuli	Outcome Measures
			Study Size (M/F)	Age	Pain Duration	Pain Intensity (0-10)	Study Size (M/F)	Age			
(Cook et al., 2004)	Fibromyalgia	USA	9 (0/9)	37 ± 5	NA	1.03 ± 0.7	9 (0/9)	35 ± 3	fMRI	Heat pain on left thenar eminence	BOLD at 1.5 T
(Napadow et al., 2006)	Carpal tunnel syndrome	USA	10 (4/6)	51.1 (31-60)	4 months - 10 years	NA	9 (3/6)	46.9 (32-59)	fMRI	Innocuous electrical stimulation to D2, 3 and 5	BOLD at 3 T
(Maihofner et al., 2007)	CRPS I- Hand	Germany	12 (2/10)	41.2 ± 2.5 (SEM)	52.2 ± 32 weeks (SEM)	3.9 ± 0.8 (SEM)	12 (2/10)	43.2 ± 2.5 (SEM)	fMRI	Finger tapping task	BOLD at 1.5 T
(Gieteling et al., 2008)	CRPS I- Hand with dystonia	Netherlands	8 (1/7)	46.4 ± 6	NA	NA	17 (2/15)	42.9 ± 9.2	fMRI	Imagining and performing wrist flexion/extension	BOLD at 3 T
(Kobayashi et al., 2009)	Low back pain	Japan	8 (5/3)	33 (22-44)	>3 months	NA	8 (8/0)	29 (22-42)	fMRI	Lumbar mechanical compression	BOLD at 3 T
(Wasan et al., 2011)	Low back pain	USA	16 (5/11)	47.4 (40-54.8) (95% CI)	6.24 years (3.9-11.8) (95% CI)	4.8 (3.8-5.9) (95% CI)	16 (5/11)	46.7 (40.1-53.2) (95% CI)	fMRI	Rest state; clinical maneuver (pain exacerbation); heat pain (affected leg)	rCBF at 3 T

(Barke et al., 2012)	Low back pain	Germany	30 (0/30)	NA	NA	NA	30 (0/30)	NA	fMRI	Photos (aversive and neutral movement/posture; general fear-inducing; neutral; spider)	BOLD at 3 T
(Bolwerk et al., 2013)	CRPS I & II-Hand and foot	Germany	12 (5/7)	61.1 ± 11.1	15.5 (4-406) weeks	5.3 ± 2.1	12 (5/7)	60.9 ± 11	fMRI	Resting state	BOLD at 1.5 T
(Liu et al., 2013)	Postherpetic neuralgia	China	11 (11/0)	66.2 ± 5.5	8.4 ± 6.2 months	8.3 ± 1	11 (11/0)	64 (56-73)	fMRI	Resting state	rCBF at 3 T
(Flodin et al., 2014)	Fibromyalgia	Sweden	16 (0/16)	48.3 (25-64)	7.6 ± 3.8 years	NA	22 (0/22)	45.7 (20-63)	fMRI	Ankle, knee and hand tasks	BOLD at 3 T
(He et al., 2014)	Temporo-mandibular disorder	China	23 (9/14)	22.4 ±3.6	14.8 ± 20.7 months	NA	20 (9/11)	23.1 ± 2.4	fMRI	Resting state	BOLD at 3 T
(Pijnenburg et al., 2015)	Low back pain	Belgium	17 (6/11)	33.3 ± 7.9	9.8 ± 8.2 years	2 ± 2	17 (5/12)	31.8 ± 8.2	fMRI	Resting state	BOLD at 3 T
(Shanahan et al., 2015)	Osteoarthritis knee	Australia	11 (6/5)	68.9 ± 6.4	NA	4.3 ± 0.8	7 (5/2)	64 ± 6.7	fMRI	15 pressure stimuli (5 different pressure intensities) on left thumb	BOLD at 3 T
(Flodin et al., 2016)	Rheumatoid arthritis	Sweden	24 (4/20)	53.8 ± 14.8	66 ± 34 months	3.4 ± 2.9	19 (3/16)	50.4 ± 16.6	fMRI	Resting state	BOLD at 3 T

(Hemington et al., 2016)	Ankylosing spondylitis-Back pain	Canada	20 (17/3)	39.4 ± 12	12.8 ± 10.1 years	NA	20 (17/3)	39.7 ± 12	fMRI	Resting state	BOLD at 3 T
(Hotta et al., 2017)	CRPS I- Hand	Finland	13 (0/13)	44.7 ± 6.9	5.2 ± 3.9 years	7.7 ± 1.7	13 (0/13)	44.1 ± 8.6	fMRI	Viewing videos of hand actions	BOLD at 3 T
(Tian et al., 2016)	Trigeminal neuropathic pain	China	20 (8/12)	52.6 ± 8.9	21.1 ± 16.2 months	7.7 ± 1.6	22 (6/16)	52.2 ± 6.1	fMRI and MRI	Resting state	BOLD and DKI analysis at 3 T
(van Velzen et al., 2016)	CRPS- Hand	Netherland	19 (0/19)	48.1 ± 11.6	110.8 ± 110.5 years	7.1 ± 1.5	19 (0/19)	49.4 ± 11.6	fMRI and MRI	Resting state	BOLD, VBM and DTI analysis at 3 T
(Moayedi et al., 2011)	Temporo-mandibular disorder	Canada	17 (0/17)	33.1 ± 11.9	9.8 ± 8.2 years	4.3 ± 1.8	17 (0/17)	32.2 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T
(Desouza et al., 2013)	Trigeminal neuropathic pain	Canada	24 (9/15)	48.5 ± 12.7	6.3 ± 3 years	NA	24 (9/15)	47.6 ± 12.3	MRI	Resting state	Cortical thickness analysis via 3.0T
(Maeda et al., 2013)	Carpal tunnel syndrome	USA	28 (8/20)	48.1 ± 9.6	8.5 ± 9.1 years	2.5 ± 0.8 (0-5)	28 (11/17)	47.3 ± 9.9	MRI	Resting state	DTI analyses at 3 T
(Wu et al., 2013)	Ankylosing spondylitis-Neuropathic pain	Canada	17 (12/5)	34.4 ± 12.4	NA	6.1 ± 1.7	17 (12/5)	34.9 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T

(Pleger et al., 2014)	CRPS I-Hand	Germany	20 (9/11)	41.8 ± 9.8	11.9 ± 14.3 months	5.3 ± 2.4	20 (9/11)	41.6 ± 9.6	MRI	Resting state	VBM analysis (?) at 1.5 T
(Ung et al., 2014)	Low back pain	USA	47 (25/22)	373. ± 12.2	8.6 ± 7.8 years	NA	47 (25/22)	37.7 ± 7.8	MRI	Resting state	VBM (SVM) analysis at 3 T
(Juottonen et al., 2002)	CRPS I-Hand	Finland	6 (0/6)	44.5 (33-54)	42.2 ± 26.2 months	5.6 ± 1.8	6 (0/6)	45.1 (34-55)	MEG	Tactile stimuli to the fingertips	Reactivity of 20-Hz motor cortex rhythm
(Shibukawa et al., 2007)	Temporo-mandibular disorder	Japan	9 (4/5)	32.4	NA	NA	8 (4/4)	30	MEG	Observation tasks of jaw- and palm-opening movements	Neuromagnetic signals
(Kirveskari et al., 2010)	CRPS I- Hand	Finland	8 (0/8)	45.5 (26-57)	5.5 ± 3.1 years	6.4 ± 1.8	8 (0/8)	46.3 28-57)	MEG	Noxious thulium–laser stimulation of both hands	Reactivity of 20-Hz motor cortex rhythm
(Grachev et al., 2000)	Low back pain	USA	9 (7/2)	45 ± 6	9 ± 5 years	6.18 ± 1.72	11 (9/2)	44 ± 3	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
(Fayed et al., 2010)	Fibromyalgia	Spain	10 (2/8)	40 ± 6.2	1.6 ± 0.3 years	NA	10 (2/8)	37.8 ± 8.7	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
(Sharma et al., 2012)	Low back pain	USA	19 (4/15)	46.1 ± 11.3	8.8 ± 7.2 years	4.5 ± 1.9	14 (3/11)	44.6 ± 14.7	MRS	Resting state	Absolute concentration of neurochemicals at 3 T

(Jacobs et al., 2010)	Low back pain	USA	10 (5/5)	39.2 ± 6.3 (95% CI)	>12 months	1.8 ± 0.26 (95%CI)	10 (5/5)	35.4 ± 5.3 (95%CI)	EEG	Arm raise	Alpha event-related desynchronization (ERD) and Bereitschaftspotentials (BP)
(Shiraishi et al., 2006)	CRPS	Japan	18 (10/8)	40.7 (21-59)	49.8 (6-252) months	NA	13 (11/2)	38.7 (27-58)	PET	Resting state	Cerebral glucose metabolism

fMRI: functional magnetic resonance imaging; MRI: magnetic resonance imaging; MEG: magnetoencephalography; MRS: magnetic resonance spectroscopy; EEG: electroencephalography; PET: positron emission computed tomography; BOLD: blood-oxygen-level-dependent contrast imaging; rCBF: regional cerebral blood flow; DTI: diffusion tensor imaging; DKI: diffusion kurtosis imaging; VBM: voxel based morphometry; SVM: support vector machines; NA: not available; SEM: standard error of the mean; CI: confidence interval. Values are mean ± standard deviation unless otherwise stated.

2.4.2 Quality and risk of bias within studies

The average score for the methodological quality assessment was 3.1 out of 5 (range between 1 and 5) (Table 2.4), with 50 studies presenting a score of 3 or higher. For the TMS methodology checklist, the average score for the reported items was 64.8% (standard deviation [SD] = 13) and for the controlled items 61.1% (13.8). All studies reported and controlled 'position and contact of electromyography (EMG) electrodes' and 'stimulation intensity'. All studies that used paired-pulse paradigms (n=16) reported the intensity of the test and conditioning pulse and the inter-stimulus interval. Participant age and sex, although reported, were not controlled. Items that were not consistently reported or controlled were: 'prior motor activity of the muscle to be tested', 'level of relaxation of the muscles other than those being tested', 'pulse shape' and 'participants' prescribed medication'.

Table 2.4 Risk of bias assessment for included studies.

Study (First author, Year)	Modified STROBE statement items						Transcranial magnetic stimulation methodology checklist	
	Source of participants	Participant selection	Methodology	Statistical analysis	Funding	Total score	Reported	Controlled
Salerno 2000	0	1	0	0	1	2	41.4%	39.3%
Schwenkreis 2003	0	1	1	1	0	3	64.3%	63%
Strutton 2003	1	0	0	1	1	3	40%	41.7%
On 2004	0	1	0	1	0	2	53.8%	52%
Eisenberg 2005	1	1	1	1	0	4	72.4%	71.4%
Krause 2005	0	0	0	1	0	1	61.5%	48%
Strutton 2005	1	0	0	1	1	3	52%	45.8%
Krause 2006	1	0	0	1	0	2	52%	37.5%
Turton 2007	0	1	0	1	1	3	46.2%	44%
Tsao 2008	0	1	1	1	1	4	73.1%	76%
Berth 2009	0	0	1	1	1	3	77%	68%
Turgut 2009	0	1	1	1	0	3	69.2%	64%
Mhalla 2010	1	1	0	1	0	3	55.2%	53.6%

Schwenkreis 2010	0	1	1	1	1	4	64.3%	66.7%
Clark 2011	0	1	0	1	1	3	54.2%	52.2%
Schwenkreis 2011	0	0	0	1	1	2	64.3%	55.6%
Tsao 2011	0	0	1	1	1	3	79.2%	82.6%
Masse-Alarie 2012	0	0	1	1	1	3	69%	71.4%
Vallence 2013	0	0	1	0	1	2	77%	68%
Kittelson 2014	0	1	1	1	1	4	72.4%	71.4%
Marker 2014	1	0	1	1	1	4	90%	82.1%
Rittig-Rasmussen 2014	1	1	0	1	1	4	57.7%	56%
Bradman 2015	0	0	0	1	1	2	61.5%	52%
Schabrun 2015 a	0	1	0	1	1	3	43.5%	43.5%
Schabrun 2015 b	1	1	1	1	1	5	77%	76%
Val Velzen 2015	1	1	0	0	1	3	57.7%	52%
Burns 2016	0	1	1	1	1	4	79.3%	75%
Caumo 2016	1	0	0	1	1	3	62.1%	46.4%
Masse-Alarie 2016 a	0	1	0	1	1	3	62.1%	59.3%

Masse-Alarie 2016 b	0	1	1	1	1	4	69%	64.3%
Rio 2016	1	1	0	1	0	3	57.7%	60%
Tarrago 2016	1	1	0	1	1	4	69%	55.6%
Morgante 2017	0	1	1	1	1	4	72.4%	77.8%
Parker 2017	0	1	1	1	1	4	96.6%	88.9%
Te 2017	1	1	1	1	1	5	75%	79.2%
Grachev 2000	0	1	1	1	1	4	NA	NA
Juottonen 2002	0	1	1	0	1	3	NA	NA
Cook 2004	0	0	0	0	1	1	NA	NA
Napadow 2006	0	1	1	1	1	4	NA	NA
Shiraishi 2006	0	1	1	0	0	2	NA	NA
Maihöfner 2007	0	1	1	0	1	3	NA	NA
Shibukawa 2007	0	1	1	1	1	4	NA	NA
Gieteling 2008	0	1	1	0	1	3	NA	NA
Kobayashi 2009	0	0	1	0	1	2	NA	NA
Fayed 2010	1	0	0	1	1	3	NA	NA

Jacobs 2010	0	0	1	1	1	3	NA	NA
Kirveskari 2010	0	0	1	1	1	3	NA	NA
Moayedi 2011	0	1	0	1	1	3	NA	NA
Wasan 2011	0	1	0	0	1	2	NA	NA
Barke 2012	1	1	0	1	0	3	NA	NA
Sharma 2012	0	1	1	1	1	4	NA	NA
Bolwerk 2013	0	1	1	1	1	4	NA	NA
Desouza 2013	0	1	0	1	1	3	NA	NA
Liu 2013	0	1	0	0	1	2	NA	NA
Maeda 2013	0	1	0	1	1	3	NA	NA
Wu 2013	0	1	0	1	1	3	NA	NA
Flodin 2014	1	1	1	1	1	5	NA	NA
He 2014	0	1	1	0	1	3	NA	NA
Pleger 2014	0	1	0	0	1	2	NA	NA
Ung 2014	0	1	0	0	1	2	NA	NA
Pijnenburg 2015	0	1	0	0	1	2	NA	NA

Shanahan 2015	0	1	0	0	1	2	NA	NA
Flodin 2016	1	1	1	0	1	4	NA	NA
Hemington 2016	0	1	0	0	1	2	NA	NA
Hotta 2016	1	1	0	0	1	3	NA	NA
Tian 2016	1	0	1	1	1	4	NA	NA
Van Velzen 2016	0	1	0	1	1	3	NA	NA

Note: Each domain would be allocated 1 point if the risk of bias was low and zero point if the risk of bias was considered high. The maximum score possible was five points.

NA: not applicable.

2.4.3 Is there evidence of altered M1 function, organisation and structure in chronic pain?

We were unable to conduct meta-analyses of these data due to the heterogeneity of methodology across the included studies. Furthermore, the effect size of the differences between the pain and healthy participants were not reported in these studies.

In neuropathic pain, three studies reported statistically significant ($p<0.05$) increases in M1 activation/connectivity in neuropathic pain populations from regional cerebral blood flow (rCBF) ((Liu et al., 2013), cluster level corrected $p<0.05$, n=22 participants, quality score=2) and blood-oxygen-level-dependent (BOLD) contrast studies ((Tian et al., 2016), n=42 participants, quality score=4; (Napadow et al., 2006), n=19 participants, quality score=4). Voxel-based morphometry (VBM) imaging showed 12-13% increase in bilateral M1 cortical thickness in trigeminal neuralgia ((Desouza et al., 2013), n=48 participants, quality score=3), and larger left M1 cortical thickness that were associated with stronger neuropathic pain symptoms in ankylosing spondylitis ((Wu et al., 2013), r=0.8, n=34 participants, quality score=3). One diffusion tensor imaging study reported that enhanced myelination (lower radial diffusivity) in the microstructure of white matter connecting primary sensory cortex and M1 contralateral to the affected side was correlated with nerve conduction velocity in carpal tunnel syndrome ((Maeda et al., 2013), r=0.72, n=56 participants, quality score=3).

In LBP, one MRI study reported increased M1 grey matter (GM) density in people with chronic LBP ((Ung et al., 2014), $p<0.001$ uncorrected for multiple comparisons, n=94 participants, quality score=2). While one study reported decreased functional connectivity in the left M1, the left supplementary motor area, and the left cerebellum when compared with healthy participants ((Pijnenburg et al., 2015), 1.88 ± 0.89SD vs. 2.64 ± 0.8SD, n=34 participants, quality score=2), the other reported increased rCBF in the left M1 ((Wasan et al., 2011), cluster-level $p<0.01$, n=32 participants, quality score=2). Two studies found no change in M1 activation/connectivity using BOLD contrast ((Kobayashi et al., 2009), n=45 participants, quality score=3) ((Barke et al., 2012), n=16 participants, quality score=2). One EEG study found altered cerebrocortical motor activity prior to an arm raise in chronic LBP participants ((Jacobs et al., 2010), n=20 participants, quality score=3). MRS studies reported conflicting findings for M1 neurochemical metabolism. One study reported no between-group difference in sensorimotor cortex ((Grachev et al., 2000), n=20 participants, quality score=4), while the other found lower N-Acetylasparate concentrations in the right M1 when compared with healthy participants ((Sharma et al., 2012), 9 ± 0.9mM vs. 10.2 ± 1.2mM, n=33 participants, quality score=4). For ankylosing spondylitis related back pain, greater functional impairment was correlated with greater M1-precuneous resting functional connectivity and impaired spinal mobility was associated with weaker M1-rostral ventromedial medulla functional connectivity on BOLD contrast ((Hemington et al., 2016), n=40 participants, quality score=2).

Findings in people with CRPS were inconsistent for M1 structure from VBM studies. One study showed increased M1 GM density ((Pleger et al., 2014), cluster-level p=0.042, corrected, n=40 participants, quality score=2), while the other showed no between-group difference in GM volume and white matter connectivity in sensorimotor cortex ((van Velzen et al., 2016), n=38 participants, quality score=3). Similarly, findings for M1 activation/connectivity from BOLD contrast were inconsistent. Two studies showed increased activation in bilateral M1 ((Maihofner et al., 2007), cluster-level p<0.0001, uncorrected, n=24 participants, quality score=3) or connectivity ((Bolwerk et al., 2013), cluster-level p<0.01, corrected, n=24 participants, quality score=4), while two showed no changes when compared with healthy participants ((Gieteling et al., 2008), n=25 participants, quality score=3) ((van Velzen et al., 2016), n=38 participants, quality score=3). There was significant between-group difference in activation of the sensorimotor cortex ((Hotta et al., 2017), p<0.05, corrected, n=26 participants, quality score=3).

In temporomandibular disorder (TMD), one VBM study reported that greater pain severity was associated with smaller GM thickness of the M1 region where the representation of the face was situated ((Moayedi et al., 2011), r=-0.83, n=34 participants, quality score=3). BOLD contrast showed decreased intrinsic neural activity in the left M1 in individuals with TMD ((He et al., 2014), p<0.05, corrected, n=43 participants, quality score=3). One MEG study found that TMD participants had significantly smaller neuromagnetic signals in M1 during observation of jaw-opening movements ((Shibukawa et al., 2007), 1±1 nAm vs. 16± 3 nAm, n=17 participants, quality score=4).

In fibromyalgia, one MRS study showed a lower myo-inositol (mI) to creatine (Cr) ratio in the left sensorimotor cortex, indicating possible M1 neuronal metabolic dysfunction ((Fayed et al., 2010), $p<0.05$, n=20 participants, quality score=3). Two studies using BOLD contrast reported conflicting findings in M1 activation/connectivity. One found no between-group difference ((Cook et al., 2004), n=18 participants, quality score=3), while the other showed decreased sensorimotor cortex connectivity ((Flodin et al., 2014), $p<0.00031$, corrected, n=38 participants, quality score=4).

One fMRI study in people with knee OA reported that the M1 representation of the affected knee was shifted 4.1 mm anteriorly (SD or confidence interval [CI] not reported) and the relative position of the knee and ankle representations were swapped when participants performed ankle and knee tasks ((Shanahan et al., 2015), n=18 participants, quality score=2). In addition, poorer performance of a knee task was associated with more anterior placement of the M1 loci in people with knee OA. In rheumatoid arthritis, one study using BOLD contrast reported increased connectivity of bilateral sensorimotor cortex with the supplementary motor and mid cingulate cortex ((Flodin et al., 2016), $p<0.00031$, corrected, n=43 participants, quality score=4).

2.4.4 Is there evidence of altered corticospinal excitability in chronic pain?

Data for rMT, aMT, MEP amplitude and latency, CSP and map volume were pooled to perform separate meta-analyses from studies using single-pulse TMS. Pooled

effect estimates for all measures revealed no difference between people with and without pain (Table 2.5; Supplementary Fig. S1-6 in Appendix A.3). There was substantial heterogeneity across all measures with the exception of MEP latency and map volume of erector spinae. For comparisons where significant heterogeneity was observed, we conducted subgroup analysis according to condition. A moderate reduction in aMT in people with chronic knee pain (three studies, 73 participants, standardised mean difference -0.52 95%CIs [-1.02, -0.02], p=0.04) (χ^2P=0.68, I^2=0%) (all studies have quality score greater than 3) (Supplementary Fig. S2 in Appendix A.3) was detected, indicating increased M1 corticospinal excitability. Seven out of 35 TMS studies (Bradnam et al., 2016; Krause et al., 2005; Krause et al., 2006; On et al., 2004; Salerno et al., 2000; Schwenkreis et al., 2011; Vallence et al., 2013) scored lower than 3 (median value) on the modified STROBE statement and were categorised as high risk-of-bias. Meta-analyses re-run after removing the high risk-of-bias TMS studies detected a large reduction in the CSP for CRPS but left only a single small study (n=20 participants) in that subgroup.

Table 2.5 Effect sizes for between group differences (people with and without pain) from meta-analyses of transcranial magnetic stimulation studies. *Pooled estimates for all measures revealed no difference between people with and without pain, with the exception of long-interval intra-cortical inhibition.*

Outcome measure	Number of included studies	Number of participants	Quality score range (max score= 5)	Standardised mean difference (95% confidence interval)
Resting motor threshold	19	604	1-5	0.01 (-0.29, 0.31)
Active motor threshold	12	357	3-5	0.11 (-0.24, 0.46)
Motor evoked potential amplitude	24	788	1-5	-0.15 (-0.38, 0.09)
Motor evoked potential latency	4	181	2-4	0.21 (-0.11, 0.52)
Cortical silent period	12	481	1-4	-0.42 (-0.85, 0.00)
Map volume- erector spinae	2	70	3	-0.24 (-0.72, 0.23)

Map volume- wrist extensor	2	46	2, 5	0.35 (-0.66, 1.36)
Short-interval intra-cortical inhibition	15	572	2-4	0.07 (-0.36, 0.50)
Long-interval intra-cortical inhibition	3	102	2-4	0.78 (0.37, 1.19)
Intra-cortical facilitation	7	249	2-4	-0.26 (-0.65, 0.14)
Short-interval intra-cortical facilitation	3	113	3-4	0.23 (-0.24, 0.70)

2.4.5 Is there evidence for altered intra-cortical facilitation and/or inhibition in chronic pain?

Sixteen studies investigated intra-cortical inhibitory and facilitatory networks using paired-pulse TMS paradigms with several different measures. A moderate increase in long-interval intra-cortical inhibition (LICI) was detected in people with pain (three studies, 102 participants, 0.78 [0.37, 1.19], p<0.001) (χ^2P=0.84, I^2=0%) (Fig. 2.2), indicating increased M1 intra-cortical inhibition. No difference between people with and without pain was found for short-interval intra-cortical inhibition (SICI), intra-cortical facilitation (ICF) or short-interval intra-cortical facilitation (SICF) (Table 5; Supplementary Fig. S7-S9 in Appendix A.3). One study appeared to mislabel ICF as SICF based on the experimental protocol and was not included in the meta-analysis (Caumo et al., 2016). There was substantial heterogeneity in the pooled effect estimates for SICI (χ^2P<0.01, I^2=80%) and ICF (χ^2P=0.04, I^2=51%). The subgroup analysis showed a moderate reduction in SICI in people with CRPS (four studies, 100 participants, -0.77 [-1.21, -0.34], p<0.01) (χ^2P=0.72, I^2=0%) (Supplementary Fig. S7 in Appendix A.3), indicating reduced M1 intra-cortical inhibition, and a moderate reduction in ICF in people with non-neuropathic pain (six studies, 151 participants, -0.53 [-0.94, -0.13], p=0.01) (χ^2P=0.24, I^2=26%) (Supplementary Fig. S8 in Appendix A.3), indicating reduced M1 intra-cortical facilitation.

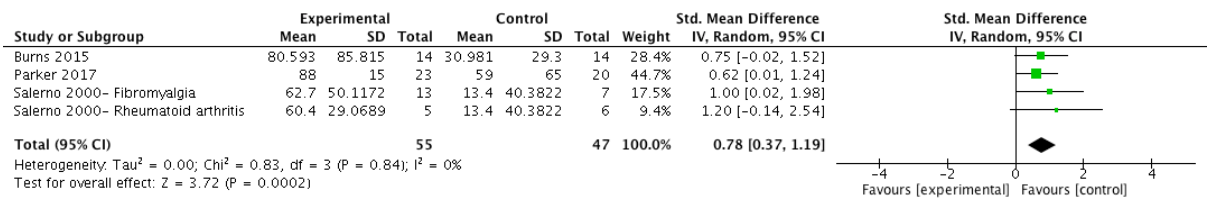

Figure 2.2 Meta-analysis forest plot for long-interval intra-cortical inhibition (LICI).

Evidence of reduced M1 intra-cortical inhibition in people with CRPS is complemented by the findings of attenuated activities of the 20-Hz cortical rhythm (which reflects decreased M1 cortical inhibition) from two MEG studies. The 20-Hz rebound duration in the right hemisphere was significantly shorter ((Juottonen et al., 2002), 357 vs. 458 ms, $p<0.03$, n=18 participants, quality score=3), and the rebound amplitude (1±1SD vs. 7±3SD fT/cm, $p=0.05$) and the reactivity (4±2SD vs. 16±5SD fT/cm, $p=0.03$) to painful hand stimuli were significantly smaller ((Kirveskari et al., 2010), n=18 participants, quality score=3) when compared with healthy participants. One PET study (n=31 participants, quality score=2) showed reduced glucose metabolism in the contralateral M1 in CRPS ((Shiraishi et al., 2006), $p<0.005$, uncorrected), suggesting possible M1 inhibition.

2.5 Discussion

This systematic review is the first to provide a comprehensive and critical review of studies investigating M1 structure, organisation and function in people with chronic pain. For a range of neurophysiological parameters, published studies provided conflicting evidence. Meta-analyses identified a moderate increase in M1 long-interval intra-cortical inhibition in people with chronic pain. Our findings suggest that the evidence for M1 changes in chronic pain populations is inconclusive for most measures.

2.5.1 Evidence for altered intra-cortical facilitation and/or inhibition in chronic pain

Pooled data from three studies investigating non-neuropathic pain provided evidence of increased LICI, indicating increased M1 intra-cortical inhibition. Increased LICI reflects upregulated $GABA_B$-mediated intra-cortical inhibition (McDonnell et al., 2006). Subgroup analyses showed reduced ICF in non-neuropathic pain, suggesting decreased intra-cortical facilitation of glutamatergic interneurons through N-methyl-D-aspartate receptors (Ziemann et al., 1998a), and reduced SICI in CRPS, suggesting M1 intra-cortical disinhibition driven by downregulated $GABA_A$-receptors (McDonnell et al., 2006; Werhahn et al., 1999). However, while our subgroup analyses were pre-planned, interpretation of these findings requires caution as there are no overall effects in the pooled estimates for SICI and ICF.

Consistent with a previous review of CRPS (Di Pietro et al., 2013a), our review also found M1 disinhibition based on MEG outcomes from two studies. The 20-Hz cortical rhythm measured in MEG is initially decreased (suppression; reflecting an activated M1) and subsequently increased (rebound; reflecting inhibited M1) and represents the functional state of M1 (Parkkonen et al., 2015; Salmelin and Hari 1994). Combined MEG and MRS demonstrated a positive correlation between 20-Hz rebound amplitude and the concentration of inhibitory neurotransmitter gamma-aminobutyric (GABA), indicating the rebound period represents GABAergic inhibition in M1 (Gaetz et al., 2011). MEG studies found a significantly shorter rebound duration of 20-Hz rhythm in both hemispheres (Juottonen et al., 2002), and weaker rebound amplitude and reactivity of 20-Hz rhythm in the contralateral hemisphere to the affected side (Kirveskari et al., 2010), indicating M1 disinhibition in CRPS. These findings suggest M1 disinhibition in CRPS, reflecting downregulated GABAergic

inhibition. The MEG findings of reduced M1 inhibition in CRPS are inconsistent with the findings of increased LICI in chronic pain from TMS studies. These inconsistencies could be explained as none of these TMS studies investigated CRPS. Although one PET study found reduced glucose metabolism in the contralateral M1 for CRPS in the group analysis, indicating possible M1 inhibition, only three (out of 18) CRPS participants demonstrated this finding in the individual analysis (Shiraishi et al., 2006). Future larger trials are needed to elucidate M1 glucose metabolism in CRPS.

2.5.2 Evidence of altered M1 structure, organisation and function in chronic pain

There is conflicting evidence for M1 changes in chronic pain, which may be explained by the heterogeneity of the underlying neurophysiological mechanisms, methodological differences, internal study biases, reporting biases, and the random play of chance, given the small sample size of the included studies. For example, heterogeneity of underlying neurophysiological mechanisms in non-specific chronic LBP has been reported (Smart et al., 2011). A mixture of neuropathic and non-neuropathic pain components were identified not only in chronic non-specific LBP (Spahr et al., 2017), but ankylosing spondylitis back pain (Wu et al., 2013), and knee and hip OA (French et al., 2017b; Hochman et al., 2013; Moreton et al., 2015; Moss et al., 2018). However, it is unclear whether a neuropathic pain subgroup exists in other pain conditions. Future studies should investigate whether distinct pain subgroups exist within chronic pain conditions and whether these subgroups present with different M1 changes.

Evidence from several different measures suggests increased M1 activation/connectivity in neuropathic pain. M1 disinhibition has been attributed to increased M1 activation (carpal tunnel syndrome), increased M1 rCBF (postherpic neuralgia) and increased M1 functional connectivity (trigeminal neuralgia) (Liu et al., 2013; Napadow et al., 2006; Tian et al., 2016), though M1 disinhibition in neuropathic pain was not supported by the finding of a reduction in MEP amplitude from a single study in people with diabetic neuropathy (Turgut and Altun 2009) (Supplementary Fig. S3 in Appendix A.3). More research is needed to elucidate the neurophysiological mechanisms driving M1 functional changes in neuropathic pain populations.

Several studies reported that impaired motor control in chronic pain was associated with M1 reorganisation or altered corticomotor physiology (Jacobs et al., 2010; Shanahan et al., 2015; Tsao et al., 2008). For example, delayed activation of the trunk muscles when performing an arm raise in chronic LBP patients was associated with smaller amplitudes of Bereitschafts potential, an EEG potential generated by M1 and the supplementary motor cortex representing movement preparation (Jacobs et al., 2010), and with increased map volume and the posterolaterally shifted M1 representation of transversus abdominis (Tsao et al., 2008). This supports the role of altered M1 in motor control impairment in musculoskeletal disorders. However, the causal relationship and the interaction between M1 changes, motor control impairment and symptom persistence in chronic pain requires further investigation.

A previous review on M1 function in CRPS could not draw a definite conclusion on M1 functional changes (Di Pietro et al., 2013a). Two recent MRI studies investigating

M1 function and structure for CRPS were included in this review which reported conflicting findings, likely due to different experimental protocols (resting state vs. observational tasks) (Hotta et al., 2017; van Velzen et al., 2016). Taken together with the other neurophysiological evidence, no conclusion on M1 changes in CRPS can be drawn from our findings.

2.5.3 Evidence of altered corticospinal excitability in chronic pain

Meta-analyses of TMS data reveal no significant change in any measure of corticospinal excitability in people with chronic pain. Although subgroup analysis finds a reduction in aMT in chronic knee pain, suggesting increased excitability in the motor system particularly in relation to neuronal and interneuronal membrane excitability (Ziemann et al., 1996), interpretation of this finding requires caution as there is no overall effect in the pooled estimate for aMT.

A previous review on corticomotor excitability in chronic pain found evidence of M1 disinhibition that was more prominent in neuropathic pain populations (Parker et al., 2016). However, our review does not find compelling evidence of M1 disinhibition when comparing people with and without pain. This discrepancy is likely due to our inclusion of more recent studies (Bradnam et al., 2016; Caumo et al., 2016; Masse-Alarie et al., 2016; 2017a; Morgante et al., 2017; Parker et al., 2017; Rio et al., 2016; Schabrun et al., 2015c; Shanahan et al., 2015; Tarrago Mda et al., 2016; Te et al., 2017) and exclusion of studies containing neurological populations (Lefaucheur et al., 2006). Also, CRPS studies were separated from neuropathic pain in our subgroup analyses as they have different diagnostic criteria and pathophysiology.

Altered M1 representation of erector spinae muscles (reduced map volume) in chronic LBP has been reported (Tsao et al., 2011), but not supported by a larger study (Schabrun et al., 2015b). Pooled map volume data from these studies found no significant difference between LBP and healthy participants. The differences between the studies in sample size and methodology such as different EMG electrodes (fine wire needle versus superficial, surface electrodes), the sizes of grid used to measure the map (5 x 7 cm versus 6 x 7 cm) and different coils used to deliver TMS could contribute to the contradictory findings of M1 reorganisation of erector spinae in LBP. Although some small single studies reported increased map volume of the wrist extensor (lateral epicondylalgia) and transversus abdominis (LBP) muscles, and decreased map volume of quadriceps (patellofemoral pain) (Supplementary Fig. S5 in Appendix A.3), meta-analyses do not support the changes in M1 representations.

2.5.4 Limitations and recommendations

Several limitations should be considered when interpreting the findings of this review. First, most included studies were small, and may be affected both by low statistical power and conversely, the propensity for small published studies to return positive and often inflated effect sizes (Button et al., 2013). Additionally, subgroup analyses are regarded as exploratory and interpretation of these findings requires caution, particularly when there is no overall effect in the pooled estimates. False positive significance tests also increase in likelihood rapidly as more subgroup analyses are performed.

TMS studies investigating M1 representations of the affected muscles in chronic pain reported the centre of gravity (CoG) as the location of M1 representation. Smudged M1 representations of affected muscles (measured by the distance between the CoG of neighbouring muscles) has been reported in chronic LBP and lateral epicondylalgia, suggesting M1 reorganisation (Schabrun et al., 2015b; Schabrun et al., 2015c; Tsao et al., 2011). However, we were unable to meta-analyse CoG data as studies reported either the coordinates of the CoG or the absolute distance between the averaged CoG for each group. Future research using TMS to investigate M1 representation of the affected muscles should report the coordinates of CoG for meta-analysis of the data. We also acknowledge that four included TMS studies were published by one of the co-authors of this review (Burns et al., 2016a; Schabrun et al., 2015b; Schabrun et al., 2015c; Te et al., 2017). To minimise the bias, reviewers who were not involved in these studies performed the risk of bias assessment.

A recent study reported that the errors of software commonly used for data analysis in fMRI studies may result in a false positive rate of up to 70% and questioned the validity of some fMRI studies (Eklund et al., 2016). It is beyond the scope of this review to discuss how these statistical issues may influence the findings of this review. However, the fMRI findings of M1 activation/connectivity and organisation for chronic pain in this review should be interpreted with caution. Several studies included in this review investigated the sensorimotor cortex rather than the primary motor cortex (Fayed et al., 2010; Flodin et al., 2016; Flodin et al., 2014; Hotta et al., 2017; van Velzen et al., 2016). It is possible that heterogeneity in the brain region

being investigated (i.e. sensorimotor vs. primary motor cortex) contributed to the inconclusive findings of this review.

2.6 Conclusion

This review provides the current evidence on M1 structure, organisation and function in chronic pain and identifies areas where further research is required. EEG, MEG, MRS and PET techniques have been rarely used to investigate M1 function in chronic pain. Data pertaining to M1 changes for conditions such as TMD, rheumatoid arthritis, neck, shoulder, and neuropathic pain are still lacking. Additionally, more research using paired-pulse TMS paradigms to investigate M1 intra-cortical facilitation/and inhibition in chronic pain is required as data are still lacking for measures of LICI and SICF. Future studies with larger sample sizes are warranted to elucidate M1 changes in chronic pain conditions and to inform treatments targeting M1.

Chapter 3

Sensorimotor and Cingulate Cortex Excitability in Acute Low Back Pain: A Cross-Sectional Study

The findings from Chapter 2 suggest that the evidence for altered plasticity in the primary motor cortex (M1) in chronic pain is inconclusive. To further explore the role of neuroplasticity in musculoskeletal pain, the acute clinical low back pain (LBP) population was investigated. This chapter reports on the findings of a cross-sectional study that aimed to examine sensorimotor and cingulate cortex excitability and M1 organisation in individuals with acute, clinical LBP compared with pain-free controls. The manuscript of this study has been submitted to the Journal of Pain and is under review.

Chapter 3. Sensorimotor and Cingulate Cortex Excitability in Acute Low Back Pain: A Cross-Sectional Study

3.1 Abstract

Sensorimotor cortex excitability is altered in both the immediate acute, and chronic stages of musculoskeletal pain. However, these changes are opposite, with decreased excitability reported in experimentally-induced acute pain (lasting minutes to hours), and increased excitability in chronic, clinical pain (lasting>6 months). It is unknown whether sensorimotor cortex excitability is altered in acute, *clinical* musculoskeletal pain (lasting<4 weeks). In 36 individuals with acute, non-specific, clinical low back pain (LBP) and 36 age- and sex-matched, pain-free controls, we investigated sensory and cingulate cortex excitability using sensory evoked potentials (SEPs), as well as excitability and organisation of the primary motor cortex using transcranial magnetic stimulation. Processing of sensory inputs was lower (smaller area of the N_{80}-N_{150}-P_{260} SEP complex) in acute LBP ($F_{1,70}$=45.28, p<0.01). Examination of specific SEP components revealed lower excitability of the secondary sensory and anterior cingulate cortices (smaller area of the N_{150} and P_{260} SEP components) in acute LBP, although inter-individual variability was high. Motor cortical map volume was lower in acute LBP ($F_{1,70}$=5.61, p=0.02). These findings demonstrate that acute LBP is characterised by lower sensorimotor and cingulate cortex excitability at the group level. However, individual variation was high, suggesting individual adaptation of different cortical strategies in acute pain.

Perspective: This is the first study to examine sensorimotor and cingulate cortex excitability in the acute stage of clinical low back pain. This information is critical for understanding the neurophysiology of acute low back pain.

3.2 Introduction

Individuals who experience low back pain (LBP) for 6 months or more ('chronic LBP') display excitability and organisation of the primary sensory (S1) and motor (M1) cortices that differs from pain-free individuals (Ung et al., 2014; Wand et al., 2011; Zhao et al., 2017). For example, studies demonstrate greater S1 excitability and a difference in the location of S1 activation in chronic LBP (Diers et al., 2007; Flor et al., 1997). Similarly, there is evidence of different M1 organisation characterised by a more posterior location and greater overlap of representations of the trunk muscles (Tsao et al., 2011; Tsao et al., 2008; 2010). Differences in M1 excitability and organisation have been associated with the severity and location of pain and/or impaired motor control (Elgueta-Cancino et al., 2018; Flor et al., 1997; Masse-Alarie et al., 2012; Schabrun et al., 2017b; Tsao et al., 2008). Despite findings of altered sensorimotor cortex excitability and organisation in the chronic stage of pain, no study has examined S1 or M1 in the acute stage of clinical LBP (pain lasting less than 4 weeks).

Sensorimotor cortex activity in the chronic stage of pain is typically characterised by *greater* S1 and M1 excitability (Diers et al., 2007; On et al., 2004; Rio et al., 2016; Turgut and Altun 2009). Conversely, experimentally-induced acute musculoskeletal pain (pain of rapid onset, lasting minutes to hours) *decreases* S1 and M1 excitability (Burns et al., 2016b). Evidence of greater excitability compared to pain-free controls in the chronic stage of pain is hypothesised to reflect maladaptive neuroplasticity and the adoption of simplified movement strategies (Hodges and Tucker 2011; Schabrun et al., 2016) (although the absence of longitudinal studies means that causality is not

yet clear), whereas in the presence of acute experimental pain, reduced sensorimotor cortex excitability has been interpreted to limit the painful movement to prevent further pain and/or injury (or threat thereof) (Lund et al., 1991; Rossi et al., 2003). These findings suggest that cortical excitability in the acute and chronic stages of pain may be in the opposite direction. However, interpretation of this difference is challenging because the nature (predictable and generally without tissue damage) and timeframe (lasting minutes to hours) of acute experimental pain differs from acute clinical pain. In a clinical context, pain is generally triggered by tissue damage and has a timeframe of pain lasting up to 4-6 weeks. It remains unclear whether S1 and M1 excitability are altered in acute clinical pain and whether these changes, if present, reflect those reported following acute experimental pain (decreased excitability) or those reported in the chronic stage (greater excitability) of pain.

The aim of this study was to compare the excitability of the sensory and cingulate cortex and the excitability and organisation of the primary motor cortex in individuals with acute (pain lasting up to four weeks), clinical, non-specific LBP with a group of pain-free controls. Based on findings from acute experimental pain models, it was hypothesised that excitability in S1 and M1 would be lower in individuals with acute LBP than pain-free controls.

3.3 Methods

3.3.1 Study design and participants

A cross-sectional study design was used to evaluate (1) sensory and cingulate cortex processing and (2) motor cortical organisation in 36 individuals experiencing an episode of acute non-specific LBP and 36 age- and sex-matched controls. The study was conducted in a university research laboratory. As there have been no studies of sensorimotor cortex excitability in acute, clinical LBP on which to base a sample size calculation, a convenience sample was used. However, the sample size was greater than that used to demonstrate changes in sensorimotor cortex excitability in chronic LBP with similar methodology (Elgueta-Cancino et al., 2018; Schabrun et al., 2017b).

Acute non-specific LBP was defined as the onset of pain between the 12th thoracic vertebra and the gluteal fold in the past 4 weeks, following a period of at least 2 months without LBP, that resulted in functional limitation (de Vet et al., 2002). Participants were recruited from primary care clinics and the community between January 2014 and April 2017 and included if they were at least 18 years of age and could provide written, informed consent. Individuals who presented with suspected nerve root involvement, suspected major spine pathology (e.g. fracture, tumour, cauda equina syndrome), other major diseases/disorders, neurological conditions, a history of spine surgery, psychiatric conditions, any other chronic pain conditions or contraindications to the use of transcranial magnetic stimulation (TMS) were excluded (Keel et al., 2001). Participant characteristics are summarised in Table 3.1. All procedures were approved by the institutional Human Research Ethics Committee (H10465) and conformed to the Declaration of Helsinki.

Table 3.1 Participant characteristics (mean and standard deviation).

	Low back pain (n=36)	Pain-free controls (n=36)
Sex (male:female)	17:19	18:18
Age (years)	34±12	29±7
Pain at time of testing (NRS)	2.8±1.9	---
Pain in the past week (NRS)	3.6±1.8	---
Pain duration (weeks)	2.4±1.2	---
Side of worst pain (right:left)	30:6	---
Number reporting first episode of low back pain	8	---

NRS – numerical rating scale.

3.3.2 Measures

All the following measures were carried out in the same session, on the same day.

