School of Population Health

The Impact of Non-Invasive Brain Stimulation on Motor Cortex Excitability and Cognition in Chronic Lower Back Pain

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DECLARATION

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

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

Human Ethics (For projects involving human participants/tissue, etc) The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee, Approval Number HR17/2015.

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GENERAL ABSTRACT

Low back pain is a major health and economic concern worldwide, with up to 80% of the general population experiencing low back pain during their lifetime. Research estimates that 20 – 40% of individuals with acute low back pain will develop to chronic lower back pain (CLBP). Despite the significant prevalence and high economic burden, the mechanisms underlying CLBP are not fully understood. The Neuromatrix Theory of pain has proposed that chronic pain results from multiple factors and cannot solely be attributed to injury. This theory suggests that the longer pain is experienced, the less likely it is to reflect actual tissue damage. As such, this has led researchers to propose that cortical changes in areas associated with pain processing may contribute to pain chronicity. Two cortical areas that form part of the salience matrix are the motor cortex and the prefrontal cortex. Research has shown that chronic pain is associated with altered motor cortex excitability and has suggested that intracortical facilitation (ICF) and short interval intracortical inhibition (SICI) may be the key mechanisms associated with the maintenance of pain. Additionally, the processing and cognitive evaluation of pain have also been reported to contribute to pain chronicity. The Dorsolateral Prefrontal Cortex (DLPFC) is a key area associated with the processing of pain. However, this processing engages significant neural resources in the DLPFC, and as a result, leaves little neural resources available for other cognitive functions of the DLPFC. While research has suggested that chronic pain is associated with altered motor cortex excitability and impaired cognitive function, it is unclear if the pattern of altered motor cortex excitability and impaired cognitive function varies across different forms of chronic pain. Understanding the neural mechanisms underlying altered motor cortex excitability is important to determine the key factors that contribute to pain chronicity in CLBP. In a similar vein, it is important to profile the specific nature of cognition in CLBP, as deficits in cognitive function contribute to pain chronicity and poor treatment outcomes.

In this thesis, I examine motor cortex excitability in people with CLBP so that the mechanisms underlying altered motor cortex excitability in CLBP can be further understood. I also examine cognitive function in people with CLBP to establish whether cognitive deficits present in a similar pattern in people with CLBP,

and whether deficits meet the criteria for mild cognitive impairment. Finally, I examine the impact of anodal-transcranial direct current stimulation (tDCS) on motor cortex excitability and cognitive function in people with CLBP to explore the potential for tDCS as a therapeutic tool in the management of CLBP.

Chapter two examined motor cortex excitability in people with CLBP and age- and gender-matched controls. Motor cortex excitability was examined using single-pulse and paired-pulse Transcranial Magnetic Stimulation. Individuals with CLBP had significantly higher resting motor threshold (indicative of decreased corticospinal excitability) and lower ICF compared to the control group. However, ICF was not associated with pain-related outcomes (pain intensity, disability, and pain catastrophising). Given ICF and SICI are interrelated, we conducted an exploratory analysis that explored the relationship between the balance of excitation and inhibition and pain intensity. Our analysis revealed a significant relationship between the balance of excitation/inhibition and pain intensity, such that increased inhibition was associated with greater pain intensity. These findings suggest CLBP is associated with altered motor cortex excitability involving glutamatergic mechanisms. It also provides evidence that pain may be a by-product of neural dysfunction when excitation and inhibition mechanisms are not balanced.

Chapter three compared cognitive functioning in people with CLBP and age- and gender-matched controls. Our analysis revealed a significant difference in four of the five cognitive domains (memory, attention and working memory, visuospatial, and language) between the two groups. Furthermore, the pattern of cognitive performance was able to correctly identify 84% of the CLBP sample, suggesting that deficits in cognition present similarly in people with CLBP. Finally, 16% of the people with CLBP met the criteria for mild cognitive impairment. We suggest that this provides support for the involvement of the prefrontal cortex in the processing and evaluation of CLBP. These findings provide evidence that attention to pain is cognitively demanding, and as such cognitive resources are diverted away from normal cognitive functioning.

Current treatment options for CLBP have been shown to provide modest short-lived improvements in pain. However, these treatments are often ineffective for long-term pain management. This may be due to treatments targeting pain relief as opposed to targeting underlying cortical mechanisms that may contribute to pain

chronicity. In light of this, chapter four examines the impact of anodal-tDCS over left DLPFC on motor cortex excitability in people with CLBP. We determined that twice weekly, 1.5mA anodal-tDCS over left-DLPFC may modulate motor cortex excitability, such that ICF and SICI were increased in the anodal group, compared to the sham group. Additionally, pain intensity and self-reported disability was reduced in the anodal group, compared to the sham group. These findings add to our understanding of the use of neuromodulation techniques to alleviate chronic pain and support the theoretical framework that restoration of abnormal motor cortex excitability may improve pain-related outcomes in people with CLBP.

Previous research has suggested that CLBP is a multidimensional condition characterised by alterations in cognition, psychological health, and quality of life. However, treatments for CLBP often fail to address these aspects of the pain experience. As such, chapter five examined the impact of anodal-tDCS over left-DLPFC on cognitive function in people with CLBP. Specifically, we examined the impact of twice weekly, 1.5mA anodal-tDCS over DLPFC on five cognitive domains (memory, attention and working memory, executive function, visuospatial, and language), compared to sham-tDCS. In addition, we also examined the impact of a-tDCS on pain-related outcomes (pain intensity, disability, and pain catastrophising), psychological health (depression, anxiety, and stress), and quality of life. We predicted that, compared to the sham-tDCS group, the anodal-tDCS group would show improvement in cognitive performance and improvement in pain-related outcomes and psychological health. However, we found that both the anodal-tDCS group and the sham-tDCS group showed significant improvement in cognitive performance at post-intervention. Additionally, both groups showed significant reduction in pain-related outcomes, and significant improvement in psychological health and quality of life. In light of these unexpected findings, we suggest that the improvements across both groups are likely reflective of a placebo effect. While the findings did not support the use of anodal-tDCS over left-DLPFC to improve cognitive functioning in people with CLBP, we suggest that these findings raise an interesting question about the potential for tDCS-induced placebo effect to be clinically beneficial in the management of CLBP.

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LIST OF ABBREVIATIONS

a-tDCS	Anodal-Transcranial Direct Current Stimulation
BNT	Boston Naming Test
CBT	Cognitive Behavioural Therapy
CLBP	Chronic Lower Back Pain
COWAT	Controlled Oral Word Association Task
DASS	Depression, Anxiety, Stress Scale
DLPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnostic Statistical Manual-5
EMG	Electromyogram
FDI	First Dorsal Interosseous
GABA	Gamma-aminobutyric Acid
GABA	Gamma-aminobutyric Acid
HVLT	Hopkins Verbal Learning Test
HVOT	Hooper Visual Organisation Test
ICF	Intracortical Facilitation
JLO	Judgement Line Orientation
LBP	Lower Back Pain
LNS	Letter Number Sequencing
MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
MEP	Motor Evoked Potential
NMDA	N-methyl-d-aspartate
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAG	Periaqueductal Gray Area
PCS	Pain Catastrophising Scale
RMDQ	Roland Morris Disability Questionnaire
rMT	Resting Motor Threshold
RVM	Rostral Ventromedial Medulla
SICI	Short Interval Intracortical Inhibition
SOC	Stockings of Cambridge
s-tDCS	Sham-Transcranial Direct Current Stimulation

tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
TMS	Transcranial Magnetic Stimulation
VAS	Visual Analogue Scale

CHAPTER ONE: GENERAL INTRODUCTION

1.0 Introduction

1.1 Chronic Pain

Chronic pain is an extensive health care problem, with one in five Australians suffering from chronic pain (Toblin et al., 2011). Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (International Association for the Study of Pain, 2011, part III). Pain involves awareness of noxious stimuli (stimuli that threatens to, or damages normal tissue) and emotional responses that result in a pattern of reactive behaviours (International Association for the Study of Pain, 2011). Pain is a very subjective sensation and so varies between individuals, even when they have suffered the same injury (International Association for the Study of Pain, 2011; Nicholas et al., 2019). The perception of pain is the process by which painful or damaging stimuli are communicated from the site of the pain to the central nervous system. However, pain intensity may not be proportional to the type or extent of the tissue damage (Moseley, 2007). Many people report pain in the absence of any pathophysiological cause (i.e., without noxious stimuli). Subjectively this pain is indistinguishable from pain with a physical cause and is therefore still considered pain (International Association for the Study of Pain, 2011. Pain is considered to be chronic when it has persisted for at least three months (Nicholas et al., 2019). The aetiology and mechanisms underlying chronic pain are not fully understood (Woolf & Mannion, 1999). It is unknown why some people develop chronic pain, while others who have suffered similar damage do not.

1.2 Classifying Pain

Pain can be classified and defined in many different ways, depending on the extent of injury and the processing in the central nervous system. Nociceptive pain is defined as pain that is associated with actual or potential non-neural tissue damage and is due to the activation of sensory neurons (nociceptors) in response to noxious stimuli (International Association for the Study of Pain, 2011). Inflammatory pain is due to actual tissue injury and inflammation and is characterised by hypersensitivity at the site of injury and adjacent tissues. Inflammatory pain typically returns to normal if the injury is controlled (Woolf & Salter, 2000). Neuropathic pain is caused

by a lesion or disease affecting the somatosensory system. Neuropathic pain can be triggered by both noxious and innocuous stimuli (Woolf, 2010). Pain can only be considered neuropathic, if a lesion is radiographically identifiable (Treede et al., 2008). Functional pain is characterised by spontaneous pain caused by noxious or innocuous stimuli. There is typically minimal evidence of inflammation, and the maintenance of functional pain is often unclear, but may be caused by abnormal central nervous system processing (Costigan et al., 2009; Woolf, 2010). Central Sensitisation can be seen in inflammatory, neuropathic, and functional pain, and is caused by hypersensitivity within the central nervous system. Central sensitisation usually normalises as lesions are resolved, however, can persist and elicit pain beyond the initial noxious stimuli (Woolf, 2011; Woolf & Salter, 2000).

The classification system for identifying pain is focused mainly on pathoanatomy, despite pain being increasingly acknowledged as a multidimensional disorder (Allegri et al., 2016). Current diagnosis systems do not consider the multitude of dimensions that underlie pain disorders (such as pain characteristics, psychological, and lifestyle), and as such cannot provide a comprehensive classification and diagnosis for different pain disorders. The lack of a comprehensive classification for pain contributes to poor health-related outcomes, lack of effective treatment and as a result may be responsible for pain maintenance (Mills et al., 2019).

1.3 Chronic Lower Back Pain

One of the most common forms of chronic pain is CLBP (Hoy et al., 2014). The injury model of low back pain proposes that the cause of acute lower back pain is typically trauma to the lower back (Vlaeyen et al., 2018). Although the pain is generally short-lived, lower back pain can persist without adequate treatment. Persistent lower back pain leads to a diagnosis of CLBP (Chanda et al., 2011). A diagnosis of CLBP is supported by the Australian Clinical Guidelines for Diagnosis of low back pain, and the persistence of the pain for at least three months. The Australian Clinical Guidelines provide a diagnostic classification for acute low back pain, and can be classified as ‘non-specific’, ‘neurological’ or ‘specific’ (Koes et al., 2001). The diagnostic criterion is supported through physical examination and, in some cases, radiography (Koes et al., 2001). Approximately 70% of lower back pain

is diagnosed as ‘non-specific’ as a definitive diagnosis cannot be reached through radiographical methods (Last & Hulbert, 2009).

The focus on pathoanatomy and the injury model in the classification of CLBP means that many contributing factors to the chronicity of lower back pain (LBP) are often not considered for diagnosis (Laslett et al., 2005). Although CLBP is considered to be a multidimensional, biopsychosocial disorder, most classification systems do not consider neurophysiological, psychological, and individual pain experiences that may be underlying pain chronicity (Rabey et al., 2015). This has resulted in the attempt to determine a specific injury or damaged structure that contributes to nociception in CLBP. However, in many cases there is minimal evidence or no known source of noxious stimuli (Laslett et al., 2005). This has resulted in CLBP being classified and diagnosed based on movement and pain response (Delitto et al., 1995; Laslett et al., 2005), despite the acknowledgement of multidimensional contributions to pain chronicity (O’Sullivan, 2005). There are currently no singular standardised guidelines for the diagnosis of CLBP (Iswarari et al., 2011; Oliveira et al., 2018). The lack of a singular, comprehensive guideline for diagnosing CLBP means that CLBP is often poorly managed and has poor treatment outcomes, with individuals with CLBP experiencing moderate to severe pain for several years (Itz et al., 2013; Müller-Schwefe et al., 2017). This could possibly stem from clinicians' restricted understanding and proficiency in managing chronic pain, hence their lack of awareness regarding the various factors that contribute to chronic pain and the requirement for a multi-faceted treatment approach (Itz et al., 2013; Müller-Schwefe et al., 2017). As such, the need for a singular, comprehensive guideline for the diagnosis of CLBP is crucial for improving CLBP outcomes.

Despite the lack of standardised guidelines for diagnosis, CLBP is the second leading cause of disability worldwide (Allegri et al., 2016; Hoy et al., 2014). In Australia, CLBP is the most common job-related disability and cause of work absence, with an estimated cost of over $4 billion on the Australian economy (Arthritis and Osteoporosis Victoria, 2013; Schofield et al., 2012). As CLBP is progressive, it is often difficult to determine the exact cause of the pain. ‘Specific’ low back pain is typically attributed to recognisable pathology, such as fractures, infection, or arthritis. However, ‘non-specific’ and ‘neurological’ back pain are not typically attributed to any recognisable pathology (Koes et al., 2001). In some cases

of CLBP, the original injury or cause of pain can be completely healed, or may not have been detectable (Anderson, 1999). In 'non-specific' acute low back pain radiography is not recommended for at least 6 weeks following injury (Allegri et al., 2016), and may contribute to the lack of recognisable pathology when the pain has become chronic. Although the cause of the pain is often no longer detectable, the pain that is being experienced is real. Little is known about why this occurs (Anderson, 1999). Due to the difficulties in diagnosing CLBP based on the above classifications, the International Association for the Study of Pain (IASP), in conjuction with the World Health Organisation have proposed the term "chronic primary pain" as the diagnostic classification for CLBP (Nicholas et al., 2019). This classification focuses on pain mechanism categories, rather than the pathophysiology of pain (Nicholas et al., 2019; Perrot et al., 2019). Chronic primary pain retains the criteria that pain must persist or reoccur for at least 3 months, but also includes pain that is associated with significant emotional and/or functional distress, and that symptoms are not better explained by another condition (Nicholas et al., 2019). This classification aims to better account for biological, psychological, and social contributors to CLBP (Nicholas et al., 2019; Perrot et al., 2019).