3.3.2.1 Pain

Pain was assessed using an 11-point numerical rating scale (NRS) anchored with 'no pain' at 0 and 'worst pain possible' at 10 on: (1) the day of testing and (2) the average pain in the past week. The duration of the current episode of LBP and any history of prior LBP were recorded.

3.3.2.2 Sensory and cingulate cortex excitability

Electroencephalography (EEG) was recorded using gold plated cup electrodes positioned over S1 (3 cm lateral and 2 cm posterior to Cz) on the side contralateral to the side of worst pain in individuals with acute LBP or the matched side in pain-free controls and referenced to Fz using the International 10/20 System (Schabrun et al.,

2015a). Electrode impedance was kept below 5 kΩ. EEG signals were amplified 50000x, band pass filtered between 5-500 Hz and sampled at 1000 Hz using a Micro1401 data acquisition system and Signal software (CED Limited, Cambridge, UK).

Sensory evoked potentials (SEPs) were recorded in response to electrical stimulation of the paraspinal muscles at L3 on the side of worst pain in individuals with acute LBP or the matched side in pain-free controls. A constant current stimulator (Digitimer, DS7AH) delivered electrical stimuli of 1 ms duration at a rate of 2/s (maximum current: 1A). A 20% variance was incorporated into the stimulus frequency to reduce accommodation. Perceptual threshold is defined as the lowest intensity of electrical stimulus the participant can detect. Stimulus intensity was set at 3x perceptual threshold and adjusted where necessary to ensure the stimuli were non-noxious. Two blocks of 500 stimuli were recorded. To exclude the potential interference of repeated sensory stimuli on motor cortical organisation, SEPs were recorded after the participants received transcranial magnetic stimulation (Schabrun et al., 2015a).

3.3.2.3 Motor cortical organisation

Surface electromyography (EMG) was recorded from the paraspinal muscles at two sites: 3 cm lateral to the spinous process of L3 and 1 cm lateral to the spinous process of L5 on the side of worst pain (or the matched side for pain-free controls) using disposable, Ag/AgCL electrodes (Noraxon USA Inc, Arizona, USA) (Lariviere et al., 2003; O'Connell et al., 2007). These sites are appropriate for assessing features of the motor cortical representation of lumbar paraspinal muscles (Schabrun et al., 2017b; Schabrun et al., 2014b; Tsao et al., 2011). Ground electrodes were placed over the

anterior superior iliac spine bilaterally. EMG data were amplified 1000x, filtered 20-1000 Hz and sampled at 2000 Hz using a Micro1401 data acquisition system and Spike2 software (CED Limited, Cambridge, UK).

An established TMS mapping procedure for the paraspinal muscles was used (Schabrun et al., 2014b). Single-pulse, monophasic stimuli (Magstim 200 stimulator/7 cm figure-of-eight coil; Magstim Co. Ltd. Dyfed, UK) were delivered to the M1 contralateral to the side of worst pain in individuals with acute LBP or the matched side in pain-free controls. The coil was positioned tangential to the skull with the handle aligned posteriorly. Participants wore a cap marked with a 6 x 7 cm grid and oriented to the vertex (point 0,0). The vertex was determined using the International 10/20 System, and aligned with the centre of the cap (coordinate 0,0)(Herwig et al., 2003). The cap was tightly fitted and the position regularly checked to ensure placement consistency. Starting at the vertex, five stimuli were delivered over each scalp site on the grid (inter-stimulus interval: 6 s) at 100% of stimulator output while participants activated the paraspinal muscles to 20% of their EMG recorded during a maximum voluntary contraction (determined as 20% of the highest root mean square [RMS] EMG for 1 s during three, 3-s maximal muscle contractions performed against manual resistance in sitting) with feedback provided on a monitor. All TMS procedures adhered to the TMS checklist for methodological quality (Chipchase et al., 2012b).

3.3.3 Data management

SEPs were analysed as area for the N_{80} component (between the first major downward deflection of the curve after stimulation and the first major negative peak, N_{80}), N_{150} component (between the first negative peak, N_{80} and second negative peak, N_{150}), P_{260} component (between the second negative peak, N_{150} and the positive deflection of the curve starting around 150 ms after stimulus onset, P_{260}), and the N_{80}-N_{150}-P_{260} SEP complex (Diers et al., 2007; Schabrun et al., 2015a). The N_{80} component is thought to derive from S1, N_{150} from the secondary sensory cortex (S2), and P_{260} from the anterior cingulate cortex (ACC) (Diers et al., 2007). The latency of the individual SEP components was calculated as the time from stimulus onset to the individual N_{80}, N_{150} and P_{260} peaks. Area measures for the individual SEP components and the N_{80}-N_{150}-P_{260} complex, and latency measures, were averaged across the two SEP blocks for each participant. A trace from a representative pain-free participant demonstrating the components that were analysed is provided in Figure 3.1.

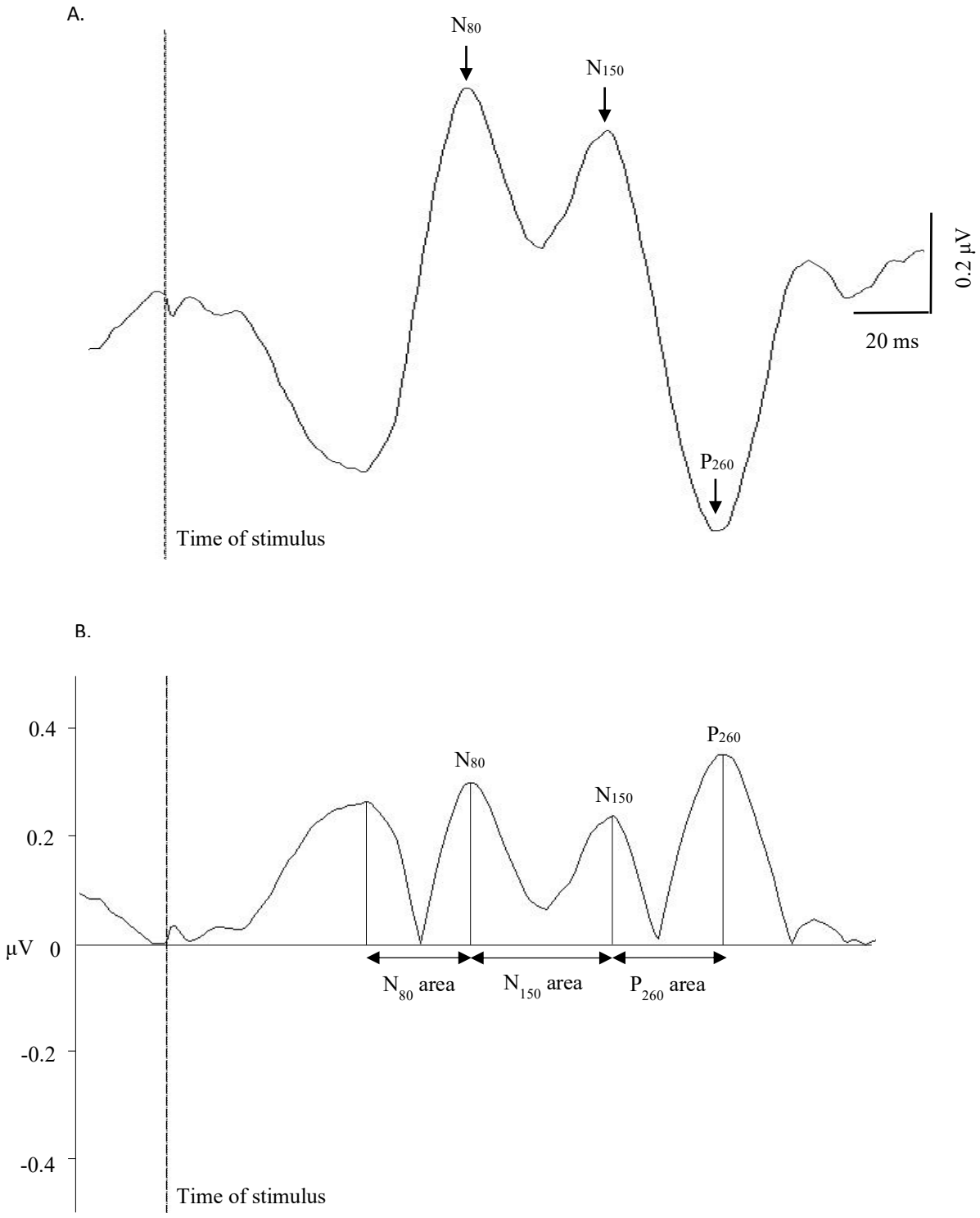

Figure 3.1 A) Raw data from a single participant demonstrating components of the sensory evoked potential used for analysis. B) Rectified version of the waveform shown in Panel A. *Any negative voltages were converted into positive value. The area under the curve of each SEP components was calculated.*

Analysis of TMS map data was performed using MATLAB 7 (The MathWorks, USA). EMG traces of the five MEPs recorded at each scalp site were averaged. MEP onset and offset were visually identified from the averaged traces and MEP amplitude calculated as the RMS EMG amplitude between the onset and offset. Background RMS EMG between 55 to 5 ms prior to stimulation was subtracted. MEP amplitudes were superimposed over the respective scalp sites to construct a topographical representation of the paraspinal muscles and normalised to the peak amplitude for each participant. Normalised values below 25% of the peak response were removed and the remaining values rescaled from 0 to 100% (Schabrun et al., 2014b; Tsao et al., 2011). Three parameters were calculated from the normalised maps. (1) Map volume (measure of total excitability of the motor cortical representation) was calculated as the sum of the mean normalised MEP amplitude at all active sites. A scalp site was considered active if the normalised MEP amplitude was equal to or greater than 25% of the peak response. (2) Centre of gravity (CoG) was calculated for each muscle using the formula: CoG = $\sum V_i \, x \, X_i \, / \sum V_i \, , \sum V_i \, x \, Y_i \, / \sum V_i$ where: V_i = mean MEP amplitude at each site with the coordinates X_i, Y_i(Uy et al., 2002a; Wassermann et al., 1992). The CoG represents an amplitude-weighted location of the map centre and is a valid and reliable measure of a motor cortical representation (Malcolm et al., 2006; Ngomo et al., 2012; Uy et al., 2002a). (3) The number of discrete peaks was determined. A scalp site was identified as a peak if its MEP amplitude was greater than 60% of the maximum MEP amplitude for an individual's map and was separated from any adjacent peaks by a reduction in MEP amplitude of at least 20% (Schabrun et al., 2014b; Tsao et al., 2011).

3.3.4 Statistical analyses

Sensory and ACC excitability and motor cortical organisation were compared between the acute LBP and control groups using one-way analyses of variance (ANOVA) with factor Group (LBP vs. control). Data that were not normally distributed were log transformed. ANOVA on ranks was performed where data were not normally distributed after log transformation. Post-hoc tests were performed using the Holm-Sidak method corrected for multiple comparisons. Pearson's correlation coefficients were used to test linear associations between measures of pain (severity and duration) and i) SEP latency and area and ii) map volume in the acute LBP group.

3.3.5 Post hoc analyses

The primary analysis demonstrated large interquartile ranges, indicating high variability, in the areas of the N_{150} and P_{260} SEP components in individuals with acute LBP. When the relationship between the N_{150} and P_{260} SEP components was investigated in people with acute LBP using a Pearson's correlation coefficient, two distinct sub-groups were revealed; one group that displayed high secondary sensory and ACC excitability and one group that displayed low secondary sensory and ACC excitability. To further explore this secondary finding, individuals with acute LBP were divided into two groups according to the median value of the areas of N_{150} and P_{260} SEP components and pain characteristics were compared between individuals with high and low excitability using one-way ANOVA. Significance was set at $p<0.05$.

3.4 Results

3.4.1 Sensory and anterior cingulate cortex excitability

The latency of the N_{150} SEP component was longer in individuals with acute LBP than pain-free controls (ANOVA on Ranks H (1)=5.49, p=0.02; Figure 3.2B). The area for the N_{80}-N_{150}-P_{260} complex was smaller in those with acute LBP than pain-free controls ($F_{1,70}$=45.28, p<0.01; Figure 3.2A). Consistent with this, areas for the individual N_{150} (ANOVA on Ranks H (1)=4.11, p=0.04) and P_{260} (ANOVA on Ranks H (1)=3.93, p=0.047) SEP components were also smaller in participants with acute LBP than pain-free controls (Figure 3.2C and 3.2D). There was no difference in the area for the N_{80} SEP component between groups (ANOVA on Ranks H (1)=2.63, p=0.11).

Table 3.2 ***Group data (mean and standard deviation) for the latency of N_{80}, N_{150}, and P_{260} components of sensory evoked potential in individuals with and without acute low back pain.***

	Low Back Pain (n=36)	**Pain-free controls (n=36)**
N_{80} SEP component (ms)	83.1±6.9	82.5±3.7
N_{150} SEP component (ms)	121.0±10.5	115.1±6.2
P_{260} SEP component (ms)	158.0±15.9	153.1±7.1

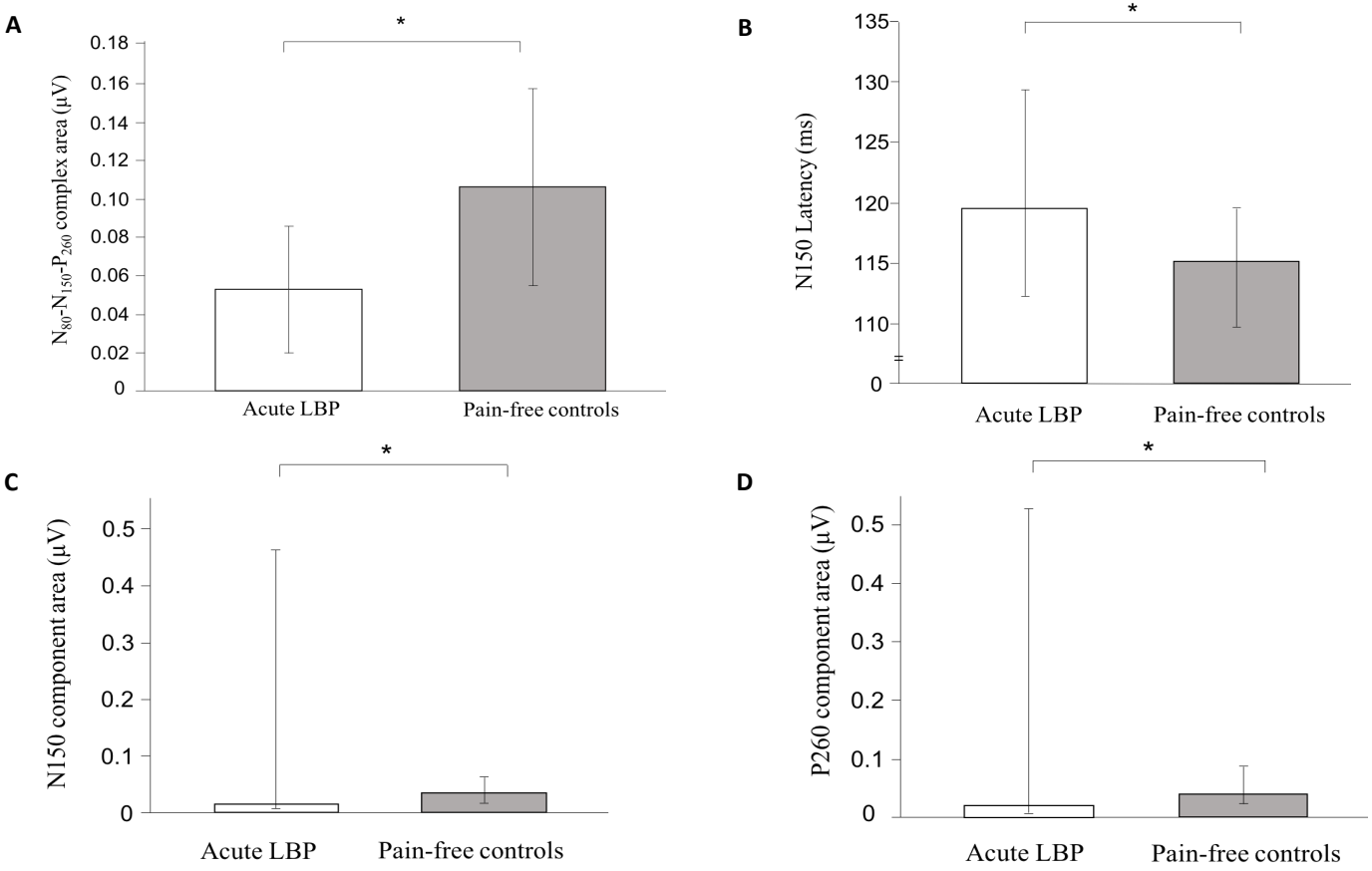

Figure 3.2 Group data (mean and standard deviation) for A) the area of the N_{80}-N_{150}-P_{260} sensory evoked potential (SEP) complex, and group data (median and interquartile range) for B) the latency of the N_{150} SEP component, C) the area of the N_{150} SEP component and D) the area of the P_{260} SEP component. *Note that the area of N_{80}-N_{150}-P_{260} SEP complex, and the N_{150} and the P_{260} SEP components was smaller in the in individuals with acute low back pain than pain-free controls. The latency of the N_{150} SEP component was later in individuals with acute low back pain than pain free-controls. *p<0.05.*

3.4.2 Post hoc analyses

Higher excitability in S2 (larger area of the N_{150} SEP component) was associated with higher excitability in ACC (larger area of the P_{260} SEP component) in individuals with acute LBP (r^2=0.84, p<0.01; Figure 3.3). The correlation analysis revealed two distinct groups: twelve individuals with high excitability in both S2 and ACC (3 individuals with first episode LBP), and 24 individuals with low excitability in both cortical regions (5 individuals with first episode LBP). Clear SEP peaks were discernible in both groups despite the difference in excitability. When pain intensity was compared between the two groups (based on the median split in both cortical regions: N_{150} area - 0.015μV, P_{260} area - 0.02μV), individuals with high excitability had significantly lower pain in the past week (2.9±1.9) than those with low excitability (4.0±1.6, $F_{1,28}$= 5.10, p=0.03).

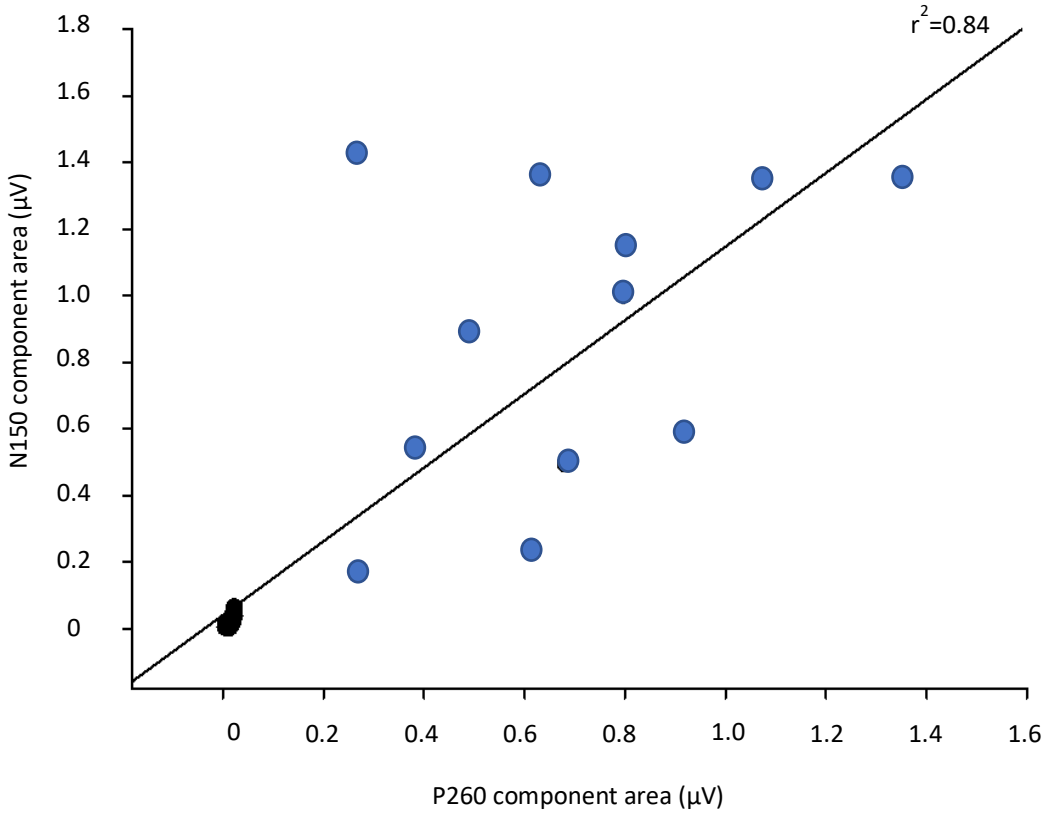

Figure 3.3 Linear correlation between the area of the N_{150} and P_{260} sensory evoked potential components in individuals with acute low back pain*. Note the two groups: 12 individuals with high excitability in both the secondary sensory and cingulate cortex and 24 individuals (clustered in the bottom left of the graph) with low excitability in both cortical regions.*

3.4.3 Motor cortical organisation

M1 map volume recorded with the EMG electrode at the L3 recording site was smaller in individuals with acute LBP than pain-free controls ($F_{1,70}$= 5.61, p=0.02; Figure 3.4). Map volume at the L5 EMG recording site did not differ between those with and without acute LBP (ANOVA on Ranks H (1)=0.50, p=0.48). There was no difference between groups for any other measure of primary motor cortex

organisation (Table 3.2). Map data from a representative individual with acute LBP and a pain-free control are provided in Figure 3.4B. There was no relationship between L3 map volume and pain intensity at the time of testing (r^2=0.01, *p*=0.95) or pain duration (r^2=0.2, *p*=0.31).

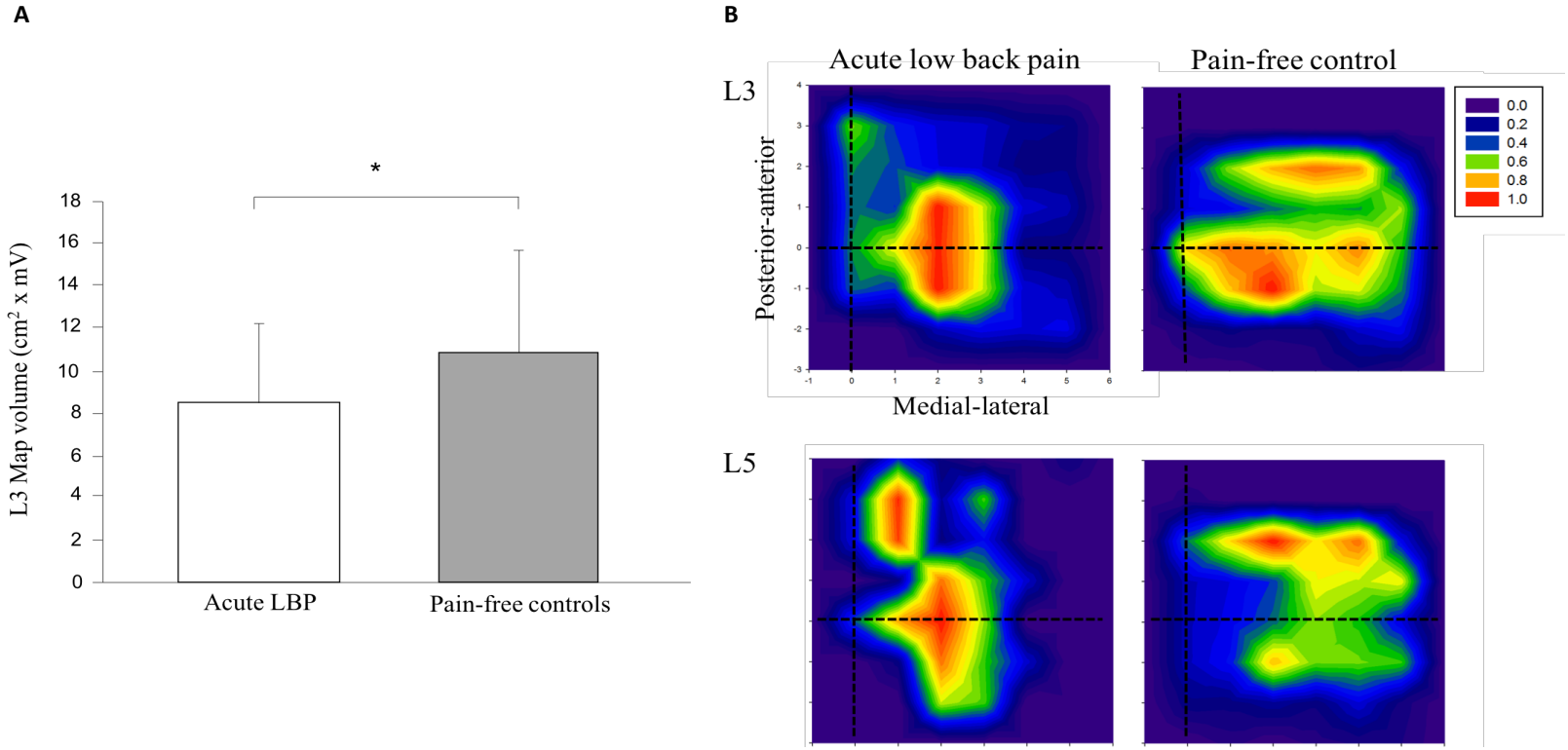

Figure 3.4. A) Group data (mean and standard deviation) for map volume at the L3 recording site. Map volume was smaller in individuals with acute low back pain than in pain-free controls. *p=0.02. B) Normalised motor cortical maps at L3 and L5 recording sites in one representative participant with acute low back pain (left images) and one representative pain-free participant (right images). *The dashed lines indicate the location of the vertex (coordinate 0,0). The coloured scale represents the proportion of the maximum motor evoked potential amplitude. Warmer colours represent higher excitability.*

Table 3.3 Group data (mean and standard deviation) for map parameters in individuals with and without acute low back pain.

	Muscle	Low Back Pain (n=36)	Pain-free controls (n=36)
CoG mediolateral location (cm)	L3	2.3±0.6	2.5±0.6
	L5	2.3±0.6	2.4±0.6
CoG posteroanterior location (cm)	L3	-0.1±1.0	-0.3±0.9
	L5	0.04±1.0	-0.2±1.0
Distance between CoG (cm)		0.5±0.3	0.4±0.3
Number of discrete peaks	L3	1.8±0.9	1.8±1.0
	L5	2.1±1.1	2.1±1.1

CoG - centre of gravity.

3.5 Discussion

This study is the first to examine sensorimotor cortex excitability in acute, clinical musculoskeletal pain. The data demonstrate smaller area of the N_{80}-N_{150}-P_{260} SEP complex, which implies "less" processing of sensory inputs in individuals with acute LBP compared with pain-free controls. Examination of specific SEP components revealed lower S2 and ACC excitability in acute LBP. Map volume of the paraspinal muscles was less in acute LBP, although measures of the map CoG and number of discrete peaks were not different, suggesting that corticomotor excitability, but not organisation, is different between individuals with acute LBP and pain-free controls. At the group level, these data suggest that acute clinical LBP is characterised by lower sensorimotor and ACC excitability. However, post hoc analysis revealed two distinct patterns of S2 and ACC excitability (high vs. low) amongst individuals with acute LBP.

This unique finding could suggest that the cortical strategy adopted in response to acute pain differs between individuals.

3.5.1 Differences in processing of non-noxious afferent input by sensory and cingulate cortices in acute LBP

SEP data demonstrated overall, less processing of non-noxious afferent inputs in the sensory and cingulate cortices (smaller area of the N_{80}-N_{150}-P_{260} complex) in individuals with acute LBP. Specifically, S2 and ACC excitability were lower (smaller areas for the individual N_{150} and P_{260} SEP components) and the peak in S2 activity was delayed (longer latency of the N_{150} SEP component) at the group level in acute LBP compared with pain-free controls. Although functional magnetic resonance imaging studies have shown altered (decreased or increased) ACC activation in response to a noxious afferent input using acute experimental pain (Zhang et al., 2014; Zhang et al., 2017), the current study is the first to provide evidence for differences in S2 and ACC excitability in acute clinical pain. S2 and ACC are involved in the emotional and motivational dimensions of pain with roles in pain perception and the integration and processing of nociceptive and non-nociceptive inputs (Apkarian et al., 2005; Casey et al., 2001; Frot et al., 2001; Fulbright et al., 2001; Treede et al., 2000). It has been shown that pain can interrupt cognition and task performance by directing attention towards the painful stimulus and away from the task (Chang and Shyu 2001; Seminowicz et al., 2004). A smaller area of the N_{150} and P_{260} SEP components in response to non-noxious afferent input in acute clinical LBP might reflect less processing of these non-nociceptive inputs. Specifically, clinical LBP may 'distract' the brain from processing other non-noxious sensory inputs. Previous studies have

shown that pain competes with the processing of non-noxious sensory inputs by diverting attentional resources (Attridge et al., 2016; Eccleston 1995).

An interesting and unique observation was that although sensory and cingulate cortex excitability were lower in individuals with acute LBP when compared to pain-free controls, variability was high. Post hoc analyses performed to explore the source of this variability revealed two distinct groups: those with high, and those with low, excitability in both S2 and ACC. The strong correlation between the SEP components attributed to S2 and ACC (r^2=0.84) suggests that S2 and ACC excitability are co-modulated in response to acute pain (although the measurement used for the N_{150} and P_{260} SEP components are drawn from the same waveform and this may lead to some overestimation of the correlation). Interestingly, those with high excitability experienced significantly less pain (2.5$\pm$1.9, N=12) than those with low excitability (4.0$\pm$1.6, N=24). This appears consistent with the hypothesis of competing demands of pain, as those with more severe pain might be expected to have greater demand on attentional resources, and greater compromise to the processing of non-noxious sensory inputs than is observed in those with less severe pain (Attridge et al., 2016; Eccleston 1995). This relationship requires detailed investigation in future studies.

S1, along with S2, is involved in sensory discrimination (Schafer et al., 2012; Zhang et al., 2017). There is evidence of decreased sensory discrimination (measured by tactile acuity) in acute experimental and chronic LBP, possibly related to adaptive (acute) and maladaptive (chronic) cortical reorganisation in S1 and S2 (Adamczyk et al., 2018a; Adamczyk et al., 2018b). Whether sensory discrimination is also affected by

acute clinical LBP and the relationship between sensory discrimination and S1/S2 excitability requires further investigation. However, contrary to our hypothesis, and to findings from acute experimental pain models, S1 excitability (area of the N_{80} SEP component) was not different in acute clinical LBP when measured in response to a non-noxious input. Using acute experimental pain models, previous studies have shown a reduction in the area of the early latency SEP components indicating decreased S1 excitability (Rossi et al., 1998; Rossi et al., 2003; Schabrun et al., 2015a; Schabrun et al., 2013), and this is supported by imaging studies showing decreased S1 activation in response to noxious stimuli (Zhang et al., 2014; Zhang et al., 2017). The discrepancy between decreased S1 excitability in studies using experimental pain models and the absence of a difference in S1 in acute clinical LBP is likely explained by different SEP protocols (noxious vs. non-noxious stimuli). The duration of pain may also influence this observation. Acute experimental pain models typically induce pain of rapid onset lasting for minutes to hours (Burns et al., 2016b) and are generally not associated with tissue damage. In the current study, individuals had experienced clinical LBP for up to 4 weeks – consistent with the clinical definition of acute LBP (Delitto et al., 2012). It is unknown whether decreased S1 excitability is also present in the very early stages (minutes to hours) of acute clinical LBP and whether this might be specific to noxious and non-noxious inputs.

Evidence suggests that the different stages of LBP may be characterised by differences in sensory and cingulate cortex excitability, but interpretation is challenging because of use of noxious and non-noxious inputs in different studies. When pain lasts for minutes to hours (induced by experimental pain models), SEP

responses evoked by both noxious and non-noxious inputs reveal reduced S1 excitability (Rossi et al., 1998; Rossi et al., 2003; Schabrun et al., 2015a; Schabrun et al., 2013). Whether there are changes in S2 and ACC excitability at this time point is unknown as relevant SEP data are absent. When LBP persists for several weeks, our findings reveal no difference in S1 excitability and lower S2 and ACC excitability in response to non-noxious stimuli. In the chronic stage of LBP, previous EEG studies have shown greater S1 excitability(Diers et al., 2007), no difference in S2 (Diers et al., 2007; Flor et al., 2004; Ladouceur et al., 2018), and inconclusive findings for ACC excitability (one study reported lower amplitude of the P_{260} component (Diers et al., 2007) and two found no difference (Flor et al., 2004; Ladouceur et al., 2018)) in response to noxious stimuli. Further, imaging studies have shown greater ACC activation in chronic LBP (Kregel et al., 2015). Future studies should investigate response to both noxious and non-noxious inputs using a longitudinal design to elucidate how sensory processing changes when LBP transitions from the acute to chronic stage and any potential relationship between these changes and symptom persistence/recovery.

3.5.2 Corticomotor excitability and organisation in acute LBP

This is the first study to demonstrate that corticomotor excitability is lower in individuals with acute clinical LBP (smaller map volume of paraspinal muscles at the L3 recording site) compared with pain-free controls. This finding is consistent with the hypothesis that corticomotor excitability is decreased in acute clinical LBP, but whether it is decreased relative to a pre-pain state for these individuals is unclear. Consistent with previous studies, lower corticomotor excitability was evident at the

L3, but not the L5, recording site (Schabrun et al., 2017b). Smaller map volume implies lower excitability of corticomotor pathways to paraspinal muscles (Schabrun et al., 2017b), consistent with findings from acute experimental pain models(Burns et al., 2016b). Although the functional relevance of lower corticomotor excitability in acute pain is unclear, it has been hypothesised that lower corticomotor excitability is a purposeful adaptation to limit provocative movements and thus limit the threat of further pain and injury (Hodges and Tucker 2011; Lund et al., 1991). As increased M1 map volume is associated with learning a motor skill with specific training (Adkins et al., 2006; Perez et al., 2004; Tyc and Boyadjian 2011), it is possible that lower M1 map volume may represent a reduced capacity to control a muscle/skill (e.g. reduced capacity to activate paraspinal muscles, or reduced lumbar segmental movement during forward bending). Conversely, as map volume is known to reduce when a motor skill is consolidated in M1, lower map volume in acute LBP could represent nervous system reinforcement of a simplified movement strategy (Nudo et al., 1996; Pascual-Leone et al., 1994). These hypotheses require future investigation.

Cross-sectional studies have provided evidence for differences in the organisation of M1 representations of paraspinal muscles (anteriorly/posteriorly shifted location and reduced number of discrete peaks) in chronic LBP (Elgueta-Cancino et al., 2018; Schabrun et al., 2017b; Tsao et al., 2011). However, whether there is a causal relationship between M1 reorganisation and LBP chronicity is unknown. In acute LBP, our data show no difference in either the CoG location or number of discrete map peaks between groups, suggesting that M1 reorganisation might not occur in the first weeks of LBP. It is possible that lower corticomotor excitability in the absence of

substantial M1 reorganisation represents an early adaptive and protective strategy in acute LBP (Hodges and Tucker 2011).

3.5.3 Limitations

Our findings suggest that the emotional and motivational dimensions of pain perception, competition for processing of non-nociceptive sensory inputs, and sensory discrimination may be altered in acute clinical LBP. However, our study did not directly investigate these components nor did we investigate the cortical response to noxious inputs. Similarly, although we postulate that lower corticomotor excitability may be associated with impaired motor control observed in the clinic, motor control in our participants was not examined. Future studies investigating neurophysiological mechanisms in acute LBP should consider measures directly examining sensorimotor function. The average pain intensity at the time of testing was 2.8 on a 11-point NRS. Future studies should seek to include individuals with greater pain severity for a wider representation of the acute clinical LBP population. Finally, this study was cross-sectional in nature and thus, causality cannot be inferred. Whether changes in M1, S2 and ACC excitability were present before the onset of acute LBP in these individuals or whether these changes relate to the development of chronic LBP has yet to be determined.

3.6 Conclusion

These data suggest that overall processing of sensory inputs and corticomotor excitability to the paraspinal muscles are lower in individuals with acute clinical LBP than pain-free controls. Specifically, SEP features attributed to processing of non-

noxious afferent input by S2 and ACC are lower at the group level in acute clinical LBP. However, these cortical features are not consistent between individuals with some displaying high S2 and ACC excitability and others displaying low excitability, and the relationship with symptoms supports the concept of pain interference. Our data provide the first information on cortical excitability in acute clinical, non-specific LBP. This information is important to understand the neurophysiological mechanisms involved in the acute stage of clinical LBP.

Chapter 4

Central pain processing does not differ between first episode and recurrent acute low back pain

The findings of Chapter 3 suggest that neuroplasticity in individuals with acute clinical low back pain is characterised by lower sensorimotor and cingulate cortex excitability with high inter-individual variability. Another important mechanism of neuroplasticity in musculoskeletal pain is central pain processing. This chapter reports on the findings from a second cross-sectional study that aimed to investigate central pain processing in individuals experiencing their first episode of acute LBP, those experiencing acute recurrent LBP and pain-free controls. The manuscript of this study is currently under review with Pain Medicine.

Chapter 4. Central pain processing does not differ between first episode and recurrent acute low back pain

4.1 Abstract

One-third of individuals with acute low back pain (LBP) experience recurrent symptoms within 12 months but the underlying mechanisms are unclear. One explanation is that individuals experiencing recurrent LBP develop altered central pain processing that predisposes to symptom recurrence. We aimed to compare central pain processing between individuals experiencing their first episode of acute LBP (N=11), recurrent acute LBP (N=11), and age- and sex-matched pain-free controls (N=11). Central pain processing was examined using pressure and heat pain threshold (PPT and HPT), nociceptive flexor withdraw reflex (NFR) and conditioned pain modulation (CPM). Other measures included pain and disability. The NFR latency was shorter in individuals experiencing their first episode of acute LBP when compared with pain-free controls (p=0.01). Descending inhibitory pain control measured by CPM was less efficient in both acute LBP groups when compared with pain-free controls. HPT and PPT did not differ between people with and without acute LBP. There were no differences between the two LBP groups for any outcome measure. These data demonstrate altered central pain processing in the acute stage of LBP. However, the degree of impairment did not differ between individuals with a first episode vs. recurrent acute LBP. These findings suggest that altered central pain processing in acute LBP is not related to a previous history of LBP.

Perspective: Central pain processing is altered in acute LBP. The degree of impairment does not differ between individuals experiencing a first episode vs. recurrent acute LBP. LBP recurrence may not be related to altered central pain processing during the acute stage of pain.

4.2 Introduction

Approximately one-third of people with an acute episode of low back pain (LBP) experience recurrence of symptoms within 12 months, with previous episode(s) of LBP being the only consistent predictor of recurrence (da Silva et al., 2017). Recurrence has been defined as a new episode of low back pain that lasts for more than 24 hours, with at least one month free of pain prior to the commencement of the new episode (Stanton et al., 2009). The mechanisms that predispose an individual to symptom recurrence are unclear, although the development of impaired central pain processing, including increased sensitivity of spinal and cortical neurons to sensory stimuli ('central sensitisation') and impaired descending inhibitory pain control, in response to an acute episode of LBP may contribute. However, whether central pain processing differs between individuals experiencing a first ever episode of acute LBP and those with a history of recurrent acute LBP is unknown.

Preliminary evidence suggests central pain processing is altered in people with acute LBP. For instance, individuals with acute LBP have lower pressure pain thresholds, higher pain in response to electrical stimuli at remote sites (areas outside the back), enlarged reflex receptive fields and lower nociceptive flexor withdrawal reflex (NFR) thresholds than healthy controls (Biurrun Manresa et al., 2013; Vuilleumier et al., 2017). These findings suggest widespread hyperalgesia, allodynia to mechanical and electrical stimuli and enhanced spinal excitability in people with acute LBP, manifestations thought to reflect central sensitisation. In contrast, evidence for impaired descending inhibitory pain control in acute LBP is mixed, with three studies demonstrating no change and one demonstrating that although the magnitude of the

descending inhibitory pain control response is unchanged in acute LBP, the duration of the response is reduced (Klyne et al., 2018; Marcuzzi et al., 2018; Mlekusch et al., 2016; Vuilleumier et al., 2017). One explanation for these mixed findings could be that the degree of impairment in descending pain inhibition is related to a previous history of LBP. Unfortunately, it is not reported whether individuals with a prior history of LBP were included in their acute LBP cohorts. It is unknown whether changes in central pain processing are consistent in people with acute LBP regardless of pain history, or whether those with recurrent LBP display greater central sensitisation and/or impaired descending pain control, than those presenting with a first episode of acute LBP.

This study aimed to compare central pain processing between individuals experiencing i) their first episode of acute non-specific LBP, ii) recurrent acute non-specific LBP, and iii) pain-free controls. We hypothesised that: (1) individuals experiencing acute LBP, with or without a previous history of LBP, would have more evidence of central sensitisation and impaired descending inhibitory pain control than pain-free controls, and (2) individuals with recurrent acute LBP would demonstrate greater central sensitisation and impaired descending inhibitory pain control than those experiencing their first episode of acute LBP.

4.3 Methods

4.3.1 Study design and participants

A cross-sectional study design was used to evaluate central sensitisation and descending inhibitory pain control in: (1) 11 individuals experiencing their first

episode of acute non-specific low back pain (LBP), (2) 11 individuals with recurrent acute non-specific LBP, and (3) 11 pain-free controls. All participants were age- and sex-matched. As there have been no studies of central pain processing in a first episode of acute LBP on which to base a sample size calculation, a convenience sample was used. Acute, non-specific LBP was defined as pain occurring between the 12th thoracic vertebra and the gluteal fold that lasted more than 24 hours but less than four weeks, and resulted in functional limitation (Delitto et al., 2012). Participants experiencing their first episode of LBP had no prior history of LBP. Participants with recurrent LBP had experienced an acute onset of LBP in the past four weeks, following a period of at least one month without LBP (de Vet et al., 2002; Stanton et al., 2009). The average time between the last episode of LBP and the current acute episode was 12.7 months (range: 2-24 months). Pain-free controls had no current pain or history of any chronic pain condition. Participants were recruited from primary care clinics and the community and were included if they were at least 18 years of age and could provide written, informed consent. Individuals who presented with suspected nerve root involvement, suspected spinal pathology (fracture, tumour, cauda equina syndrome), other major diseases/disorders, neurological conditions, a history of spine surgery, psychiatric conditions, any chronic pain conditions or contraindications to conditioned pain modulation techniques (e.g. loss of sensation) were excluded. Participant characteristics are summarised in Table 4.1. All procedures were approved by the institutional Human Research Ethics Committee (H10465) and conformed to the Declaration of Helsinki.

Table 4.1 Participant Characteristics (mean and standard deviation).

	First episode acute LBP	Recurrent acute LBP	Pain-free controls
Age	28.5 ± 5	28.6 ± 4.9	28.6 ± 4.2
Sex (male/female)	6:5	6:5	6:5
Site of Pain (left/right)	9:2	9:2	---
Pain intensity at testing (NRS)	2.7 ± 2.7	2.8 ± 2.1	---
Average pain intensity past 7 days (NRS)	3.6 ± 2.7	3.7 ± 2.1	---
Pain duration (weeks)	1.7 ± 1.4	1.8 ± .15	---
PCS-Total score	8 ± 8.8	10.4 ± 8.5	---
RMDQ	4 ± 4.7	5.5 ± 5.3	---
DASS-21 Depression	1.2 ± 1.2	3.3 ± 4.1	0.72 ± 1
DASS-21 Anxiety	0.8 ± 1.4	2.3 ± 2.4	1.5 ± 1.5
DASS-21 Stress	2.7 ± 2.8	5.3 ± 3.8	3.7 ± 3.4

NRS- Numerical Rating Scale; PCS- Pain Catastrophising Scale; RMDQ- Roland Morris Disability Questionnaire; DASS-21- Depression Anxiety Stress Scale-21.