1.4 Contributors to Non-Specific Back Pain

While non-specific LBP is, by definition, not attributed to recognisable, known pathology, a number of potential contributing factors have been identified. These factors, although not necessarily the cause of non-specific LBP, are considered to affect progression (Anderson, 1999; see the Lancet series on LBP for a comprehensive review, Foster et al 2018; Hartvigsen et al., 2018). Research suggests there is a significant association between non-specific LBP and disc degeneration (Cheung et al., 2009; de Schepper et al., 2010; Endean et al., 2011). This includes disc space narrowing, degeneration, and herniation. Although this pathology has been identified through clinical imaging, a meta-analysis by Endean et al. (2011) reported that none of these lesions could be attributed to the cause of non-specific LBP on an individual level. Endean et al. (2011) suggested that this is because abnormalities are common in people who are asymptomatic, and that these abnormalities typically do not coincide with pain development.

Research suggests that LBP may be a form of musculoskeletal pain, which is often caused by an injury to the muscles, ligaments, nerves, or related soft tissues that support the spine (Jackson & Simpson, 2006; Treede et al., 2015). Musculoskeletal pain can also be caused by general every day 'wear and tear', or overuse of the muscle tissues. This has led researchers to investigate if non-specific LBP may be associated with repetitive mechanical movements associated with certain occupations. However, multiple systematic reviews have found that it is unlikely that mechanical factors were independently causative of LBP. Mechanical factors included occupational sitting and posture (Roffey et al., 2010a), pulling or pushing (Roffey et al., 2010b), lifting or carrying (Wai et al., 2010a), and bending and twisting (Wai et al., 2010b). While pain has been shown to have a profound effect on motor function, including restricted movement, changes in muscle tension and impaired muscle coordination (Schabrun & Hodges, 2012), research suggests these changes in motor function are a result, rather than a cause of LBP. For example, a person with LBP may be afraid to bend down because they fear it might hurt or exacerbate the injury. This suggests mechanical factors are more likely associated with fear of movement or fear of re-injury rather than a direct cause of injury (Mercier & Léonard, 2011; Vlaeyen et al., 1995).

Age has also been considered a contributing factor to non-specific LBP. Until recently, it was believed young adults did not experience LBP unless caused by a chronic, life-threatening disease or injury. Jeffries et al. (2007) reported that adolescents and young adults were just as likely to report LBP as older adults. Although prevalence rates are similar, older adults are more likely to report poor health outcomes as a direct result of non-specific LBP. Older adults are more likely to report poor health-related quality of life and higher levels of functional disability than younger adults (Meyer et al., 2007). Despite this, older adults, particularly men, are less likely to seek treatment (Ferreira et al., 2010; Hicks et al., 2008). Balagué et al. (2012) suggest that people do not seek treatment for acute LBP, as it is unlikely to be associated with serious disease. Reoccurrence of LBP is a leading contributor to individuals seeking treatment, with approximately 10% of acute LBP progressing to persistent LBP (Costa et al., 2012; Costa et al., 2009; Ferreira et al., 2010). A systematic review (Costa et al., 2012) reported that while most participants with acute LBP recovered within 12 weeks, less than half of participants with persistent

LBP were recovered at 12 months, with reoccurence of LBP identified as a prognostic factor for persistent LBP (Costa et al., 2012; Coste et al., 2004; Pengel et al., 2003).

Psychosocial factors have also been identified as contributing to non-specific LBP. Research suggests that psychosocial factors are more predictive of pain and disability in LBP than anatomical factors (Corrêa et al., 2022; Stewart & Loftus et al., 2018). A systematic review reported that depression, anxiety, and pain catastrophising increase the risk of pain chronicity in LBP (Nieminen et al., 2021). Depression is a common comorbidity among individuals with acute and chronic LBP. A systematic review and meta-analysis reported that depression did not contribute to pain intensity but is associated with increased disability and poor recovery in acute LBP (Nieminen et al., 2021). In CLBP, depression is associated with increased pain intensity, disability, and poor recovery (Nieminen et al., 2021). Current treatment guidelines for LBP also identify anxiety as a risk factor for poor prognosis (Hayden et al., 2008). High levels of state anxiety are associated with an increased risk of transition to CLBP and higher levels of pain-related disability (Hallegraeff et al., 2020). Bener et al. (2022) reported the frequency and severity of anxiety were significantly higher in individuals with LBP compared to those without LBP. Additionally, anxiety is often comorbid with depression in individuals with CLBP (Oliveira et al., 2019). In individuals with chronic pain, anxiety and depression are correlated with poor treatment outcomes and satisfaction with treatment (Bair et al., 2008; McCracken et al., 2002). This has also been supported in individuals with CLBP, with anxiety and depression associated with low treatment satisfaction, pain severity, functional, social, and emotional disability (Oliveira et al., 2019).

Pain catastrophising is a maladaptive response to pain that is associated with increased pain intensity, increased disability, and disengagement of attention from pain (Borkum, 2010; Peters et al., 2005; Picavet et al., 2002; Seminowicz & Davis, 2007). People who report high pain catastrophising tend to exaggerate the threat and intensity of pain sensations (Quartana et al., 2009). Research investigating pain catastrophising following surgery reported that pre-surgery pain catastrophising scores predicted post-surgery pain (Pavlin et al., 2005). Similar results were found in people with CLBP (Picavet et al., 2002). This suggests that pain catastrophising

levels may predispose people to develop and/or maintain chronic pain (Seminowicz & Davis, 2007). Current Treatment options for CLBP

There are a number of different treatment options available for people with CLBP. Pharmacological intervention is the most common form of prescribed treatment for acute non-specific back pain. As pain continues, other treatment options, such as surgical and/or non-pharmacological interventions, are often explored.

1.4.1 Pharmacological Intervention

1.4.1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a form of analgesic medication that is typically prescribed for the treatment of inflammatory conditions, such as musculoskeletal pain (Ho et al. 2018). NSAIDs are the most commonly used form of analgesic medication, and are available as both over-the-counter medication and prescription medication (Chou et al., 2017b). Common types of NSAIDs include ibuprofen, aspirin, Celebrex®, and Voltaren®. Over-the-counter NSAIDs are effective for acute pain conditions, and work relatively quickly. As such, over-the counter NSAIDs are often considered the 'first-line' analegisc agent during acute, or subchronic phases (Peck et al., 2021). Over-the-counter NSAIDs are not typically recommended for long-term pain management, as they only have a short action time and may need to be used as often as every 4 – 6 hours. The use of over-the-counter NSAIDs is only recommended for up to 10 days for pain relief, without consultation with a doctor (Ong et al., 2007). Prescription NSAIDs may be prescribed in a range of different doses, however, are typically much stronger than over-the-counter NSAIDs. Prescribed NSAIDs are typically taken once or twice a day, and a prescribed for long-term health conditions, such as chronic pain, rheumatoid arthritis, and chronic musculoskeletal conditions (Ong et al., 2007).