4.3.2 Measures

4.3.2.1 Pain and disability

Pain severity was assessed using an 11-point numerical rating scale (NRS) anchored with 'no pain' at zero and 'worst pain possible' at 10. The duration of the current episode of LBP was recorded for all participants at the time of testing. Disability was assessed using the Roland Morris Disability Questionnaire (RMDQ), a reliable and valid tool in the LBP population (Roland and Morris 1983). The RMDQ has 24 items

with the score totaled from the number of items checked by each participant. A higher score indicates greater disability.

4.3.2.2 Central sensitisation

Three measures were used to assess sensitisation of the central nervous system:

(i) Nociceptive flexor withdrawal reflex (NFR): Surface electromyography was recorded from the biceps femoris muscle on the side of worst LBP (or the matched side in pain-free controls). Electrical stimuli were delivered to the sural nerve within the retromalleolar pathway according to a variable interval schedule of 20 s. Each trial consisted of a volley of five 1-ms rectangular pulses with a 3-ms inter-pulse interval. Stimulus intensity was increased in 4 mA increments until a NFR was detected and then decreased in 2 mA increments until the reflex was absent. The NFR threshold was determined as the lowest stimulator intensity that elicited a NFR. The stimulus intensity was then set at 120 % of the NFR threshold and five trials recorded. The NFR was identified as the multiphasic response occurring 90-180 ms after each stimulus. The magnitude of the reflex response was assessed as the area under the curve (root mean square). During the NFR assessment, participants rated their pain severity on an 11-point NRS (Chang et al., 2017). The NFR is a reliable experimental test (intersession coefficient of variation = 16.9%, intraclass coefficient [ICC] = 0.82) (Micalos et al., 2009).

(ii) Heat pain thresholds (HPTs): were measured using the conditioned pain

modulation system (Thermal Sensory Analyzer, TSA-2001, Q-Sense-CPM, Medoc Ltd, Ramat Yishai, Israel). A 30 x 30 mm Peltier-based thermode was placed on the skin. The temperature started at 32°C and increased at a rate of 0.5°C/s. Participants were instructed to push a button when the sensation of heat first turned to one of pain. For both LBP groups, HPTs were measured at the site of worst LBP, the opposite side of the lumbar region and the ventral aspect of the forearm on the side of worst pain. For pain-free controls, HPTs were measured 3 cm lateral to the L3 spinous process bilaterally and over the ventral aspect of the forearm of the dominant hand. Three measures were made at each site and the average at each site used for analyses. HPT measures have been shown to be reliable in LBP populations (coefficient of repeatability [CR], 7.4◦C) (Vuilleumier et al., 2015).

(iii) Pressure pain thresholds (PPTs): A handheld pressure algometer (Somedic, Hörby, Sweden, probe size 1cm^2) was applied at the site of worst LBP and over a remote site (thumbnail ipsilateral to the side of worst pain) in both LBP groups. For pain-free controls, PPTs were measured 3 cm lateral to the L3 spinous process on the side of the dominant hand and over the thumbnail of the dominant hand. Pressure was applied at a rate of 40 kPa/s and participants used a hand-held trigger to indicate when the sensation of pressure first changed to one of pain. Three measures were made at each site and averaged for analysis. PPT measures have

demonstrated acceptable reliability in LBP population (CR, 162.7 kPa) (Vuilleumier et al., 2015).

4.3.2.3 Descending inhibitory pain control

Descending inhibitory pain control was assessed as the change in pain perceived in one body region (test stimulation [TS], pressure pain threshold) as a result of pain induced in another body region (conditioned stimulation [CS], heat pain). Pressure (pressure pain threshold) was used as the test stimulus and heat pain (1°C above the heat pain threshold) as the conditioned stimulus using a conditioned pain modulation (CPM) System (Thermal Sensory Analyzer, TSA-2001, Q-Sense-CPM, Medoc Ltd, Ramat Yishai, Israel). Three PPTs were measured before the application of heat pain (TS_1). Heat pain was then applied via a 30 x 30 mm thermode. Three PPTs were re-measured 30 seconds after applying heat pain (TS_2). Participants were instructed to rate their pain on a numerical rating scale (0-100) at 0 s, 30 s and at the end of the trial. Pain scores were maintained between 50 and 80/100 during testing. Participants completed two trials in random order: i) pressure at the site of worst LBP and heat on the opposite forearm; ii) pressure at the ipsilateral forearm and heat on the low back opposite to the side of worst pain. This is a standard procedure (type and sites of stimuli) to induce a CPM response (Klyne et al., 2015). The magnitude of the CPM response was measured as TS_2 minus TS_1. A positive value indicates a normal CPM response. The CPM paradigm has shown good intrasession reliability (ICC > 0.75) (Lewis et al., 2012a).

4.3.2.4 Psychosocial questionnaires

Psychosocial factors were assessed using the following questionnaires. Pain-free controls completed only the DASS-21.

(i) The Pain Catastrophising Scale- a reliable and valid, 13-item self-report instrument to assess patients' thoughts and feelings about pain in the domains of magnification, rumination and helplessness(Osman et al., 2000).

(ii) The Depression Anxiety Stress Scale- 21 (DASS 21) - a reliable and valid, 21-item self-administered questionnaire to measure negative emotional states of depression, anxiety and stress (Parkitny and McAuley 2010). Higher scores in the subscales indicate more severe condition of depression, anxiety and stress.

4.3.3 Statistical analyses

Pain characteristics (severity and duration), and scores from the RMDQ and the Pain Catastrophising Scale were compared between individuals with a first episode of acute LBP and those with acute, recurrent LBP using Wilcoxon signed rank tests. The scores from the DASS 21 were compared between groups (first episode, recurrent, pain-free) using the Kruskal-Wallis test. Outcome measures for sensitisation and descending inhibitory pain control were compared between groups (first episode, recurrent, pain-free) using a one-way analyses of variance (ANOVA). Data that were not normally distributed were log transformed. ANOVA on ranks was performed where data were not normally distributed after log transformation. Post-hoc tests were performed using the Holm-Sidak method corrected for multiple comparisons. A $P<0.05$ was considered significant. Results are presented as means and standard

deviations in the text unless otherwise stated.

4.4 Results

4.4.1 Pain characteristics and psychosocial factors

Participants in both LBP groups had experienced a similar duration of pain (W=-1, Z=-0.06 *p*=1.0), and had similar pain severity at the time of testing (W=3, Z=0.15, *p*=0.92) and in the past seven days (W=-7, Z=-.042, *p*=0.73) (Table 4.1). There were no differences between the two LBP groups in RMDQ score (W=17, Z=0.87, *p*=0.43), PCS total scores (W=-13, Z=-0.58, *p*=0.58) or any of the subscales (rumination W=-32, Z=-1.43, *p*=0.18; magnification W=-12, Z=-0.6, *p*=0.56; helplessness W=-1, Z=-0.05, *p*=1.0). There were no between-group differences for the DASS 21 (depression: Kruskal-Wallis H (2)=2.25, *p*=0.33; anxiety: Kruskal-Wallis H (2)=3.62, *p*=0.16; stress: Kruskal-Wallis H (2)=2.34, *p*=0.31).

4.4.2 Central pain processing measures

4.4.2.1 Nociceptive withdrawal reflex

NFR responses could not be elicited in two participants experiencing their first episode of LBP as they were unable to tolerate electrical stimuli to the sural nerve. There was a significant between-group difference in NFR latency ($F_{2, 28}$=5.23, *p*=0.01). Post hoc analyses revealed a shorter NFR latency in individuals experiencing their first episode of acute LBP (n=9) when compared with pain-free controls (*p*=0.01), but no difference between those with a first episode and recurrent acute LBP (*p*=0.09) or between those with recurrent acute LBP and pain-free controls (*p*=0.25) (Figure 4.1). There were no between-group differences for NFR amplitude (ANOVA on Ranks H

(2)=1.39, *p*=0.50), threshold (ANOVA on Ranks H (2)=3.68, *p*=0.16) or NFR pain intensity ($F_{2, 28}$=0.92, *p*=0.41).

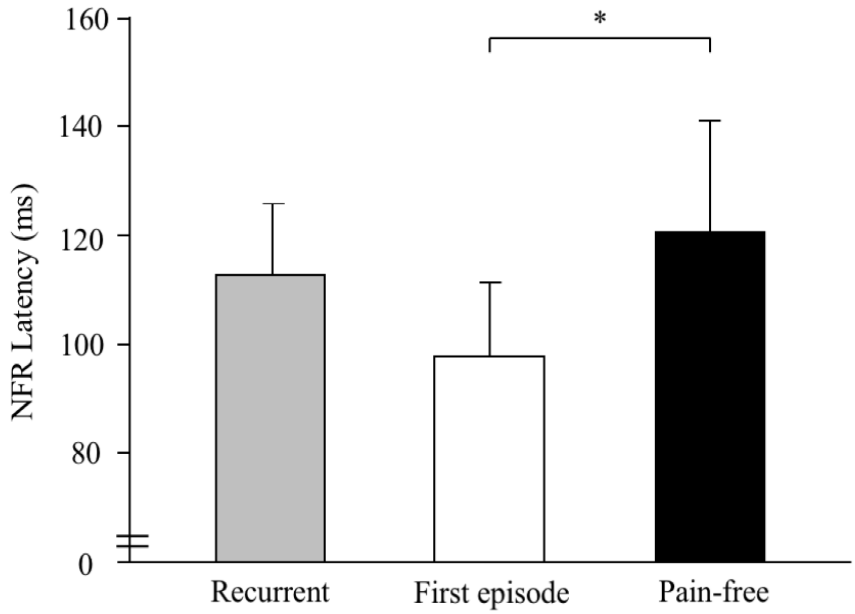

Figure 4.1 Group data (mean and standard deviation) demonstrating the latency of the nociceptive flexor withdraw reflex (NFR) in individuals with recurrent acute low back pain (LBP), individuals with their first episode of acute LBP, and pain-free controls. **p=0.01 between groups.*

4.4.2.2 Heat and pressure pain thresholds

HPTs could not be assessed in two participants experiencing their first episode of LBP (n=9) due to a loss of thermal sensation and PPTs could not be assessed in one participant experiencing their first episode of LBP (n=10) due to the intensity of their pain. There were no significant between-group differences in HPTs at the lumbar (LBP site $F_{2, 28}$=0.39, *p*=0.68; opposite to LBP site $F_{2, 28}$=0.73, *p*=0.49) or forearm ($F_{2, 28}$=0.20,

p=0.82) sites. Similarly, there were no between-group differences in PPTs measured at either the lumbar (ANOVA on Ranks H (2)=3.38, *p*=0.18) or thumb (ANOVA on Ranks H (2)=3.49, *p*=0.18) sites.

4.4.2.3 Descending inhibitory pain control

Responses could not be assessed in three participants experiencing their first episode of LBP (n=8) (two participants did not have HPT measures while the conditioned stimulus was unable to induce the required pain intensity within the safety limit of the CPM device in one participant) and in one pain-free participant (n=10) (unable to induce the required pain intensity within the safety limit). In one pain-free control, the CPM response was only elicited when PPTs were measured at the lumbar site. When heat pain was applied at the lumbar region opposite to the side of worst LBP, the change in PPT at the forearm was different between groups ($F_{2, 25}$=5.95, *p*=0.01) (Figure 4.2). Post hoc analyses revealed a greater increase in the PPT in pain-free controls (reflective of a normal CPM response) when compared with individuals experiencing their first episode of LBP (*p*=0.01) and in those with acute recurrent LBP (*p*=0.04). There was no difference between individuals with acute recurrent LBP and those with a first episode of LBP (*p*=0.28). When heat pain was applied at the forearm opposite to the side of LBP, there was no difference in the PPT response between groups ($F_{2, 26}$=3.16, *p*=0.06).

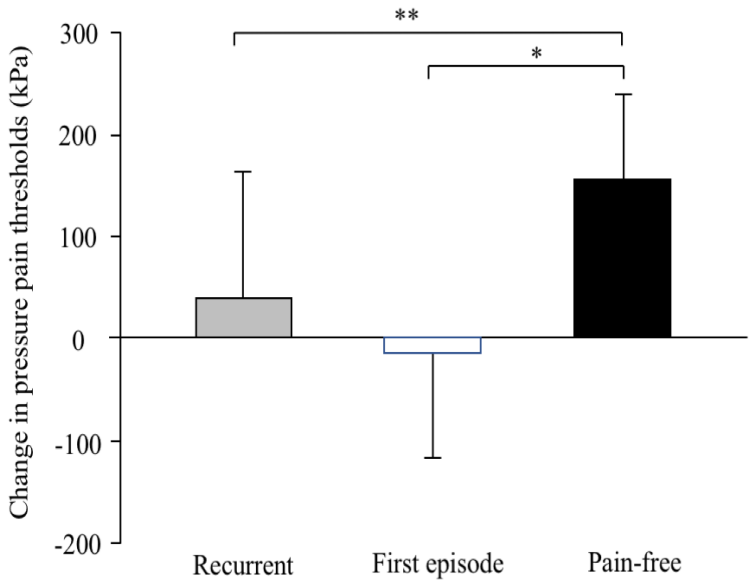

Figure 4.2 Group data (mean and standard deviation) demonstrating the conditioned pain modulation (CPM) response in individuals with recurrent acute low back pain (LBP), individuals with their first episode of acute LBP, and pain-free controls. **P=0.01 between groups and **P=0.04 between groups.*

4.5 Discussion

This preliminary study is the first to compare central pain processing, including central sensitisation and descending inhibitory pain control, between individuals with a first ever episode of acute LBP and those with recurrent acute LBP. Individuals experiencing a first episode of acute LBP had increased spinal excitability (shorter NFR latency) when compared with pain-free controls but there was no difference between the two LBP groups. Individuals experiencing acute LBP, with or without a previous history of LBP, demonstrated less efficient descending inhibitory pain control when compared with pain-free controls. Our findings provide evidence that

descending inhibitory pain control is altered in the acute stage of LBP. However, contrary to our hypothesis, individuals with recurrent acute LBP did not demonstrate a greater degree of impairment than those experiencing their first episode of acute LBP. These findings suggest that LBP recurrence may not be related to altered central pain processing in the acute stage of pain.

4.5.1 The role of altered central pain processing in recurrent LBP

Recurrent episodes of acute LBP are common, and it is now acknowledged that this clinical pattern reflects a persistent condition with a variable course, rather than a serious of unrelated occurrences of pain (Dunn et al., 2013; Hartvigsen et al., 2018). This definition suggests the presence of biopsychosocial changes that do not resolve during a period of relative remission, predisposing to recurrence of LBP. A number of authors have suggested that altered central pain processing may be one mechanism that contributes to recurrence of LBP (Graven-Nielsen and Arendt-Nielsen 2010; Hartvigsen et al., 2018; Nijs et al., 2016; Vierck 2006; Wand and O'Connell 2008; Woolf 2011).

Central pain processing can be evaluated in humans through exploration of central sensitisation and descending inhibitory pain control mechanisms. These mechanisms are believed to play a critical role in determining an individual's pain experience (Fields 2004; Heinricher et al., 2009; Nir et al., 2012). For instance, pain facilitation occurring via central sensitisation mechanisms produces hyperalgesia in response to injury (or the threat of injury) that is thought to enhance the healing of injured tissue (Sterling 2010; Woolf 2011). Conversely, descending inhibitory pain control

downregulates nociceptive input resulting in analgesia that is thought to assist with escape from potentially dangerous situations (Heinricher et al., 2009; Millan 2002). Although these mechanisms are adaptive in the short-term, central sensitisation and deficient descending inhibitory pain control have been implicated in the pathogenesis of musculoskeletal pain when pain is idiopathic and persists beyond normal tissue healing times. For instance, systematic reviews demonstrate increased spinal excitability in a range of chronic musculoskeletal pain disorders including primary headache, fibromyalgia, chronic knee pain and whiplash injury (Lim et al., 2011), widespread hyperalgesia in chronic shoulder and osteoarthritis knee pain (Noten et al., 2017; Suokas et al., 2012), and impaired descending inhibitory pain control in fibromyalgia, headache, arthritis, and some visceral and neurological conditions (Lewis et al., 2012b). These findings provide a basis for the hypothesis that central sensitisation (manifesting as increased spinal excitability and widespread hyperalgesia) and deficient descending inhibitory pain control contribute to the development of chronic and recurrent musculoskeletal pain (Graven-Nielsen and Arendt-Nielsen 2010; Nijs et al., 2016; Vierck 2006; Wand and O'Connell 2008; Woolf 2011). However, evidence in support of this hypothesis is limited as i) few studies make the distinction between chronic continuous, and chronic recurrent pain, and ii) research investigating central pain processing in recurrent musculoskeletal pain conditions is scarce.

Only two studies have examined central pain processing in recurrent LBP, reporting normal descending inhibitory pain control and an absence of widespread hyperalgesia in this population (Goubert et al., 2017; O'Neill et al., 2011). Notably,

both studies provide evidence of altered central pain processing in chronic continuous LBP (Goubert et al., 2017; O'Neill et al., 2011). Our data extend these findings by examining central pain processing in the acute stage of LBP, demonstrating that although descending inhibitory pain control is less efficient during an acute episode of LBP, this does not differ based on a previous history of LBP. Taken together, these data suggest that altered central pain processing is not a distinguishing feature of recurrent acute LBP and suggest that changes in central pain processing develop as a consequence of sustained, rather than episodic, pain.

4.5.2 Mechanisms underpinning recurrent LBP are unclear

Although longitudinal studies that examine the same individuals during periods of remission and recurrence are needed to confirm that altered central pain processing does not play a role in recurrent LBP, the findings of this preliminary study suggest that other mechanisms may be important. Although evidence is limited, previous studies have shown that individuals with recurrent LBP have delayed activation of the deep back muscles on the previously painful side and greater trunk stiffness while performing trunk perturbation tasks during a period of remission (Hodges et al., 2009; MacDonald et al., 2009). These data have been interpreted to reflect the adoption of maladaptive movement strategies that persist even when pain is absent and that may compromise spinal loading and predispose to LBP recurrence (Hodges et al., 2009; Larsen et al., 2018; MacDonald et al., 2009). This hypothesis is supported by a loss of discrete motor cortical organisation of the paraspinal muscles in individuals experiencing chronic recurrent LBP (Schabrun et al., 2017b), suggesting a possible association between motor cortical reorganisation and recurrent LBP. In addition,

psychosocial factors such as depression, anxiety, pain catastrophizing and pain self-efficacy may be relevant to the development of recurrent LBP. For example, symptoms of depression and work-related factors (e.g. low decision authority and low job satisfaction) increased risk of recurrent LBP and may play an important role in symptom recurrence (Pinheiro et al., 2015; Taylor et al., 2014; van den Heuvel et al., 2004). Indeed, evidence suggests that psychosocial factors can influence central pain processing (Goodin et al., 2009; Nir et al., 2012; Tesarz et al., 2016). However, in the current study psychosocial factors were not different between those experiencing their first episode of acute LBP and those with recurrent acute LBP. Further research is needed to identify the biopsychosocial factors that contribute to the development of recurrent LBP.

4.5.3 Limitations

This preliminary study has several limitations. As the first study to compare central pain processing in individuals with recurrent acute LBP and those with a first episode of acute LBP, there were insufficient data on which to base a sample size calculation. While we can likely rule out the large effects of the past history of LBP on altered central pain processing in the acute stage of LBP, we acknowledge that we may not be powered to detect less notable effects. Future studies with a larger sample size are needed to confirm the current findings. Further, research indicates that a history of three or more previous episodes of LBP triples the odds of recurrent pain within 12 months (Machado et al., 2017). Thus, individuals reporting 3 or more previous episodes of LBP may have greater changes in central pain processing than those reporting one or two previous episodes of LBP. However, our sample size was

insufficient to investigate an effect of the number of previous LBP episodes on central pain processing. Finally, the average acute pain intensity at the time of testing was relatively mild (2.7 and 2.8 points on a 11-point NRS) for the two acute LBP groups. Future studies should seek to include individuals with a greater intensity of acute pain to represent a wider acute LBP population.

4.6 Conclusion

This study confirms the presence of altered central pain processing in acute non-specific LBP compared with pain-free controls. However, there is no difference in central pain processing between individuals with a first episode and recurrent acute LBP. These data suggest that altered central pain processing in acute LBP is not related to an individual's previous history of LBP.

Chapter 5

Addition of Transcranial Direct Current Stimulation to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

The findings of Studies 2 to 4 provide new insight into neuroplasticity in chronic and acute musculoskeletal pain. To provide a clinical context for these findings, this chapter reports the findings from a pilot randomised controlled trial that investigated a novel therapy that combines non-invasive brain stimulation and exercise for chronic pain. The content has been published in *Chang WJ, Bennell KL, Hodges PW, Hinman RS, Young CL, Buscemi V, Liston MB, Schabrun SM. Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: A pilot randomised controlled trial. PLoS One. 12:e0180328, 2017.* A copy of this publication is provided in Appendix C. **Note:** the protocol of this study has been published in *Chang WJ, Bennell KL, Hodges PW, Hinman RS, Liston MB, Schabrun SM. Combined exercise and transcranial direct current stimulation intervention for knee osteoarthritis: protocol for a pilot randomised controlled trial. BMJ open. 5:e008482, 2015*. A copy of this publication is provided in Appendix D.

Chapter 5. Addition of Transcranial Direct Current Stimulation to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

5.1 Abstract

A randomised, assessor- and participant-blind, sham-controlled trial was conducted to assess the safety and feasibility of adding transcranial direct current stimulation (tDCS) to quadriceps strengthening exercise in knee osteoarthritis (OA), and provide data to inform a fully powered trial. Participants were randomised to receive active tDCS+exercise (AT+EX) or sham tDCS+exercise (ST+EX) twice weekly for 8 weeks whilst completing home exercises twice per week. Feasibility, safety, patient-perceived response, pain, function, pressure pain thresholds (PPTs) and conditioned pain modulation (CPM) were assessed before and after treatment. Fifty-seven people were screened for eligibility. Thirty (52%) entered randomisation and 25 (84%) completed the trial. One episode of headache in the AT+EX group was reported. Pain reduced in both groups following treatment (AT+EX: $p<0.001$, partial $\eta^2=0.55$; ST+EX: $p=0.026$, partial $\eta^2=0.18$) but no between-group differences were observed ($p=0.18$, partial $\eta^2=0.08$). Function improved in the AT+EX ($p=0.01$, partial $\eta^2=0.22$), but not the ST+EX ($p=0.16$, partial $\eta^2=0.08$) group, between-group differences did not reach significance ($p=0.28$, partial $\eta^2=0.052$). AT+EX produced greater improvements in PPTs than ST+EX ($p<0.05$) (superolateral knee: partial $\eta^2=0.17$; superior knee: partial $\eta^2=0.3$; superomedial knee: partial $\eta^2=0.26$). CPM only improved in the AT+EX group but no between-group difference was observed ($p=0.054$, partial $\eta^2=0.158$). This study provides the first feasibility and safety data for the addition of tDCS to quadriceps strengthening exercise in knee OA. Our data suggest AT+EX may improve

pain, function and pain mechanisms beyond that of ST+EX, and provides support for progression to a fully powered randomised controlled trial.

5.2 Introduction

Knee osteoarthritis (OA) is a prevalent and costly health problem with no known cure. Approximately 10% of people aged over 60 years experience significant pain, physical dysfunction and reduced quality of life as a result of knee OA, and this figure is rising rapidly (Vos et al., 2012). The development of low cost, non-drug, non-surgical treatments to improve patient outcomes has been identified as a key priority area by people living with OA (Gierisch et al., 2014).

Strengthening exercise is the cornerstone of conservative management for knee OA and is recommended in all clinical guidelines internationally (Hochberg et al., 2012; McAlindon et al., 2014). Although exercise is effective in knee OA, meta-analyses indicate treatment benefits are at best, moderate, for pain and physical function, and small in quality of life (Fransen et al., 2015). Novel treatments that enhance the benefits of strengthening exercise through synergistic mechanistic effects are one avenue that might further improve exercise outcomes for people with knee OA.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique with the potential to enhance the effectiveness of exercise in knee OA. Weak direct currents are applied to the brain via scalp electrodes to increase (anodal stimulation) or decrease (cathodal stimulation) the excitability of neurons in the region below the electrode and in distant interconnected areas (Lang et al., 2005; Miranda et al., 2006; Wagner et al., 2007). As increased cortical excitability in the primary motor cortex (M1) is associated with motor learning (Bagce et al., 2013; Hirano et al., 2015; Jensen et al., 2005; Ljubisavljevic 2006), anodal tDCS of M1 is

thought to increase the brain's responsiveness to the afferent input generated by subsequent treatments such as motor training and peripheral electrical stimulation, a phenomenon known as priming (Reis and Fritsch 2011; Schabrun and Chipchase 2012b; Schabrun et al., 2014a). In addition, evidence from healthy individuals and groups with chronic pain suggests anodal tDCS applied to the primary motor cortex (M1) can reduce pain through modulation of pain processing in cortical and subcortical regions, facilitation of descending anti-nociceptive pathways, and induction of synaptic change, reminiscent of neuroplasticity, in underlying brain regions (Fenton et al., 2009; Fregni et al., 2006a; Fregni et al., 2006b; Nitsche et al., 2005b). On this basis, applying anodal tDCS to M1 in addition to the established exercise therapy for knee OA has the potential to bolster the mechanistic and clinical effects of exercise through two mechanisms: i) 'priming' the brain to increase its responsiveness to the corticomotor benefits of exercise (e.g. increased cortical excitability, enhanced voluntary muscle activation, strength gains, improved muscle coordination and motor control) and/or; ii) additive and complementary effects on pain system function which has been argued as an outcome of exercise (Koltyn and Arbogast 1998). Thus, the combined application of tDCS and exercise may enhance mechanistic and clinical outcomes in knee OA. However, there has been no research investigating the effect of tDCS combined with exercise therapy in people with osteoarthritic pain.

Only one study has attempted to combine tDCS with exercise for treatment of chronic pain (Mendonca et al., 2016). That study demonstrated greater decreases in pain intensity and anxiety, as well as a trend towards a greater reduction in depression, in

individuals with fibromyalgia when tDCS was delivered during aerobic exercise than when tDCS or exercise were delivered alone. These data suggest that tDCS may bolster the effects of exercise in chronic pain.

This pilot randomised clinical trial aimed to: i) determine the safety, feasibility and patient-perceived response of adding tDCS to an exercise program for knee OA; and ii) provide data to inform a sample size calculation for a fully-powered trial based on trends of efficacy in pain, physical function and pain system function should these be observed.

5.3 Methods

This randomised, assessor- and participant-blinded controlled trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry: ACTRN12613001320741. Ethical approval was obtained from Western Sydney University's Human Research Ethics Committee (H10184). All participants provided written informed consent.

5.3.1 Participants

Individuals who met the criteria of the American College of Rheumatology (ACR) clinical classification for idiopathic knee OA (Altman et al., 1986) were recruited between September 2014 and August 2015 in Sydney, Australia. The post-intervention assessment of the trial was completed in November 2015. The ACR criteria include the presence of knee pain plus at least three of the following six items: age over 50 years, morning stiffness lasting less than 30 minutes, crepitus, bony

tenderness, bony enlargement and no palpable warmth. A minimum pain score of 40 on a 100mm visual analogue scale (VAS) on walking in the past week was required. Exclusion criteria are detailed in the protocol paper (Appendix D) (Chang et al., 2015a). Participants were permitted to continue their usual medications for the duration of the trial. Medication type and dosage were recorded at the baseline assessment. Potential participants completed an on-line or telephone screening questionnaire to determine eligibility. Eligible individuals were contacted to confirm their willingness to participate and to arrange baseline assessment. A single investigator (W-JC), blinded to the group allocation of the participants, performed participant recruitment, screening, and testing.

5.3.2 Procedures

Participants were randomly allocated to: 1) active tDCS plus exercise (AT+EX); or 2) sham tDCS plus exercise (ST+EX). The randomisation schedule was concealed in consecutively numbered, sealed opaque envelopes. An investigator not involved in recruitment and assessment prepared and provided the envelopes to the treating physiotherapists who revealed group allocation. Participants received 20 minutes of either active or sham tDCS immediately prior to 30 minutes of one-to-one supervised strengthening exercise, twice weekly for eight weeks (16 sessions). tDCS was applied before exercise therapy based on findings of greatest clinical benefit in individuals with stroke when tDCS is applied before, and not during or after, a second therapy (Giacobbe et al., 2013). Treatment duration was based on previous studies that reported that at least 12 supervised exercise sessions are required for optimum results in knee OA (Juhl et al., 2014). The knee with worst symptoms was assessed

and treated if bilateral knee OA was present. Assessment and treatment were performed in the laboratory at Western Sydney University. Physiotherapists with more than five years experience were trained in tDCS and delivered both the tDCS (active and sham) and exercise therapies. All participants were instructed to complete home exercises twice per week.

5.3.3 tDCS

tDCS was delivered via two 35 cm^2 surface sponge electrodes using a direct current stimulator (DC-STIMULATOR, neuroConn, Ilmenau, Germany) while participants sat quietly. The active electrode (anode) was placed over M1 contralateral to the side of the worst knee and the reference electrode (cathode) over the contralateral supraorbital region (Zaghi et al., 2011). The primary motor cortex has emerged as one of the most effective and reliable sites for tDCS in the treatment of pain, producing improvements in pain analogous to those of FDA approved pharmaceuticals in other musculoskeletal pain conditions with considerably fewer side-effects (Marlow et al., 2013). Current intensity was ramped up (0 mA to 1 mA) and down (1 mA to 0 mA) over 10 seconds at the beginning and end of the stimulation period. The stimulation protocol was selected based on tDCS literature (Brunoni et al., 2012). For sham stimulation, electrodes were placed in an identical position. Stimulation was turned on for 15 seconds, then off, to provide the initial itching sensation. Participants were informed that they may or may not perceive any sensation during stimulation (Gandiga et al., 2006). The success of participant blinding was assessed at post-intervention assessment using a Yes/No response to a series of questions to determine whether treatment allocation was divulged to participants before

completion of the trial (Chang et al., 2015a).

5.3.4 Exercise therapy

Standardised quadriceps strengthening exercises (5 in total) known to be effective in knee OA were performed with ankle cuff weights or resistance bands where appropriate (Fransen et al., 2015; Lange et al., 2008). Each exercise was performed in 3 sets of 10 repetitions with a 30s break between sets. The exercises are described in detail in the protocol paper (Chang et al., 2015a). The exercise program was progressed as defined in the protocol. The starting level and when to progress the exercise were determined for each individual by the treating physiotherapists based on participant feedback and the therapist's clinical judgement. Cuff weights/resistance bands were given to participants to perform their supervised exercises (at the same dosage) at home. Home exercise diaries with instructions were provided for recording the number of sessions, the type and number of exercises performed and any adverse reactions. Diaries were collected at the post-intervention assessment.

5.3.5 Measures

Baseline and post-intervention assessments were performed within one week of commencing or completing the 8-week treatment. *Feasibility* was measured as the: (i) number of treatment sessions attended by each participant, (ii) number of drop-outs in each treatment group, (iii) proportion of participants recruited from the total number screened, (iv) willingness of each participant to undergo therapy on an 11-point numerical rating scale (NRS) with 'not at all willing' at 0 and 'very willing' at 10

(baseline only), and (v) number of home exercise sessions completed. *Safety* was assessed as any adverse reaction reported upon verbal questioning by the treating physiotherapists at each session (Carlesso et al., 2010). The description of any adverse reaction, its severity and duration and how the adverse reaction was managed were documented.

5.3.5.1 *Pain, function and perceived effect of treatment*

Pain and function were measured using: (i) a 100 mm VAS for pain on walking over the past week with terminal descriptors of 'no pain' (score 0 mm) and 'worst pain imaginable' (score 100 mm), (ii) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (5 items, total score = 20) and physical function (17 items, total score = 68) subscales (Williams et al., 2012). The reliability of the VAS in OA has been demonstrated (Bellamy 1997). The WOMAC is a disease-specific valid and reliable instrument for knee OA (Bellamy et al., 1988). Participants' perceived response to therapy was assessed at post-intervention assessment using a 7-point Likert scale ranging from "completely recovered" to "vastly worsened" (Dworkin et al., 2005).

5.3.5.2 *Pain mechanisms*

The protocol for each measure is described in detail in the protocol paper (Chang et al., 2015a). In brief, the following measures were made:

(i) Pressure pain thresholds (PPTs) were measured at two remote sites: a) ipsilateral tibialis anterior (10 cm distal to the tibial tuberosity), b) ipsilateral extensor carpi radialis longus (10 cm distal to the lateral

epicondyle of the humerus); and eight sites at the worst knee (Figure 5.1): c) inferomedial- 2 cm distal to the inferior medial edge of patella; d) inferolateral- 2 cm distal to the interior lateral edge of patella; e) lateral- 3 cm lateral the mid point of the lateral patellar border; f) superolateral- 2 cm proximal to the superior lateral edge of patella; g) superior- 2 cm proximal to the mid point of the superior patellar border; h) superomedial- 2 cm medial to the superior medial edge of patellar; i) medial- 3 cm medial to the mid point of the medial patellar border; and j) centre of the patella (Arendt-Nielsen et al., 2010). The average of three measurements at each site was used in the analysis. The reliability of PPT in OA knee has been demonstrated (ICC = 0.83 [0.72-0.90]) (Wylde et al., 2011).

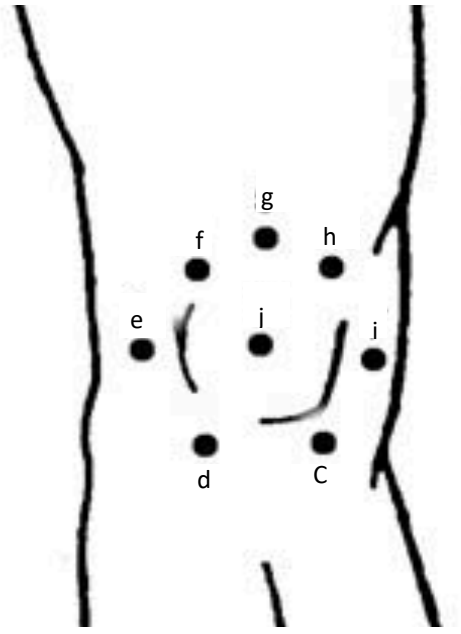

Figure 5.1 Pressure pain thresholds measured at eight sites of the worst knee. *Note: this is an example of a right osteoarthritic knee pain (adapted from Arendt-Nielsen et al., 2010).*

(ii) Heat pain thresholds (HPTs) were measured at the worst knee (medial knee joint line, patella and lateral knee joint line) and the ventral aspect of the forearm (10 cm distal from the elbow crest) on both sides. The average of three measurements at each site was used in the analysis. HPT measure has moderate reliability in OA knee (ICC = 0.77 [0.62-0.87]) (Wylde et al., 2011).

(iii) CPM was examined as a change in pain perceived in one body region (test stimulation [TS], pressure pain threshold) as a result of pain induced in another body region (conditioned stimulation [CS], heat pain). Participants completed two trials in random order: i) TS at the worst knee and CS at the contralateral forearm; ii) TS at the contralateral forearm and CS at the ipsilateral forearm. The CPM paradigm has demonstrated good intrasession reliability (ICC > 0.75) (Lewis et al., 2012a).

(iv) Nociceptive flexor withdrawal reflex (NFR) was measured using surface stimulating electrodes applied at a retromalleolar location along the expected location of the sural nerve on the side of the worst knee. Recording electrodes were positioned over the belly of the biceps femoris muscle. The intensity needed to evoke a response in biceps femoris, indicating activation of the NFR, the latency of the onset of the NFR response, the EMG amplitude of the NFR response (quantified as the area of the root mean square amplitude between onset and offset of the response) and the subjective pain score on a NRS (0-10) experienced from the sural nerve stimulus were recorded. The NFR is a reliable experimental test (intersession CV_{SEM} = 16.9%, ICC = 0.82) (Micalos et al., 2009).

5.3.6 Data analysis

A CONSORT (Moher et al., 2012) diagram was used to describe the flow of the participants and to summarise the eligibility, recruitment and follow-up rates throughout the trial. *T*-tests were used for between-group comparisons of baseline characteristics. Data distribution was tested for skewness, kurtosis and normality (Shapiro-Wilk test) prior to conducting the *T*-tests. The analyses of pain, function and pain system function were performed according to intention-to-treat analysis. Missing data were not replaced. To confirm the appropriateness of the statistical analysis plan for a full randomised controlled trial, repeated Measures Analysis of Variance (Rizzo et al., 2014) were conducted to compare baseline and post-intervention scores for each outcome, in each group. An analysis of covariance (ANCOVA) was used to assess between-group changes in pain, function and pain mechanisms, where group allocation was the fixed factor and the corresponding baseline outcome values were covariates (Van Breukelen 2006). Prior to conducting the analysis of variance and covariance tests, the normality (Shapiro-Wilk test) and the homogeneity of variances were tested. Results are presented as means and standard deviations unless otherwise stated.

5.4 Results

5.4.1 Feasibility

Fifty-seven people were screened for eligibility. Thirty-two (56%) met the inclusion criteria and attended baseline assessment. Two declined to participate after completing baseline assessment. Thirty screened participants (52%) were enrolled in

the study and randomly allocated to a treatment group (Figure 5.1). Twenty-five enrolled participants (84%) (13 in the AT+EX group and 12 in the ST+EX group) completed the treatment and post-intervention assessment. The dropout rate was 16% (13% [n=2] in the AT+EX group and 20% [n=3] in the ST+EX group). In the AT+EX group, one participant withdrew after having an unrelated fall at home and the second relocated to another city. In the ST+EX group, one participant was unable to continue the study while simultaneously receiving physiotherapy after a rotator cuff repair surgery and two withdrew due to traveling distance required to attend treatments. The treatment attendance rate was 80% (14±1.7 sessions) in the AT+EX group and 78% (13.7±2.7 sessions) in the ST+EX group. The AT+EX group completed 14.7 (±2.3) home exercise sessions while the ST+EX group completed 11.3 (±5.2) sessions (out of 16). The demographic characteristics of all participants at baseline were similar between groups (Table 5.1). Blinding was successful; no participant reported that the type of tDCS stimulation was divulged before completing the post-intervention assessment. Eleven (73%) participants in the AT+EX group and seven (47%) in the ST+EX group correctly guessed their treatment group. The outcome assessor reported that the treatment allocation of participants was not divulged before the trial completion.

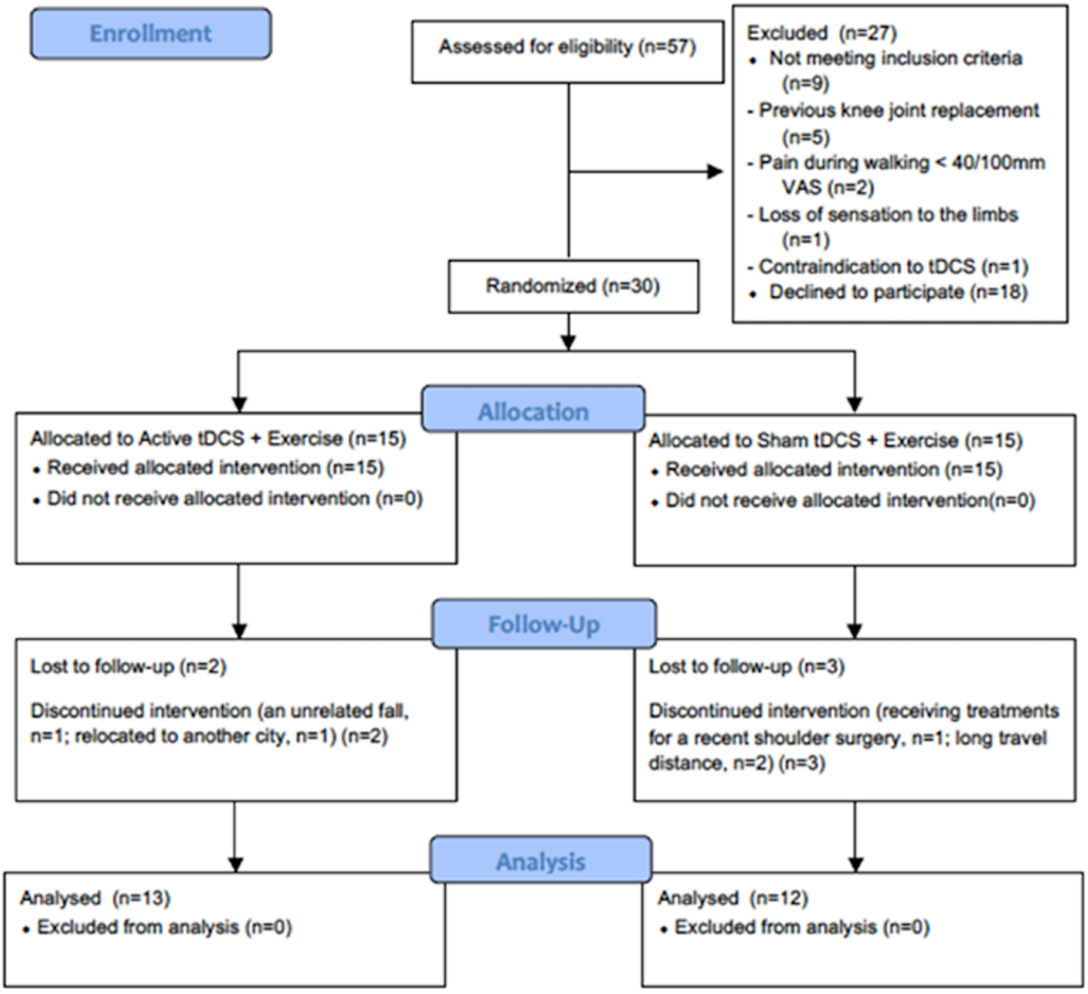

Figure 5.2 Consort diagram for flow of participants through the trial.

Table 5.1 Baseline characteristics of participants (mean and standard deviation).

	Active tDCS + Exercise (N=15)	Sham tDCS + Exercise (N=15)
Age (year)	59.8±9.1	64.1±11.1
Gender (male/female)	4/11	6/9
Height (metre)	1.6±0.08	1.6±0.11
Weight (kg)	89.0±13.3	84.5±16.4
Body Mass Index (kg/metre^2)	31.3±3.5	30.5±9.1
Duration of symptoms (years)	7.2±5.3	9±7.3
Previous knee arthroscopy	4	6
Bilateral OA knee pain	12	10
Side of worst knee pain (left/right)	4/11	8/7
Willingness to undergo treatment at baseline (out of 10)	9.4±1.1	9.8±0.3
Expected treatment effects		
Minimal improvement	3(20%)	1(6%)
Moderate improvement	6(40%)	7(47%)
Large improvement	6(40%)	7(47%)
Pain on walking (visual analog scale, 100 mm)	59.8±15.2	56.4±19.7
WOMAC *Total score*	55±16.0	48±10.7
Pain	11±3.9	9.9±3.2
Physical function	38.8±11.9	33.2±7.7

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

5.4.2 Safety

One participant in the AT+EX group reported increased pain and swelling in her worst knee at week 6 of the treatment with no precipitating factors identified and was diagnosed with a first episode of gout (no previous history) by her general practitioner. She completed the trial after her symptoms settled. Two adverse reactions to tDCS were documented; one participant in the AT+EX group reported a single episode of headache after one treatment session and later withdrew from the study due to a fall at home. One participant in the ST+EX group reported a single incident of a painful sensation under the tDCS electrode when the current intensity was ramped up at the beginning of stimulation. tDCS was ceased immediately and the painful sensation resolved. The participant returned to complete the study after the incident and reported no further adverse reactions. No adverse reactions to, or concerns regarding the implementation of, the exercise program were identified.

5.4.3 Perceived participant response to treatment

All participants in the AT+EX group and 84 % in the ST+EX group reported an improvement in their knee OA symptoms following treatment (Figure 5.2). No participant reported that knee symptoms worsened with either treatment.