1.4.1.2 Opioids and Benzodiazepine.

Opioids are a type of narcotic analgesic that acts on the nervous system by binding to opioid receptors and inhibiting the release of neurotransmitters. Endogenous opioids (naturally occurring in the brain) regulate nociceptive

information, while exogenous opioid agonists (medication) produce analgesia (Feng et al., 2012). Opioids are typically only available through prescription, and include; codeine, morphine, hydrocodone, and oxycodone. Opioids are fast-acting medication and are typically prescribed to treat severe pain conditions that do not respond well to NSAIDs (Chou et al., 2007). The use of opioid medication must be overseen by a doctor/physician due to potential side effects and addictive nature of opioids (Chou et al., 2007).

Benzodiazepines are a form of depressant drug that has a 'tranquiliser' type effect on the brain (Guina & Merrill, 2018). Benzodiazepines may be prescribed for analgesic effects in chronic pain, but may also be prescribed for anxiety-related reasons (Dellemijn & Fields, 1994; Pergolizzi & LeQuang, 2020). Benzodiazepines are prescribed to treat excessive activity in the nerves. Benzodiazepines work by enhancing the effect of inhibitory neurotransmitters (gamma-aminobutyric acid), which reduces excessive brain activity (Griffin et al., 2013). Benzodiazepines are fast-acting medication and are typically prescribed in chronic pain to treat muscles spasms, and anxiety-related reasons, such as pain catastrophizing (Pergolizzi & LeQuang, 2020). Benzodiazepines are only available through prescription, and include: diazepam, alprazolam, lorazepam, and Temazepam. Similar to opioids, the use of benzodiazepines must be overseen by a doctor/physician due to potential side effects and addictive nature of benzodiazepines (Pergolizzi & LeQuang, 2020).

1.4.1.3 Anti-Depressants.

Although anti-depressants are commonly used and prescribed for mental health conditions, anti-depressants are also considered an effective treatment for chronic pain (Verdu et al., 2008). While the analgesic effect of anti-depressants is not well understood, tricyclic anti-depressants are reported to be most effective in alleviating pain (Sansone & Sansone, 2008; Verdu et al., 2008). Tricyclic anti-depressants help to restore normal neurotransmitter function and reduce pain signals (Dharmshaktu et al., 2012). Anti-depressants have no immediate effect on chronic pain, and may take at least a week to have any effect (Obata, 2017). Anti-depressants are only available through prescription, and include: amitriptyline, Clomipramine, desipramine, and nortiptyline. Use of anti-depressants must be overseen by a

doctor/physician due to potential side effects and addictive nature (Verdu et al., 2008).

1.4.2 Effectiveness of Pharmacological Intervention.

NSAID's are the most commonly prescribed and over-the-counter medication for LBP, and are considered a 'first-line' treatment option (Chou et al., 2017b). A systematic review by Roelofs et al. (2008) reported that NSAID's were effective for short-term pain relief in acute LBP and CLBP. In acute LBP, the use of NSAID's was associated with a reduction in pain, and an improvement in functioning, compared to placebo (Roelofs et al., 2008). The use of NSAID's was also associated with a reduction in use of other analgesics (Roelofs et al., 2008). In CLBP, NSAID's were associated with a reduction in pain, compared to placebo (Roelofs et al., 2008). However, there is little evidence that NSAID's are more effective than other over-the-counter medications, such as paracetamol. Roelofs et al. (2008) reported that there is moderate evidence that NSAID's are equally effective for pain relief and functioning in acute LBP, when compared with paracetamol. In CLBP, there is limited evidence that NSAID's are more effective than paracetamol in reducing pain (Roelofs et al., 2008). Furthermore, no differences were reported between type of NSAID and pain relief.

A meta-analysis by Martell et al. (2007) examined the effectiveness of opioids vs placebo in reducing CLBP. Martell et al. (2007) reported that few studies met the criteria for inclusion in the meta-analysis and should be interpreted with caution. While Martell et al. (2007) summarised that they could not definitively conclude that opioids were effective at reducing CLBP, individual studies suggest that opioids may at least be more effective than placebo in reducing pain. In response to these results, a systematic review by Deshpande et al. (2007), re-analysed the included papers, but pooled the results for the placebo and other analgesic groups. This re-analysis revealed no significant difference between the opioid group and the pooled placebo and analgesic group. A systematic review and meta-analysis by Chaparro et al. (2014) reported that opioids are effective for mild pain relief for short-term management of CLBP in comparison to placebo. Chaparro et al. (2014) suggested that no definitive conclusions could be made regarding long-term

management of CLBP with opioids, due to the lack of research investigating the effectiveness of opioids for longer than 12 weeks.

A systematic review by Furlan et al. (2006) reported that only strong opioids, such as oxycodone, were effective in reducing pain in comparison to placebo. Similar results were found by Kalso et al. (2004), who reported only Class 3 opioids, such as morphine, were effective in reducing pain. While strong opioids have been found to be statistically better at reducing pain in CLBP, there was no reported change in overall function (Furlan et al., 2006; Kalso et al., 2004). Chaparro et al (2014) also reported little evidence for functional improvement following opioid treatment, despite evidence for a small reduction in pain. This suggests that a reduction in pain may not coincide with a clinically meaningful improvement in function (Deshpande et al., 2007). However, these findings may be influenced by the short-term studies (less than 12 weeks). The efficacy of opioids improving functional outcomes in CLBP in the long-term are unknown (Chaparro et al, 2014; Deshpande et al., 2007).

Despite conflicting research into the efficacy of opioids for CLBP, opioids are still commonly described for short and long-term management of CLBP. Martell et al. (2007) reported that as high as 66% of people diagnosed with CLBP were prescribed opioids to manage pain. While Martell et al. (2007) reported that opioids may be effective for short-term relief, they reported that long-term use was associated with increased risk of drug addiction and poor medication-taking behaviour. They reported the prevalence of lifetime substance abuse disorders in those using opioids for pain management in CLBP was as high as 56 per cent, while current abuse disorders were as high as 43 per cent. Martell et al. (2007) reported that as high as 24 per cent of those prescribed opioids for CLBP were using the medication outside of prescribed guidelines.

Benzodiazepines are often prescribed to manage acute pain, such as muscle spasms, which can occur in chronic pain. However, the use of benzodiazepines for the management of CLBP is controversial. Some clinical guidelines recommend the use of benzodiazepines for CLBP, while other guidelines do not recommend the use of benzodiazepines, either alone or in conjunction with other medication (Koes et al., 2001). A systematic review by Chou et al (2017b) reported that benzodiazepines were no more effective than placebo in reducing acute LBP pain. In CLBP, the use

of benzodiazepines was associated with an increased likelihood of reducing pain, in comparison to placebo (Salzmann et al., 1992). For functional improvement, no difference was found in functional scores between the use of diazepam and placebo for acute LBP. In comparison to placebo, diazepam was less likely to be associated with large reductions in pain (Brötz et al., 2010). Despite the conflicting evidence into the effectiveness of benzodiazepines in CLBP, benzodiazepines are still commonly recommended, particularly in individuals who are nonresponsive to NSAIDs or opioids (Koes et al., 2010).