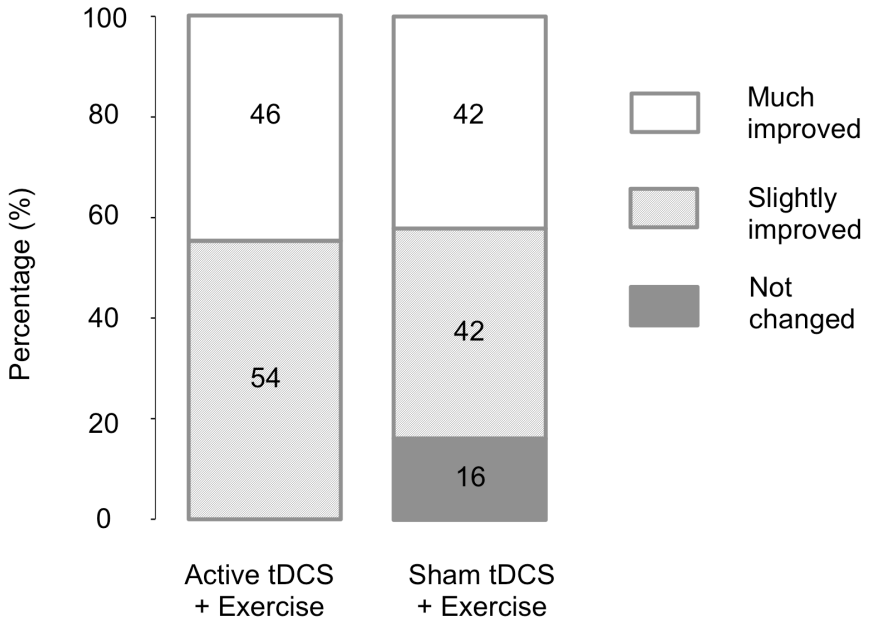

Figure 5.3 Percentage of participants reporting perceived improvement across categories from 'not changed' to 'much improved'. *Note: no participants reported that their condition worsened after either intervention.*

5.4.4 Pain and function

Pain during walking (100 mm VAS) reduced in both groups at post-intervention (ANOVA: AT+EX group: $p<0.001$, partial $\eta^2=0.55$; ST+EX group: $p=0.026$, partial $\eta^2=0.18$) (Table 5.2) (Figure 5.3). Pain reduction in the AT+EX group was double that observed in the ST+EX group (AT+EX group: -41.4 mm, 95%CI -30.7 to -52.2; ST+EX group: -20.7 mm, 95%CI -7.1 to -34.3; Figure 5.4). The between-group difference was in favour of the AT+EX group (mean difference=-13.0, 95%CI -32.6 to 6.5; ANCOVA: $p=0.18$, partial $\eta^2=0.08$). Scores on the WOMAC pain subscale followed a similar pattern (Table 5.2).

Table 5.2 Group data (mean and 95% confidence interval) for pain and function outcome measures.

	Baseline		**Post-intervention**		**Difference within groups (Follow up – Baseline) [a]**		**Difference between groups; adjusted mean [b]**	
	AT+EX (N=15)	**ST+EX (N=15)**	**AT+EX (N=13)**	**ST+EX (N=12)**	**AT+EX (N=13)**	**ST+EX (N=12)**	**AT+EX minus ST+EX**	**P value between groups**
Pain VAS (100 mm)	59.9(67.6,52.1)	56.5(66.5,46.5)	24.1(33.4,14.8)*	33.7(49.0,18.5)*	-41.4(-30.7,-52.2)	-20.7(-7.1,-34.3)	-13.0(-32.6,6.5)	.18
WOMAC								
Total score	55.0(63.1,46.9)	48.0(53.4,42.6)	36.8(45.3,28.2)*	39.1(47.1,31.0)	-16.7(-6.0,-27.3)	-8.1(-1.3,-14.8)	-6.2(-18.8,6.3)	.31
Pain subscale	11.0(13.0,9.0)	9.9(11.6,8.3)	7.5(9.2,5.7)*	7.4(9.3,5.5)	-3.8(-1.0,-6.5)	-2.2(-0.5,-3.8)	-0.6(-3.4,2.3)	.69
Physical function subscale	38.9(44.9,32.8)	33.3(37.2,29.3)	26.0(32.3,19.7)*	27.8(33.8,21.7)	-10.9(-3.3,-18.5)	-4.9(0.2,-10.0)	-4.8(-14.0,4.3)	.28

AT + EX = active tDCS + exercise, ST + EX = sham tDCS + exercise; VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. [a] A negative number indicates improvement at post-intervention. [b] A negative number favours the AT + EX group. *$p < 0.05$.

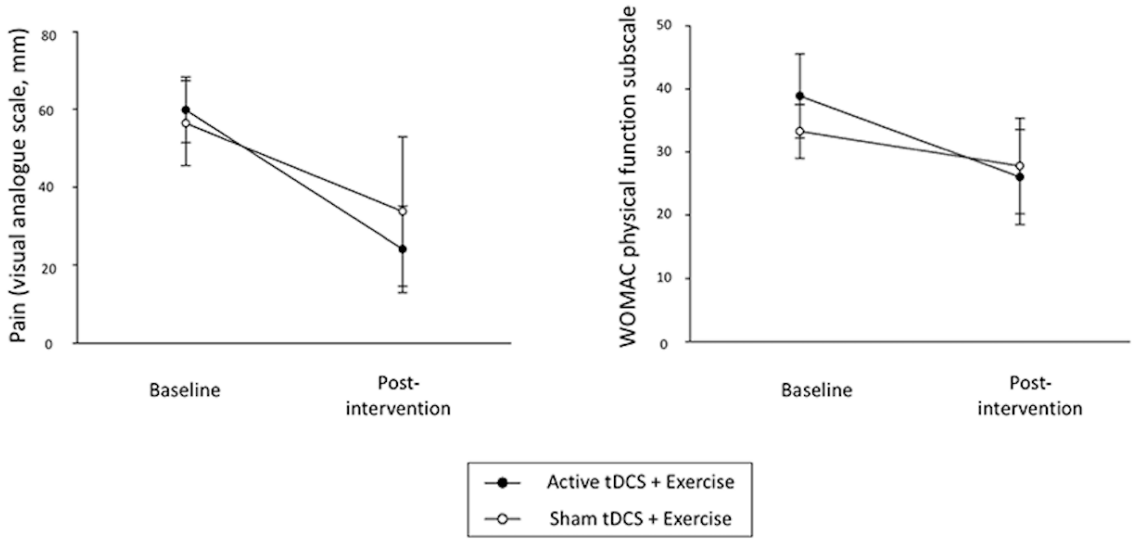

Figure 5.4 Pain and WOMAC physical function subscale (mean and 95% confidence interval) pre- and post-interventions. *Active tDCS + exercise produced improvements in pain and function but sham tDCS + exercise only produced improvement in pain.*

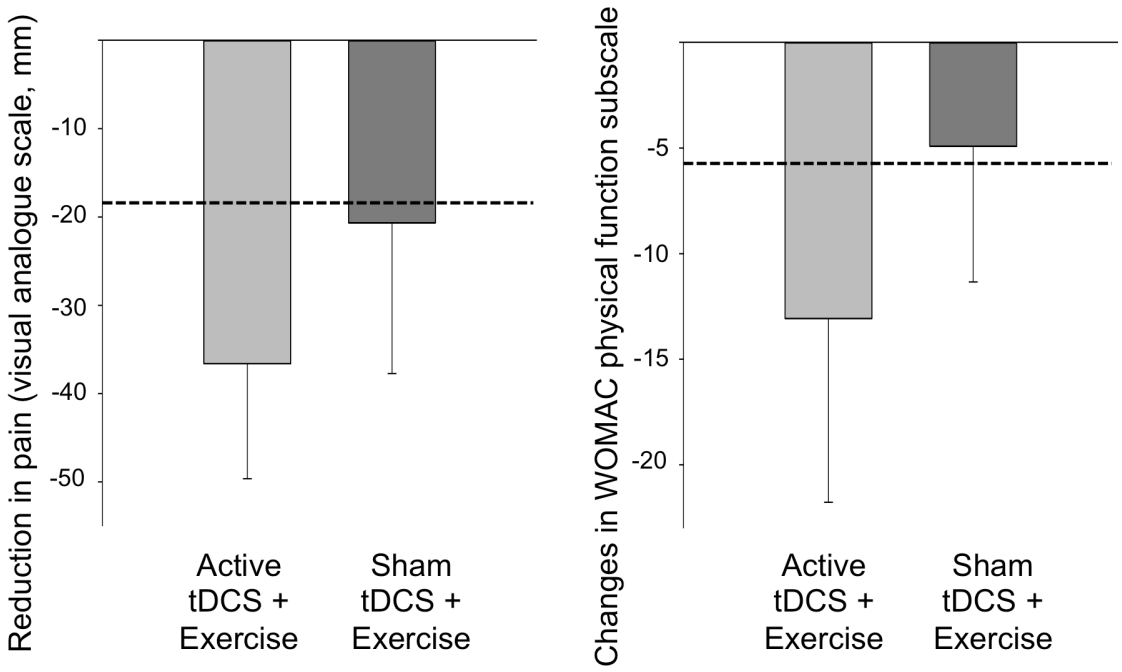

Figure 5.5 Group change in pain (left panel) and WOMAC physical function subscale (right panel). *The graph showed within-group changes (mean and 95% confidence interval) in pain and function following 8 weeks of either active tDCS + exercise or sham tDCS + exercise. Note: larger negative scores indicate greater improvements in pain and function. The dotted line indicates the minimal clinically important change for each outcome.*

Improvements in physical function (WOMAC subscale) were observed in the AT+EX (ANOVA: p=0.01, partial η^2=0.22), but not the ST+EX group (ANOVA: p=0.16, partial η^2=0.08) at post-intervention (AT+EX: -10.9 units, 95%CI -3.3 to -18.5; ST+EX: -4.91 units, 95%CI 0.2 to -10.0; Figures 5.3 and 5.4). Between-group comparisons did not

reach statistical significance (mean difference = -4.8, 95%CI -14.0 to 4.3; ANCOVA: p=0.28, partial η^2=0.052).

5.4.5 Pain mechanisms

PPTs increased (i.e. a greater amount of pressure was required to be perceived as painful) to a greater extent in the AT+EX group for the superolateral, superior, and superomedial knee sites when compared with the ST+EX group (ANCOVA: p<0.05; partial η^2=0.169, partial η^2=0.301, partial η^2=0.262 respectively) (Figure 5.5). Conditioned pain modulation, which is proposed to measure descending pain inhibition (TS at the worst knee and CS at the contralateral forearm), improved from baseline in the AT+EX group (25.6 kPa, 95%CI 47.2 to 4.1, ANOVA: p=0.032, partial η^2=0.17) but not in the ST+EX group (-27.1 kPa, 95%CI 24.6 to -78.8, ANOVA: p=0.41, partial η^2=0.03) (see Supplementary S1 Table in Appendix C.1). However, there were no between-group differences (mean difference=39.0, 95%CI -0.7, 78.6; ANCOVA: p=0.054, partial η^2=0.158). No within- or between-group differences were found for any other measure, including the NFR (Supplementary Tables S1, S2 and S3 in Appendix C.1-C.3).

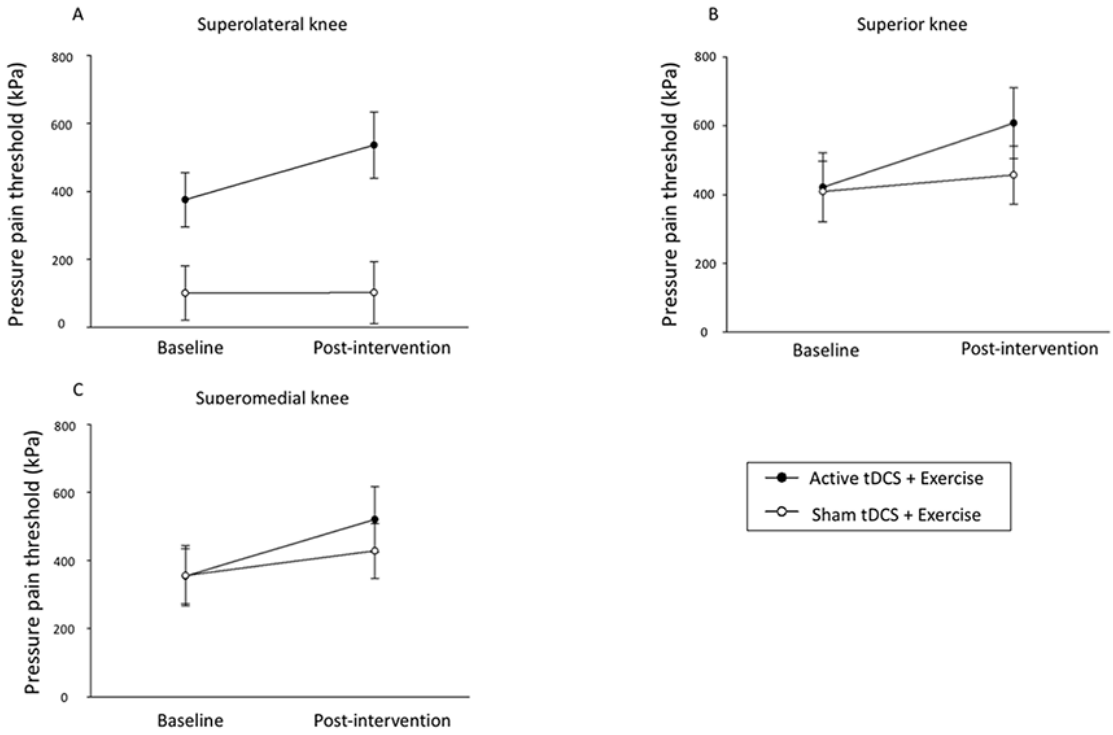

Figure 5.6 Pressure pain thresholds (mean and 95% confidence interval) pre- and post-interventions at three knee sites. *Active tDCS + exercise produced greater improvements in pressure pain thresholds at all three sites following 8 weeks of treatment compared with sham tDCS + exercise (A = superolateral knee; B = superior knee; C = superomedial knee).*

5.4.6 Sample size calculation

The minimum clinically important difference to be detected in OA trials is a change in pain of 18 mm and a change in function of six units (Tubach et al., 2005). We require a sample size of 99 participants per intervention arm (198 in total) at 90% power and 5% significance level to detect a mean difference of this magnitude, assuming a small effect size (0.3) and allowing for a maximum dropout rate of 20%.

5.5 Discussion

This is the first study to investigate the addition of tDCS to a quadriceps strengthening exercise in knee OA. Our study demonstrates that this treatment combination is feasible and appears to be safe in this population. Further, our preliminary evidence indicates that adding tDCS to exercise may be a promising approach for improving pain, physical function and pain mechanisms in knee OA. These results provide data to inform a fully powered clinical trial to examine the effect of this novel treatment on the symptoms and pain mechanisms associated with knee OA.

5.5.1 Adding tDCS to exercise for knee OA is feasible and safe

Attendance rates for treatments and post-intervention assessment were both above 80%, indicating that a larger randomised controlled trial to evaluate the efficacy of this treatment in this population is feasible (Ribeiro et al., 2014). No barriers to implementation of the interventions or outcome measures were identified in this study. Therefore, the methodology used in this study can be implemented in a larger study without any major amendments. Adverse reactions to tDCS during (e.g. fatigue) and after (headache, nausea or insomnia) stimulation have been reported in previous studies (Mendonca et al., 2016; O'Connell et al., 2011; Poreisz et al., 2007). We documented only two adverse reactions that could be attributed to tDCS: one episode of headache in the AT+EX group and one episode of a painful sensation during the initial ramping up of the electric current in the ST+EX group. No adverse reactions were documented in response to the exercise treatment. The overall incidence rate of adverse reactions in this study is lower than those reported in either the tDCS or knee OA literature (Bennell et al., 2014; Poreisz et al., 2007), indicating

that the implementation of a tDCS and exercise treatment is likely to be safe in knee OA.

5.5.2 The effects of adding tDCS to exercise on pain, function and pain mechanisms

Previous studies have investigated the analgesic effect of tDCS in chronic pain conditions such as low back pain (O'Connell et al., 2013; Schabrun et al., 2014a), chronic pelvic pain (Fenton et al., 2009), fibromyalgia (Lee et al., 2012; Mendonca et al., 2011; Mendonca et al., 2016) and neuropathic pain after spinal cord injury (Mehta et al., 2015) with conflicting results. This study is the first to use tDCS in knee OA and to combine tDCS with strengthening exercise in any pain condition. Consistent with evidence of strengthening exercise in knee OA (Fransen et al., 2015; Uthman et al., 2013), both groups reported reduced pain following the 8-week treatment. However, in the AT+EX group, effects on pain were more than double the minimal clinically important difference (MCID) of 20 mm for this outcome (Tubach et al., 2005), and double those observed in the ST+EX group. The improvement in physical function following AT+EX also exceeded the MCID of 6 units on the WOMAC physical function subscale in knee OA (Tubach et al., 2005).

Sensitivity to pressure was reduced to a greater extent (increase in PPTs) following AT+EX than ST+EX. CPM (presumed to indicate descending pain inhibition) also demonstrated similar results. The potentially superior effects on pain system function observed with AT+EX may reflect a summative effect of the two treatments on pain mechanisms. Pain in knee OA is considered to include contributions from both peripheral nociceptive afferents in the knee joint structures, as well as

sensitization, both peripherally and centrally, and the relative contribution of each will vary between individuals. Recognition of the role of central sensitisation in knee OA is increasing. From one perspective, persistent nociceptive input from joint structural changes in knee OA can increase the synaptic excitability and efficiency in the central pain pathway and result in central sensitisation, characterised by local and widespread hyperalgesia (Fingleton et al., 2015; Moreton et al., 2015), augmented spinal excitability and deficits in descending pain inhibition (Lluch et al., 2014; Woolf 2011). Multiple other factors contribute to this process including unhealthy pain cognitions and a host of biological processes. Pain intensity in many individuals with knee OA is associated with hyperalgesia and impaired descending pain inhibition, and for many the relationship with radiographic changes is weak (Arendt-Nielsen et al., 2015). Exercise is known to have an anti-nociceptive effect at both peripheral and central levels (Hoffman et al., 2004; Koltyn and Arbogast 1998; Millan 2002; O'Leary et al., 2007), and the potential to reduce the “pain” sensitivity in the central nervous system, in chronic pain conditions (Nijs et al., 2015). Anodal tDCS can modulate pain processing at central level (Nitsche et al., 2005b) and increase the brain’s receptiveness to other interventions through a ‘priming’ effect by modulating the excitability of cortical neurons/networks (Schabrun and Chipchase 2012a). Adding anodal tDCS to exercise may induce complementary effects on pain mechanisms and bolster the brain’s responsiveness to the analgesic effects of exercise, leading to greater clinical benefits in knee OA. The relationship between a tDCS and exercise treatment, pain mechanisms and clinical benefits requires investigation in a larger randomised controlled trial.

An alternative explanation for our findings is that tDCS primed/enhanced the corticomotor training effects of strengthening exercise. Previous studies of tDCS combined with strength training in healthy individuals have shown a greater capacity for high volume training, lower perceived exertion during training, improved motor control and larger increases in corticomotor excitability than can be achieved with strength training alone (Hendy and Kidgell 2013; Lattari et al., 2016). These effects may lead to greater improvements in knee joint control and mechanical benefits for the knee, reducing pain and disability. Future studies should include measures of muscle strength and motor control to further evaluate this possibility.

tDCS is a relatively inexpensive and portable device and for health professionals already trained in the therapeutic use of electric current, such as physiotherapists, minimal training would be required to ensure safe and effective application. Although not currently used in the clinical setting, tDCS could be easily integrated into clinical practice if beneficial effects on knee OA are established in a future larger trial. A fully powered randomised controlled trial is required to determine whether this treatment produces superior clinical benefits in knee OA.

5.5.3 Limitations

This study had several limitations. First, by design the study included a small sample size that was not intended to provide sufficient power to definitively determine the efficacy of adding tDCS to exercise treatment for knee OA. Therefore, the results must be interpreted with caution. Second, the short follow-up period in this study may have been too brief to determine between-group differences. A larger clinical

trial with longer follow-up periods is required. Third, we did not record any changes in the participants' medication (type and dosage) during this trial. The dosage of the participants' usual medication was only recorded at the baseline. Future trials should record any changes in participants' use of medication during the trial to evaluate the relationship between pain and the use of medication. Finally, the treating physiotherapists delivered both the tDCS and exercise treatment, and were not blind to group allocation. However, our exercise protocol was well established with clear instructions for how to progress each exercise (Chang et al., 2015a) and the treating therapists were instructed to strictly adhere to the protocol to minimise any potential bias. Future trials should seek to blind the treating therapists to the tDCS condition.

5.6 Conclusion

This pilot study provides the first feasibility and safety data for the addition of tDCS to strengthening exercise in people with knee OA. Although not powered to assess between-group differences, our study suggests that the addition of active tDCS to exercise may improve pain, function and pain mechanisms in knee OA beyond that of sham tDCS with exercise, and in excess of MCIDs for pain and function in this population. A fully powered randomised controlled trial with longer follow up is now justified to determine the clinical benefit of this novel treatment for knee OA.

Chapter 6

General Discussion

The overarching aim of this thesis was to investigate and target specific neurophysiological mechanisms (sensorimotor cortex plasticity and central pain processing) in musculoskeletal pain. This chapter will discuss and synthesise findings from the four studies. Future directions for research, clinical implications, and limitations will also be presented.

Chapter 6. General Discussion

6.1 Contribution of this thesis to the body of evidence

Musculoskeletal pain is a highly prevalent and costly health problem, yet our understanding of the condition is limited, and existing treatments are largely ineffective. Literature suggests that maladaptive neuroplasticity, characterised by sensorimotor cortex organisation and altered central pain processing, plays a role in the development of chronic pain and disability in musculoskeletal conditions. However, although there is early cross-sectional evidence to support a role for maladaptive neuroplasticity in *chronic* musculoskeletal pain, a systematic review of this evidence is lacking and relevant data in the *acute* stage of pain are absent. A better understanding of neuroplasticity is essential to advance our knowledge of the pathophysiology of musculoskeletal pain and to guide the development of effective treatment.

Cross-sectional evidence drawn from individual studies suggests that maladaptive neuroplasticity in the primary motor cortex (M1) is present in chronic musculoskeletal pain and is associated with symptoms of pain and movement dysfunction. However, a systematic evaluation of the evidence for altered M1 plasticity in chronic pain across studies has not been performed. This information is essential given that maladaptive neuroplasticity is a prevailing theory for why pain becomes chronic in this field. To this end, Study 1 provided the first comprehensive evaluation of the evidence for altered M1 plasticity in chronic pain. Meta-analyses showed increased M1 long-interval intra-cortical inhibition (LICI) in chronic pain.

However, for most neurophysiological measures, evidence for altered M1 plasticity in chronic pain populations was inconclusive.

A second gap in our knowledge relates to the evidence for neuroplasticity in acute pain. While there is moderate to strong evidence for reduced sensorimotor cortex excitability in response to acute experimentally-induced pain (Burns et al., 2016b), relevant data for acute, *clinical* musculoskeletal pain are absent. Similarly, research investigating central pain processing in acute clinical musculoskeletal pain is limited and findings are conflicting (Marcuzzi et al., 2015). The inconsistency of the current evidence could be explained by the presence of distinct subgroups of individuals with different degrees of impairment in central pain processing that could in turn, be an important determinant of pain outcome; yet this possibility has received limited attention. To address these knowledge gaps, Study 2 provided the first evidence of sensory, motor and cingulate cortex excitability and M1 organisation in acute clinical musculoskeletal pain and Study 3 provided the first exploration of central pain processing in acute LBP based on the presence or absence of a prior history of LBP. These data demonstrate that acute low back pain (LBP) is characterised by lower sensorimotor and cingulate cortex excitability when compared with pain-free individuals but, inter-individual variability is high. Further, although impaired descending inhibitory pain control is present in acute LBP, the degree of impairment does not differ between individuals with a first episode vs. recurrent acute LBP.

To provide a clinical context for the results from studies 1-3, Study 4 investigated the effect of a combined transcranial direct current stimulation (tDCS) and exercise

treatment on neuroplasticity (specifically central pain processing) and clinical outcomes in chronic pain. The combined application of tDCS and exercise is thought to synergistically modulate neuroplasticity in chronic pain to improve clinical outcomes beyond that which can be achieved with exercise alone. Study 4 provided the first feasibility and safety data for the addition of tDCS to a strengthening exercise program in chronic pain. Results suggest that adding anodal tDCS to exercise is feasible and safe, and may improve pain, function and central pain processing beyond that of sham tDCS and exercise. These data provide support for progression to a fully powered randomised controlled trial.

Each of these studies makes a unique and novel contribution to the body of evidence. The following sections provided an integrated discussion of these studies in the context of pain and neuroplasticity. Future directions for research are integrated throughout the discussion.

6.2 Maladaptive neuroplasticity in chronic musculoskeletal pain

Maladaptive neuroplasticity is the dominant theory used to explain why some people develop chronic musculoskeletal pain in this field (Apkarian et al., 2011; Harris 1999; Mansour et al., 2014). Although the identification of a pathoanatomical source of pain is useful in the diagnosis and treatment of some acute musculoskeletal disorders, this approach provides little therapeutic value in conditions such as non-specific LBP, especially when symptoms of pain and disability persist longer than expected tissue healing times (Pelletier et al., 2015; Wand et al., 2011). The discovery that the central nervous system can change and adapt throughout life (i.e. neuroplasticity), has

provided a potential mechanistic explanation for the development of symptom chronicity and could also explain the limited success of conventional treatments (Pelletier et al., 2015). However, despite the maladaptive plasticity hypotheses receiving considerable attention in the field, direct evidence remains elusive.

Systematic reviews provide a method to systematically integrate findings from individual studies while also considering study quality and are designed to provide an exhaustive summary of the available literature on a given topic. Although this methodology has been used to provide some evidence for sensorimotor cortex organisation and altered central pain processing in chronic pain populations (Di Pietro et al., 2013a; b; Fingleton et al., 2015; Lewis et al., 2012b; Noten et al., 2017; Parker et al., 2016; Sanzarello et al., 2016; Suokas et al., 2012), previous systematic reviews were limited to specific pain conditions (i.e. complex regional pain syndrome), were contaminated by inclusion of neurological conditions (i.e. migraine) or failed to include data acquired across a range of neurophysiological methods.

Study 1 of this thesis was therefore the first to systematically evaluate the evidence for altered M1 structure, organisation and function using a comprehensive range of neurophysiological measures in a clearly defined chronic pain population. Interestingly, although 67 studies were included in the systematic review, the synthesised results were inconclusive, and for most neurophysiological measures, findings of altered M1 plasticity were inconsistent between studies. A number of possibilities could explain this finding. First, these data could be interpreted to suggest that maladaptive neuroplasticity in M1 does not in fact, underpin chronic

pain. Indeed, although maladaptive neuroplasticity is the basis for many theories on the persistence and recurrence of pain (Apkarian et al., 2011; Flor et al., 1997; Maihofner et al., 2003), some research contradicts this hypothesis. For example, while the maladaptive neuroplasticity theory suggests that greater phantom pain should be associated with a greater loss in cortical representation of the missing limb, recent research shows instead, that worse phantom limb pain is associated with greater representation of the missing hand in the primary sensorimotor cortex (Makin et al., 2013). The authors suggest that the preserved cortical representation of the missing hand following limb amputation is driven by ongoing phantom pain experience, indicating neuroplasticity in chronic pain can be adaptive. If this finding were confirmed, it would challenge the prevailing mechanistic theory in the field and suggest that mechanisms other than maladaptive M1 plasticity underpin the development and maintenance of chronic pain. What is clear is that more studies are needed across a range of pain conditions before definitive conclusions can be made regarding the presence of altered M1 plasticity in chronic musculoskeletal pain.

A second explanation is that current evidence is simply insufficient and too heterogenous at this time to determine whether maladaptive M1 neuroplasticity is present in chronic pain. Indeed, although 67 studies were included, evidence was synthesised according to neurophysiological method used and pain condition evaluated resulting in a small number of studies that in most cases, were unable to be pooled for meta-analysis. In addition, the overall methodological quality of the included studies was at best moderate (3.1 out of 5). A larger number of high quality studies using consistent methodologies and pain populations is urgently needed to

determine whether maladaptive M1 neuroplasticity is a feature of chronic musculoskeletal pain conditions.

Finally, the results of the systematic review could be explained if the neurophysiological mechanisms underpinning chronic pain differ between individuals. Emerging evidence indicates that subgroups of individuals characterised by the presence of neuropathic pain exist within some chronic pain populations (e.g. non-specific LBP, ankylosing spondylitis back pain and osteoarthritis) (French et al., 2017a; Moreton et al., 2015; Moss et al., 2018; Smart et al., 2011; Spahr et al., 2017; Wu et al., 2013). In particular, signs of neuropathic pain are demonstrated in one third of individuals with chronic LBP (Freynhagen et al., 2006), nearly 25% of individuals with hip or knee osteoarthritis (French et al., 2017a) and 65% of individuals with ankylosing spondylitis back pain (Wu et al., 2013). Importantly, neuropathic pain severity is associated with increased M1 grey matter – a marker of neuroplasticity (Wu et al., 2013). Thus, individuals who present with neuropathic pain may demonstrate different M1 functional changes (e.g. decreased intracortical inhibition) compared with those who present with non-neuropathic pain (Schwenkreis et al., 2010). Despite this, most previous studies do not separate people with chronic pain into different subgroups for analysis. Future research should seek to determine whether different pain phenotypes display different alterations in M1 plasticity.

6.3 Maladaptive neuroplasticity in acute musculoskeletal pain

In the absence of sufficient data to definitively determine whether maladaptive M1 plasticity exists in the chronic stage of pain, another approach to explore this question is through the evaluation of individuals in the acute stage of pain. Surprisingly however, there has been limited research in acute clinical pain and little is known about neuroplasticity in the first 4-6 weeks after pain onset. Understanding early mechanistic changes is essential to facilitate early intervention and treatment approaches in future.

This thesis investigated sensorimotor cortex excitability (Study 2) and central pain processing (Study 3) using a range of neurophysiological tests in individuals with acute clinical LBP. These studies revealed for the first time, that acute clinical LBP is characterised by i) lower overall sensory processing (specifically, lower secondary sensory (S2) and anterior cingulate (ACC) cortex excitability), ii) lower corticomotor excitability and iii) impaired descending inhibitory pain control when compared with pain-free controls. These findings likely reflect the presence of adaptive, protective strategies in response to acute clinical LBP. Specifically, the finding of lower overall sensory processing could be explained by the '*competing demands of pain*' theory where the presence of pain is thought to 'distract' the brain, diverting attentional resources away from the processing of non-nociceptive afferents (Attridge et al., 2016; Eccleston 1995). Similarly, lower corticomotor excitability is thought to reflect a protective motor strategy used to constrain provocative movements (Hodges and Tucker 2011) while impaired descending inhibitory pain control is considered a protective strategy that upregulates pain sensitivity to promote tissue healing and prevent further injury in acute pain (Staud 2012; Sterling 2010; Woolf 2011).

Together, these findings indicate the presence of adaptive neuroplasticity in acute clinical musculoskeletal pain that is focussed on protection of the injured part. These data suggest that if neuroplasticity does become maladaptive in chronic pain, these changes develop after the acute stage (i.e. >4-6 weeks after pain onset), highlighting the need for longitudinal research that spans the acute, transitional and chronic stages of musculoskeletal pain. Future research should use longitudinal study designs to determine the time-point where plasticity becomes maladaptive and how this relates to symptom chronicity.

A unique and exciting finding from this thesis was the discovery of subgroups within the acute clinical LBP population characterised by differences in S2 and ACC excitability (Study 2). This thesis is the first to show that individuals with high S2 and ACC excitability in the acute stage of pain experience significantly less pain than those with low excitability in these brain regions. These data suggest individuals adopt different cortical strategies in response to non-noxious afferent input that could be relevant to long-term pain outcome. For example, it is plausible that individuals experiencing more severe pain might have greater demands on attentional resources, and thus, have greater compromise to processing of non-noxious sensory afferent input leading to maladaptive cortical organisation and persistent pain. If this finding were confirmed, low S2 and ACC excitability in the acute stage of pain could represent a risk factor for the development of chronic pain. This hypothesis requires further detailed investigation in an appropriately powered cohort study.

In contrast to findings for S2 and ACC, this thesis failed to demonstrate different subgroups in the acute stage of pain based on prior pain history when mechanisms of central pain processing were considered. Indeed, this thesis reveals that acute recurrent LBP is not associated with altered central pain processing, suggesting that other mechanisms such as sensorimotor cortical plasticity may contribute to pain recurrence. For example, preliminary evidence shows that individuals with chronic *recurrent* LBP demonstrate a shift in the M1 representation of the deep abdominal muscle and a loss of discrete M1 representation of the paraspinal muscles (Schabrun et al., 2017b; Tsao et al., 2008), suggesting a possible link between LBP recurrence and M1 reorganisation. However, whether sensorimotor cortical plasticity predisposes individuals with a past history of musculoskeletal pain to symptom recurrence needs to be examined in future studies.

6.4 A novel treatment to target neuroplasticity in chronic musculoskeletal pain

Although maladaptive neuroplasticity is the prevailing theory for chronic pain in this field, few treatments exist that directly target this mechanism. This thesis is the first to explore a combined treatment of tDCS and strengthening exercise that targets altered central pain processing in chronic musculoskeletal pain. Study 4 showed promising findings and suggested that the application of tDCS over M1 prior to exercise may enhance the therapeutic and mechanistic effects of exercise for individuals with knee osteoarthritis. Specifically, when tDCS was combined with exercise, greater effects on pain and physical function were observed when compared with exercise alone (sham tDCS plus exercise). In fact, improvements following 8 weeks of active tDCS plus exercise exceeded the minimal clinically

important difference for both pain and function in this population (Tubach et al., 2005). In addition, the combined tDCS and exercise intervention demonstrated positive effects on central pain processing in knee osteoarthritis characterised by a decrease in sensitivity to pressure stimuli (measured using pressure pain thresholds) and improved descending inhibitory pain control (measured using CPM).

While strengthening exercise is known to improve knee osteoarthritic pain, the mechanisms of effect are unclear (Runhaar et al., 2015). Increased knee extensor strength has been shown to partially mediate the beneficial effects of strengthening exercise on pain and physical function in individuals with knee osteoarthritis (Hall et al., 2018). Previous studies investigating tDCS combined with strength training in healthy individuals have shown a greater capacity for high volume training, lower perceived exertion during training, improved motor control and larger increases in corticomotor excitability than that can be achieved with strength training alone (Hendy and Kidgell 2013; Lattari et al., 2016). Adding tDCS to exercise may enhance the effects of exercise on knee extensor strength and lead to greater effects on pain and physical function for knee osteoarthritis. Measures of quadriceps strength are needed in the future trials to better understand the mechanisms underpinning the therapeutic effects of tDCS and exercise.

Another explanation of larger improvements in pain and function observed when tDCS was combined with exercise could be the synergistic effects of these interventions on central pain processing (Schabrun and Chipchase 2012b). Exercise applied alone is known to reduce mechanical pain sensitivity and improve descending

inhibitory pain control in knee osteoarthritis (Fingleton et al., 2017; Henriksen et al., 2014). Similarly, research shows that tDCS applied over M1 reduces mechanical pain sensitivity and enhances descending inhibitory pain control (Castillo-Saavedra et al., 2016; Flood et al., 2016; Vaseghi et al., 2014). While both interventions exert positive effects on central pain processing (Fenton et al., 2009; Fregni et al., 2006a; Fregni et al., 2006b; Garcia-Larrea et al., 1999; Koltyn and Arbogast 1998; Koltyn et al., 2014; Millan 2002; Nitsche et al., 2005a; Strafella et al., 2004), the mechanisms underpinning the effects of combining tDCS and exercise on knee osteoarthritic pain remain unclear and require further investigation.

Emerging evidence suggests that only some subgroups of individuals in knee osteoarthritis (approximately 40%) have an impaired CPM response (Arendt-Nielsen et al., 2015; Egsgaard et al., 2015; Osgood et al., 2015). Notably, these individuals demonstrate worsened pain sensitivity following exercise whereas those with normal CPM demonstrate improved pain sensitivity following exercise (Fingleton et al., 2017). A deficient analgesic response to exercise is thought to reflect impaired descending inhibitory pain control and may explain clinical observations of pain exacerbation following exercise in some individuals and contribute to the moderate effects of exercise on knee osteoarthritic pain observed in systematic reviews (Fransen et al., 2015). Further, preliminary evidence shows that individuals with greater CPM impairment have greater pain reduction following tDCS (Castillo-Saavedra et al., 2016). Combined application of tDCS and exercise may improve descending inhibitory pain control and enhance the analgesic effects of exercise in these subgroups. The

effect of tDCS combined with exercise on different subgroups of individuals with chronic pain is an important area for future research.

This study is the first to use tDCS to bolster the effects of strengthening exercise in any musculoskeletal condition. A knee osteoarthritis population was selected to test this novel treatment as robust systematic review evidence demonstrates that exercise is effective in knee osteoarthritis with moderate effects on pain and disability (Fransen et al., 2015). Our data indicate that a combined treatment of tDCS and strengthening exercise is feasible and safe for this population. Given the trend toward superior clinical and mechanistic effects observed in Study 4, the next step is to conduct a fully powered, randomised controlled trial, with an estimated sample size of 198 participants in total (99 per intervention arm), to determine the efficacy of this novel therapy.

6.5 Clinical implications

This thesis provides new insight into the neurophysiological mechanisms of musculoskeletal pain that advance knowledge of this condition as well as inform the development of novel treatments for individuals with chronic pain. Pain and movement dysfunction are the primary reasons that individuals with musculoskeletal pain conditions seek treatment (Hodges and Smeets 2015; O'Sullivan 2005) However, current treatments are suboptimal. A better understanding of the underlying neurophysiological mechanisms, and the development and testing of treatments that target these mechanisms could lead to better clinical outcomes (Woolf et al., 2004). For example, as altered sensorimotor excitability is present in musculoskeletal pain,

therapeutic techniques that modulate cortical excitability may potentially have beneficial effects on pain. Strengthening exercise, peripheral electrical stimulation (PES) using protocols that induce muscle contraction (Chipchase et al., 2011; Hendy and Kidgell 2013; Lattari et al., 2016) and anodal tDCS (Nitsche et al., 2003b; Nitsche and Paulus 2000; 2001) could be used to increase M1 cortical excitability in acute musculoskeletal pain. Multimodal interventions such as PES and exercise (Barsi et al., 2008; Khaslavskaia and Sinkjaer 2005), tDCS and PES (Schabrun et al., 2014a), and tDCS and exercise (Chang et al., 2017) may provide novel treatment options for acute or chronic musculoskeletal pain that can specifically decrease or increase cortical excitability. Further work is needed to determine effective treatment protocols for these neuromodulatory interventions in musculoskeletal pain. Characterising the specific neurophysiological mechanisms present across different musculoskeletal pain conditions and at the individual level is essential for the successful transition of these interventions from laboratory to clinical practice.

Inconsistent evidence and high variability between individuals highlight the importance of identifying distinct subgroups defined by neurophysiological mechanism and providing mechanism-specific, tailored treatment. For example, while knee osteoarthritic pain is traditionally considered as nociceptive in nature, subgroups of individuals with central sensitisation and neuropathic pain have been identified (Egsgaard et al., 2015; French et al., 2017a). Neuropathic pain in knee osteoarthritis is shown to be associated with central sensitisation (Hochman et al., 2013). Evidence suggests that individuals with central sensitisation in knee osteoarthritis have poor outcomes following guideline-based physiotherapy (O'Leary

et al., 2018) and have less pain relief following total joint replacement (Arendt-Nielsen et al., 2018; Petersen et al., 2016). As our preliminary evidence shows that adding tDCS to exercise may have positive effects on central pain processing, this intervention may provide greater clinical outcomes for individuals who present with central sensitisation and neuropathic pain than for those who present with predominantly nociceptive pain. Further, while the effectiveness of adding tDCS to exercise for knee osteoarthritis requires confirmation in future larger trials, our preliminary data provide a foundation for translating this approach into other chronic pain conditions (e.g. LBP and neck pain) where exercise is the recommended treatment.

6.6 Limitations

In the previous chapters, limitations of Study 1-4 are acknowledged and discussed and therefore, the limitations presented here are those relevant to this thesis as a whole. First, the potential influence of small studies cannot be excluded in this thesis. Small sample sizes are known to demonstrate low statistical power with a propensity to return positive results and inflated effect sizes due to relatively larger effects of sampling variation and random error (Ioannidis 2008). Although Study 1 was a systematic review and meta-analysis in design, the effects of small studies should be acknowledged as the sample sizes of included studies were small (9-54). As there were no relevant studies in acute, clinical LBP on which to base sample size calculations, convenience samples were used in Study 2 and Study 3. The possibility of low statistical power to detect between-group changes in measures of M1 organisation and central pain processing should be acknowledged and addressed in

future studies. Although Study 4 was not intended to provide sufficient power to determine the effectiveness of adding tDCS to exercise for knee osteoarthritis, caution is required when interpreting the findings due to the small sample size. Overall, it is essential that the findings described in Study 2-4 are tested in replication studies with larger sample sizes and sufficient statistical power.

Second, although this thesis examined the presence of altered neuroplasticity in musculoskeletal pain, causality cannot be confirmed. As studies included in the systematic review (Study 1) were cross-sectional, the causal relationship between any finding of altered M1 plasticity and chronic pain remains unknown and warrants further investigation. Similarly, although the findings observed in Study 2 and 3 demonstrated altered sensorimotor cortical excitability and impaired descending inhibitory pain control in acute clinical LBP, the causal relationship between acute musculoskeletal pain and neuroplasticity cannot be inferred and therefore should be explored in future research. Third, potential risk of bias in each study should be acknowledged. The investigator in Study 2 and 3 was not blind to the groups. Although the outcome assessor and participants were blind in Study 4, the treating physiotherapists were not blind to group allocation. Future studies should consider these factors to enhance the rigor of neurophysiological research in musculoskeletal pain.

Further, this thesis explored only M1 neuroplasticity and central pain processing in musculoskeletal pain. Other mechanisms including plasticity in other brain regions and the spinal cord, inflammation and psychosocial factors could be relevant. There

is a rich body of evidence for psychological changes in musculoskeletal pain. For example, several systematic reviews indicate that the development of chronic pain is associated with psychological factors such as low level of self-efficacy (Martinez-Calderon et al., 2018; Primdahl et al., 2011), fear avoidance (Leeuw et al., 2007; Pincus et al., 2006), pain catastrophising (Sullivan et al., 1998) and depression (Pinheiro et al., 2015). Thus, this thesis focused on exploring the biological aspect of pain. Similarly, systematic reviews provide some evidence for plasticity in other brain regions (e.g. bilateral medial frontal cortex, thalamus, insula) in chronic pain (Cauda et al., 2014; Kregel et al., 2015; Yuan et al., 2017), although there is variability between studies and the functional relevance of these changes is unclear. As longitudinal data are absent, the causal relationship between brain changes and chronic pain cannot be inferred. Notably, relevant research in acute pain is also lacking. While a recent systematic review provides evidence for functional and structural changes in brain regions involved in processing emotion and cognition in chronic LBP (Ng et al., 2018), it is unknown how psychological factors might interact with neuroplasticity and whether these interactions determine clinical outcome of musculoskeletal pain. Further, emerging evidence suggests that systemic inflammation is observed in individuals with acute and chronic musculoskeletal pain (Klyne et al., 2017; Shimura et al., 2013; Wang et al., 2008) and subgroups with distinct inflammatory and psychological profiles in the acute stage of pain have different outcomes (Klyne et al., 2018). While the interaction between systemic inflammation and psychosocial factors influences symptoms in musculoskeletal pain (Edwards et al., 2011; Kelly et al., 2011; Mullington et al., 2010; Okifuji and Hare 2015; Wang et al., 2010), whether these factors also interact with neuroplasticity is

unknown. More research is needed to elucidate the relationship between neuroplasticity, systemic inflammation and psychosocial factors in musculoskeletal pain and to guide the development of novel treatments that specifically target these mechanisms.