Although not its primary function, anti-depressants have been shown to have analgesic properties (McQuay et al., 1996). A meta-analysis by Salerno et al. (2002) reported that anti-depressants have a small, but significant, effect on pain intensity in CLBP, when compared to placebo. Consistent with these findings, a review by Schnitzer et al. (2004) also reported that anti-depressants were more effective at reducing pain, when compared to placebo. Conversely, a systematic review by Urquhart et al. (2008) reported that there is no clear evidence that anti-depressants are more effective than placebo in CLBP. In the studies included in the review, five of the studies reported no difference in pain relief between anti-depressants and placebo (Jenkins et al., 1976; Goodkin et al., 1990; Atkinson et al., 1999; Dickens et al., 2000; Katz et al., 2005), while three studies reported anti-depressants were more effective at reducing pain than placebo (Atkinson et al., 1998; Atkinson 1999; Atkinson et al., 2007). In 4 reviews examining the effectiveness of anti-depressants in CLBP, two reviews reported that anti-depressants were effective at reducing pain (Salerno et al., 2002; Schnitzer et al., 2004), one review reported anti-depressants were ineffective (Urquhart et al, 2008), and one review suggested that pain relief was dependent on type of anti-depressant (Staiger et al., 2003). A recent meta-analysis reported that serotonin-noradrenaline reuptake inhibitors reduced back pain, but that tricyclic and other forms of anti-depressants did not reduce back pain (Ferreira et al., 2021). Despite the conflicting research into the effectiveness of anti-depressants for pain relief in CLBP, research suggests that up to 23% of doctors/physicians prescribe anti-depressants for LBP (Di Iorio et al., 2000).

Few studies have compared the effectiveness of all forms of pharmacological treatments in CLBP. While studies have examined the effectiveness of medication either on their own, or in conjunction with another form of medication (e.g.,

NSAID's vs NSAID's plus opioids), the findings are often inconsistent. There is no clear evidence that one form of medication is better than another or that any particular combination of medications are more effective in reducing pain (Chou et al., 2017b). The lack of consistent findings may be due to study limitations, such as small sample sizes, variation in type of CLBP, and engagement in other treatment (e.g., previous surgery, and non-pharmacological treatments; Chou et al., 2017b). Despite this, guidelines for the management of CLBP typically recommend all of the described medications. It is generally acknowledged that over-the-counter analgesics and NSAID's are 'first-line' options, with the use of opioids, benzodiazepines, and anti-depressants considered on a case-by-case basis (Koes et al., 2010).

1.4.3 Surgical Intervention

Although only a small number of those diagnosed with non-specific CLBP require surgery, the rates of surgical intervention for CLBP is increasing (Weinstein et al., 2006). Typically, surgery is considered in people who show signs of a degenerative condition, such as degenerative disc disease, or spinal trauma. In non-specific CLBP, surgery is still considered potential treatment avenue when there are signs of spinal degeneration. This includes when the cause of degeneration is likely due to normal ageing, or general 'wear and tear', and unlikely to be attributed to the cause of pain (van Tulder et al., 2006). The most common forms of surgery for non-specific CLBP are spinal fusion and lumbar disc replacement (Chou et al., 2009). Spinal fusion involves 'welding' multiple vertebrae (small bones of the spine) together. This allows the vertebrae to heal together, into one large vertebrae, and increases spinal stabilisation. To achieve this, an intervertebral disc is removed and replaced with a bone graft or plastic cage. Metal rods and screw may also be used to aid the fusion (Allen et al., 2009). Spinal fusion is typically considered when there is a narrowing of space between vertebrae, which can cause pressure on the spinal cord. Narrowing of the vertebrae is typically associated with normal ageing (Chou et al., 2009; van Tulder et al., 2006). Lumbar disc replacement involves replacing an entire disc with a metal or plastic artificial disc. Lumbar discs cushion and separate the vertebrae of the spine. Lumbar disc replacement is considered when one or two degenerative discs are compressing on a nerve, causing pain and limited mobility. The13rtificeal disc is designed to replicate the disc's natural movement, reduce

inflammation and spinal instability. As a result, lumbar disc replacement should reduce pain (Lin & Wang, 2006).

1.4.4 Effectiveness of Surgical Intervention.

A review by van Tulder et al. (2006) examined the research into the effectiveness of spinal fusion for reducing pain in CLBP. Van Tulder et al (2006) reported that results into the effectiveness of spinal fusion for CLBP are conflicting. Fritzell et al. (2001) compared lumbar fusion with physiotherapy. They reported that spinal fusion was more effective at reducing pain when compared to physiotherapy. Furthermore, spinal fusion was also effective in reducing disability, and overall improvement and return to work, when compared to physiotherapy. However, all participants in the physiotherapy group reported having completed previous physiotherapy treatment without success and may explain the lack of improvement in this study. In comparison, Brox et al (2003) compared lumbar fusion with a rehabilitation intervention that contained an educational component and a three-week exercise program. Brox et al (2003) reported no significant differences in reported pain, disability, or return to work at one-year follow up. This is consistent with Fairbank et al's (2005) findings that there were no significant differences between the spinal fusion group and a 15-day exercise and education intervention group in pain, disability, and quality of life at two-year follow up.

1.4.5 Non-pharmacological Intervention

Non-pharmacological interventions include a range of general and tailored approaches for the treatment of CLBP. Some common non-pharmacological interventions for CLBP include: exercise therapy (individualised or group-focused), manual therapy (spinal manipulation), massage, acupuncture, educational programs, nerve stimulation, and heat or cold therapy. Exercise therapies aim to reduce pain and improve function by engaging in activities that target specific muscle groups and improve postural musculature and stabilisation (Hayden et al., 2021). Manual therapy involves the manipulation of the spine and/or pelvis, and typically involves high-velocity thrust techniques (Standaert et al., 2011). Massage therapy involves tissue manipulation via applied pressure using the hands, or a massage device (van Middelkoop et al., 2011). Acupuncture involves the insertion of fine needles into the

skin at certain parts of the body to produce therapeutic effects (Pyne & Shenker, 2008). Acupuncture is traditionally based on Chinese medicine, but Western medicine has integrated acupuncture in the treatment of chronic pain, with a focus on needling specific pressure points to induce pain relief (Pyne & Shenker, 2008). Educational programs, often referred to as 'back schools', are training programs that provide lessons on exercises aimed at treating CLBP (Straube et al., 2016). One of more common types of nerve stimulation is transcutaneous electrical nerve stimulation (TENS). TENS is a peripheral stimulation technique that delivers a low electrical current across the skin and is designed to inhibit the transmission of pain signals (Johnson, 2007). Cold therapy involves the application of ice packs, cold gel packs and/or cold compress to reduce inflammation in the injured tissue. Heat therapy involves the application of hot water bottles, heat pads, heat wraps, and/or hot baths to stimulate vasodilation and increase blood flow. The increase in blood flow is thought to promote healing in the injured tissue (French et al., 2006).

The most common psychological-based therapies for the treatment of LBP are cognitive behavioural therapy (CBT) and mindfulness (Anheyer et al., 2017; Hajihasani et al., 2019; Richmond et al., 2015). CBT for LBP focuses on increasing pain education, implementing and maintaining adaptive coping strategies, and implementing problem-solving strategies to cope with pain (Yang et al., 2022). The key mechanisms of action of CBT for CLBP include a reduction in psychological distress (depression and anxiety) and catastrophising, and an increase in pain self-efficacy (Hanscom et al., 2015). CBT for CLBP aims to address and reduce the impact of psychological contributors on chronic pain, and ultimately reduce the pain experience (i.e., reduce pain intensity and functional, social, and emotional disability; Petrucci et al., 2022).Mindfulness interventions for chronic pain typically focus on mindfulness-based stress reduction and mindfulness-based cognitive therapy (Cramer et al., 2012). These interventions involve a combination of meditation, yoga, body scan techniques (Bishop et al., 2004), mindful exercise (Tsang et al., 2008), and acceptance and commitment therapy (Veehof et al., 2011). While research on the mechanisms underlying how mindfulness-based interventions improve chronic pain has produced conflicting results, there is some level of agreement that mindfulness-based interventions improve mental and emotional functioning, which may reduce the pain experience (Harrison et al., 2017).

1.4.6 Effectiveness of Non-pharmacological Intervention

Research suggests that multiple non-pharmacological interventions are associated with small to moderate improvements in pain and functioning in CLBP (Chou et al., 2017a). An American Pain Society review found that exercise therapy was associated with greater pain relief than no exercise, but there was no significant effect on function (Chou et al., 2007). In comparison, a systematic review by van Middelkoop et al (2010), reported reduced pain and improved function following exercise therapy, when compared to usual care treatment. However, this improvement was reduced at long-term follow-up. Motor control exercises have been reported to be more beneficial in improving pain-related outcomes in CLBP compared to general exercise in the short and immediate term (Inani & Selkar, 2013; Macedo et al., 2012; Stankovic et al., 2012). However, other studies have reported that this improvement is no longer significant at long-term follow-up (Byström et al., 2013). In a systematic review, Chou et al (2017a) reported that no clear differences were observed in over twenty trials examining the impact of other types of exercise therapy.

Effectiveness of massage therapy has been difficult to determine due to the variety of massage techniques and because massage is often combined with other interventions (Chou et al., 2017a). Chou et al (2016) reported that massage, when combined with another intervention, provided greater therapeutic benefits than standalone interventions (i.e., no massage). Massage, combined with exercise therapy, has been shown to reduce pain and improve function in CLBP, however the effect was only small and short-lived (Ajimsha et al., 2014; Zhang et al., 2015). A meta-analysis examining the effect of acupuncture in CLBP reported that acupuncture reduced pain intensity, disability and improved quality of life compared to no treatment. However, the improvements following acupuncture did not significantly differ to improvements following sham-acupuncture (Xu et al., 2013). Xu et al. (2013) reported that the effects of acupuncture were likely due to the non-specific effects of manipulation, rather than the acupuncture itself. Research examining the impact of TENS on pain-outcomes have provided conflicting results. A small trial found that TENS was associated with reduced pain immediately following treatment, compared with sham-TENS (Cheing & Hui-Chan, 1999). Another trial reported that TENS did not improve pain-outcomes following 6-weeks

of treatment, however, after 3-months TENS was associated with greater likelihood of experiencing reduced pain (Buchmuller et al., 2012). However, systematic reviews have reported that TENS does not improve pain outcomes any more than sham-TENS, and TENS was not more effective than other forms of treatment (e.g., exercise, interferential therapy; Chou et al., 2016; Chou et al., 2017a; van Middelkoop et al., 2011).

Research has reported conflicting evidence for psychosocial based therapies for the treatment of CLBP A meta-analysis examined the effect of CBT versus mindfulness-based stress reduction on pain outcomes in CLBP (Petrucci et al., 2021). CBT was reported to reduce pain intensity, disability, fear-avoidance beliefs, and improve quality of life compared to controls (usual care). Mindfulness-based stress reduction was reported to reduce pain intensity and improve quality of life compared to controls (usual care). CBT was more effective than mindfulness-based stress reduction at reducing disability, and Mindfulness-based stress reduction was more effective than CBT in improving quality of life. However, neither CBT and/or mindfulness reduced depression or the number of days with pain compared to controls (usual care; Petrucci et al., 2021). In comparison, a systematic review and meta-analysis reported that in CLBP, psychological-based therapies were most effective when combined with physiotherapy (Ho et al., 2020). Additionally, it was reported that the type of psychological-based therapy that was most effective differed between individuals who experienced different pain symptoms (e.g., those with leg pain responded better to CBT, while those without leg pain responded better to pain education; Ho et al., 2020). Ho et al. (2020) reported that while psychological-based therapies were beneficial to reducing pain and disability in the short-term, the clinical effectiveness of the therapy diminishes in the long term (≥12 months), suggesting that psychological-based therapies may only be beneficial for CLBP in the short-term.Although research has shown some support for existing treatment options in the management of CLBP, these treatments typically result in small to modest short-term improvements and are often ineffective for long-term pain management (Chou et al., 2017a; Chou et al., 2017b). Additionally, these treatments are often only focused on pain and physical symptom management. Research and pain management institutions have recently begun to adopt a multidisciplinary approach to the treatment of chronic pain (i.e., combination of pharmacological and

non-pharmacological treatments). However, limited physician/health care provider knowledge on the treatment of pain means the psychosocial components of CLBP are often poorly addressed (García-Martínez et al., 2022; Lewis & Battaglia, 2019). CLBP is, however, increasingly being acknowledged as a multidimensional condition that cannot simply be explained by injury. This is particularly evident for non-specific CLBP, where evidence of injury is often healed or undetectable. This has led researchers to postulate on factors that may be contributing to the persistence of pain even when the injury is healed (Moseley & Flor, 2012). A number of different theories of pain have sought to account for pain persistence in the absence of injury.

1.5 The Neuromatrix Theory

The Neuromatrix theory conceptualises pain as a multidimensional experience that cannot solely be attributed to injury (Melzack, 2001, Moseley, 2007). The Neuromatrix Theory suggests that the pain experience results from multiple factors (Melzack, 2001). In accord with the theory, pain is a central nervous system response that occurs when the body is perceived to be under threat (Iannetti & Mouraux, 2010; Moseley, 2007). Pain is considered to be a conscious experience, as the pain response is produced by perceived danger to body tissues without the activation of nociceptor fibers (Moseley & Flor, 2012). Nociceptors are sensory neurons that alert the brain to potentially damaging noxious stimuli (Melzack, 2001; Moseley, 2007; Moseley & Flor, 2012). The theory suggests that pain is not necessarily an accurate reflection of the state of body tissues and that pain can exist beyond potential tissue damage (Moseley & Flor, 2012).

The Neuromatrix theory proposes that the relationship between pain and body tissue becomes less predictable as the pain persists (Moseley, 2007). In persistent pain, sensory neurons become sensitised to nociception and pain networks become more sensitive as the pain persists (Moseley, 2007; Moseley & Flor, 2012). In line with this, formerly non-painful stimuli are perceived to be painful regardless of their potential (or not) to damage body tissue (Moseley, 2007). The longer pain is experienced, the less likely it is to reflect actual or potential tissue damage (Moseley & Flor, 2012; Mylius et al., 2006). In accord with the theory, cortical changes may contribute to the maintenance of the pain experience (Moseley & Flor, 2012; Mylius

et al., 2006). In the case of persistent pain, the cortical representation of the body part in the primary sensory motor cortex can be distorted and is associated with increased pain levels and chronicity (Lotze & Moseley, 2007; Moseley & Flor, 2012).