6.7 Conclusion

This thesis makes a novel and substantial contribution to our understanding of neuroplasticity in musculoskeletal pain and provides the foundation for the exploration of novel interventions to reduce pain and disability. Specifically, this thesis provides evidence that i) M1 structural, organisational and functional changes are inconsistent in chronic pain, ii) neuroplasticity in acute LBP is characterised by lower sensorimotor and cingulate cortex excitability and impaired descending inhibitory pain control when compared with pain-free individuals, and iii) adding tDCS to exercise may improve pain, function and pain mechanisms in knee osteoarthritis beyond that of exercise applied alone. Notably, subgroups distinguished by high or low S2 and ACC excitability may represent individual adaptation of different cortical strategies that relate to the processing of non-noxious input in acute LBP and could be relevant for pain outcome, whereas subgroups determined by a past history of LBP do not differ in central pain processing in acute LBP. Future studies with larger sample sizes and longitudinal study designs are needed to elucidate the evidence of altered M1 plasticity in chronic pain and to confirm findings of decreased sensorimotor cortex excitability and altered central pain processing in acute pain. Finally, a fully powered randomised controlled trial is necessary to determine the therapeutic effects of adding tDCS to exercise treatment for knee osteoarthritis.

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Appendix A

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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 19, No 4 (April), 2018: pp 341-359
Available online at www.jpain.org and www.sciencedirect.com

Critical Review

Altered Primary Motor Cortex Structure, Organization, and Function in Chronic Pain: A Systematic Review and Meta-Analysis

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Abstract: **Chronic pain can be associated with movement abnormalities. The primary motor cortex (M1) has an essential role in the formulation and execution of movement. A number of changes in M1 function have been reported in studies of people with chronic pain. This review systematically evaluated the evidence for altered M1 structure, organization, and function in people with chronic pain of neuropathic and non-neuropathic origin. Database searches were conducted and a modified STrengthening the Reporting of OBservational studies in Epidemiology checklist was used to assess the methodological quality of included studies. Meta-analyses, including preplanned subgroup analyses on the basis of condition were performed where possible. Sixty-seven studies (2,290 participants) using various neurophysiological measures were included. There is conflicting evidence of altered M1 structure, organization, and function for neuropathic and non-neuropathic pain conditions. Meta-analyses provided evidence of increased M1 long-interval intracortical inhibition in chronic pain populations. For most measures, the evidence of M1 changes in chronic pain populations is inconclusive.**

Perspective: ***This review synthesizes the evidence of altered M1 structure, organization, and function in chronic pain populations. For most measures, M1 changes are inconsistent between studies and more research with larger samples and rigorous methodology is required to elucidate M1 changes in chronic pain populations.***

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Key words: *Chronic pain, primary motor cortex, neuroplasticity, meta-analysis.*

Chronic pain conditions such as low back pain (LBP), neck pain, and knee osteoarthritis (OA) are leading causes of disability globally[107] and are associated with significant and rising health care and socioeconomic costs.[50] Despite this, effective treatment remains elusive.

People with chronic pain conditions commonly present with abnormalities of movement. For example, excessive finger flexion has been reported during grip release in chronic lateral elbow pain, greater hip adduction and internal rotation during stair climbing in lateral hip pain, and delayed onset of trunk muscle activation during

W.-J.C., M.B.L., and S.M.S. received salary support from the National Health and Medical Research Council of Australia and G.A. from an Australian Postgraduate Award.
The authors have no conflicts of interest to declare.
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
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1526-5900/$36.00
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https://doi.org/10.1016/j.jpain.2017.10.007

arm elevation in recurrent LBP.[3,33,97] As a result, rehabilitation to target movement dysfunction is a treatment for musculoskeletal pain. However, treatment success with this approach is limited[1,71] and there is debate regarding the type, quantity, and timing of interventions needed to effectively target movement dysfunction in chronic musculoskeletal pain or indeed whether such an approach is warranted.[2,30,31]

The physiological basis of movement dysfunction in pain is poorly understood. The primary motor cortex (M1) has an essential role in the formulation and execution of movement and is likely to have a role in movement abnormalities. Indeed, a recent systematic review provided evidence of reduced M1 output (ie, corticospinal excitability) in response to acute muscle pain that may represent an adaptive mechanism to protect against further pain or injury.[9] Similarly, studies investigating M1 in experimental models of progressively developing, sustained muscle pain show altered M1 organization (increased representations of painful muscles) and function (reduced M1 inhibition) 4 days after pain onset.[77] Studies have reported that changes in M1 structure, organization, and function may also be present when pain becomes chronic. For example, associations have been reported between the severity of pain and/or the degree of movement dysfunction in chronic musculoskeletal disorders such as low back, elbow, and patellofemoral pain and reorganization of the M1 representation (ie, greater representational overlap, reduced number of discrete peaks) of muscles in the region of pain.[78,79,94] However, it is unclear whether M1 reorganization presents in other chronic pain conditions and whether it can be observed via different neurophysiological methods.

Previous reviews examining changes in M1 in chronic pain have been restricted to specific pain conditions or by the neurophysiological method used to assess M1. For instance, a systematic review revealed limited evidence for bilateral M1 disinhibition in complex regional pain syndrome (CRPS) of the upper limb.[20] Whether similar alterations in M1 are present in other forms of chronic pain is unknown. Indeed, it has been suggested that M1 disinhibition may occur in chronic neuropathic but not chronic nociceptive pain.[82] A second systematic review reported similar findings of disinhibition across a range of chronic pain conditions (including migraine) but was restricted to data obtained using transcranial magnetic stimulation (TMS).[65] The integration of information on M1 structure, organization, and function across 1) a range of neuropathic and non-neuropathic conditions, and 2) using a range of complementary neurophysiological techniques, is necessary to provide comprehensive information on whether M1 is altered in chronic pain. This information is timely because of the range of treatment techniques being tested that target the M1 in chronic pain.[12,56,74,80]

The aim of this review was to systematically evaluate the evidence of altered M1 structure, organization, and function in chronic pain conditions of neuropathic and non-neuropathic origin across a range of neurophysiological methods.

Methods

The protocol of this review was prospectively registered with the International Prospective Register of Systematic Reviews (registration number CRD42015014823) and has been published elsewhere.[13] This review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[46]

Search Strategy

The search was conducted in 5 electronic databases (PubMed, MEDLINE, Embase, PsychINFO, and CINAHL) from inception to February 2017, using key words and medical subject headings terms related to chronic pain and M1 organization/function (Supplementary Appendix 1). The reference list of eligible studies and relevant reviews were manually searched for additional articles.

Eligibility Criteria

Inclusion criteria were: 1) full text studies published in English, including in press or accepted studies, 2) adult (aged older than 18 years) humans with non-neuropathic or neuropathic pain, 3) duration of pain >3 months,[64] 4) investigated and reported measures of the organization and/or function of the M1 (regardless of the anatomical or functional definition used) using TMS, magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), magnetic

Table 1. Summary of M1 Structural, Organizational, and Functional Constructs and Their Associated Neurophysiological Methods and Outcome Measures

	M1 STRUCTURE	*M1 ORGANIZATION*	*M1 FUNCTION*
Neurophysiological methods and outcome measures	MRI: cortical thickness (VBM); white matter structure (diffusion tensor imaging)	fMRI: activation/connectivity (rCBF, BOLD) TMS: M1 representation (map volume, CoG of M1 representation)	TMS: corticospinal excitability (rMT, aMT, MEP amplitude and latency, CSP); ICF/intracortical inhibition EEG: cerebrocortical motor activity MEG: 20-Hz cortical rhythm (rebound amplitude/duration, reactivity) MRS: neurochemical metabolism PET: glucose metabolism

Abbreviation: rMT, resting motor threshold.

resonance spectroscopy (MRS), or positron emission tomography (PET; Table 1). Studies were excluded if: 1) included participants presented chronic pain associated with neurological disorders, cancer, or visceral pain, or 2) the study did not include a healthy control group or used the unaffected limb or body side as a control. Cross-sectional or prospective studies, including case-control and randomized controlled trials that provided baseline data with information relevant to the review objective and that met the eligibility criteria, were included.

Study Selection

Search results were imported into Endnote X7 (Clarivate Analytics, Philadelphia, PA). After removing duplicates, 2 reviewers independently screened titles and abstracts of all studies to remove those not relevant to the review objective. The full text of all remaining studies were retrieved and evaluated according to the eligibility criteria. If there was uncertainty or disagreement, a third reviewer was consulted.

Data Extraction

Two independent reviewers extracted the following data: pain condition, country of origin, study design and setting, inclusion/exclusion criteria, source of participants, sample size, participant demographic characteristics, duration and severity of chronic pain, neurophysiological methods, specifics of the investigative model, type and location of stimulation, and outcomes (ie, M1 excitability, representation, reactivity, neurochemical or glucose metabolism). Any disagreements were resolved in consensus with a third reviewer. If data were missing, authors were contacted a maximum of 3 times, after which the data were considered irretrievable.

Quality and Risk of Bias Assessment

Study quality and risk of bias were assessed by 2 independent reviewers using a modified version of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for cross-sectional and cohort studies.[57,103,104] Disagreements were resolved by consensus with a third reviewer. The modified STROBE statement investigated potential for bias in 5 domains: 1) source of participants, 2) participant selection, 3) methodology, 4) statistical analysis, and 5) funding (Supplementary Appendix 2). Each domain would be allocated 1 point if the risk of bias was low and no point if the risk of bias was considered high. The maximum score possible was 5 points. For studies using TMS, an additional methodological quality assessment was undertaken using an adapted version of the TMS methodological checklist.[14] Two items that were not relevant for this review were removed from the checklist (item 22—time between days of testing—and item 30—size of the unconditioned motor evoked potential [MEP] controlled). Each domain that was reported (*r*) and/or controlled (*c*) was allocated 1 point. In total, the maximum score possible for the reported and controlled items of the TMS methodological checklist were, respectively, 26 and 25 for single-pulse TMS, and 29 and 28 for paired-pulse TMS. The ratio of the summed score relative to the maximum score for the reported (r/[26 or 29] $\times$ 100) and controlled (c/[25 or 28] $\times$ 100) items was calculated. The median percentage for the reported and controlled items was then calculated. TMS studies received 1 point in the methodology category of the modified STROBE statement if the percentage of reported and controlled items were both greater than the median value.

Data Synthesis

Meta-analyses were performed to aggregate the data from TMS studies. Because of increased heterogeneity in the methodology of included studies, a narrative synthesis was used to summarize the findings of studies using other neurophysiological methods.[84] TMS outcome measures (resting and active motor threshold [aMT], MEP amplitude and latency, cortical silent period (CSP), map volume, intracortical inhibition and facilitation) were pooled and separate meta-analyses were performed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Cohen d effect sizes were used to analyze effect estimates (d ≤.2, small; .5, moderate; ≥.8, large).[16] Meta-analyses were performed using a random effects model when data from at least 2 studies addressing that outcome were accessible. Statistically significant heterogeneity was identified using the χ^2 test and was considered when χ^2 $P < .10$. The I^2 statistic was used to evaluate the degree of heterogeneity. Substantial heterogeneity was considered present when $I^2 > 50\%$.[35] Meta-analyzed data are presented as effect estimates (standardized mean difference [SMD] with 95% confidence intervals [CIs]).

Subgroup and Sensitivity Analysis

Preplanned subgroup analyses were conducted according to the type of musculoskeletal condition where significant heterogeneity was identified. The median value of the modified STROBE statement score of the TMS studies was used as a cutoff point to divide studies into either low or high risk of bias groups. The influence of high risk of bias studies was examined by rerunning the analysis with those studies excluded.

Results

The initial search identified 5,028 records, from which 120 full text articles were retrieved to assess eligibility. Sixty-nine studies met the inclusion criteria in the review. The authors of 14 studies were contacted to request additional data pertaining to M1 function. Two studies were excluded as a result of unsuccessful attempts to acquire these data.[18,106] Thus, a total of 67 studies were included in this review. The study flow chart can be seen in Fig 1.

Study Characteristics

The included studies encompassed 7 neurophysiological methods: TMS (n = 35 studies), functional MRI (fMRI;

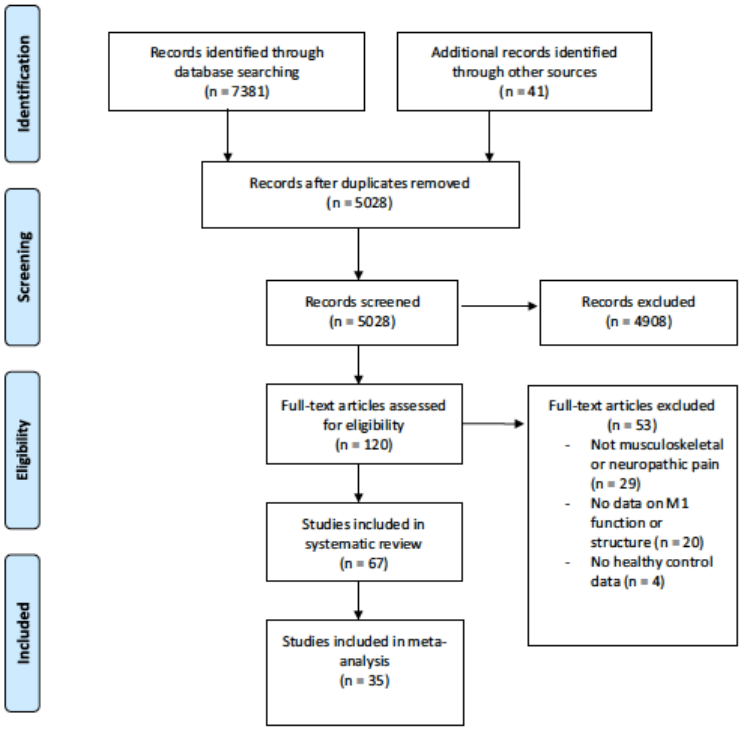

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the screening and inclusion of studies.

n = 16 studies), MRI (n = 6 studies), MEG (n = 3 studies), MRS (n = 3 studies), EEG (n = 1 study), and PET (n = 1 study). Two studies investigated functional as well as structural MRI changes.[95,101] In total, the included studies involved 1,248 chronic pain (20 different pain conditions) and 1,042 healthy participants. CRPS (n = 16 studies) and LBP (n = 16 studies) were the most frequently investigated conditions.

Five studies investigated 2 or more chronic pain conditions.[11,72,73,75,82] Participant sex (n = 4 studies) and age (n = 3 studies), pain intensity (n = 22 studies), and the duration of the pain (n = 7 studies) were not reported by some of the included studies. The characteristics of included studies are summarized in Tables 2 and 3.

Quality and Risk of Bias Within Studies

The average score for the methodological quality assessment was 3.1 of 5 (range = 1–5; Table 4), with 50 studies presenting a score of ≥3. For the TMS methodology checklist, the average score for the reported items was 64.8% (SD = 13) and for the controlled items 61.1% (SD = 13.8). All studies reported and controlled position and contact of electromyography electrodes and stimulation intensity. All studies that used paired-pulse paradigms (n = 16) reported the intensity of the test and conditioning pulse and the interstimulus interval. Participant age and sex, although reported, were not controlled. Items that were not consistently reported or controlled were: previous motor activity of the muscle to be tested, level of relaxation of the muscles other than those being tested, pulse shape, and participants' prescribed medication.

Is There Evidence of Altered M1 Function, Organization, and Structure in Chronic Pain?

We were unable to conduct meta-analyses of these data because of the heterogeneity of methodology across the included studies. Furthermore, the effect size of the differences between the pain and healthy participants were not reported in these studies.

In neuropathic pain, 3 studies reported statistically significant ($P < .05$) increases in M1 activation/connectivity in neuropathic pain populations from regional cerebral blood flow (rCBF)[47] (cluster level corrected $P < .05$, n = 22 participants, quality score = 2) and blood oxygen level-dependent (BOLD) contrast studies (n = 42 participants, quality score = 4[95]; n = 19 participants, quality score = 4[62]). Voxel-based morphometry (VBM) imaging showed 12% to 13% increase in bilateral M1 cortical thickness in

Table 2. Characteristics of Studies using TMS

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Salerno et al[75]	Fibromyalgia; rheumatoid arthritis	France	13 (0/13); 5 (0/5)	50.1 ± 5.6; 50.0 ± 5.1 (SEM)	NA	NA	13 (NA)	49.1 ± 5 (SEM)	Double cone coil on cortical representation of the target muscles	Single and paired pulses	First dorsal interosseous, tibialis anterior	rMT, MEP amplitude, CSP, SICI, ICF, LICI
Schwenkreis et al[81]	CRPS I: hand	Germany	25 (9/16)	49.1 ± 13.8	26.1 ± 47 Months	NA	20 (10/10)	20 to 78 (95% CI)	Circular coil (14 cm) on vertex	Single and paired pulses, monophasic*	First dorsal interosseous	rMT, MEP amplitude, SICI, ICF
Strutton et al[91]	Chronic sciatica	United Kingdom	9 (NA)	NA	NA	NA	7 (NA)	NA	Double cone coil on hotspot	Single pulse, monophasic*	Tibialis anterior, lateral gastrocnemius	rMT, aMT
On et al[63]	Patello-femoral pain	Turkey	13 (0/13)	25 ± 8.1 (SEM)	3.46 ± 1.9 Years (SEM)	NA	13 (0/13)	25.1 ± 7.4 (SEM)	Circular coil (9 cm) on hotspot	Single pulse, monophasic	Vastus medialis obliques, vastus lateralis, extensor digitorum brevis	MEP amplitude
Eisenberg et al[21]	CRPS I: hand; CRPS I: foot	Israel	6 (4/2); 6 (5/1)	33 ± 12.7; 32 ± 9	31 ± 41 Months; 20 ± 21 months	7.3 ± 3.1; 6.7 ± 2.3	14 (10/4)	30.9 ± 12.7	Figure of 8 coil (9 cm) on hotspot	Single and paired pulses, monophasic*	Abductor pollicis brevis	SICI
Krause et al[43]	CRPS I: hand	Germany	12 (2/10)	55.9 ± 15.6	NA	NA	10 (NA)	42.4	Figure of 8 coil (9 cm) on hotspot	Single pulse, monophasic*	Long extensor muscle	rMT, MEP amplitude, CSP
Strutton et al[92]	LBP	United Kingdom	24 (15/9)	39.1 ± 2.2	NA	NA	11 (7/4)	35.9 ± 3.2	Double cone coil on vertex	Single pulse, monophasic*	Erector spinae	aMT, MEP latency, CSP
Krause et al[44]	CRPS: hand	Germany	14 (4/10)	37 (17–72)	>6 Months	NA	10	38 (24–63)	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic*	Long extensor muscle	rMT, MEP amplitude, map volume
Turton et al[99]	CRPS I: hand	United Kingdom	8 (1/7)	45 ± 13	6.6 ± 4.9 Years	6.3 ± 1.4	8 (1/7)	45 ± 13	Figure of 8 coil (9.5 m) on hotspot	Single pulse, monophasic*	Abductor pollicis brevis	MEP amplitude
Tsao et al[97]	LBP	Australia	11 (5/6)	24 ± 7	5.6 ± 4.2 Years	5.5 ± 2	11 (4/7)	23 ± 3	Figure of 8 coil (7 cm) and double cone coil (11 cm) on hotspot and M1	Single pulse, monophasic	Transversus abdominus	rMT, aMT, map volume
Berth et al[5]	Rotator cuff tear	Germany	10 (10/0)	64.9 ± 4.6	>6 Months	NA	13 (10/3)	27.2 ± 8.1	Figure of 8 coil on hotspot	Single pulse, monophasic*	Deltoid	MEP amplitude

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Table 2. Continued

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Turgut et al[98]	Diabetic neuropathic pain	Turkey	20 (5/15)	63.9 ± 7.3	12.4 ± 6.7 Years	8.1 ± 1.3	30 (14/16)	58.3 ± 6.5	Circular coil (14 cm) on hotspot	Single pulse, NA	First dorsal interosseous	rMT, MEP amplitude, MEP latency, CSP
Mhalla et al[57]	Fibromyalgia	France	21 (0/21)	52.2 ± 10.4	14.1 ± 11.9 Years	5.5 ± 1.3	21 (0/21)	46.7 ± 11.6	Figure of 8 coil	Single and paired pulses, NA	First dorsal interosseous	rMT, SICI, ICF
Schwenkreis et al[82]	Neuralgia: hand; OA: hand	Germany	26 (14/12); 20 (10/10)	50.9 ± 11.7; 56.6 ± 10.2	39.3 ± 44.8 Months; 35.6 ± 42.9 months	4.7 ± 2.1; 3.9 ± 2	14 (6/8)	58.8 ± 12.7	Circular coil (14 cm) on vertex	Single and paired pulses, monophasic	First dorsal interosseous	rMT, SICI, ICF
Clark et al[15]	LBP	United States	10 (5/5)	23.7 ± 6.1	3.2 ± 3.1 Years	2.6 ± 1.6	10 (5/5)	22.9 ± 1.9 (SEM)	Custom-modified 110-mm double cone coil on vertex	Single pulse, NA	Erector spinae	MEP amplitude
Schwenkreis et al[83]	Fibromyalgia	Germany	16 (2/14)	48.7 ± 8.4	NA	NA	23 (7/16)	37.7 ± 11.5	Circular coil (14 cm) on vertex	Single and paired pulses, mono-phasic*	Forearm superficial flexor	rMT, MEP amplitude, CSP, SICI, ICF
Tsao et al[96]	LBP	Australia	9 (4/5)	25 ± 3.4	3.6 ± 2.3 Years	4.7 ± 1.1	11 (5/6)	24 ± 5	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic	Deep multifidus, erector spinae	Map volume
Masse-Alarie et al[54]	LBP	Canada	13 (6/7)	53.7 ± 7.4	16 ± 10 Years	2.9 ± 2.5	9 (4/5)	48.7 ± 6.8	Double cone coil (7 cm) on hotspot	Single and paired pulses, mono-phasic	Transversus abdominus, internal oblique	MEP amplitude, SICI
Vallence et al[105]	Chronic tension type headache	Australia	11 (5/6)	35 ± 13.2	NA	NA	18 (7/11)	28 ± 8 (unclear)	Figure of 8 (9 cm) on hotspot	Single pulse, mono-phasic*	Abductor pollicis brevis	rMT, MEP amplitude
Kittelson et al[41]	OA knee	United States	17 (8/9)	63.9 ± 1.8 (SEM)	NA	NA	20 (10/10)	58.3 ± 2.5 (SEM)	Double cone coil on hotspot	Single and paired pulses, mono-phasic*	Vastus lateralis	rMT, MEP amplitude, SICI, ICF
Marker et al[51]	Neck pain	United States	9 (2/7)	42.4 ± 11	>12 Months	1.7 ± 1.4	8 (4/4)	31.5 ± 14.5	Figure of 8 coil (7 cm) on hotspot	Single and paired pulses, mono-phasic	Upper trapezius	rMT, aMT, MEP amplitude, SICI
Rittig-Rasmussen et al[73]	Neck pain; knee pain	Denmark	20 (14/6); 15 (10/5)	29 ± 7; 27 ± 6	>3 Months	1.7 ± .6 1.5 ± .6	15 (12/3)	25 ± 3.5	Figure of 8 coil on hotspot	Single pulse, monophasic	Upper trapezius, abductor pollicis brevis	aMT, MEP amplitude, MEP latency
Bradnam et al[7]	Shoulder pain	Australia	8 (1/7)	64.9 (49–75)	>12 Months	4.4 ± 1.2	18 (9/8)	41.3 (20–68)	Figure of 8 (7 cm) on hotspot	Single pulse, monophasic*	Infraspinatus	aMT, MEP amplitude, CSP
Schabrun et al[78]	LBP	Australia	27 (13/14)	30 ± 9	5.3 ± 4 Years	4.6 ± 1.9	23 (12/11)	27 ± 5	Figure of 8 coil on M1	Single pulse, monophasic	L3 and L5 erector spinae	Map volume

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Table 2. Continued

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Schabrun et al[79]	Lateral epicondylalgia	Australia	11 (5/6)	44 ± 11	9 ± 6 Months	2.7 ± 2	11 (5/6)	42 ± 11	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic*	Extensor carpi radialis brevis, extensor digitorum	rMT, MEP amplitude, map volume
Van Velzen et al[101]	CRPS I: hand	Netherlands	12 (2/10)	51 ± 9.5	88 ± 26.9 Months	6.7 ± 1.8	12 (1/11)	52 ± 13	Figure of 8 coil on hotspot	Single pulse, biphasic*	First dorsal interosseous	rMT, MEP amplitude
Burns et al[8]	Lateral epicondylalgia	Australia	14 (4/10)	41.5 ± 9.9	37.3 ± 74.8 Months	3.5 ± 2.8	14 (4/10)	42.1 ± 11.1	Circular coil (9 cm) on hotspot	Single and paired pulses, monophasic*	Extensor carpi radialis brevis	rMT, aMT, MEP amplitude, SICI, ICF, LICI
Caumo et al[11]	Myofascial pain; fibromyalgia; OA knee	Brazil	54 (0/54); 19 (0/19); 27 (0/27)	46.1 ± 12.1; 50.4 ± 8.8; 64.4 ± 7.8	NA	7.2 ± 2.2; 7.9 ± 1.9; 6.3 ± 2.2	14 (0/14)	32.4 ± 10.8	Figure of 8 coil on M1	Single and paired pulses	First dorsal interosseous	MEP amplitude, CSP, SICI, ICF
Masse-Alarie et al[53]	LBP	Canada	35 (20/15)	38 ± 14.6	65.8 ± 72.8 Months	4.2 ± 2.1	13 (6/7)	37.6 ± 12.5	Double cone coil on hotspot	Single and paired pulses, monophasic	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
Masse-Alarie et al[52]	LBP	Canada	11 (6/5)	33.8 ± 12.5	NA	2 ± 1.9	13 (6/7)	37.6 ± 12.5	Double cone coil (7 cm) on hotspot	Single and paired pulses, monophasic*	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
Rio et al[72]	Patellar tendon pain; anterior knee pain	Australia	11 (10/1); 10 (6/4)	26 (18–37); 26.5 (18–37)	90 Months (5–192); 9 months (12–264) (median)	5.4 ± 2.0; 5.0 ± 2.4	8 (7/1)	26 (18–37) (median)	Double cone coil (110 mm) on hotspot	Single pulse, monophasic*	Rectus femoris	aMT
Tarrago et al[93]	OA knee	Brazil	21 (0/21)	64.5 ± 7.72	6.73 ± 2.53 Years	NA	10 (0/10)	34.1 ± 11.64	Figure of 8 coil on hotspot	Single and paired pulses	First dorsal interosseous	rMT, MEP amplitude, CSP, SICI, ICF
Morgante et al[60]	CRPS I: hand	United States	10 (1/9)	48.2 ± 5.5 (SE)	11.3 ± 1.8 Months (SE)	8.1 ± .73	10 (1/9)	48.3 ± 12.5 (SE)	Figure of 8 coil on hotspot	Single and paired pulses, monophasic	Abductor pollicis brevis	rMT, aMT, CSP, SICI, ICF
Parker et al[66]	OA hand	New Zealand	23 (6/17)	72 ± 6	13.5 ± 13.1 years	NA	20 (6/14)	71 ± 7	Figure of 8 coil on hotspot	Single and paired pulses, monophasic	First dorsal interosseous	rMT, MEP amplitude, CSP, SICI, LICI, SICF
Te et al[94]	Patello-femoral pain	Australia	11 (3/8)	21 ± 7	29 ± 6 months	2.3 ± 2.2	11 (3/8)	24 ± 6	Figure of 8 coil on M1	Single pulse, monophasic	Rectus femoris, vastus lateralis, vastus medialis	aMT, map volume

Abbreviations: M, male; F, female; SEM, standard error of the mean; NA, not available; rMT, resting motor threshold; SE, standard error.
NOTE. Values are mean ± SD unless otherwise stated.
*Information obtained from the stimulator manufacturer's website.

Table 3. Characteristics of Included Studies Using Other Neurophysiological Methods

			Chronic pain participants				Healthy participants				
Reference	Condition	Country	Study size (M/F)	Age	Pain duration	Pain intensity (0–10)	Study size (M/F)	Age	Modality	Stimuli	Outcome measures
Cook et al[17]	Fibromyalgia	United States	9 (0/9)	37 ± 5	NA	1.03 ± .7	9 (0/9)	35 ± 3	fMRI	Heat pain on left thenar eminence	BOLD at 1.5 T
Napadow et al[62]	Carpal tunnel syndrome	United States	10 (4/6)	51.1 (31–60)	4 months to 10 years	NA	9 (3/6)	46.9 (32–59)	fMRI	Innocuous electrical stimulation to digit 2, 3, and 5	BOLD at 3 T
Maihöfner et al[49]	CRPS I: hand	Germany	12 (2/10)	41.2 ± 2.5 (SEM)	52.2 ± 32 weeks (SEM)	3.9 ± .8 (SEM)	12 (2/10)	43.2 ± 2.5 (SEM)	fMRI	Finger tapping task	BOLD at 1.5 T
Gieteling et al[28]	CRPS I: hand with dystonia	Netherlands	8 (1/7)	46.4 ± 6	NA	NA	17 (2/15)	42.9 ± 9.2	fMRI	Imagining and performing wrist flexion/extension	BOLD at 3 T
Kobayashi et al[42]	LBP	Japan	8 (5/3)	33 (22–44)	>3 Months	NA	8 (8/0)	29 (22–42)	fMRI	Lumbar mechanical compression	BOLD at 3 T
Wasan et al[108]	LBP	United States	16 (5/11)	47.4 (95% CI = 40–54.8)	6.24 years (95% CI = 3.9–11.8)	4.8 (95% CI = 3.8–5.9)	16 (5/11)	46.7 (95% CI = 40.1–53.2)	fMRI	Rest state; clinical maneuver (pain exacerbation); heat pain (affected leg)	rCBF at 3 T
Barke et al[4]	LBP	Germany	30 (0/30)	NA	NA	NA	30 (0/30)	NA	fMRI	Photos (aversive and neutral movement/posture; general fear-inducing; neutral; spider)	BOLD at 3 T
Bolwerk et al[6]	CRPS I and II: hand and foot	Germany	12 (5/7)	61.1 ± 11.1	15.5 (4–406) Weeks	5.3 ± 2.1	12 (5/7)	60.9 ± 11	fMRI	Resting state	BOLD at 1.5 T
Liu et al[47]	Postherpetic neuralgia	China	11 (11/0)	66.2 ± 5.5	8.4 ± 6.2 Months	8.3 ± 1	11 (11/0)	64 (56–73)	fMRI	Resting state	rCBF at 3 T
Flodin et al[25]	Fibromyalgia	Sweden	16 (0/16)	48.3 (25–64)	7.6 ± 3.8 Years	NA	22 (0/22)	45.7 (20–63)	fMRI	Ankle, knee, and hand tasks	BOLD at 3 T
He et al[32]	Temporo-mandibular disorder	China	23 (9/14)	22.4 ± 3.6	14.8 ± 20.7 Months	NA	20 (9/11)	23.1 ± 2.4	fMRI	Resting state	BOLD at 3 T
Pijnenburg et al[69]	LBP	Belgium	17 (6/11)	33.3 ± 7.9	9.8 ± 8.2 Years	2 ± 2	17 (5/12)	31.8 ± 8.2	fMRI	Resting state	BOLD at 3 T
Shanahan et al[85]	OA knee	Australia	11 (6/5)	68.9 ± 6.4	NA	4.3 ± .8	7 (5/2)	64 ± 6.7	fMRI	15 Pressure stimuli (5 different pressure intensities) on left thumb	BOLD at 3 T
Flodin et al[24]	Rheumatoid arthritis	Sweden	24 (4/20)	53.8 ± 14.8	66 ± 34 Months	3.4 ± 2.9	19 (3/16)	50.4 ± 16.6	fMRI	Resting state	BOLD at 3 T
Hemington et al[34]	Ankylosing spondylitis, back pain	Canada	20 (17/3)	39.4 ± 12	12.8 ± 10.1 Years	NA	20 (17/3)	39.7 ± 12	fMRI	Resting state	BOLD at 3 T
Hotta et al[37]	CRPS I: hand	Finland	13 (0/13)	44.7 ± 6.9	5.2 ± 3.9 Years	7.7 ± 1.7	13 (0/13)	44.1 ± 8.6	fMRI	Viewing videos of hand actions	BOLD at 3 T
Tian et al[95]	Trigeminal neuropathic pain	China	20 (8/12)	52.6 ± 8.9	21.1 ± 16.2 Months	7.7 ± 1.6	22 (6/16)	52.2 ± 6.1	fMRI and MRI	Resting state	BOLD and DKI analysis at 3 T
Van Velzen et al[102]	CRPS: hand	Netherland	19 (0/19)	48.1 ± 11.6	110.8 ± 110.5 Years	7.1 ± 1.5	19 (0/19)	49.4 ± 11.6	fMRI and MRI	Resting state	BOLD, VBM and DTI analysis at 3 T

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Table 3. Continued

			Chronic pain participants				Healthy participants				
Reference	Condition	Country	Study size (M/F)	Age	Pain duration	Pain intensity (0–10)	Study size (M/F)	Age	Modality	Stimuli	Outcome measures
Moayedi et al[58]	Temporomandibular disorder	Canada	17 (0/17)	33.1 ± 11.9	9.8 ± 8.2 Years	4.3 ± 1.8	17 (0/17)	32.2 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T
Desouza et al[19]	Trigeminal neuropathic pain	Canada	24 (9/15)	48.5 ± 12.7	6.3 ± 3 Years	NA	24 (9/15)	47.6 ± 12.3	MRI	Resting state	Cortical thickness analysis via 3 T
Maeda et al[48]	Carpal tunnel syndrome	United States	28 (8/20)	48.1 ± 9.6	8.5 ± 9.1 Years	2.5 ± .8 (0–5)	28 (11/17)	47.3 ± 9.9	MRI	Resting state	DTI analyses at 3 T
Wu et al[110]	Ankylosing spondylitis, neuropathic pain	Canada	17 (12/5)	34.4 ± 12.4	NA	6.1 ± 1.7	17 (12/5)	34.9 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T
Pleger et al[70]	CRPS I: hand	Germany	20 (9/11)	41.8 ± 9.8	11.9 ± 14.3 Months	5.3 ± 2.4	20 (9/11)	41.6 ± 9.6	MRI	Resting state	VBM analysis (?) at 1.5 T
Ung et al[100]	LBP	United States	47 (25/22)	373. ± 12.2	8.6 ± 7.8 Years	NA	47 (25/22)	37.7 ± 7.8	MRI	Resting state	VBM (SVM) analysis at 3 T
Juottonen et al[39]	CRPS I: hand	Finland	6 (0/6)	44.5 (33–54)	42.2 ± 26.2 Months	5.6 ± 1.8	6 (0/6)	45.1 (34–55)	MEG	Tactile stimuli to the fingertips	Reactivity of 20-Hz motor cortex rhythm
Shibukawa et al[87]	Temporomandibular disorder	Japan	9 (4/5)	32.4	NA	NA	8 (4/4)	30	MEG	Observation tasks of jaw- and palm-opening movements	Neuromagnetic signals
Kirveskari et al[40]	CRPS I: hand	Finland	8 (0/8)	45.5 (26–57)	5.5 ± 3.1 Years	6.4 ± 1.8	8 (0/8)	46.3 28–57)	MEG	Noxious thulium laser stimulation of both hands	Reactivity of 20-Hz motor cortex rhythm
Grachev et al[29]	LBP	United States	9 (7/2)	45 ± 6	9 ± 5 Years	6.18 ± 1.72	11 (9/2)	44 ± 3	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
Fayed et al[23]	Fibromyalgia	Spain	10 (2/8)	40 ± 6.2	1.6 ± .3 Years	NA	10 (2/8)	37.8 ± 8.7	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
Sharma et al[86]	LBP	United States	19 (4/15)	46.1 ± 11.3	8.8 ± 7.2 Years	4.5 ± 1.9	14 (3/11)	44.6 ± 14.7	MRS	Resting state	Absolute concentration of neurochemicals at 3 T
Jacobs et al[38]	LBP	United States	10 (5/5)	39.2 ± 6.3 (95% CI)	>12 months	1.8 ± .26 (95%CI)	10 (5/5)	35.4 ± 5.3 (95%CI)	EEG	Arm raise	Alpha event-related desynchronization and Bereitschafts potentials
Shiraishi et al[88]	CRPS	Japan	18 (10/8)	40.7 (21–59)	49.8 (6–252) Months	NA	13 (11/2)	38.7 (27–58)	PET	Resting state	Cerebral glucose metabolism

Abbreviations: M, male; F, female; NA, not available; SEM, standard error of the mean; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; SVM, support vector machine.
NOTE. Values are mean ± SD unless otherwise stated.

Table 4. Risk of Bias Assessment for Included Studies

	Modified STROBE statement items						*TMS methodology checklist*	
Reference	*Source of participants*	*Participant selection*	*Methodology*	*Statistical analysis*	*Funding*	*Total score*	*Reported*	*Controlled*
Salerno et al[75]	0	1	0	0	1	2	41.4%	39.3%
Schwenkreis et al[81]	0	1	1	1	0	3	64.3%	63%
Strutton et al[91]	1	0	0	1	1	3	40%	41.7%
On et al[63]	0	1	0	1	0	2	53.8%	52%
Eisenberg et al[21]	1	1	1	1	0	4	72.4%	71.4%
Krause et al[43]	0	0	0	1	0	1	61.5%	48%
Strutton et al[92]	1	0	0	1	1	3	52%	45.8%
Krause et al[44]	1	0	0	1	0	2	52%	37.5%
Turton et al[99]	0	1	0	1	1	3	46.2%	44%
Tsao et al[97]	0	1	1	1	1	4	73.1%	76%
Berth et al[5]	0	0	1	1	1	3	77%	68%
Turgut et al[98]	0	1	1	1	0	3	69.2%	64%
Mhalla et al[57]	1	1	0	1	0	3	55.2%	53.6%
Schwenkreis et al[82]	0	1	1	1	1	4	64.3%	66.7%
Clark et al[15]	0	1	0	1	1	3	54.2%	52.2%
Schwenkreis et al[83]	0	0	0	1	1	2	64.3%	55.6%
Tsao et al[96]	0	0	1	1	1	3	79.2%	82.6%
Masse-Alarie et al[54]	0	0	1	1	1	3	69%	71.4%
Vallence et al[105]	0	0	1	0	1	2	77%	68%
Kittelson et al[41]	0	1	1	1	1	4	72.4%	71.4%
Marker et al[51]	1	0	1	1	1	4	90%	82.1%
Rittig-Rasmussen et al[73]	1	1	0	1	1	4	57.7%	56%
Bradman et al[7]	0	0	0	1	1	2	61.5%	52%
Schabrun et al[78]	0	1	0	1	1	3	43.5%	43.5%
Schabrun et al[79]	1	1	1	1	1	5	77%	76%
Van Velzen et al[101]	1	1	0	0	1	3	57.7%	52%
Burns et al[8]	0	1	1	1	1	4	79.3%	75%
Caumo et al[11]	1	0	0	1	1	3	62.1%	46.4%
Masse-Alarie et al[52]	0	1	0	1	1	3	62.1%	59.3%
Masse-Alarie et al[53]	0	1	1	1	1	4	69%	64.3%
Rio et al[72]	1	1	0	1	0	3	57.7%	60%
Tarrago et al[93]	1	1	0	1	1	4	69%	55.6%
Morgante et al[60]	0	1	1	1	1	4	72.4%	77.8%
Parker et al[66]	0	1	1	1	1	4	96.6%	88.9%
Te et al[94]	1	1	1	1	1	5	75%	79.2%
Grachev et al[29]	0	1	1	1	1	4	NA	NA
Juottonen et al[39]	0	1	1	0	1	3	NA	NA
Cook et al[17]	0	0	0	0	1	1	NA	NA
Napadow et al[62]	0	1	1	1	1	4	NA	NA
Shiraishi et al[88]	0	1	1	0	0	2	NA	NA
Maihöfner et al[49]	0	1	1	0	1	3	NA	NA
Shibukawa et al[87]	0	1	1	1	1	4	NA	NA
Gieteling et al[28]	0	1	1	0	1	3	NA	NA
Kobayashi et al[42]	0	0	1	0	1	2	NA	NA
Fayed et al[23]	1	0	0	1	1	3	NA	NA
Jacobs et al[38]	0	0	1	1	1	3	NA	NA
Kirveskari et al[40]	0	0	1	1	1	3	NA	NA
Moayedi et al[58]	0	1	0	1	1	3	NA	NA
Wasan et al[108]	0	1	0	0	1	2	NA	NA
Barke et al[4]	1	1	0	1	0	3	NA	NA
Sharma et al[86]	0	1	1	1	1	4	NA	NA
Bolwerk et al[6]	0	1	1	1	1	4	NA	NA
Desouza et al[19]	0	1	0	1	1	3	NA	NA
Liu et al[47]	0	1	0	0	1	2	NA	NA
Maeda et al[48]	0	1	0	1	1	3	NA	NA
Wu et al[110]	0	1	0	1	1	3	NA	NA
Flodin et al[25]	1	1	1	1	1	5	NA	NA
He et al[32]	0	1	1	0	1	3	NA	NA

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Table 4. Continued

	Modified STROBE statement items						TMS methodology checklist	
Reference	Source of participants	Participant selection	Methodology	Statistical analysis	Funding	Total score	Reported	Controlled
Pleger et al[70]	0	1	0	0	1	2	NA	NA
Ung et al[100]	0	1	0	0	1	2	NA	NA
Pijnenburg et al[69]	0	1	0	0	1	2	NA	NA
Shanahan et al[85]	0	1	0	0	1	2	NA	NA
Flodin et al[24]	1	1	1	0	1	4	NA	NA
Hemington et al[34]	0	1	0	0	1	2	NA	NA
Hotta et al[37]	1	1	0	0	1	3	NA	NA
Tian et al[95]	1	0	1	1	1	4	NA	NA
Van Velzen et al[102]	0	1	0	1	1	3	NA	NA

Abbreviations: STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; NA not available.
NOTE: Each domain would be allocated 1 point if the risk of bias was low and zero point if the risk of bias was considered high. The maximum score possible was five points. NA: not applicable.

trigeminal neuralgia[19] (n = 48 participants, quality score = 3), and larger left M1 cortical thickness that were associated with stronger neuropathic pain symptoms in ankylosing spondylitis[110] (r = .8, n = 34 participants, quality score = 3). One diffusion tensor imaging study reported that enhanced myelination (lower radial diffusivity) in the microstructure of white matter connecting primary sensory cortex and M1 contralateral to the affected side was correlated with nerve conduction velocity in carpal tunnel syndrome[48] (r = .72, n = 56 participants, quality score = 3).

In LBP, 1 MRI study reported increased M1 gray matter (GM) density in people with chronic LBP[100] ($P < .001$ uncorrected for multiple comparisons, n = 94 participants, quality score = 2). Although 1 study reported decreased functional connectivity in the left M1, the left supplementary motor area, and the left cerebellum compared with healthy participants[69] (1.88 ± 0.89 SD vs 2.64 ± 0.8 SD, n = 34 participants, quality score = 2), the other reported increased rCBF in the left M1[108] (cluster-level $P < .01$, n = 32 participants, quality score = 2). Two studies reported no change in M1 activation/connectivity using BOLD contrast (n = 45 participants, quality score = 3,[42] and n = 16 participants, quality score = 2[4]). One EEG study reported altered cerebrocortical motor activity before an arm raise in chronic LBP participants[38] (n = 20 participants, quality score = 3). MRS studies reported conflicting findings for M1 neurochemical metabolism. One study reported no between group difference in sensorimotor cortex[29] (n = 20 participants, quality score = 4), whereas the other reported lower N-acetylasparate concentrations in the right M1 compared with healthy participants[86] (9 ± .9 mM vs 10.2 ± 1.2 mM, n = 33 participants, quality score = 4). For ankylosing spondylitis-related back pain, greater functional impairment was correlated with greater M1–precuneous resting functional connectivity and impaired spinal mobility was associated with weaker M1–rostral ventromedial medulla functional connectivity on BOLD contrast[34] (n = 40 participants, quality score = 2).