1.6.1 Pain Networks. No single cortical area is responsible for pain (Moseley, 2007). Although many cortical areas are activated during pain, some cortical areas are activated more often than others (Moseley, 2003). These areas form the 'salience matrix' (previously referred to as the 'pain matrix'). Areas that are thought to be involved in the perception of pain include the primary and secondary somatosensory cortex, anterior cingulate cortex, prefrontal cortex, insular cortex, amygdala, thalamus, cerebellum and the periaqueductal gray area (PAG; the prefrontal cortex, specifically the Dorsolateral Prefrontal Cortex, and the PAG are discussed in more detail in section 1.8). The somatosensory cortex has been reported to encode the sensory-discriminative aspect of pain (e.g., location and sensation; Sun et al., 2023). The anterior cingulate cortex is key to processing the emotional and affective experience of pain (Sun et al., 2023). The insular cortex is also thought to play a role in the emotional and affective-motivational experience of pain and has been shown to be involved in the perception of pain intensity (Labrakakis, 2023). The amygdala is another area that is involved in the emotional-affective experience of pain and is also reported to be key in pain modulation (Neugebauer, 2015). The thalamus is involved in the sensory-discriminative and affective-motivational aspects of pain and is a key relay structure between areas of the pain network (Aziz & Ahmad, 2006). The cerebellum has a cross-modal role, and is involved in sensorimotor and affective processing, and pain modulation (Moulton et al., 2010).

Since the original inception of the 'pain matrix,' other areas have also been proposed to play a key tole in the processing and modulation of pain. These areas include the motor cortex (Castillo Saavedra et al., 2014; Gan et al., 2022; Negrini-Ferrari et al., 2021; Vaseghi et al., 2015b) and the dorsolateral prefrontal cortex (DLPFC; Andrade et al., 2017; Brighina et al., 2011; Vaseghi et al., 2015a; Vaseghi et al., 2015b). The motor cortex is reported to modulate chronic pain via the glutamatergic system (Negrini-Ferrari et al., 2021) and may also be associated with the release of endogenous opioids in the interconnected pain network (Lopes et al., 2019; Maarrawi et al., 2013). The DLPFC is associated with the cognitive-attentional

evaluation and emotional response to pain (Kong et al., 2006; Mylius et al., 2006; Pacheco-Barrios et al., 2020).

1.7 The Salience Matrix: Plasticity in the Motor Cortex

Neuroplasticity describes the brain's ability to change and adapt (Bosnar Puretić & Demarin, 2012). Neuroplasticity is the central nervous systems adaption of anatomical structures (neuronal pathways and synapses) and functional organisation due to changes in behaviour, environment and learning (Pascual-Leone et al., 2005). Acquisition of new knowledge and skills causes change through formation of new neuronal circuits and reinforcement of pre-established neuronal pathways (Pascual-Leone et al., 2005). After repeated use of the new information, neurons related to that activity are simultaneously activated and neural pathways are strengthened. The strengthening of existing connections is fundamental to learning and neuroplasticity (Pascual-Leone et al., 2005).

The potential for plastic change has been demonstrated in the adult motor cortex. Plastic changes in the motor cortex result from learning, pathological changes, sensory experience, or as a consequence of trauma (Pascual-Leone et al., 2005). Motor cortex function is dependent on healthy inhibitory and excitatory systems (Bosnar Puretić & Demarin, 2012). These systems, aided by the interaction of neurotransmitters and cellular receptors, determine the neuronal excitability level (motor cortex excitability). Inhibition is facilitated by the action of gamma-aminobutyric acid (GABA) on GABAA and GABAB receptors (McDonnell et al., 2006). Excitation is aided by the action of glutamate on N-methyl-d-aspartate (NMDA), and non-NMDA receptors (Bosnar Puretić & Demarin, 2012). These systems are not irrevocably fixed and can be reorganised through learning, pathological changes and trauma. Inhibitory and excitatory systems play a crucial role in facilitating plastic changes (Bosnar Puretić & Demarin, 2012; McDonnell et al., 2006).

There is increasing support that motor-control dysfunction in chronic pain is associated with pain-related plasticity (Massé-Alarie & Schneider, 2016; Parker et al., 2016). Research in CLBP indicates that the lumbar spinal muscles exhibit reduced cortico-spinal excitability (Strutton et al., 2005). This reduction in cortico-spinal excitability has also been reported in fibromyalgia (Mhalla et al., 2010).

Mhalla et al (2010) suggested that fibromyalgia is associated with a global decrease in intracortical modulation. In comparison, Massé-Alarie et al. (2012; 2017) reported no significant difference in cortico-spinal excitability between CLBP and controls. Although studies have produced conflicting results, there is some evidence to suggest that people with pain demonstrate abnormal motor cortex excitability (Parker et al., 2016). The lack of consistent findings in global excitability has led to investigating if specific intracortical mechanisms may underlie changes in excitability in chronic pain.

1.8 Short Intracortical Inhibition and Intracortical Facilitation

It has been proposed that intracortical inhibition and facilitation are the principal mechanisms underlying changes in cortical plasticity (Lotze & Moseley, 2007). Short intracortical inhibition (SICI) prevents neurons firing in an undesirable way. Reduced SICI results in less than optimal firing of neurons (McDonnell et al., 2006; Ziemann et al., 1996). Conversely, intracortical facilitation (ICF) is described as the lowering of the activation threshold of a certain pathway. ICF typically occurs as a result of repeated use of that pathway, whereby activation is reinforced. For example, neurons processing pain may be activated just by the thought of pain rather than actually experiencing pain (Ziemann et al., 1996). Although SICI and ICF are distinct neural mechanisms, it is likely that both excitatory and inhibitory changes occur at the same time (Ziemann et al., 1996).

ICF and SICI provide a measure of glutamatergic (excitatory) and GABA (inhibitory) neurotransmitters (Cash et al., 2017). GABA and glutamate are believed to be key neurotransmitters involved in the pathophysiology of pain, such that neurochemical levels of glutamate and GABA may be unique to different pain conditions (Peek et al., 2020). This suggests that glutamate and GABA levels may serve as biomarkers for specific pain conditions (Peek et al., 2020). Research has shown that altered levels of GABA and glutamate are associated with pain sensitivity (Zunhammer et al., 2016). Research in CLBP has reported decreased levels of glutamate (Gussew et al., 2011). N-Acetylaspartate, which acts on excitatory glutamate receptors, has also been shown to be reduced in CLBP (Sharma et al., 2012). Gussew et al. (2011) suggested that this decrease in levels of glutamate may be due to altered glutamatergic mechanisms in response to chronic pain processing.