Findings in people with CRPS were inconsistent for M1 structure from VBM studies. One study showed increased M1 GM density[70] (cluster-level $P = .042$, corrected, n = 40 participants, quality score = 2), whereas the other showed no between group difference in GM volume and white matter connectivity in sensorimotor cortex[102] (n = 38 participants, quality score = 3). Similarly, findings for M1 activation/connectivity from BOLD contrast were inconsistent. Two studies showed increased activation in bilateral M1[49] (cluster-level $P < .0001$, uncorrected, n = 24 participants, quality score = 3) or connectivity[6] (cluster-level $P < .01$, corrected, n = 24 participants, quality score = 4), whereas 2 showed no changes compared with healthy participants (n = 25 participants, quality score = 3,[28] and n = 38 participants, quality score = 3[102]). There was a significant between group difference in activation of the sensorimotor cortex[37] ($P < .05$, corrected, n = 26 participants, quality score = 3).

In temporomandibular disorder (TMD), 1 VBM study reported that greater pain severity was associated with smaller GM thickness of the M1 region where the representation of the face was situated[58] (r = –.83, n = 34 participants, quality score = 3). BOLD contrast showed decreased intrinsic neural activity in the left M1 in individuals with TMD[32] ($P < .05$, corrected, n = 43 participants, quality score = 3). One MEG study reported that TMD participants had significantly smaller neuromagnetic signals in M1 during observation of jaw-opening movements[87] (1 ± 1 nano amp meter vs 16 ± 3 nano amp meter, n = 17 participants, quality score = 4).

In fibromyalgia, 1 MRS study showed a lower myoinositol to creatine ratio in the left sensorimotor cortex, indicating possible M1 neuronal metabolic dysfunction[23] ($P < .05$, n = 20 participants, quality score = 3). Two studies using BOLD contrast reported conflicting findings in M1 activation/connectivity. One reported no between group difference[17] (n = 18 participants, quality score = 3), whereas the other showed decreased sensorimotor cortex connectivity[25] ($P < .00031$, corrected, n = 38 participants, quality score = 4).

One fMRI study in people with knee OA reported that the M1 representation of the affected knee was shifted 4.1 mm anteriorly (SD or CI not reported) and the relative position of the knee and ankle representations were swapped when participants performed ankle and knee tasks[85] (n = 18 participants, quality score = 2). In

Table 5. Effect Sizes for Between Group Differences (People With and Without Pain) From Meta-Analyses of TMS Studies. Pooled Estimates for All Measures Revealed No Difference Between People With and Without Pain, With the Exception of LICI

Outcome measure	Number of included studies	Number of participants	Quality score range (maximum score = 5)	SMD (95% CI)
Resting motor threshold	19	604	1 to 5	.01 (–.29 to .31)
AMT	12	357	3 to 5	.11 (–.24 to .46)
MEP amplitude	24	788	1 to 5	–.15 (–.38 to .09)
MEP latency	4	181	2 to 4	.21 (–.11 to .52)
Cortical silent period	12	481	1 to 4	–42 (–.85 to .00)
Map volume: erector spinae	2	70	3	–.24 (–.72 to .23)
Map volume: wrist extensor	2	46	2 to 5	.35 (–.66 to 1.36)
SICI	15	572	2 to 4	.07 (–.36 to .50)
LICI	3	102	2 to 4	.78 (.37–1.19)
ICF	7	249	2 to 4	–.26 (–.65 to .14)
SICF	3	113	3 to 4	.23 (–.24 to .70)

addition, poorer performance of a knee task was associated with more anterior placement of the M1 loci in people with knee OA. In rheumatoid arthritis, 1 study using BOLD contrast reported increased connectivity of bilateral sensorimotor cortex with the supplementary motor and midcingulate cortex[24] ($P < .00031$, corrected, n = 43 participants, quality score = 4).

Is There Evidence of Altered Corticospinal Excitability in Chronic Pain?

Data for resting motor threshold, aMT, MEP amplitude and latency, CSP, and map volume were pooled to perform separate meta-analyses from studies using single-pulse TMS. Pooled effect estimates for all measures revealed no difference between people with and without pain (Table 5; Supplementary Figs 1–6). There was substantial heterogeneity across all measures with the exception of MEP latency and map volume of erector spinae.

For comparisons in which significant heterogeneity was observed, we conducted subgroup analysis according to condition. A moderate reduction in aMT in people with chronic knee pain (3 studies, 73 participants, SMD = –.52, 95% CI = –1.02 to –.02, $P = .04$, χ^2 $P = .68$, $I^2 = 0\%$; all studies have quality score >3; Supplementary Fig 2) was detected, indicating increased M1 corticospinal excitability.

Seven of 35 TMS studies[7,43,44,63,75,83,105] scored lower than 3 (median value) on the modified STROBE statement and were categorized as high risk of bias. Meta-analyses rerun after removing the high risk of bias TMS studies detected a large reduction in the CSP for CRPS but left only a single small study (n = 20 participants) in that subgroup.

Is There Evidence for Altered Intra-Cortical Facilitation and/or Inhibition in Chronic Pain?

Sixteen studies investigated intracortical inhibitory and facilitatory networks using paired-pulse TMS paradigms with several different measures. A moderate increase in long-interval intracortical inhibition (LICI) was detected in people with pain (3 studies, 102 participants, SMD = .78, 95% CI = .37–1.19, $P < .001$, χ^2 $P = .84$, $I^2 = 0\%$; Fig 2), indicating increased M1 intracortical inhibition. No difference between people with and without pain was found for short-interval intracortical inhibition (SICI), intra-cortical facilitation (ICF) or short-interval ICF (SICF; Table 5, Supplementary Figs 7–9). One study appeared to mislabel ICF as SICF on the basis of the experimental protocol and was not included in the meta-analysis.[11] There was substantial heterogeneity in the pooled effect estimates for SICI (χ^2 $P < .01$, $I^2 = 80\%$) and ICF (χ^2 $P = .04$, $I^2 = 51\%$). The subgroup analysis showed a moderate reduction in SICI in people with CRPS (4 studies, 100 participants, SMD = –.77, 95% CI = –1.21 to –.34, $P < .01$, χ^2 $P = .72$, $I^2 = 0\%$; Supplementary Fig 7), indicating reduced M1 intracortical inhibition, and a moderate reduction in ICF in people with non-neuropathic

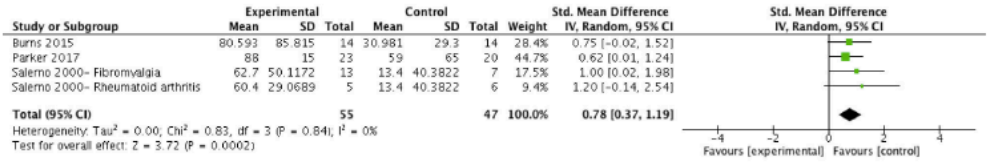

Figure 2. Meta-analysis forest plot for LICI.

pain (6 studies, 151 participants, SMD = −.53, 95% CI = −.94 to −.13, $P = .01$, χ^2 $P = .24$, $I^2 = 26\%$; Supplementary Fig 8), indicating reduced M1 ICF.

Evidence of reduced M1 intracortical inhibition in people with CRPS is complemented by the findings of attenuated activities of the 20-Hz cortical rhythm (which reflects decreased M1 cortical inhibition) from 2 MEG studies. The 20-Hz rebound duration in the right hemisphere was significantly shorter[39] (357 vs 458 ms, $P < .03$, n = 18 participants, quality score = 3), and the rebound amplitude (1 ± 1 SD vs 7 ± 3 SD femtotesla/cm, $P = .05$) and the reactivity (4 ± 2 SD vs 16 ± 5 SD femtotesla/cm, $P = .03$) to painful hand stimuli were significantly smaller[40] (n = 18 participants, quality score = 3) compared with healthy participants. One PET study (n = 31 participants, quality score = 2) showed reduced glucose metabolism in the contralateral M1 in CRPS[88] ($P < .005$, uncorrected), suggesting possible M1 inhibition.

Discussion

To our knowledge, this systematic review is the first to provide a comprehensive and critical review of studies investigating M1 structure, organization, and function in people with chronic pain. For a range of neurophysiological parameters, published studies provided conflicting evidence. Meta-analyses identified a moderate increase in M1 LICI in people with chronic pain. Our findings suggest that the evidence for M1 changes in chronic pain populations is inconclusive for most measures.

Evidence for Altered ICF and/or Inhibition in Chronic Pain

Pooled data from 3 studies investigating non-neuropathic pain provided evidence of increased LICI, indicating increased M1 intracortical inhibition. Increased LICI reflects upregulated γ-aminobutyric acid $(GABA)_B$-mediated intracortical inhibition.[55] Subgroup analyses showed reduced ICF in non-neuropathic pain, suggesting decreased ICF of glutamatergic interneurons through N-methyl-D-aspartate receptors,[111] and reduced SICI in CRPS, suggesting M1 intracortical disinhibition driven by downregulated $GABA_A$-receptors.[55,109] However, although our subgroup analyses were preplanned, interpretation of these findings requires caution because there are no overall effects in the pooled estimates for SICI and ICF.

Consistent with a previous review of CRPS,[20] our review also found M1 disinhibition on the basis of MEG outcomes from 2 studies. The 20-Hz cortical rhythm measured in MEG is initially decreased (suppression; reflecting an activated M1) and subsequently increased (rebound; reflecting inhibited M1) and represents the functional state of M1.[68,76] Combined MEG and MRS showed a positive correlation between 20-Hz rebound amplitude and the concentration of the inhibitory neurotransmitter GABA, indicating the rebound period represents GABAergic inhibition in M1.[27] MEG studies reported a significantly shorter rebound duration of 20-Hz rhythm in both hemispheres,[39] and weaker rebound amplitude and reactivity of 20-Hz rhythm in the hemisphere contralateral to the affected side,[40] indicating M1 disinhibition in CRPS. These findings suggest M1 disinhibition in CRPS, reflecting downregulated GABAergic inhibition. The MEG findings of reduced M1 inhibition in CRPS are inconsistent with the findings of increased LICI in chronic pain from TMS studies. These inconsistencies could be explained because none of these TMS studies investigated CRPS. Although 1 PET study reported reduced glucose metabolism in the contralateral M1 for CRPS in the group analysis, indicating possible M1 inhibition, only 3 (of 18) CRPS participants showed this finding in the individual analysis.[88] Future larger trials are needed to elucidate M1 glucose metabolism in CRPS.

Evidence of Altered M1 Structure, Organization, and Function in Chronic Pain

There is conflicting evidence for M1 changes in chronic pain, which may be explained by the heterogeneity of the underlying neurophysiological mechanisms, methodological differences, internal study biases, reporting biases, and the random play of chance, because of the small sample sizes of the included studies. For example, heterogeneity of underlying neurophysiological mechanisms in nonspecific chronic LBP has been reported.[89] A mixture of neuropathic and non-neuropathic pain components were identified not only in chronic nonspecific LBP,[90] but ankylosing spondylitis back pain,[110] and knee and hip OA.[26,36,59,61] However, it is unclear whether a neuropathic pain subgroup exists in other pain conditions. Future studies should investigate whether distinct pain subgroups exist within chronic pain conditions and whether these subgroups present with different M1 changes.

Evidence from several different measures suggests increased M1 activation/connectivity in neuropathic pain. M1 disinhibition has been attributed to increased M1 activation (carpal tunnel syndrome), increased M1 rCBF (postherpic neuralgia), and increased M1 functional connectivity (trigeminal neuralgia)[47,62,95] though M1 disinhibition in neuropathic pain was not supported by the finding of a reduction in MEP amplitude from a single study in people with diabetic neuropathy[98] (Supplementary Fig 3). More research is needed to elucidate the neurophysiological mechanisms driving M1 functional changes in neuropathic pain populations.

Several studies reported that impaired motor control in chronic pain was associated with M1 reorganization or altered corticomotor physiology.[38,85,97] For example, delayed activation of the trunk muscles when performing an arm raise in chronic LBP patients was associated with smaller amplitudes of Bereitschafts potential, an EEG potential generated by M1 and the supplementary motor cortex representing movement preparation,[38] and with increased map volume and the posterolaterally shifted M1 representation of transversus abdominis.[97] This supports the role of altered M1 in motor control impairment in musculoskeletal disorders. However, the causal relationship and the interaction between M1 changes, motor

control impairment, and symptom persistence in chronic pain requires further investigation.

A previous review on M1 function in CRPS could not draw a definite conclusion on M1 functional changes.[20] Two recent MRI studies investigating M1 function and structure for CRPS were included in this review, which reported conflicting findings, likely because of different experimental protocols (resting state vs observational tasks).[37,102] Taken together with the other neurophysiological evidence, no conclusion on M1 changes in CRPS can be drawn from our findings.

Evidence of Altered Corticospinal Excitability in Chronic Pain

Meta-analyses of TMS data revealed no significant change in any measure of corticospinal excitability in people with chronic pain. Although subgroup analysis found a reduction in aMT in chronic knee pain, suggesting increased excitability in the motor system particularly in relation to neuronal and interneuronal membrane excitability,[112] interpretation of this finding requires caution because there is no overall effect in the pooled estimate for aMT.

A previous review on corticomotor excitability in chronic pain reported evidence of M1 disinhibition that was more prominent in neuropathic pain populations.[65] However, our review did not find compelling evidence of M1 disinhibition when people with and without pain were compared. This discrepancy is likely because of our inclusion of more recent studies[7,11,52,53,60,66,72,79,85,93,94] and exclusion of studies containing neurological populations.[45] Also, CRPS studies were separated from neuropathic pain in our subgroup analyses because they have different diagnostic criteria and pathophysiology.

Altered M1 representation of erector spinae muscles (reduced map volume) in chronic LBP has been reported,[96] but not supported by a larger study.[78] Pooled map volume data from these studies found no significant difference between LBP and healthy participants. The differences between the studies in sample size and methodology such as different electromyography electrodes (fine wire needle vs superficial, surface electrodes), the sizes of grid used to measure the map (5×7 cm versus 6×7 cm), and different coils used to deliver TMS could contribute to the contradictory findings of M1 reorganization of erector spinae in LBP. Although some small single studies reported increased map volume of the wrist extensor (lateral epicondylalgia) and transversus abdominis (LBP) muscles, and decreased map volume of quadriceps (patellofemoral pain; Supplementary Fig 5), meta-analyses do not support the changes in M1 representations.

Limitations and Recommendations

Several limitations should be considered when interpreting the findings of this review. First, most included studies were small, and may be affected by low statistical power as well as conversely, the propensity for small published studies to return positive and often inflated effect sizes.[10] Additionally, subgroup analyses are regarded as exploratory and interpretation of these findings requires caution, particularly when there is no overall effect in the pooled estimates. False positive significance tests also increase in likelihood rapidly as more subgroup analyses are performed.

TMS studies investigating M1 representations of the affected muscles in chronic pain reported the center of gravity (CoG) as the location of M1 representation. Smudged M1 representations of affected muscles (measured by the distance between the CoG of neighboring muscles) has been reported in chronic LBP and lateral epicondylalgia, suggesting M1 reorganization.[78,79,96] However, we were unable to meta-analyze CoG data because studies reported either the coordinates of the CoG or the absolute distance between the averaged CoG for each group. Future research using TMS to investigate M1 representation of the affected muscles should report the coordinates of CoG for meta-analysis of the data. We also acknowledge that 4 included TMS studies were published by 1 of the coauthors of this review.[8,78,79,94] To minimize the bias, reviewers who were not involved in these studies performed the risk of bias assessment.

A recent study reported that the errors of software commonly used for data analysis in fMRI studies may result in a false positive rate of up to 70% and questioned the validity of some fMRI studies.[22] It is beyond the scope of this review to discuss how these statistical issues may influence the findings of this review. However, the fMRI findings of M1 activation/connectivity and organization for chronic pain in this review should be interpreted with caution. Several studies included in this review investigated the sensorimotor cortex rather than the M1.[23-25,37,102] It is possible that heterogeneity in the brain region being investigated (ie, sensorimotor vs M1) contributed to the inconclusive findings of this review.

Conclusions

This review provides the current evidence on M1 structure, organization, and function in chronic pain and identifies areas where further research is required. EEG, MEG, MRS, and PET techniques have been rarely used to investigate M1 function in chronic pain. Data pertaining to M1 changes for conditions such as TMD, rheumatoid arthritis, neck, shoulder, and neuropathic pain are still lacking. Additionally, more research using paired-pulse TMS paradigms to investigate M1 ICF/and inhibition in chronic pain is required because data are still lacking for measures of LICI and SICF. Future studies with larger sample sizes are warranted to elucidate M1 changes in chronic pain conditions and to inform treatments targeting M1.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2017.10.007.

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Appendix A.1 Search strategy for MEDLINE

1. Chronic pain or
2. Pain or
3. (Chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temporomandib* or complex or regional or burning mouth or back-ache or back*ache or lumbago or fibromyalg*) or
4. (Reflex near/4 dystroph*) or
5. (Sudeck* near/2 atroph*) or
6. Whip-lash or whip*lash or polymyalg* or
7. (Failed back near/4 surg*) or
8. (Failed back near/4 syndrome*)
9. 1 or 2 or 3or 4 or 5 or 6 or 7 or 8
10. MRI or
11. Magnetic resonance imaging or
12. fMRI or
13. functional magnetic resonance imaging or
14. blood oxygen-level dependent contrast or
15. BOLD contrast or
16. Electroencephalogra* or
17. Electrophysiolog* or
18. EEG or
19. MEG or
20. Magnetoencephalogra* or

21. Positron emission tomography or

22. PET or

23. Voxel-based morphometry or

24. VBM or

25. CT scan or

26. Computed tomography or

27. Computerised axial tomography or

28. Computerized axial tomography or

29. Transcranial magnetic stimulation or

30. TMS or

31. Neural inhibition or

32. Brain mapping or

33. Evoked potentials

34. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

35. Motor cortical or

36. Sensorimotor cortex or

37. Motor cortex/physiopathology or

38. Pain neuromatrix or

39. Neuroanatom*or

40. Neuroplastic*

41. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

42. 9 and 38 and 48

Appendix A.2 Risk of bias assessment

1. Sources of participants

- Were the sources of the participants of the study (both patients and healthy controls) reported?

2. Sample selection

- Were the patient population comparable to the healthy population in terms of age and gender?

3. Methodology:

3.1 Was the technique conducted properly?

- TMS studies will be assessed by the checklist
- fMRI/MRI studies will be assessed by the following two items (Coppieters et al 2016):
    - Whether the researchers performed visual inspection of the MRI data quality (eg, head motion).
    - Scores whether manual exclusion in case of low data quality and/or data adjustment
    - was included in the preprocessing pipeline
- MRS studies should report the following specifics: single or multiple voxel spectroscopy; echo time (TE), repetition time (TR), field strength, MRS sequence software (ie. STEAM or PRESS), post-processing software (i.e. LCModel or Scion Image) and metabolite ration/concentration.

4. Statistical analysis

4.1 Was data analysis adequately performed?

For fMRI studies: the following criteria should be met (Lin 2014):

- Whether the type of group-wise statistical inference (e.g. random or fixed effect) was reported.
- Whether correction of multiple comparison was applied to the resulted images

4.2 Did the authors provided measures of central tendency (i.e., mean, median) and variability (i.e., standard deviation, 95% confidence intervals, interquartile ranges)?

5. Funding

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

Appendix A.3

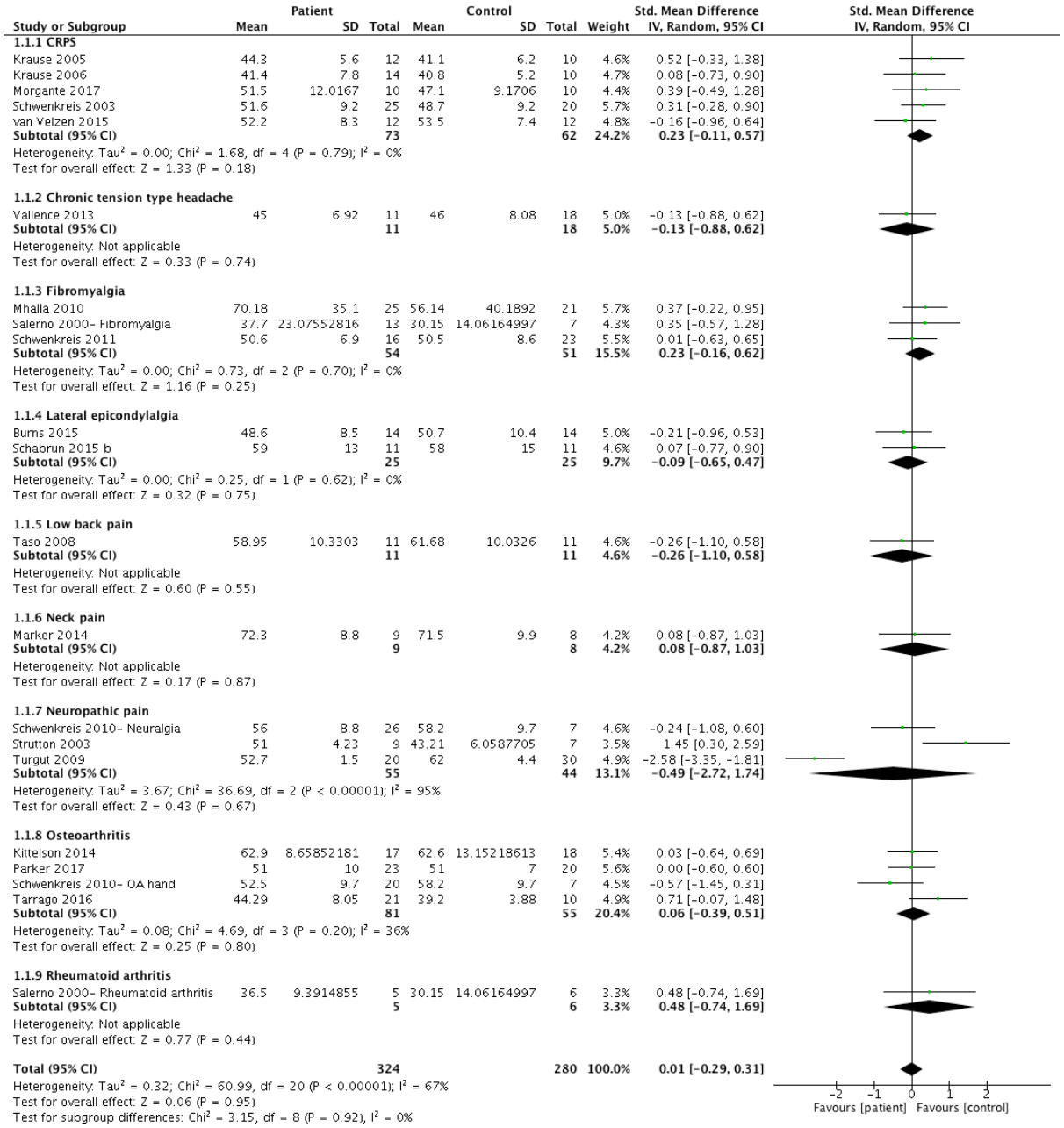


Figure S1. Meta-analysis forest plot for rest motor threshold (rMT).

Appendix A.3 (continued)

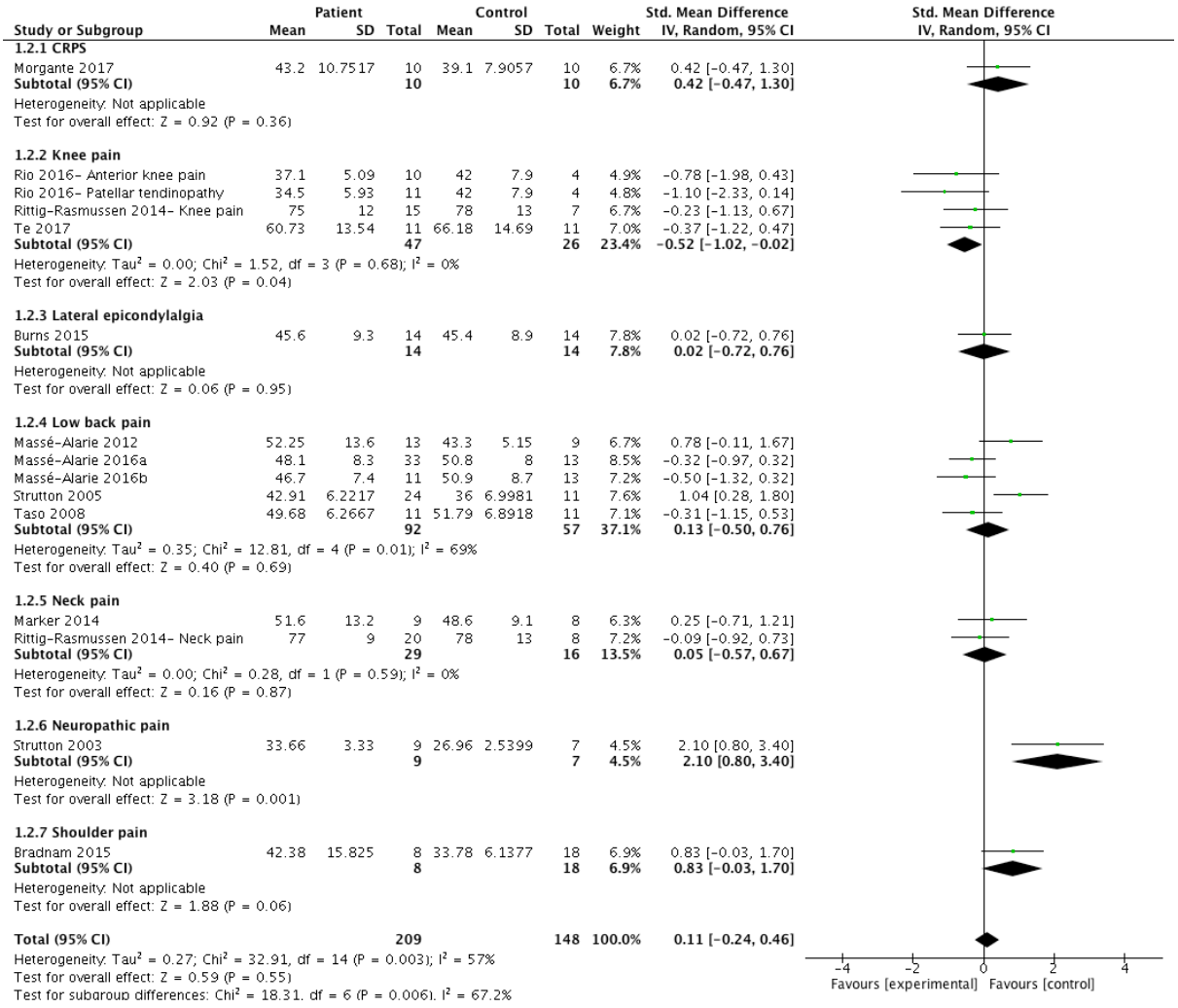


Figure S2. Meta-analysis forest plot for active motor threshold (aMT).

Appendix A.3 (continued)

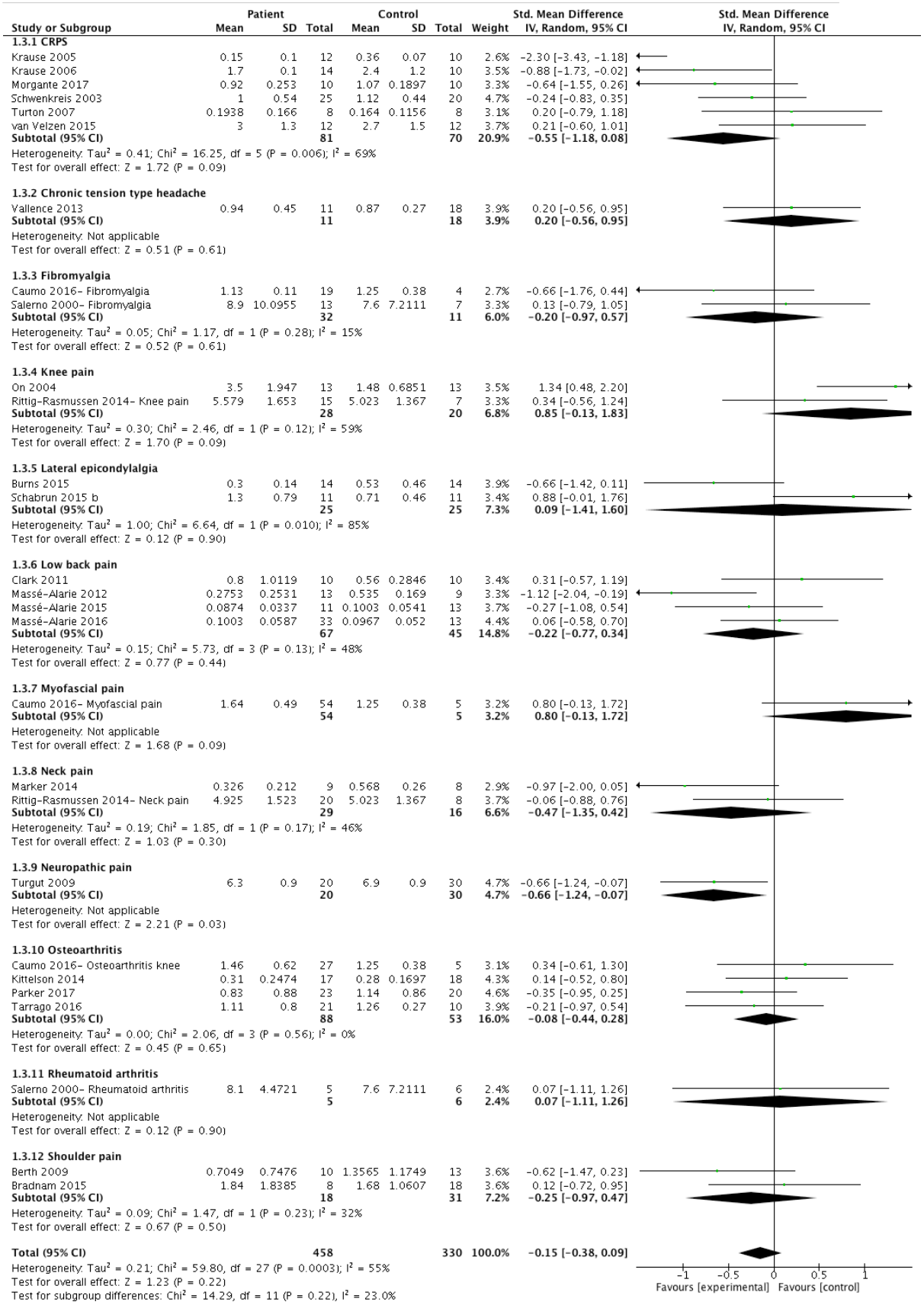


Figure S3. Meta-analysis forest plot for motor evoked potential (MEP) amplitude.

Appendix A.3 (continued)

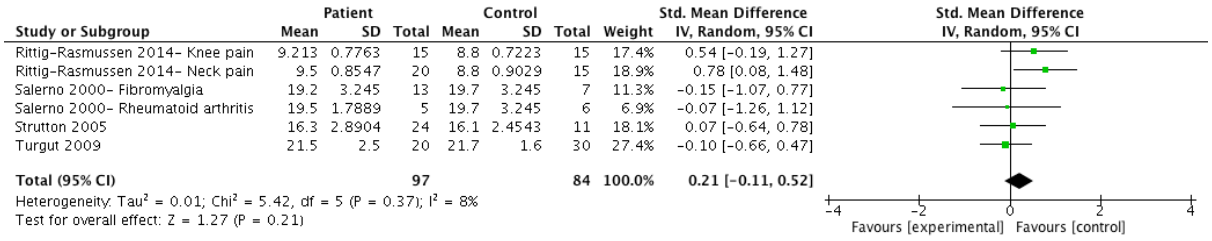


Figure S4. Meta-analysis forest plot for motor evoked potential (MEP) latency.

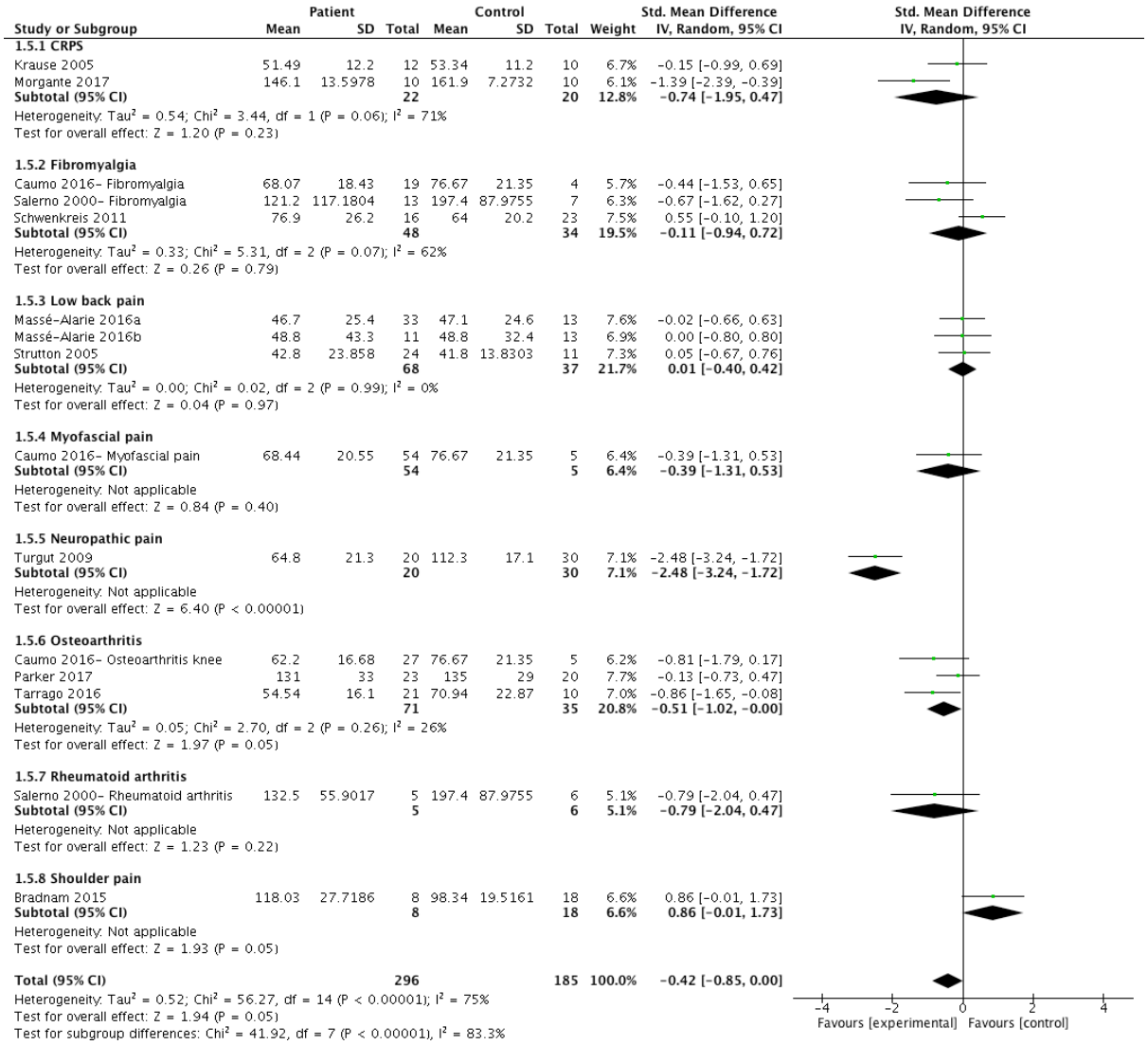


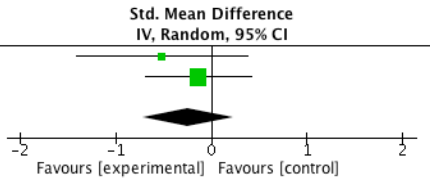
Figure S5. Meta-analysis forest plot for cortical silent period (CSP).

Appendix A.3 (continued)

A. Map volume- Erector spinae

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Tsao 2011	6.7	2.693	9	8.9	4.9121	11	27.7%	-0.52 [-1.42, 0.38]
Schabrun 2015 a	9.8	5.11	27	10.51	5.1	23	72.3%	-0.14 [-0.69, 0.42]
Total (95% CI)			**36**			**34**	**100.0%**	**-0.24 [-0.72, 0.23]**

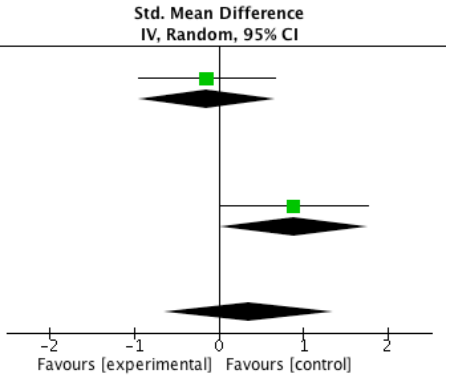
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)



B. Map volume- Wrist extensor

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 CRPS								
Krause 2006	15.6	8.2	14	16.8	7.6	10	51.5%	-0.15 [-0.96, 0.67]
Subtotal (95% CI)			**14**			**10**	**51.5%**	**-0.15 [-0.96, 0.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
2.2.2 Lateral epicondylalgia								
Schabrun 2015 b	15.5	13.1	11	6.4	4.9	11	48.5%	0.89 [0.00, 1.77]
Subtotal (95% CI)			**11**			**11**	**48.5%**	**0.89 [0.00, 1.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.96 (P = 0.05)								
Total (95% CI)			**25**			**21**	**100.0%**	**0.35 [-0.66, 1.36]**

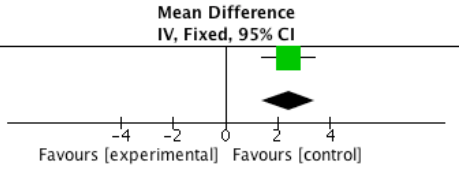
Heterogeneity: Tau² = 0.34; Chi² = 2.83, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Chi² = 2.83, df = 1 (P = 0.09), I² = 64.7%



C. Map colume- Transversus abdominus

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Taso 2008	7.6	1.2	11	5.2	1.2	11	100.0%	2.40 [1.40, 3.40]
Total (95% CI)			**11**			**11**	**100.0%**	**2.40 [1.40, 3.40]**

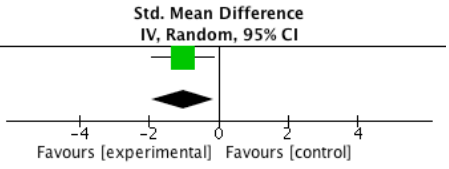
Heterogeneity: Not applicable
Test for overall effect: Z = 4.69 (P < 0.00001)



D. Map volume- Vastus lateralis

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Te 2017	7.1	1.9	11	10.8	4.5	11	100.0%	-1.03 [-1.93, -0.13]
Total (95% CI)			**11**			**11**	**100.0%**	**-1.03 [-1.93, -0.13]**

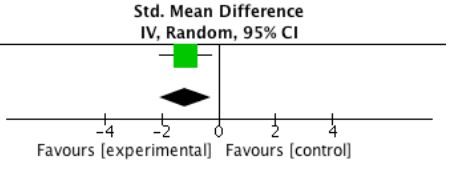
Heterogeneity: Not applicable
Test for overall effect: Z = 2.24 (P = 0.02)



E. Map volume- Vastus medialis

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Te 2017	5.3	2	11	8.7	3.4	11	100.0%	-1.17 [-2.09, -0.25]
Total (95% CI)			**11**			**11**	**100.0%**	**-1.17 [-2.09, -0.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)



F. Map volume- Rectus femoris

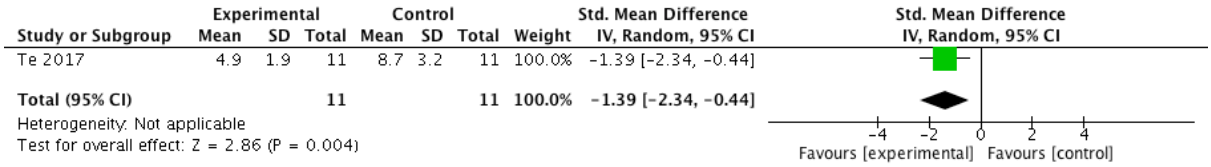


Figure S6. Meta-analysis forest plots for map volume.

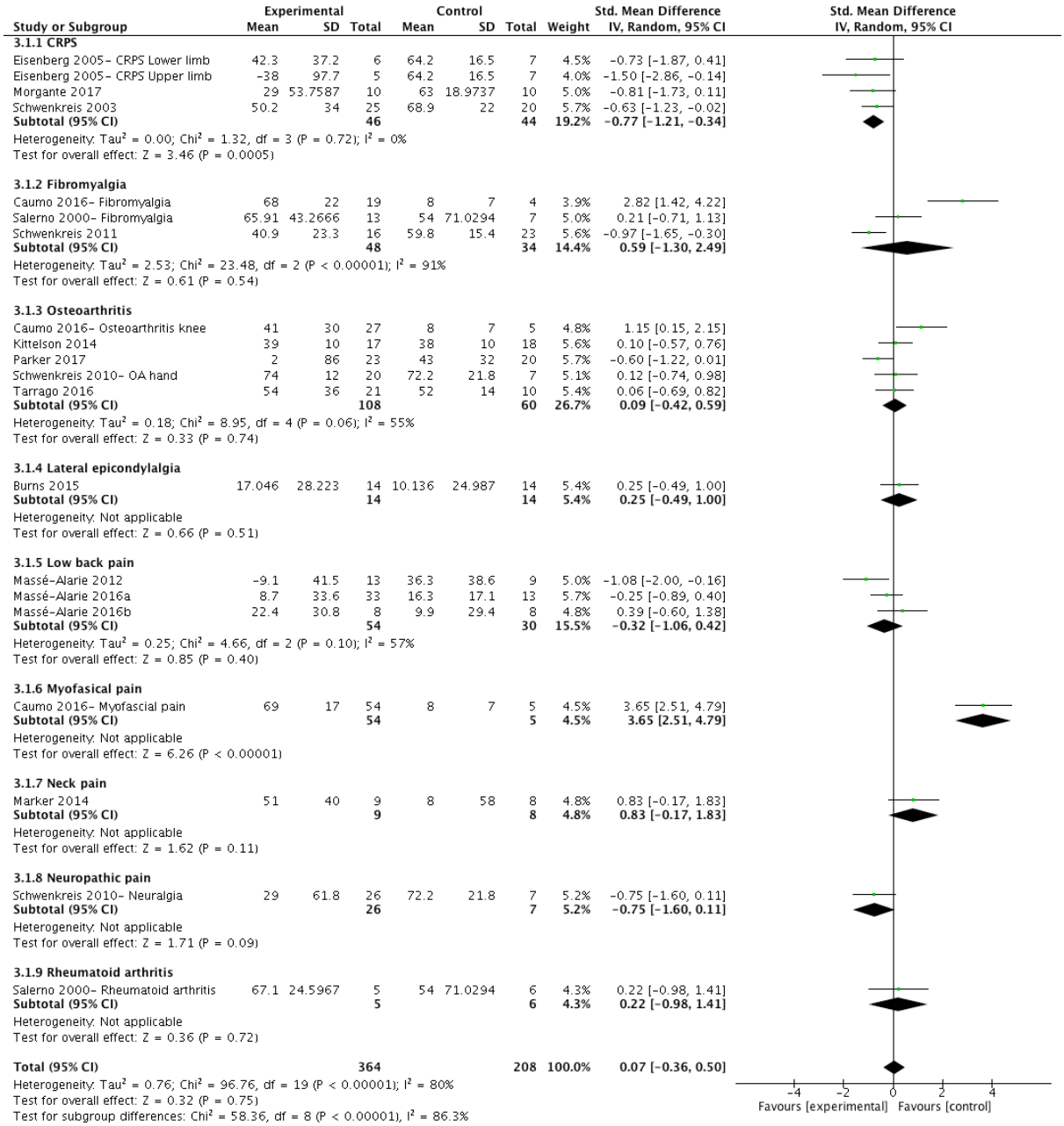


Figure S7. Meta-analysis forest plot for short-interval intra-cortical inhibition (SICI).

Appendix A.3 (continued)

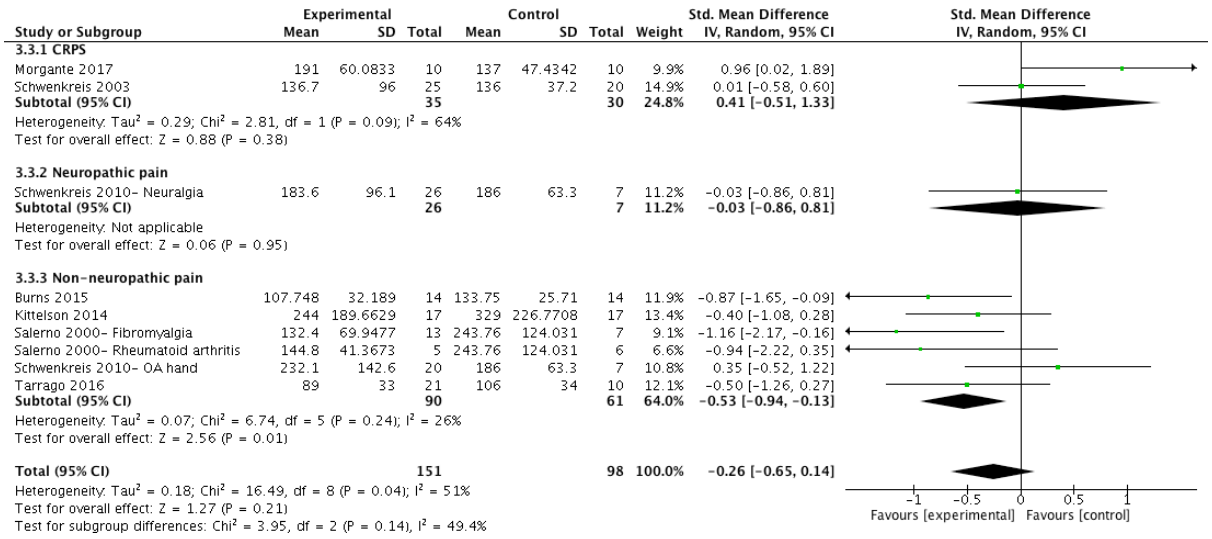


Figure S8. Meta-analysis forest plot for intra-cortical facilitation (ICF).

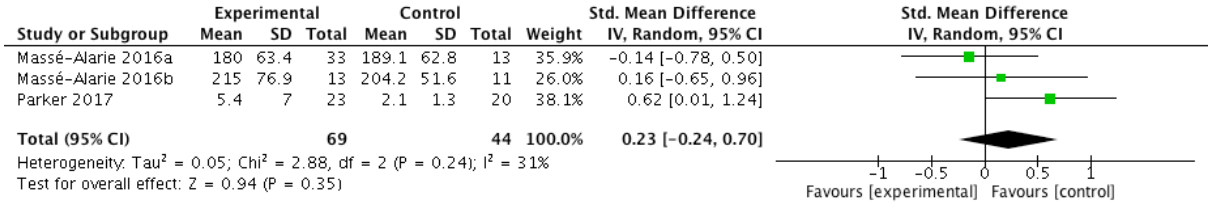


Figure S9. Meta-analysis forest plot for short-interval intra-cortical facilitation (SICF).

Appendix B

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Open Access Protocol

BMJ Open

Organisation and function of the primary motor cortex in chronic pain: protocol for a systematic review and meta-analysis

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To cite: Chang W-J, O'Connell NE, Burns E, *et al*. Organisation and function of the primary motor cortex in chronic pain: protocol for a systematic review and meta-analysis. *BMJ Open* 2015;**5**: e008540. doi:10.1136/bmjopen-2015-008540

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-008540).

Received 20 April 2015
Revised 26 August 2015
Accepted 2 September 2015

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ABSTRACT

Introduction: Primary motor cortical (M1) adaptation in the form of altered organisation and function is hypothesised to underpin motor dysfunction observed in chronic pain. The aim of this review is to assess the evidence for altered M1 organisation and function in chronic pain.

Methods and analysis: Systematic review and meta-analysis. We will search electronic databases with predetermined search terms to identify relevant studies and evaluate the studies for inclusion and risks of bias. Two independent reviewers will extract data. Any disagreement will be resolved through a third reviewer. Cross-sectional or prospective studies published in English before May 2015 that investigate M1 organisation and function in chronic pain will be included if they meet the eligibility criteria. Primary outcomes will include M1 cortical excitability, spatial cortical representation, the function of inhibitory and facilitatory intracortical networks, cortical reactivity and cortical glucose metabolism. Clinical measures such as pain and disability will be included where the correlation with the primary outcomes of M1 organisation and function were investigated in the included studies.

Ethics and dissemination: This systematic review does not require ethical approval. The results of this review will be submitted for peer-reviewed publication regardless of outcome and will be presented at relevant conferences.

Trial registration number: Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42015014823).

Strengths and limitations of this study

- Altered organisation and function of primary motor cortex (M1) is implicated in chronic pain. However, to the best of our knowledge, this is the first systematic review of M1 changes across multiple chronic pain conditions.
- Two independent reviewers will assess articles for inclusion and conduct data extraction and risk of bias assessment.
- Data analyses will include meta-analyses where appropriate, as well as subgroup and sensitivity analyses.

INTRODUCTION

Musculoskeletal disorders are a common cause of disability and result in significant social and economic costs.[1] An estimated 10%, 5% and 4% of the global population with low back pain (LBP), neck pain and knee osteoarthritis, respectively, live with disability[1] with pain being the main symptom of musculoskeletal disorders, especially in the chronic stage. In the USA, nearly 30% of the adult population live with pain.[2]

Movement dysfunction associated with pain is commonly observed in the clinic and is a key focus of rehabilitation. For instance, when musculoskeletal pain is present, deficits in force production, amplitude and speed of movement, muscle coordination and postural control are reported.[3–5] Despite this, the physiological basis and clinical relevance of movement dysfunction in pain is poorly understood. There is considerable debate regarding the type, quantity and timing of movement-based treatments, if any, needed to effectively target motor dysfunction in persistent musculoskeletal pain disorders.[6–8]

The primary motor cortex (M1) is a key driver of motor output and may therefore contribute to movement dysfunction in pain, making it a potential target for therapy. There is emerging evidence of altered M1 organisation and function across a range of chronic pain conditions. For example, M1 topographical representations generated using transcranial magnetic stimulation (TMS) show greater overlap and a reduced

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number of discrete peaks in chronic low back[9–11] and elbow pain,[12] and these changes are associated with pain severity and/or motor dysfunction. Similarly, there is evidence for increased signal with movement of the affected hand in complex regional pain syndrome (CRPS) using functional MRI[13] and evidence of reduced GABAergic and glutamatergic M1 function in fibromyalgia that is associated with fatigue.[14]

To our knowledge, only one published systematic review has investigated M1 organisation and function in chronic pain, and this was restricted to CRPS.[15] That review revealed limited evidence of bilateral M1 disinhibition in CPRS of the upper limb.[15] However, it is unknown whether similar alterations in M1 are present in other forms of chronic pain. Indeed, one previous study has suggested that M1 disinhibition may occur in chronic neuropathic but not chronic nociceptive pain.[16] This review will be the first to systematically and critically evaluate the evidence for altered M1 organisation and function, across a range of measurement tools, in chronic pain conditions of neuropathic and non-neuropathic origin. Understanding how M1 organisation and function is altered in chronic pain is essential to inform the design and testing of treatment strategies that seek to target M1 in pain.

Here, we present the protocol for a review that aims to evaluate the evidence for altered M1 organisation and function in chronic pain conditions of neuropathic or non-neuropathic origin. This protocol is prepared according to the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines.[17] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42015014823).

METHODS AND ANALYSIS

Review question

What is the evidence for altered M1 organisation and function in chronic pain conditions of neuropathic and non-neuropathic origin?

Search strategy

The methods for this systematic review have been developed according to the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[18] The search strategy will be implemented in two stages.

1. Searches will be conducted in PubMed, MEDLINE, EMBASE, PsychINFO and CINAHL databases to identify relevant literature. Key words and medical subject headings (MeSH) related to chronic pain, neuroimaging and the brain will be used; for example: chronic pain, positron emission tomography, functional magnetic resonance imaging, BOLD contrast, Electroencephalogra*, Magnetoencephalogra*, transcranial magnetic stimulation, motor cortical and sensorimotor cortex. The full search terms are listed in online supplementary appendix 1. The combination of chronic pain, neuroimaging and brain search terms will be used in varying combinations to identify relevant literature. Search strategies will be customised to suit each database. The main search strategy is included in online supplementary appendix 1.
2. The reference lists of eligible articles and relevant reviews will be manually searched for additional articles.

Type of participants

Participants should be adults (aged over 18 years) experiencing chronic, musculoskeletal pain of neuropathic or non-neuropathic origin. Neuropathic pain is defined as 'pain caused by a lesion or disease of somatosensory nervous system'.[19] Non-neuropathic pain is defined as pain without an identifiable lesion or disease of the somatosensory nervous system.[20] Studies investigating visceral or cancer pain will be excluded. No restriction is placed on the sex of participants. The duration of pain experienced by participants should be greater than 3 months as this duration is commonly defined as the chronic phase of pain.[21] Cross-sectional or prospective studies will be included in the initial search if they meet the eligibility criteria. Prospective studies including case–control and randomised controlled trials will only be included if their baseline data provide information relevant to the review objective.

Inclusion criteria

1. Full-text studies, including in press or accepted studies, published in English prior to May 2015.
2. Studies conducted on adult humans with chronic non-neuropathic or neuropathic pain.
3. Studies that investigate the organisation and/or function of the M1 (regardless of the anatomical or functional definition used) with the following techniques: TMS, MRI, positron emission tomography, EEG and magnetoencephalography.
4. Studies including data from a healthy control group.

Exclusion criteria

1. Studies including participants with chronic pain not of musculoskeletal origin, for example, pain associated with spinal cord injury, stroke, cancer or visceral pain.
2. Studies that do not include a healthy control group or that use the unaffected limb or body side as a control. It is recognised that widespread symptoms remote from the original injury site can be observed in chronic pain.[22] Thus, using an unaffected limb or body side as a comparison is not considered an appropriate control.

Primary outcomes

Eligible studies should report one of the following measurements of M1 organisation and/or function: cortical excitability, spatial representations, inhibitory or

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facilitatory intracortical networks, reactivity and/or glucose metabolism as outcomes for analysis in this review. Clinical measures such as pain and disability will be included where these are correlated with the primary outcomes of M1 organisation and function.

Data management

Two reviewers will independently evaluate the title and abstract of all studies identified through the search against the inclusion and exclusion criteria. Any duplicate studies will be removed. The full text of all eligible studies will then be retrieved. EndNote X7 will be used during the review process to avoid duplicating references. If the reviewer is uncertain about the eligibility of any study, its full text will be obtained for further information. An additional reviewer will be consulted should there be any uncertainty or disagreement of the eligibility of studies. Excluded studies and the reasons for exclusion will be recorded.

Data extraction

A customised data extraction form (see online supplementary appendix 2) will be piloted on two studies not directly related to this review, and then used to extract data. Two independent reviewers will conduct data extraction. Any disagreements will be resolved through a third reviewer. The following data will be extracted: (1) participant-specific data such as condition, duration and severity of chronic pain, sample size in each group, sex and age; (2) neurophysiological methods and outcomes, specifics of the investigative model such as type and location of stimulation, how M1 was anatomically or functionally defined, neuroimaging findings in M1 excitability, representation, reactivity and glucose metabolism; (3) pain scores. Other outcome measurements such as quantitative sensory tests and movement dysfunction will be extracted if they are correlated with the primary outcomes. If data are missing, authors will be contacted a maximum of three times, after which the data will be considered irretrievable.

Risk of bias (quality) assessment

To assess the risk of bias of the included studies, we will use the STROBE statement for cross-sectional and cohort studies (see online supplementary appendix 3) and items relevant to case–control studies from the Cochrane Collaboration tool for assessing the risk of bias.[23–25] Methodological quality pertaining directly to the use of TMS will be assessed via a TMS methodological checklist (see online supplementary appendix 4).[26] Two independent reviewers will undertake the assessment of risk of bias and methodological quality. Any disagreement will be resolved by a third reviewer.

Strategy for data synthesis

A quantitative synthesis is planned to aggregate the data from all types of chronic pain conditions. Parameters such as cortical excitability (resting or active motor thresholds, intracortical inhibition, intracortical facilitation), spatial representation (map volume, BOLD response), M1 reactivity or M1 glucose metabolism will be pooled to perform separate meta-analyses using OpenMetaAnalyst. Cohen's d effect sizes will be used to analyse effect estimates: $d \leq 0.2$ is small, 0.5 represents medium, ≥ 0.8 is considered large.[27] Data will be pooled for an outcome by using a random-effects model if data from at least two studies addressing that outcome are accessible. The χ^2 test will be used to identify statistically significant heterogeneity, and statistically significant heterogeneity will be considered existent when χ^2 $p<0.10$. The I^2 statistic will be used to evaluate the degree of heterogeneity. Substantial heterogeneity will be considered existent when I^2 >50%.[28] All data will be presented as effect estimates (with 95% CIs). Where quantitative synthesis of the extracted data is not appropriate, a narrative synthesis will be used to summarise the study findings about functional and structural changes of M1.[17]

Analysis of subgroups or subsets

Where significant heterogeneity is found, we will conduct subgroup analysis according to the type of pain conditions (LBP, CRPS, fibromyalgia, peripheral neuropathic pain or peripheral tendinopathy), duration of pain, sex of participants and type of treatment participants were receiving at the time cortical data were collected.

Sensitivity analysis

The included studies will be given a score when assessing their methodological quality. For example, studies will score one point if they meet the criteria of 1 of the 22 items from the STROBE statement, hence a maximum 22 points can be scored. The median value of the overall scores of eligible studies will be used as the cut-off point to divide the studies into either the low or high risk of bias group. We will then examine the influence of including studies at high risk of bias by running the analysis with those studies excluded.

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Contributors W-JC, NEO, EB, LSC, MBL and SMS were each involved in the conception, design, writing and editing of the study protocol. The final protocol was approved by W-JC, NEO, EB, LSC, MBL and SMS.

Funding W-JC, MBL and SMS received salary support from the National Health and Medical Research Council of Australia.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix B.1

Appendix 1 Draft search strategy for MEDLINE

1. Chronic pain or
2. Pain or
3. (Chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temporomandib* or complex or regional or burning mouth or back-ache or back*ache or lumbago or fibromyalg*) or
4. (Reflex near/4 dystroph*) or
5. (Sudeck* near/2 atroph*) or
6. Whip-lash or whip*lash or polymyalg* or
7. (Failed back near/4 surg*) or
8. (Failed back near/4 syndrome*)
9. 1 or 2 or 3or 4 or 5 or 6 or 7 or 8
10. MRI or
11. Magnetic resonance imaging or
12. fMRI or
13. functional magnetic resonance imaging or
14. blood oxygen-level dependent contrast or
15. BOLD contrast or
16. Electroencephalogra* or
17. Electrophysiolog* or
18. EEG or
19. MEG or
20. Magnetoencephalogra* or
21. Positron emission tomography or
22. PET or
23. Voxel-based morphometry or
24. VBM or
25. CT scan or
26. Computed tomography or
27. Computerised axial tomography or
28. Computerized axial tomography or
29. Transcranial magnetic stimulation or
30. TMS or
31. Neural inhibition or
32. Brain mapping or
33. Evoked potentials
34. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
35. Motor cortical or
36. Sensorimotor cortex or
37. Motor cortex/physiopathology or
38. Pain neuromatrix or
39. Neuroanatom*or
40. Neuroplastic*
41. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
42. 9 and 38 and 48

Appendix B.2

Appendix 2 Pilot Data Extraction Sheet

Authors (year)	Participants					Healthy control		Neurophysiological method			Other outcome measures		
	Condition	Sex/ Number	Age	Pain duration	Pain severity	Sex/ Number	Age	Type	Specifics	Findings	(Y/N)	Methods	Findings

Appendix B.3

Appendix 3 STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Score
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			**Score**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	
		Total Score	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article:
Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ,Poole C, Schlesselman JJ, Egger M; STROBE Initiative. **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.** (Freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix B.4

Appendix 4 Transcranial Magnetic Stimulation Methodological Checklist

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

Appendix C

PLOS ONE

RESEARCH ARTICLE

Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: A pilot randomised controlled trial

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Citation: Chang W-J, Bennell KL, Hodges PW, Hinman RS, Young CL, Buscemi V, et al. (2017) Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: A pilot randomised controlled trial. PLoS ONE 12(6): e0180328. https://doi.org/10.1371/journal.pone.0180328

Editor: Alessio Avenanti, University of Bologna, ITALY

Received: October 24, 2016

Accepted: June 13, 2017

Published: June 30, 2017

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This trial was funded by Arthritis Australia (The Zimmer Australia Grant). W-JC (1094434), PWH (1002190), KLB (1058440), MBL (1059116) and SMS (1105040) receive salary support from the National Health and Medical Research Council of Australia, RSH from the Australian Research Council (FT#130100175) and VB from a Western

Abstract

A randomised, assessor- and participant-blind, sham-controlled trial was conducted to assess the safety and feasibility of adding transcranial direct current stimulation (tDCS) to quadriceps strengthening exercise in knee osteoarthritis (OA), and provide data to inform a fully powered trial. Participants were randomised to receive active tDCS+exercise (AT+EX) or sham tDCS+exercise (ST+EX) twice weekly for 8 weeks whilst completing home exercises twice per week. Feasibility, safety, patient-perceived response, pain, function, pressure pain thresholds (PPTs) and conditioned pain modulation (CPM) were assessed before and after treatment. Fifty-seven people were screened for eligibility. Thirty (52%) entered randomisation and 25 (84%) completed the trial. One episode of headache in the AT+EX group was reported. Pain reduced in both groups following treatment (AT+EX: $p<0.001$, partial $\eta^2 = 0.55$; ST+EX: $p = 0.026$, partial $\eta^2 = 0.18$) but no between-group differences were observed ($p = 0.18$, partial $\eta^2 = 0.08$). Function improved in the AT+EX ($p = 0.01$, partial $\eta^2 = 0.22$), but not the ST+EX ($p = 0.16$, partial $\eta^2 = 0.08$) group, between-group differences did not reach significance ($p = 0.28$, partial $\eta^2 = 0.052$). AT+EX produced greater improvements in PPTs than ST+EX ($p<0.05$) (superolateral knee: partial $\eta^2 = 0.17$; superior knee: partial $\eta^2 = 0.3$; superomedial knee: partial $\eta^2 = 0.26$). CPM only improved in the AT+EX group but no between-group difference was observed ($p = 0.054$, partial $\eta^2 = 0.158$). This study provides the first feasibility and safety data for the addition of tDCS to quadriceps strengthening exercise in knee OA. Our data suggest AT+EX may improve pain, function and pain mechanisms beyond that of ST+EX, and provides support for progression to a fully powered randomised controlled trial.

Sydney University Postgraduate Research Award. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Knee osteoarthritis (OA) is a prevalent and costly health problem with no known cure. Approximately 10% of people aged over 60 years experience significant pain, physical dysfunction and reduced quality of life as a result of knee OA, and this figure is rising rapidly [1]. The development of low cost, non-drug, non-surgical treatments to improve patient outcomes has been identified as a key priority area by people living with OA [2].

Strengthening exercise is the cornerstone of conservative management for knee OA and is recommended in all clinical guidelines internationally [3, 4]. Although exercise is effective in knee OA, meta-analyses indicate treatment benefits are at best, moderate, for pain and physical function, and small in quality of life [5]. Novel treatments that enhance the benefits of strengthening exercise through synergistic mechanistic effects are one avenue that might further improve exercise outcomes for people with knee OA.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique with the potential to enhance the effectiveness of exercise in knee OA. Weak direct currents are applied to the brain via scalp electrodes to increase (anodal stimulation) or decrease (cathodal stimulation) the excitability of neurons in the region below the electrode and in distant interconnected areas [6–8]. As increased cortical excitability in the primary motor cortex (M1) is associated with motor learning [9–12], anodal tDCS of M1 is thought to increase the brain's responsiveness to the afferent input generated by subsequent treatments such as motor training and peripheral electrical stimulation, a phenomenon known as priming [13–15]. In addition, evidence from healthy individuals and groups with chronic pain suggests anodal tDCS applied to the primary motor cortex (M1) can reduce pain through modulation of pain processing in cortical and subcortical regions, facilitation of descending anti-nociceptive pathways, and induction of synaptic change, reminiscent of neuroplasticity, in underlying brain regions [16–19]. On this basis, applying anodal tDCS to M1 in addition to the established exercise therapy for knee OA has the potential to bolster the mechanistic and clinical effects of exercise through two mechanisms: i) 'priming' the brain to increase its responsiveness to the corticomotor benefits of exercise (e.g. increased cortical excitability, enhanced voluntary muscle activation, strength gains, improved muscle coordination and motor control) and/or; ii) additive and complementary effects on pain system function which has been argued as an outcome of exercise [20]. Thus, the combined application of tDCS and exercise may enhance mechanistic and clinical outcomes in knee OA. However, there has been no research investigating the effect of tDCS combined with exercise therapy in people with osteoarthritic pain.

Only one study has attempted to combine tDCS with exercise for treatment of chronic pain [21]. That study demonstrated greater decreases in pain intensity and anxiety, as well as a trend towards a greater reduction in depression, in individuals with fibromyalgia when tDCS was delivered during aerobic exercise than when tDCS or exercise were delivered alone. These data suggest that tDCS may bolster the effects of exercise in chronic pain.

This pilot randomised clinical trial aimed to: i) determine the safety, feasibility and patient-perceived response of adding tDCS to an exercise program for knee OA; and ii) provide data to inform a sample size calculation for a fully-powered trial based on trends of efficacy in pain, physical function and pain system function should these be observed.

Participants and methods

This randomised, assessor- and participant-blinded, controlled trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry: ACTRN12613001320741. Ethical approval was obtained from Western Sydney University's Human Research Ethics Committee (H10184). All participants provided written informed consent.

Participants

Individuals who met the criteria of the American College of Rheumatology (ACR) clinical classification for idiopathic knee OA [22] were recruited between September 2014 and August 2015 in Sydney, Australia. The post-intervention assessment of the trial was completed in November 2015. The ACR criteria include the presence of knee pain plus at least three of the following six items: age over 50 years, morning stiffness lasting less than 30 minutes, crepitus, bony tenderness, bony enlargement and no palpable warmth. A minimum pain score of 40 on a 100mm visual analogue scale (VAS) on walking in the past week was required. Exclusion criteria are detailed in the protocol paper (Supplementary S1 File) [23]. Participants were permitted to continue their usual medications for the duration of the trial. Medication type and dosage were recorded at the baseline assessment. Potential participants completed an on-line or telephone screening questionnaire to determine eligibility. Eligible individuals were contacted to confirm their willingness to participate and to arrange baseline assessment. A single investigator (W-JC), blinded to the group allocation of the participants, performed participant recruitment, screening, and testing.

Procedures

Participants were randomly allocated to: 1) active tDCS plus exercise (AT+EX); or 2) sham tDCS plus exercise (ST+EX). The randomisation schedule was concealed in consecutively numbered, sealed opaque envelopes. An investigator not involved in recruitment and assessment prepared and provided the envelopes to the treating physiotherapists who revealed group allocation. Participants received 20 minutes of either active or sham tDCS immediately prior to 30 minutes of one-to-one supervised strengthening exercise, twice weekly for eight weeks (16 sessions). tDCS was applied before exercise therapy based on findings of greatest clinical benefit in individuals with stroke when tDCS is applied before, and not during or after, a second therapy [24]. Treatment duration was based on previous studies that reported that at least 12 supervised exercise sessions are required for optimum results in knee OA [25]. The knee with worst symptoms was assessed and treated if bilateral knee OA was present. Assessment and treatment were performed in the laboratory at Western Sydney University. Physiotherapists with more than five years experience were trained in tDCS and delivered both the tDCS (active and sham) and exercise therapies. All participants were instructed to complete home exercises twice per week.

tDCS. tDCS was delivered via two 35 cm^2 surface sponge electrodes using a direct current stimulator (DC-STIMULATOR, neuroConn, Ilmenau, Germany) while participants sat quietly. The active electrode (anode) was placed over M1 contralateral to the side of the worst knee and the reference electrode (cathode) over the contralateral supraorbital region [26]. The primary motor cortex has emerged as one of the most effective and reliable sites for tDCS in the treatment of pain, producing improvements in pain analogous to those of FDA approved pharmaceuticals in other musculoskeletal pain conditions with considerably fewer side-effects [27]. Current intensity was ramped up (0 mA to 1 mA) and down (1 mA to 0 mA) over 10 seconds at the beginning and end of the stimulation period. The stimulation protocol was selected based on tDCS literature [28]. For sham stimulation, electrodes were placed in an identical position. Stimulation was turned on for 15 seconds, then off, to provide the initial itching sensation. Participants were informed that they may or may not perceive any sensation during stimulation [29]. The success of participant blinding was assessed at post-intervention assessment using a Yes/No response to a series of questions to determine whether treatment allocation was divulged to participants before completion of the trial [23].

Exercise therapy. Standardised quadriceps strengthening exercises (5 in total) known to be effective in knee OA were performed with ankle cuff weights or resistance bands where

appropriate [5, 30]. Each exercise was performed in 3 sets of 10 repetitions with a 30s break between sets. The exercises are described in detail in the protocol paper [23]. The exercise program was progressed as defined in the protocol. The starting level and when to progress the exercise were determined for each individual by the treating physiotherapists based on participant feedback and the therapist's clinical judgement. Cuff weights/resistance bands were given to participants to perform their supervised exercises (at the same dosage) at home. Home exercise diaries with instructions were provided for recording the number of sessions, the type and number of exercises performed and any adverse reactions. Diaries were collected at the post-intervention assessment.

Measures

Baseline and post-intervention assessments were performed within one week of commencing or completing the 8-week treatment. *Feasibility* was measured as the: (i) number of treatment sessions attended by each participant, (ii) number of drop-outs in each treatment group, (iii) proportion of participants recruited from the total number screened, (iv) willingness of each participant to undergo therapy on an 11-point numerical rating scale (NRS) with 'not at all willing' at 0 and 'very willing' at 10 (baseline only), and (v) number of home exercise sessions completed. *Safety* was assessed as any adverse reaction reported upon verbal questioning by the treating physiotherapists at each session [31]. The description of any adverse reaction, its severity and duration and how the adverse reaction was managed were documented.

Pain, function and perceived effect of treatment. Pain and function were measured using: (i) a 100 mm VAS for pain on walking over the past week with terminal descriptors of 'no pain' (score 0 mm) and 'worst pain imaginable' (score 100 mm), (ii) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (5 items, total score = 20) and physical function (17 items, total score = 68) subscales [32]. The reliability of the VAS in OA has been demonstrated [33]. The WOMAC is a disease-specific valid and reliable instrument for knee OA [34]. Participants' perceived response to therapy was assessed at post-intervention assessment using a 7-point Likert scale ranging from "completely recovered" to "vastly worsened".

Pain mechanisms. The protocol for each measure is described in detail in the protocol paper [23]. In brief, the following measures were made:

1. Pressure pain thresholds (PPTs) were measured at two remote sites: a) ipsilateral tibialis anterior (10 cm distal to the tibial tuberosity), b) ipsilateral extensor carpi radialis longus (10 cm distal to the lateral epicondyle of the humerus); and eight sites at the worst knee: c) inferomedial- 2 cm distal to the inferior medial edge of patella; d) inferolateral- 2 cm distal to the interior lateral edge of patella; e) lateral- 3 cm lateral the mid point of the lateral patellar border; f) superolateral- 2 cm proximal to the superior lateral edge of patella; g) superior- 2 cm proximal to the mid point of the superior patellar border; h) superomedial- 2 cm medial to the superior medial edge of patellar; i) medial- 3 cm medial to the mid point of the medial patellar border; and j) centre of the patella [35]. The average of three measurements at each site was used in the analysis. The reliability of PPT in OA knee has been demonstrated (ICC = 0.83 [0.72–0.90]) [36].
2. Heat pain thresholds (HPTs) were measured at the worst knee (medial knee joint line, patella and lateral knee joint line) and the ventral aspect of the forearm (10 cm distal from the elbow crest) on both sides. The average of three measurements at each site was used in the analysis. HPT measure has moderate reliability in OA knee (ICC = 0.77 [0.62–0.87]) [36].
3. CPM was examined as a change in pain perceived in one body region (test stimulation [TS], pressure pain threshold) as a result of pain induced in another body region (conditioned

stimulation [CS], heat pain). Participants completed two trials in random order: i) TS at the worst knee and CS at the contralateral forearm; ii) TS at the contralateral forearm and CS at the ipsilateral forearm. The CPM paradigm has demonstrated good intrasession reliability (ICC > 0.75) [37].

4. Nociceptive flexor withdrawal reflex (NFR) was measured using surface stimulating electrodes applied at a retromalleolar location along the expected location of the sural nerve on the side of the worst knee. Recording electrodes were positioned over the belly of the biceps femoris muscle. The intensity needed to evoke a response in biceps femoris, indicating activation of the NFR, the latency of the onset of the NFR response, the EMG amplitude of the NFR response (quantified as the area of the root mean square amplitude between onset and offset of the response) and the subjective pain score on a NRS (0–10) experienced from the sural nerve stimulus were recorded. The NFR is a reliable experimental test (intersession CV_{SEM} = 16.9%, ICC = 0.82) [38].

Data analysis

A CONSORT [39] diagram was used to describe the flow of the participants and to summarise the eligibility, recruitment and follow-up rates throughout the trial. *T*-tests were used for between-group comparisons of baseline characteristics. Data distribution was tested for skewness, kurtosis and normality (Shapiro-Wilk test) prior to conducting the *T*-tests. The analyses of pain, function and pain system function were performed according to intention-to-treat analysis. Missing data were not replaced. To confirm the appropriateness of the statistical analysis plan for a full randomised controlled trial, repeated Measures Analysis of Variance [40] were conducted to compare baseline and post-intervention scores for each outcome, in each group. An analysis of covariance (ANCOVA) was used to assess between-group changes in pain, function and pain mechanisms, where group allocation was the fixed factor and the corresponding baseline outcome values were covariates [41]. Prior to conducting the analysis of variance and covariance tests, the normality (Shapiro-Wilk test) and the homogeneity of variances were tested. Results are presented as means and standard deviations unless otherwise stated.

Results

Feasibility

Fifty-seven people were screened for eligibility. Thirty-two (56%) met the inclusion criteria and attended baseline assessment. Two declined to participate after completing baseline assessment. Thirty screened participants (52%) were enrolled in the study and randomly allocated to a treatment group (Fig 1). Twenty-five enrolled participants (84%) (13 in the AT+EX group and 12 in the ST+EX group) completed the treatment and post-intervention assessment. The dropout rate was 16% (13% [n = 2] in the AT+EX group and 20% [n = 3] in the ST+EX group). In the AT+EX group, one participant withdrew after having an unrelated fall at home and the second relocated to another city. In the ST+EX group, one participant was unable to continue the study while simultaneously receiving physiotherapy after a rotator cuff repair surgery and two withdrew due to traveling distance required to attend treatments. The treatment attendance rate was 80% (14±1.7 sessions) in the AT+EX group and 78% (13.7±2.7 sessions) in the ST+EX group. The AT+EX group completed 14.7 (±2.3) home exercise sessions while the ST+EX group completed 11.3 (±5.2) sessions (out of 16). The demographic characteristics of all participants at baseline were similar between groups (Table 1). Blinding was successful; no participant reported that the type of tDCS stimulation was divulged before completing the

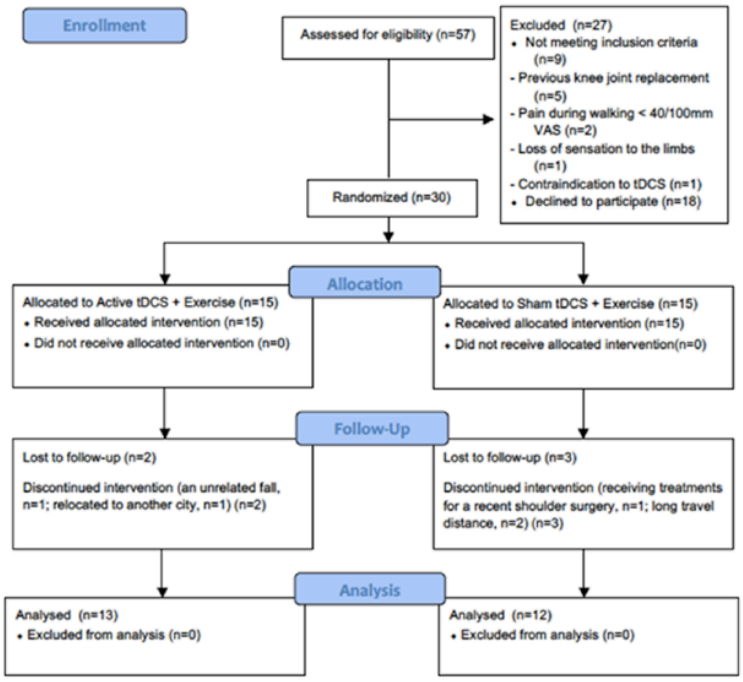

Fig 1. Consort diagram for flow of participants through the trial.

https://doi.org/10.1371/journal.pone.0180328.g001

post-intervention assessment. Eleven (73%) participants in the AT+EX group and seven (47%) in the ST+EX group correctly guessed their treatment group. The outcome assessor reported that the treatment allocation of participants was not divulged before the trial completion.

Safety

One participant in the AT+EX group reported increased pain and swelling in her worst knee at week 6 of the treatment with no precipitating factors identified and was diagnosed with a first episode of gout (no previous history) by her general practitioner. She completed the trial after her symptoms settled. Two adverse reactions to tDCS were documented; one participant in the AT+EX group reported a single episode of headache after one treatment session and later withdrew from the study due to a fall at home. One participant in the ST+EX group reported a single incident of a painful sensation under the tDCS electrode when the current intensity was ramped up at the beginning of stimulation. tDCS was ceased immediately and the painful sensation resolved. The participant returned to complete the study after the incident and reported no further adverse reactions. No adverse reactions to, or concerns regarding the implementation of, the exercise program were identified.

Perceived participant response to treatment

All participants in the AT+EX group and 84% in the ST+EX group reported an improvement in their knee OA symptoms following treatment (Fig 2). No participant reported that knee symptoms worsened with either treatment.

Table 1. Baseline characteristics of participants (mean and standard deviation).

	Active tDCS + Exercise (N = 15)	Sham tDCS + Exercise (N = 15)
Age (year)	59.8±9.1	64.1±11.1
Gender (male/female)	4/11	6/9
Height (metre)	1.6±0.08	1.6±0.11
Weight (kg)	89.0±13.3	84.5±16.4
Body Mass Index (kg/metre^2)	31.3±3.5	30.5±9.1
Duration of symptoms (years)	7.2±5.3	9±7.3
Previous knee arthroscopy	4	6
Bilateral OA knee pain	12	10
Side of worst knee pain (left/right)	4/11	8/7
Willingness to undergo treatment at baseline (out of 10)	9.4±1.1	9.8±0.3
Expected treatment effects		
Minimal improvement	3(20%)	1(6%)
Moderate improvement	6(40%)	7(47%)
Large improvement	6(40%)	7(47%)
Pain on walking (visual analog scale, 100 mm)	59.8±15.2	56.4±19.7
WOMAC *Total score*	55±16.0	48±10.7
Pain	11±3.9	9.9±3.2
Physical function	38.8±11.9	33.2±7.7

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

https://doi.org/10.1371/journal.pone.0180328.t001

Pain and function

Pain during walking (100 mm VAS) reduced in both groups at post-intervention (ANOVA: AT+EX group: $p<0.001$, partial $\eta^2 = 0.55$; ST+EX group: $p = 0.026$, partial $\eta^2 = 0.18$) (Table 2) (Fig 3). Pain reduction in the AT+EX group was double that observed in the ST+EX group (AT+EX group: -41.4 mm, 95%CI -30.7 to -52.2; ST+EX group: -20.7 mm, 95%CI -7.1 to -34.3; Fig 4). The between-group difference was in favour of the AT+EX group (mean difference = -13.0, 95%CI -32.6 to 6.5; ANCOVA: $p = 0.18$, partial $\eta^2 = 0.08$). Scores on the WOMAC pain subscale followed a similar pattern (Table 2).

Improvements in physical function (WOMAC subscale) were observed in the AT+EX (ANOVA: $p = 0.01$, partial $\eta^2 = 0.22$), but not the ST+EX group (ANOVA: $p = 0.16$, partial $\eta^2 = 0.08$) at post-intervention (AT+EX: -10.9 units, 95%CI -3.3 to -18.5; ST+EX: -4.91 units, 95%CI 0.2 to -10.0; Figs 3 and 4). Between-group comparisons did not reach statistical significance (mean difference = -4.8, 95%CI -14.0 to 4.3; ANCOVA: $p = 0.28$, partial $\eta^2 = 0.052$).

Pain mechanisms

PPTs increased (i.e. a greater amount of pressure was required to be perceived as painful) to a greater extent in the AT+EX group for the superolateral, superior, and superomedial knee sites when compared with the ST+EX group (ANCOVA: $p<0.05$; partial $\eta^2 = 0.169$, partial $\eta^2 = 0.301$, partial $\eta^2 = 0.262$ respectively) (Fig 5). Conditioned pain modulation, which is proposed to measure descending pain inhibition (TS at the worst knee and CS at the contralateral forearm), improved from baseline in the AT+EX group (25.6 kPa, 95%CI 47.2 to 4.1, ANOVA: $p = 0.032$, partial $\eta^2 = 0.17$) but not in the ST+EX group (-27.1 kPa, 95%CI 24.6 to -78.8, ANOVA: $p = 0.41$, partial $\eta^2 = 0.03$) (see Supplementary S1 Table). However, there were no

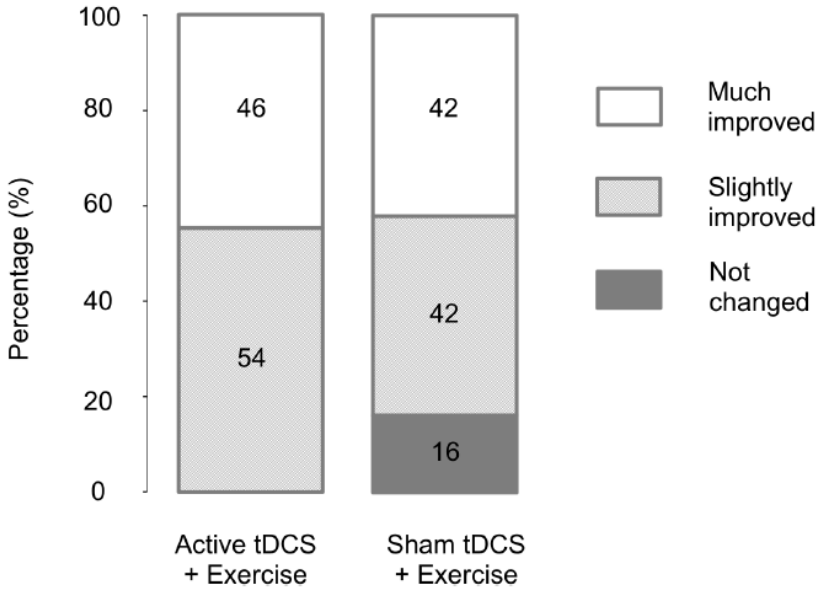

Fig 2. Percentage of participants reporting perceived improvement across categories from 'not changed' to 'much improved'. Note: no participants reported that their condition worsened after either intervention.

https://doi.org/10.1371/journal.pone.0180328.g002

between-group differences (mean difference = 39.0, 95%CI -0.7, 78.6; ANCOVA: p = 0.054, partial η^2 = 0.158). No within- or between-group differences were found for any other measure, including the NFR (Supplementary S1, S2 and S3 Tables).

Table 2. Group data (mean and 95% confidence interval) for pain and function outcome measures.

	Baseline		Post-intervention		Difference within groups (Follow up–Baseline) [a]		Difference between groups; adjusted mean [b]	
	AT+EX (N = 15)	ST+EX (N = 15)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX minus ST+EX	P value between groups
Pain VAS (100 mm)	59.9 (67.6,52.1)	56.5 (66.5,46.5)	24.1 (33.4,14.8)*	33.7 (49.0,18.5)*	-41.4(-30.7,-52.2)	-20.7(-7.1,-34.3)	-13.0(-32.6,6.5)	.18
WOMAC								
Total score	55.0 (63.1,46.9)	48.0 (53.4,42.6)	36.8 (45.3,28.2)*	39.1 (47.1,31.0)	-16.7(-6.0,-27.3)	-8.1(-1.3,-14.8)	-6.2(-18.8,6.3)	.31
Pain subscale	11.0 (13.0,9.0)	9.9(11.6,8.3)	7.5(9.2,5.7)*	7.4(9.3,5.5)	-3.8(-1.0,-6.5)	-2.2(-0.5,-3.8)	-0.6(-3.4,2.3)	.69
Physical function subscale	38.9 (44.9,32.8)	33.3 (37.2,29.3)	26.0 (32.3,19.7)*	27.8 (33.8,21.7)	-10.9(-3.3,-18.5)	-4.9(0.2,-10.0)	-4.8(-14.0,4.3)	.28

AT + EX = active tDCS + exercise, ST + EX = sham tDCS + exercise; VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] A negative number indicates improvement at post-intervention.

[b] A negative number favours the AT + EX group.

*p < 0.05.

https://doi.org/10.1371/journal.pone.0180328.t002

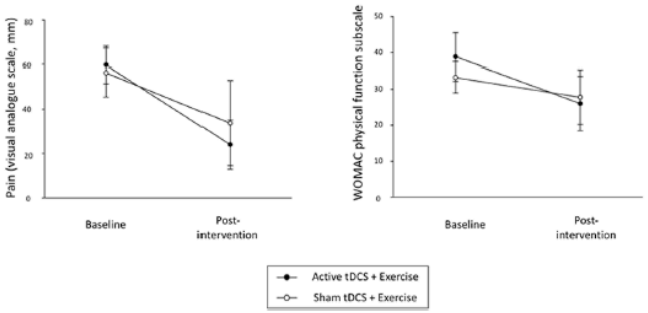

Fig 3. Pain and WOMAC physical function subscale (mean and 95% confidence interval) pre- and post-interventions. Active tDCS + exercise produced improvements in pain and function but sham tDCS + exercise only produced improvement in pain.

https://doi.org/10.1371/journal.pone.0180328.g003

Sample size calculation

The minimum clinically important difference to be detected in OA trials is a change in pain of 18 mm and a change in function of six units [42]. We require a sample size of 99 participants per intervention arm (198 in total) at 90% power and 5% significance level to detect a mean difference of this magnitude, assuming a small effect size (0.3) and allowing for a maximum dropout rate of 20%.

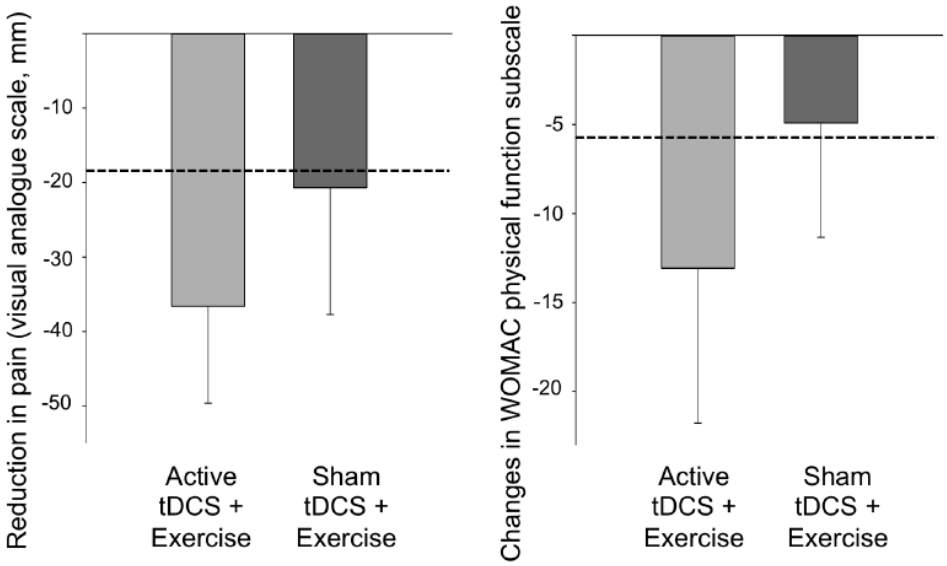

Fig 4. Group change in pain (left panel) and WOMAC physical function subscale (right panel). The graph showed within-group changes (mean and 95% confidence interval) in pain and function following 8 weeks of either active tDCS + exercise or sham tDCS + exercise. Note: larger negative scores indicate greater improvements in pain and function. The dotted line indicates the minimal clinically important change for each outcome.

https://doi.org/10.1371/journal.pone.0180328.g004

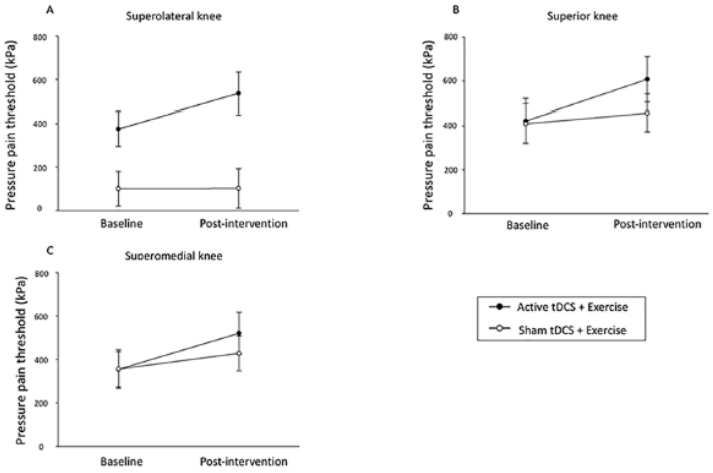

Fig 5. Pressure pain thresholds (mean and 95% confidence interval) pre- and post-interventions at three knee sites. Active tDCS + exercise produced greater improvements in pressure pain thresholds at all three sites following 8 weeks of treatment compared with sham tDCS + exercise (A = superolateral knee; B = superior knee; C = supperomedial knee).

https://doi.org/10.1371/journal.pone.0180328.g005

Discussion

This is the first study to investigate the addition of tDCS to a quadriceps strengthening exercise in knee OA. Our study demonstrates that this treatment combination is feasible and appears to be safe in this population. Further, our preliminary evidence indicates that adding tDCS to exercise may be a promising approach for improving pain, physical function and pain mechanisms in knee OA. These results provide data to inform a fully powered clinical trial to examine the effect of this novel treatment on the symptoms and pain mechanisms associated with knee OA.

Attendance rates for treatments and post-intervention assessment were both above 80%, indicating that a larger randomised controlled trial to evaluate the efficacy of this treatment in this population is feasible [43]. No barriers to implementation of the interventions or outcome measures were identified in this study. Therefore, the methodology used in this study can be implemented in a larger study without any major amendments. Adverse reactions to tDCS during (e.g. fatigue) and after (headache, nausea or insomnia) stimulation have been reported in previous studies [21, 44, 45]. We documented only two adverse reactions that could be attributed to tDCS: one episode of headache in the AT+EX group and one episode of a painful sensation during the initial ramping up of the electric current in the ST+EX group. No adverse reactions were documented in response to the exercise treatment. The overall incidence rate of adverse reactions in this study is lower than those reported in either the tDCS or knee OA literature [44, 46], indicating that the implementation of a tDCS and exercise treatment is likely to be safe in knee OA.

Previous studies have investigated the analgesic effect of tDCS in chronic pain conditions such as low back pain [15, 47], chronic pelvic pain [18], fibromyalgia [21, 48, 49] and neuropathic pain after spinal cord injury [50] with conflicting results. This study is the first to use tDCS in knee OA and to combine tDCS with strengthening exercise in any pain condition. Consistent with evidence of strengthening exercise in knee OA [5, 51], both groups reported reduced pain following the 8-week treatment. However, in the AT+EX group, effects on pain

were more than double the minimal clinically important difference (MCID) of 20 mm for this outcome [42], and double those observed in the ST+EX group. The improvement in physical function following AT+EX also exceeded the MCID of 6 units on the WOMAC physical function subscale in knee OA [42].

Sensitivity to pressure was reduced to a greater extent (increase in PPTs) following AT+EX than ST+EX. CPM (presumed to indicate descending pain inhibition) also demonstrated similar results. The potentially superior effects on pain system function observed with AT+EX may reflect a summative effect of the two treatments on pain mechanisms. Pain in knee OA is considered to include contributions from both peripheral nociceptive afferents in the knee joint structures, as well as sensitization, both peripherally and centrally, and the relative contribution of each will vary between individuals. Recognition of the role of central sensitisation in knee OA is increasing. From one perspective, persistent nociceptive input from joint structural changes in knee OA can increase the synaptic excitability and efficiency in the central pain pathway and result in central sensitisation, characterised by local and widespread hyperalgesia [52, 53], augmented spinal excitability and deficits in descending pain inhibition [54, 55]. Multiple other factors contribute to this process including unhealthy pain cognitions and a host of biological processes. Pain intensity in many individuals with knee OA is associated with hyperalgesia and impaired descending pain inhibition, and for many the relationship with radiographic changes is weak [56]. Exercise is known to have an anti-nociceptive effect at both peripheral and central levels [20, 57–59], and the potential to reduce the "pain" sensitivity in the central nervous system, in chronic pain conditions [60]. Anodal tDCS can modulate pain processing at central level [16] and increase the brain's receptiveness to other interventions through a 'priming' effect by modulating the excitability of cortical neurons/networks [61]. Adding anodal tDCS to exercise may induce complementary effects on pain mechanisms and bolster the brain's responsiveness to the analgesic effects of exercise, leading to greater clinical benefits in knee OA. The relationship between a tDCS and exercise treatment, pain mechanisms and clinical benefits requires investigation in a larger randomised controlled trial.

An alternative explanation for our findings is that tDCS primed/enhanced the corticomotor training effects of strengthening exercise. Previous studies of tDCS combined with strength training in healthy individuals have shown a greater capacity for high volume training, lower perceived exertion during training, improved motor control and larger increases in corticomotor excitability than can be achieved with strength training alone [62, 63]. These effects may lead to greater improvements in knee joint control and mechanical benefits for the knee, reducing pain and disability. Future studies should include measures of muscle strength and motor control to further evaluate this possibility.

tDCS is a relatively inexpensive and portable device and for health professionals already trained in the therapeutic use of electric current, such as physiotherapists, minimal training would be required to ensure safe and effective application. Although not currently used in the clinical setting, tDCS could be easily integrated into clinical practice if beneficial effects on knee OA are established in a future larger trial. A fully powered randomised controlled trial is required to determine whether this treatment produces superior clinical benefits in knee OA.

This study had several limitations. First, by design the study included a small sample size that was not intended to provide sufficient power to definitively determine the efficacy of adding tDCS to exercise treatment for knee OA. Therefore, the results must be interpreted with caution. Second, the short follow-up period in this study may have been too brief to determine between-group differences. A larger clinical trial with longer follow-up periods is required. Third, we did not record any changes in the participants' medication (type and dosage) during this trial. The dosage of the participants' usual medication was only recorded at the baseline. Future trials should record any changes in participants' use of medication during the trial to

evaluate the relationship between pain and the use of medication. Finally, the treating physiotherapists delivered both the tDCS and exercise treatment, and were not blind to group allocation. However, our exercise protocol was well established with clear instructions for how to progress each exercise [23] and the treating therapists were instructed to strictly adhere to the protocol to minimise any potential bias. Future trials should seek to blind the treating therapists to the tDCS condition.

This pilot study provides the first feasibility and safety data for the addition of tDCS to strengthening exercise in people with knee OA. Although not powered to assess between-group differences, our study suggests that the addition of active tDCS to exercise may improve pain, function and pain mechanisms in knee OA beyond that of sham tDCS with exercise, and in excess of MCIDs for pain and function in this population. A fully powered randomised controlled trial with longer follow up is now justified to determine the clinical benefit of this novel treatment for knee OA.

Supporting information

S1 Table. Group data (mean and 95% confidence interval) for heat pain thresholds, conditioned pain modulation and nociceptive withdraw reflex. AT+EX = active tDCS + exercise, ST+EX = sham tDCS + exercise, HPT = heat pain threshold, CPM = conditioned pain modulation, NFR = nociception flexor withdraw reflex, RMS = root mean square.
(DOCX)

S2 Table. Group data (mean and 95% confidence interval) for pressure pain thresholds. AT+EX = active tDCS + exercise, ST+EX = sham tDCS + exercise; Knee 1 = 2 cm distal to the inferior medial edge of patella, Knee 2 = 2 cm distal to the interior lateral edge of patella, Knee 3 = 3 cm lateral the mid point of the lateral patellar border, Knee 4 = 2 cm proximal to the superior lateral edge of patella, Knee 5 = 2 cm proximal to the mid point of the superior patellar border, Knee 6 = 2 cm medial to the superior medial edge of patellar, Knee 7 = medial to the mid point of the medial patellar border, Knee 8 = centre of the patella.
(DOCX)

S3 Table. Effect size (Cohen's *d*) of difference within groups for pain, function and pain mechanisms. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; Knee 1 = 2 cm distal to the inferior medial edge of patella, Knee 2 = 2 cm distal to the interior lateral edge of patella, Knee 3 = 3 cm lateral the mid point of the lateral patellar border, Knee 4 = 2 cm proximal to the superior lateral edge of patella, Knee 5 = 2 cm proximal to the mid point of the superior patellar border, Knee 6 = 2 cm medial to the superior medial edge of patellar, Knee 7 = medial to the mid point of the medial patellar border, Knee 8 = centre of the patella; RMS = root mean square.
(DOCX)

S4 Table. CONSORT 2010 checklist of information to include when reporting a randomised trial.
(DOC)

S1 File. Protocol paper manuscript.
(PDF)

Author Contributions

Conceptualization: Wei-Ju Chang, Kim L. Bennell, Paul W. Hodges, Rana S. Hinman, Siobhan M. Schabrun.

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Appendix C.1

Table S1. Group data (mean and 95% confidence interval) for heat pain thresholds, conditioned pain modulation and nociceptive flexor withdraw reflex.

		Baseline		Follow-up		Difference within groups (Follow up – Baseline)		Difference between groups; adjusted mean[a]	
		AT+EX (N = 15)	ST+EX (N = 15)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX minus ST+EX	P value between groups
HPT (°C)	**Medial knee**	44.8 (45.8, 43.8)	44.9 (46.2, 43.5)	45.3 (46.0, 44.6)	45.1 (46.1, 44.1)	0.3 (0.9, -0.3)	0.9 (2.1, -0.3)	-0.2 (-1.4, 1.0)	.58
	Anterior knee	44.2 (45.5, 42.8)	44.8 (45.9, 43.7)	44.6 (45.8, 43.4)	44.7 (46.4, 43.0)	-0.6 (1, -2.2)	0.2 (1.8, -1.3)	-0.2 (-2.5, 2.0	.82
	Lateral knee	45.5 (46.5, 44.5)	46.2 (47.0, 45.4)	45.7 (46.5, 44.9)	46.5 (47.5, 45.5)	-0.1 (0.4, -0.6)	0.6 (1.6, -0.5)	-0.8 (-2.1, 0.6)	.24
	Ipsilateral forearm	42.6 (44.2, 41.0)	43.7 (44.9, 42.5)	44.4 (45.5, 44.4)	44.5 (45.3, 43.8)	1.7 (2.7, 0.7)	1.2 (2.3, 0.1)	-0.8 (-2.2, 0.6)	.67
	Contralateral forearm	43.4 (44.8, 42.0)	43.1 (44.4, 41.8)	44.6 (45.9, 43.2)	44.7 (45.5, 43.9)	1.4 (2.3, 0.4)	2.0 (3.5, 0.4)	-0.5 (-2.2, 1.1)	.79

CPM (kPa)	**Knee/ Arm**	44.2	(72.6, 15.7)	73.8	(115.1, 32.34)	88.1 *	(110.6, 65.6)	51.7	(75.4, 28.0)	25.7	(47.2, 4.1)	-27.1	(24.6, -78.8)	39.0	(-0.7, 78.6)	.054			
	Arm/Arm	18.3	(43.1, -6.3)	26.5	(53.9, -0.8)	61.3	(94.2, 28.4)	46.9	(73.4, 20.5)	19.6	(31.9, 7.2)	21.1	(56.3, -14.1)	3.5	(-36.5, 43.4)	.85			
NFR	**Threshold (mA)**	135.4	(184.3, 86.6)	102.7	(144.6, 60.8)	167.0	(229.1, 104.9)	132.9	(180.6, 85.2)	13.0	(37.5, -11.5)	13.4	(50.4, -23.6)	8.4	(-46.3, 63.2)	.75			
	Latency (ms)	125.2	(135.4, 115.1)	122.5	(135.2, 109.8)	130.6	(143.1, 118.0)	116.5	(128.4, 104.5)	10.9	(24.2, -2.4)	-8.9	(2.4, -20.1)	14.6	(-3.9, 33.1)	.11			
	Amplitude (RMS)	0.12	(0.19, 0.05)	0.15	(0.24, 0.06)	0.08	(0.1, 0.07)	0.1	(0.15, 0.06)	-0.06	(0.02, -0.14)	-0.04	(0.03, -0.12)	-0.01	(-0.07, 0.04)	.56			

AT+EX = active tDCS + exercise, ST+EX = sham tDCS + exercise, HPT = heat pain threshold, CPM = conditioned pain modulation, NFR = nociception flexor withdraw reflex, RMS = root mean square. [a] Value adjusted for baseline scores using ANCOVA. * Indicates statistically significant (p<0.05) improvement from baseline within each treatment group.

Appendix C.2

Table S2. Group data (mean and 95% confidence interval) for pressure pain thresholds.

	Baseline		Follow-up		Difference within groups (Follow up – Baseline)		Difference between groups; adjusted mean[a]	
	AT+EX (N = 15)	ST+EX (N = 15)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX (N = 13)	ST+EX (N = 12)	AT+EX minus ST+EX	P value between groups
Ipsilateral forearm	345.7 (424.0, 267.4)	294.2 (347.4, 240.9)	445.8 (535.0, 356.7)	335.7 (386.1, 285.4)	78.2 (191.1, -34.6)	52.4 (116.1, -11.3)	85.2 (352.7, 515.2)	.15
Ipsilateral tibialis anterior	349.2 (427.6, 270.9)	369.1 (453.3, 285.0)	500.9 (557.4, 444.4) **	441.7 (496.5, 386.8)	116.5 (230, 2.9)	80.3 (148.4, 122.0)	60.2 (-27.4, 148.0)	.16
Knee 1	451.5 (568.0, 334.9)	473.5 (587.4, 359.6)	612.8 (723.4, 502.2)	560.6 (658.8, 462.4)	126.1 (183.5, 68.9)	751.2 (182.4, -32.1)	55.8 (-60.7, 172.3)	.33
Knee 2	409.1 (507.5, 310.7)	429.3 (517.5, 341.0)	611.5 (718.5, 504.5) **	578.4 (672.1, 484.8) **	196.1 (279.6, 112.7)	165.7 (283.5, 47.9)	25.6 (-117.2, 168.4)	.71
Knee 3	344.6 (420.4, 268.66)	338.0 (388.3, 287.7)	499.8 (573.2, 426.4) **	444.6 (524.3, 365.0) **	155.7 (222.8, 88.7)	96.5 (157.0, 36.1)	49.3 (-45.7, 144.4)	.29

Knee 4	375.9 (449.1, 302.7)	340.9 (414.3, 267.5)	536.8 (618.4, 455.2) **	409.3 (481.8, 336.9)	192.9 (244.1, 141.7)	82.1 (139.0, 25.3)	110.2 (4.8, 215.7)	.041*
Knee 5	421.8 (513.8, 329.8)	409.6 (490.0, 329.2)	608.3 (693.9, 522.7) **	457.7 (525.0, 390.4)	194.4 (258.7, 130.2)	52.6 (106.0, -0.7)	164.8 (56.5, 273.1)	.005*
Knee 6	353.9 (428.0, 279.8)	355.7 (436.5, 275.0)	520.5 (601.0, 439.9) **	428.2 (492.5, 363.8)	178.1 (232.8, 123.4)	59.9 (108.7, 11.3)	123. 5 (34.1, 212.9)	.009*
Knee 7	311.1 (370.1, 252.0)	326.9 (385.4, 268.4)	466.3 (535.4, 397.2) **	448.1 (489.9, 406.3) **	159.1 (198.9, 119.3)	110.8 (146.0, 75.7)	58.1 (-19.0, 135.1)	.13
Knee 8	384.2 (455.0, 313.2)	388.3 (463.0, 313.5)	538.5 (620.0, 457.0) **	488.0 (583.8, 392.1)	160.9 (216.1, 105.7)	102.5 (199.1, 59.1)	40.4 (-84.4, 165.1)	.50

AT+EX = active tDCS + exercise, ST+EX = sham tDCS + exercise; Knee 1 = 2 cm distal to the inferior medial edge of patella, Knee 2 = 2 cm distal to the interior lateral edge of patella, Knee 3 = 3 cm lateral the mid point of the lateral patellar border, Knee 4 = 2 cm proximal to the superior lateral edge of patella, Knee 5 = 2 cm proximal to the mid point of the superior patellar border, Knee 6 = 2 cm medial to the superior medial edge of patellar, Knee 7 = medial to the mid point of the medial patellar border, Knee 8 = centre of the patella. * Between group P < 0.05. [a] Value adjusted for baseline scores using ANCOVA. ** Indicates statistically significant (p<0.05) improvement from baseline within each treatment group.

Appendix C.3

***Table S3. Effect size (Cohen's d) of difference within groups for pain, function and pain mechanisms*.**

		Active tDCS + Eexercise	Sham tDCS + Exercise
Pain (Visual analogue scale)		-1.95	-0.77
WOMAC	**Total score**	-0.79	-0.61
	Pain subscale	-0.70	-0.66
	Physical function subscale	-0.73	-0.49
Heat pain threshold	**Medial knee**	0.28	0.39
	Anterior knee	-0.18	0.08
	Lateral knee	-0.10	0.27
	Ipsilateral forearm	0.88	0.56
	Contralateral forearm	0.70	0.65
Pressure pain threshold	**Knee 1**	1.36	0.32
	Knee 2	1.32	0.61
	Knee 3	1.30	0.68

	Knee 4	1.44	0.73
	Knee 5	1.30	0.50
	Knee 6	1.61	0.62
	Knee 7	2.06	1.60
	Knee 8	1.18	0.54
	Ipsilateral tibialis anterior	0.49	0.37
	Ipsilateral forearm	0.75	0.52
Nociception flexor withdraw reflex	**Threshold**	0.27	0.18
	Latency	0.42	-0.40
	RMS	-0.38	-0.28
Conditioned pain modulation	**Knee/Arm**	0.77	-0.27
	Arm/Arm	0.86	0.30

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; Knee 1 = 2 cm distal to the inferior medial edge of patella, Knee 2 = 2 cm distal to the interior lateral edge of patella, Knee 3 = 3 cm lateral the mid point of the lateral patellar border, Knee 4 = 2 cm proximal to the superior lateral edge of patella, Knee 5 = 2 cm proximal to the mid point of the superior patellar border, Knee 6 = 2 cm medial to the superior medial edge of patellar, Knee 7 = medial to the mid point of the medial patellar border, Knee 8 = centre of the patella; RMS = root mean square.

Appendix C.4

CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable

Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	5
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken	5
concealment mechanism		to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5-6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9-10
recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10-11

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13-16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-19
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable

Appendix D

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Open Access Protocol

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Combined exercise and transcranial direct current stimulation intervention for knee osteoarthritis: protocol for a pilot randomised controlled trial

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To cite: Chang W-J, Bennell KL, Hodges PW, *et al*. Combined exercise and transcranial direct current stimulation intervention for knee osteoarthritis: protocol for a pilot randomised controlled trial. *BMJ Open* 2015;**5**:e008482. doi:10.1136/bmjopen-2015-008482

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-008482).

Received 15 April 2015
Revised 18 June 2015
Accepted 17 July 2015

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ABSTRACT

Introduction: Osteoarthritis (OA) is a major health problem and a leading cause of disability. The knee joint is commonly affected, resulting in pain and physical dysfunction. Exercise is considered the cornerstone of conservative management, yet meta-analyses indicate, at best, moderate effect sizes. Treatments that bolster the effects of exercise, such as transcranial direct current stimulation (tDCS), may improve outcomes in knee OA. The aims of this pilot study are to (1) determine the feasibility, safety and perceived patient response to a combined tDCS and exercise intervention in knee OA, and (2) provide data to support a sample size calculation for a fully-powered trial should trends of effectiveness be present.

Methods and analysis: A pilot randomised, assessor-blind and participant-blind, sham-controlled trial. 20 individuals with knee OA who report a pain score of 40 or more on a 100 mm visual analogue scale on walking, and meet a priori selection criteria will be randomly allocated to receive either: (1) active tDCS plus exercise, or (2) sham tDCS plus exercise. All participants will receive 20 min of either active or sham tDCS immediately prior to 30 min of supervised muscle strengthening exercise twice a week for 8 weeks. Participants in both groups will also complete unsupervised home exercises twice per week. Outcome measures of feasibility, safety, pain, disability and pain system function will be assessed immediately before and after the 8-week intervention. Analyses of feasibility and safety will be performed using descriptive statistics. Statistical analyses will be used to determine trends of effectiveness and will be based on intention-to-treat as well as per protocol.

Ethics and dissemination: This study was approved by the institutional ethics committee (H10184). Written informed consent will be obtained from all participants. The results of this study will be submitted for peer-reviewed publication.

Trial registration number: ANZCTR365331.

Strengths and limitations of this study

- A randomised, assessor-blind and participant-blind, sham-controlled trial.
- Our study is the first to provide information on the feasibility and safety of a combined brain stimulation and exercise intervention in knee osteoarthritis.
- If trends of effectiveness are present, may provide data for a fully powered trial.
- This is a feasibility study and as such, is not powered to determine treatment effectiveness.
- The treating physiotherapist is not blinded to group allocation.

INTRODUCTION

Osteoarthritis (OA) is a major public health problem and a leading cause of disability. The knee joint is commonly affected and it is estimated that 10% of people aged over 60 years experience knee OA symptoms,[1] resulting in substantial pain and physical dysfunction.[2 3] Current evidence demonstrates beneficial effects of exercise therapy on pain and physical function in knee OA, without the common and sometimes serious side effects associated with pharmacological and surgical interventions.[4] Consequentially, exercise is considered the cornerstone of conservative management and is recommended in all clinical guidelines internationally.[5 6] Although exercise is effective in knee OA, meta-analyses indicate its treatment benefits are moderate for pain (standardised mean difference (SMD) −0.49, 95% CI −0.39 to −0.59) and physical function (SMD −0.52, 95% CI −0.39 to −0.64),[7] and are similar to those achieved with pharmacological treatments.[8] Novel treatments that bolster the effect of exercise therapy have the potential to further improve outcomes in knee OA.

OA is a joint disorder that affects the cartilage and bone. Although pain is often attributed to localised joint pathology, research has shown that pain intensity does not always

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correlate with the severity of joint structural damage or the presence of inflammation.[9 10] This discrepancy may be explained by the presence of a central component to persistent pain in knee OA. For example, nociceptive input from structural joint changes in OA may enhance the excitability and efficiency of synapses in the central pain pathway, a phenomenon termed central sensitisation.[11] In support of this hypothesis, a recent systematic review demonstrated that central sensitisation contributes to persistent OA pain, characterised by local and widespread hyperalgesia (such as reduced pressure and thermal pain thresholds), increased spinal excitability (increased nociceptive flexion withdraw reflex), and deficits in descending pain processing (altered conditioned pain modulation).[12] Treatments that target central sensitisation and pain processing may, therefore, be effective in knee OA.

The safe and painless application of weak direct electrical currents over the scalp (transcranial direct current stimulation, tDCS) is a novel intervention that has the potential to reduce central sensitisation and improve pain processing in knee OA. Using surface electrodes, direct current applied to the brain can increase (anodal stimulation) or decrease (cathodal stimulation) excitability of the region below the electrode as well as distant interconnected areas.[13–15] Studies of healthy individuals and patients with persistent pain suggest anodal tDCS applied to the primary motor cortex can reduce pain, a finding thought to be explained by direct effects of stimulation on the cortex and thalamus,[16–21] as well as 'downstream' effects on the anterior cingulate cortex and upper brain stem.[22 23] However, there has been no research investigating the effect of tDCS, whether applied alone or in combination with other interventions, in people with osteoarthritic pain. Exercise, moreover, can exert central as well as peripheral effects. Exercise treatments can alter sensory input from the periphery by modification of muscle control (ie, muscle coordination and strength) and through improved proprioception to enhance control of the affected joint, thus reducing nociceptor discharge and enhancing normal sensory input. Centrally, exercise is known to have an analgesic effect that reduces pain sensitivity in healthy individuals.[24 25] This is thought to be due to activation of opioidergic mechanisms and enhanced descending pain control systems.[26 27] Treatments that modify peripheral inputs (exercise), and treatments that modify processing of these inputs at the supraspinal level (tDCS and exercise) may summate to produce greater effects on pain and function. In addition, tDCS has the potential to increase the brain's receptiveness to other interventions by increasing cortical excitability, a phenomenon known as priming.[28] Thus, tDCS may optimise the responsiveness of the brain to exercise and improve outcomes beyond that which can be achieved with tDCS or exercise alone. Despite this, no study has examined the effect of a combined tDCS and exercise intervention in any persistent pain condition.

Therefore, the aims of this pilot randomised controlled trial are to (1) determine the feasibility, safety and perceived patient response to a combined tDCS and exercise intervention in knee OA and (2) provide data to support a sample size calculation for a fully-powered trial should trends of effectiveness be present.

METHODS AND ANALYSIS

Trial design

We will conduct a pilot randomised, assessor-blind and participant-blind, controlled trial. The trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacological treatment,[29] and the template for intervention description and replication (TIDieR) checklist and guide.[30] It has been prospectively registered with the Australian and New Zealand Clinical Trials Registry (365331).

Participants

Participants with knee OA that meet the American College of Rheumatology clinical classification for idiopathic knee OA criteria[31] will be recruited from the community. The criteria include the presence of knee pain plus at least three of the following six items: age over 50 years, morning stiffness lasting less than 30 min, crepitus, bony tenderness, bony enlargement and no palpable warmth. A minimum pain score of 40 on a 100 mm visual analogue scale (VAS) on walking in the last week will be required. The main exclusion criteria are: (1) knee surgery in the past 6 months; (2) knee joint replacement or high tibial osteotomy on the affected side; (3) other muscular, joint or neurological conditions affecting lower limb function; (4) unable to walk unaided; (5) currently undertaking a structured exercise programme for knee OA or (6) contraindications to tDCS (eg, epilepsy) or conditioned pain modulation techniques (eg, loss of sensation). Participants can continue to use their normal medication for the duration of the trial. The type of medication and dosage used will be recorded at the baseline assessment.

Recruitment

Participants will be recruited from local arthritis support groups, social media and healthcare providers (medical practitioners, rheumatologists and physiotherapists). Potential participants will first complete an online screening questionnaire to determine their eligibility. Those who meet the inclusion criteria will be contacted by one of the investigators to confirm their willingness to participate in the trial and to arrange the baseline assessment of outcomes. Participants will provide written informed consent on arrival for baseline assessment.

Randomisation

Participants will be individually randomised on a 1:1 basis to the active or control groups in equal numbers. The randomisation schedule will be concealed in

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consecutively numbered, sealed opaque envelopes. An investigator not involved in recruitment or assessment will provide the envelope to the treating clinician who will reveal group allocation.

Blinding

Participants and the outcome assessor will be blinded to group allocation. The treating physiotherapist will deliver the tDCS intervention and the exercise therapy and will, therefore, not be blinded to group allocation. The success of participant blinding will be assessed at the follow-up assessment using a 'yes/no' response to the question "Do you feel you received the real brain stimulation?" and a 10 cm VAS of the individual's confidence in that judgement. Participants will also be asked "Why do you believe you received the real/sham brain stimulation?" and "Was it divulged to you whether you were receiving real brain stimulation or not?". The success of assessor blinding will be determined at the completion of the follow-up assessment for each participant using a 'yes/no' response to the question "Did you know which intervention group the participant was assigned to before completion of the follow-up assessment?" and "If you answer 'yes', how was it divulged to you?".

Intervention

Participants will be randomly allocated to one of two treatment groups: (1) active tDCS plus exercise or (2) sham tDCS plus exercise. All participants will receive 20 min of either active or sham tDCS immediately prior to 30 min of supervised muscle strengthening exercise, two times per week for 8 weeks. A qualified physiotherapist who is trained in the use of tDCS will deliver the tDCS interventions and the exercise therapy in a consulting room of the UniClinic at the University of Western Sydney. The physiotherapist has a Bachelor of Science in Physiotherapy and 6 years of clinical experience. Participants in both groups will also be instructed to complete home exercises twice per week to mimic typical clinical practice. Outcome measures will be assessed immediately before and immediately after the 8-week intervention.

Transcranial direct current stimulation

Participants will be comfortably seated in an armchair while receiving tDCS and will be asked to remain quiet for the duration of the intervention. tDCS will be delivered for 20 min using a direct current stimulator (DC-STIMULATOR, neuroConn, Ilmenau, Germany) via two 35 cm^2 surface sponge electrodes. The active electrode (anode) will be placed over the primary motor cortex contralateral to the side of worst pain and the reference electrode (cathode) over the contralateral supraorbital region.[21] Current intensity will be ramped up (0–1 mA) and down (1–0 mA) over 10 s at the beginning and end of the stimulation period. For sham stimulation, electrodes will be placed in an identical position. Stimulation will be turned on for 15 s and then off, to provide the initial itching sensation. Participants will be informed that they may or may not perceive any sensation during the treatment. This procedure has been shown to effectively blind participants to the stimulation condition.[32]

Exercise

Immediately following the tDCS intervention, participants will start one-to-one exercise therapy supervised by the physiotherapist. A standardised set of quadriceps strengthening exercises that are known to be effective in knee OA (table 1) will be performed with ankle cuff weights or resistance bands where necessary.[7 33]

Exercise intensity will be progressed by the physiotherapist as appropriate for each participant. Each exercise session will last 30 min. A home exercise plan will be developed, monitored and progressed by the physiotherapist for each participant. An exercise diary with written and visual instructions for each exercise (including dosage) will be provided to each participant. The exercise diary will include space for participants to outline which exercises were completed, how many repetitions were performed and any comments regarding the home exercise programme (eg, whether pain was present, whether any exercises were difficult and if applicable, the reason why exercises were unable to be completed). The exercise diary will be returned to the investigator at the follow-up assessment session.

As the aim of this trial is to use tDCS to boost the effect of exercise, the intervention duration has been selected based on the number of sessions required to achieve efficacious outcomes using exercise alone in knee OA. An 8-week exercise duration period has been chosen based on evidence that at least 12 sessions of supervised exercise are required for exercise to be effective in knee OA,[7] with a number of studies demonstrating symptom improvement in knee OA after 8–12 weeks of exercise.[34] Thus, 8 weeks (16 sessions) should be sufficient to show improvement in this population.

Outcome measurements

Baseline and follow-up assessments will be performed within 1 week of the participant starting or completing the intervention, respectively. All outcome measures will be performed in the research laboratories of the University of Western Sydney.

Measures of pain and function

Knee pain and function will be measured using (1) a 100 mm VAS with pain on walking over the last week self-assessed with terminal descriptors of 'no pain' (score 0 mm) and 'extreme pain' (score 100 mm). (2) The Western Ontario and McMaster Universities (WOMAC) OA index (24 items, total score=96) (Likert V.3.1) and its pain subscale (7 items, total score=28) and physical function subscale (17 items, total score=68). This is a disease-specific self-report instrument that has been

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Table 1 Description of the strengthening exercise programme with images, progression and repetitions

Exercise Description	Progression	Repetitions
1. *Knee extensor strengthening* ▸ Seated knee extensions with ankle weights ▸ In a seated position, slowly straighten symptomatic knee until it is fully straight ▸ Hold for 5 s and then lower slowly	Ankle weights	3 sets of 10 30 s break period in between sets
2. *Hip abductor strengthening* Level 1: ▸ Side lying hip abduction with ankle weights ▸ Keep body still and knee straight, and lift affected leg up ▸ Do not swing affected leg forward ▸ Keep heel of foot higher than toes and behind hips while lifting leg straight upwards towards the ceiling ▸ Hold for 5 s and then lower slowly	Increase ankle weights or progress to level 2	3 sets of 10 30 s break period in between sets
Level 2: ▸ Standing hip abduction with thera-band elastic resistance band ▸ Place looped thera-band elastic resistance band around both legs just above the ankle ▸ Adequate tension on the elastic band and correct upright posture, with shoulders and hips both facing forward, is required prior to starting the exercise ▸ The back of a chair or a wall can be used to provide support ▸ Hold for 5 s and then lower slowly	Increase thera-band elastic band resistance	3 sets of 10 30 s break period in between sets
3. *Weight-bearing knee/hip extensor strengthening* Level 1: ▸ Partial wall squats (option shown is to add thera-band elastic band around knees to incorporate the hip abductor muscles) ▸ Stand with one foot 30 cm away from the wall with feet apart and turned inwards ▸ With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times ▸ Knees must go past the toes during the squat exercise ▸ Hold position for 5 s	Increase resistance by adding thera-band elastic resistance band or if already in use increase elastic band resistance strength Progress further to level 2	3 sets of 10 30 s break period in between sets
Level 2: ▸ Sit-to-stand (option to add thera-band elastic band around knees to incorporate hip abductor muscles) ▸ Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support ▸ Lean forward over toes so that the buttocks are lifted and hips go under the trunk ▸ Hold for 3 s with buttocks slightly off the chair before sitting back down slowly	Increase resistance by adding thera-band resistance elastic band or If already in use increase elastic band resistance strength Progress further to level 3	3 sets of 10 30 s break period in between sets
Level 3: ▸ Alternate split sit-to-stand ▸ Place the foot of the unaffected leg 10 cm in front of the other foot	Increase depth of squat	3 sets of 10 30 s break period in between sets

Continued

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Table 1 Continued

Exercise Description	Progression	Repetitions
▸ Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee ▸ Hold for 3 s with buttocks slightly off the chair before sitting back down, slowly		
Level 3+: ▸ Split partial wall squats ▸ Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee ▸ Stop when symptomatic knee is bent to approximately 60° (less if painful) ▸ Hold for 5 s and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times	Increase depth of squat	3 sets of 10 30 s break period in between sets
4. *Hamstring strengthening seated knee extensions* ▸ Place a looped thera-band elastic resistance band around the leg of a heavy table or chair ▸ Seated in a chair, place the symptomatic leg in the looped thera-band elastic band with the knee slightly bent ▸ Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt ▸ Hold for 5 s	Increase elastic band resistance	3 sets of 1030 s break period in between sets
5. *Steps* (A). Step ups: ▸ Place symptomatic leg onto the step ▸ Slowly step up onto the step ▸ Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground	First increase the height of the step and second, add weight Weight can be held across the chest with both hands or use two hand weights	3 sets of 10 30–60 s break period in between sets
(B). Step downs: ▸ Start with both legs standing on top of the step ▸ Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground ▸ Then straighten the affected knee slowly to return to the starting position ▸ The knee of the affected leg must point forward during the movement	First increase the height of the step and second, add weight Weight can be held across the chest with both hands or use two hand weights	3 sets of 10 30–60 s break period in between sets

Progression through the levels is an important component of the programme.

shown to be valid, reliable and responsive in an extensive range of studies of people with OA. (3) Global perceived effect of treatment, where each participant's perceived response to therapy is assessed using a seven-point Likert scale ranging from 'completely recovered' to 'vastly worsened'. This outcome will only be used in the follow-up assessment.

Measures of pain mechanisms

Measures of pain mechanisms will be performed in the same order for all participants.

I. Pressure pain thresholds (PPT): PPT will be measured using a hand-held pressure algometer (FORCE TEN FDX compact digital force gauge, Wagner Instruments, USA). The probe (size 1 cm^2) will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports that the sensation of pressure has changed to pain. PPTs will be measured three times at each of the following sites: (1) ipsilateral tibialis anterior (10 cm distal to the tibial tuberosity) and (2) ipsilateral extensor carpi radialis longus (10 cm distal to the lateral epicondyle of the humerus) and eight sites in the peripatellar region:

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(1) 2 cm distal to the inferior medial edge of patella; (2) 2 cm distal to the interior lateral edge of patella; (3) 3 cm lateral to the midpoint of the lateral patellar border; (4) 2 cm proximal to the superior lateral edge of patella; (5) 2 cm proximal to the midpoint of the superior patellar border; (6) 2 cm proximal to the superior medial edge of patellar; (7) 3 cm medial to the midpoint of the medial patellar border and (8) centre of the patella.[35] The average of the three measurements at each site will be used in the analysis. PPT measures have been shown to be reliable in knee OA (intraclass correlation coefficient (ICC) =0.83 (0.72–0.90)).[36]

II. Heat pain thresholds (HPT): HPT will be measured using the conditioned pain modulation system (Thermal Sensory Analyser, TSA-2001, Q-Sense-CPM, Medoc Ltd, Ramat Yishai, Israel). A 30×30 mm Peltier-based thermode will be placed on the skin. The temperature will start at 32°C and increase at a rate of 0.5°C/s. Participants will push a button when the sensation of heat first turns to a sensation of pain. HPTs will be measured around the peripatellar region (3 sites: medial, patella and lateral knee joint lines) and at the bilateral ventral aspect of the forearm (10 cm distal from the elbow crest). Three measurements will be recorded at each site and the average at each side will be analysed. HPT measure have been shown to have moderate reliability in knee OA (ICC=0.77 (0.62–0.87)).[36]

III. Conditioned pain modulation (CPM): CPM is a well-established, reliable and safe measure of pain processing that is thought to indicate the function of descending pain control systems. This is examined as a change in the pain perceived in one body region (test stimulation) as a result of pain induced in another body region (conditioned stimulation). We will use PPT measurement as the test stimulation and heat pain (1°C above HPT) as the conditioned stimulation using the CPM System (Thermal Sensory Analyser, TSA-2001, Q-Sense-CPM, Medoc Ltd). Three PPTs (test stimulation) will be measured before the application of heat pain (conditioned stimulation). The heat pain will then be applied via a 30×30 mm thermode. Three PPT measurements will be repeated 30 s after applying the conditioned stimulation. Participants will be asked to rate their pain during conditioned stimulation on a numeric rating scale (0–100) at 0 s, 30 s and at the end of the trial. Pain scores will be maintained between 50/100 and 80/100 during testing. Participants will complete two trials in random order: (1) test stimulation at knee and conditioned stimulation at the contralateral forearm and (2) test stimulation at the contralateral forearm and conditioned stimulation at the ipsilateral forearm. The CPM paradigm has shown good intrasession reliability (ICC>0.75).[37]

IV. Nociceptive flexor withdrawal reflex (NFR): NFR is a measure of central sensitisation and descending pain control systems, and was used in previous studies investigating central sensitisation in knee OA.[38] Surface stimulating electrodes will be positioned at a retromalleolar location along the sural nerve on the side of the painful knee. Recording electrodes will be positioned over the belly of the biceps femoris muscle. Stimulation will consist of five rectangular pulses of 1 ms duration with a 3 ms interval, and will proceed using an up and down staircase method. The intensity needed to evoke a response from the biceps femoris (indicating activation of the NFR), the area of the NFR response and the subjective pain threshold will be recorded. The NFR is a reliable experimental test (intersession coefficient of variation (CV_{SEM})=16.9%, ICC=0.82).[39]

Sample size and analysis

This is a pilot study designed to generate data that can be used to inform a future large randomised controlled trial should the intervention appear feasible, safe and show trends of effectiveness. Thus, we have selected a sample size of 10 individuals per group, or a total of 20 participants. A sample size of 20 participants was selected as this is considered achievable within the time frame allocated for completion of the pilot study according to study recruitment rates within the laboratory. We aim to evaluate key trial parameters, such as recruitment and retention of participants, randomisation, levels of missing data and preliminary indications of effectiveness, to inform calculation of a sample size for powering a full trial. As this was a pilot study, a prospective sample size calculation was not conducted.

Data for feasibility and safety will be analysed using descriptive statistics. The percentage of participants who (1) meet the inclusion criteria, (2) agree to be randomised, (3) complete the intervention and (4) attend the follow-up assessment will be calculated. Feasibility will be measured as (1) the number of sessions attended by each participant, (2) number of drop-outs in each group, (3) proportion of participants recruited from the total number screened, (4) willingness of each participant to undergo therapy on an 11-point numerical rating scale with 'not at all willing' at 0 and 'very willing' at 10 (measured at baseline) and (5) the number of home exercise sessions completed. Safety will be presented as any adverse reaction reported on verbal questioning by the treating physiotherapist at each session. An adverse reaction is defined by WHO as "a response to a drug [intervention] which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" and that likely has a causal relationship with the intervention.[40] A mild tingling or itching sensation under the electrodes, fatigue, headache, nausea and insomnia have been reported as potential adverse reactions following tDCS.[41] Potential adverse reactions as a result of the physical component of the intervention

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(muscle strengthening exercise) may include increased pain or muscle soreness around the knee joint and thigh. As potential adverse reactions are distinct for each component of the intervention, and as this trial includes a control group receiving sham tDCS, while both groups receive exercise, it should be possible to attribute any reported adverse reactions to either tDCS or exercise. The treating physiotherapist will record a description of any adverse reactions along with the severity, duration and how the adverse reaction was managed. The number of participants reporting adverse reactions, and the duration and severity of the adverse reactions will be reported.

To determine trends of effectiveness, analyses of pain, disability and pain system function will be performed according to intention-to-treat and per protocol using analysis of variance (ANOVA) to assess the changes within groups and the differences between groups over time (pre/post). Repeated measures of ANOVA will be used with factors of intervention (active tDCS/sham tDCS) and time (pre-intervention/post-intervention) as separate two-level factors. Effect size will be determined using partial η^2 from planned contrasts. The size of the treatment effects will be used to determine whether it is worthwhile to conduct a full randomised controlled trial in the future.[42 43] Given the pilot nature of this trial, missing data will not be replaced. Bonferroni post hoc tests will be applied if appropriate. The α will be set at 0.05.

Means and standard deviations (SDs) for measures of pain, function and pain mechanisms will be used to perform a sample size estimate. Power will be set at 80% to detect between-group differences, with an α of 0.05 and a drop-out rate based on that of the pilot trial. SigmaPlot will be used to analyse the data in this trial.

DISSEMINATION

All participants will provide written informed consent following verbal and written explanation of the study protocol and the opportunity to ask questions. Participants are free to withdraw from the trial at any time without prejudice to future treatment. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators.

TRIAL STATUS

This trial is currently recruiting and is expected to be completed (including follow-up testing) by August 2015.

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Funding This work was supported by Arthritis Australia (The Zimmer Australia Grant). W-JC, PWH, KLB, MBL and SMS received salary support from the National Health and Medical Research Council of Australia, and RSH from the Australian Research Council.

Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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