Evidence for alterations in intracortical mechanisms in chronic pain, including CLBP, is inconclusive (Chang et al., 2018). One study reported a decrease in corticospinal excitability in CLBP but did not examine intracortical mechanisms, SICI and ICF (Strutton et al., 2005). Massé-Alarie et al. (2016) reported reduced SICI in people with CLBP compared to controls. There were, however, no significant differences between short ICF or cortical silent period (MasséI-Alarie et al., 2016). Massé-Alarie et al. (2017) reported no difference in SICI and short ICF between people with CLBP and controls. In comparison, decreased SICI has been reported in those with chronic hand pain (Lefaucheur et al., 2006), and fibromyalgia, where both SICI and ICF levels are reduced compared to controls (Mhalla et al., 2010). Differences observed between the different studies may be due to the muscle targeted by TMS (e.g., studies targeting the site/muscle of pain versus studies targeting a site/muscle not associated with pain). Although this can make the comparison between studies difficult, individual study findings of altered excitability provide evidence that people with chronic pain exhibit abnormal motor cortex excitability, and that this abnormality is associated with increased pain levels (Lefaucheur et al., 2006). This suggests SICI and ICF may be the key mechanisms associated with the maintenance of pain (Schabrun & Hodges, 2012).

1.9 Salience Matrix: The Dorsolateral Prefrontal Cortex

The prefrontal cortex plays a key role in pain modulation and in the cognitive evaluation of pain (Lorenz et al., 2003, Melzack, 2001; Mylius et al., 2006). The cognitive evaluation of pain involves the appraisal of the pain sensation and the emotional response associated with that sensation (Kong et al., 2006). The emotional response is the result of cognitive processing that occurs following the evaluation of a painful sensation (Kong et al., 2006). Cognitive evaluative mechanisms contribute to pain chronicity, as these mechanisms can increase the perceived threat of pain and activity in the salience matrix (Moseley, 2003). This increased activity in the salience matrix increases projections between the DLPFC and the PAG (Witney et al., 2018). The DLPFC projects to the PAG via a neural pathway that involves connections between several intermediate structures, such as the medial prefrontal cortex, ventrolateral prefrontal cortex, and the perigenual anterior cingulate cortex (Chen et al., 2013; Vaseghi et al., 2014). This pathway between the DLPFC and the PAG is

thought to play a key role in the top-down modulation of pain perception (Seminowicz & Moayedi, 2017). The PAG receives pain sensory signals from the spinal cord, where the pain signal is interpreted to generate a pain response (Ossipov, 2012). The DLPFC modulates the activity of the PAG through inhibitory and excitatory processes and can therefore modulate the perception of pain (Brighina et al., 2011, Lorenz et al., 2003). Additionally, the pathway between the DLPFC and the PAG is thought to play a role in the modulation of emotional and cognitive processes (Seminowicz & Moayedi, 2017). As the DLPFC plays a key role in the cognitive and emotional evaluation of pain, the DLPFC can exert control over pain processing in the PAG, such that the DLPFC is able to alter the subjective experience of pain (e.g., shift attentional focus away from pain; Hadjipavlou et al., 2006). While the DLPFC can exert control to ensure an appropriate pain response, the attentional demand of processing pain can also impact the availability of cognitive resources (Moseley, 2003). Increased attention to pain impacts cognitive function, decision making and memory. Attending to pain is highly cognitively demanding and as such, leaves little resources available in the DLPFC for normal functioning (Moseley, 2003).

There are several theories about why cognition may be impaired in chronic pain. One theory suggests that the processing of nociceptors engages a significant amount of neural resources in the DLPFC. As a result, there are fewer neural resources available for other cognitive functions of the DLPFC, such as executive functions, planning skills and working memory (Berryman et al., 2013; Seminowicz & Davis, 2007). It has also been suggested that decreased cortical inhibition impacts the length (time) of activation in the DLPFC during pain processing. As a result, the DLPFC is unable to shift attention away from the pain to allow resources for cognitive functioning (Berryman et al., 2013). This suggests that chronic pain may interrupt and consume resources responsible for normal cognitive functioning (Smith & Ayres, 2014).

1.10 Cognitive Impairment and Chronic Pain

Studies in chronic pain have reported impaired cognitive functioning across many different cognitive domains (Berryman et al., 2013; Moriarty et al., 2011). A systematic review by Berryman et al. (2013) reported deficits in multiple working

memory domains in chronic pain. People with chronic pain performed poorly on measures of verbal working memory, non-verbal working memory and attention and working memory compared to healthy controls (Berryman et al., 2013). It has been suggested that the cognitive processing of chronic pain uses working memory resources, which results in impaired working memory (Smith & Ayres, 2014). Deficits have been reported in verbal, visual and spatial memory for those with CLBP (Jorge et al., 2009). Ling et al. (2007) reported that people with CLBP were more likely to report problems with their everyday memory performance than those without chronic pain. As working memory is important for learning, people with chronic pain demonstrate poor retention and transference of new information (Smith & Ayres, 2014). These impairments can hinder rehabilitation and activities of daily living in people with chronic pain.

Deficits in executive functioning have also been identified in chronic pain. A systematic review by Moriarty et al. (2011) reported that tasks involving more complex executive-type function and attention switching are more likely to be affected by chronic pain compared to less complex, automatic tasks. In an attention task, people with chronic pain showed increased errors and reduced reaction time compared to healthy controls, suggesting that chronic pain is associated with impaired attentional control (Moriarty et al., 2011; Veldhuijzen et al., 2006). People with chronic pain performed poorly on tasks that involve higher executive functioning, such as emotional decision making (Apkarian et al., 2004; Moriarty et al., 2011; Verhoeven et al., 2011). In CLBP, performance on emotional decision making tasks was impaired compared to healthy controls (Apkarian et al., 2004). This suggests that higher cognitive functions such as decision making and planning are impaired in CLBP (Apkarian et al., 2004). Impairments in decision making and planning is associated with disengagement from everyday activities and poor quality of life (QOL) in people with chronic pain (Hoy et al., 2014; Roth et al., 2005).

1.11 Non-invasive Brain Stimulation in Chronic Pain

Given the mounting evidence that chronic pain is associated with altered cortical excitability, research has recently begun to consider the potential for non-invasive brain stimulation as a potential tool in the management of CLBP. Non-invasive brain stimulation techniques can modulate neuronal activity, such that it can

modulate specific neural networks associated with pain processing (Xiong et al., 2022). The majority of research examining non-invasive brain stimulation in chronic pain focuses on stimulation of the motor cortex (Patricio et al., 2021). However, research suggests that the target brain region for stimulation may vary between chronic pain conditions (Knotkova et al., 2021; Xiong et al., 2022).

1.11.1 Brain Stimulation over Motor Cortex in Chronic Pain

Transcranial Magnetic Stimulation (TMS) is a non-invasive, painless technique that delivers a weak electrical current to neurons via a magnetic pulse. TMS is typically used to measure cortical excitability (Wassermann et al., 2008). rTMS is a form of repetitive TMS that can be used to disrupt cortical activity by exciting or inhibiting cortical function (Wassermann et al., 2008). Many studies have examined if rTMS induces changes in motor cortex excitability and pain levels in chronic pain. A review by Leo and Latif (2007) reported that rTMS over the motor cortex restored motor cortex excitability and reduced neuropathic pain. Leo and Latif (2007) suggested that rTMS enhances GABA activity and so improves motor cortex excitability. In chronic neuropathic hand pain, intracortical inhibition was reduced in the motor cortex corresponding to the painful hand (Lefaucheur et al., 2006). This defective intracortical inhibition was restored to normal following rTMS over the motor cortex and was associated with reduced pain (Lefaucheur et al., 2006). Lefaucheur et al (2006) suggested that the analgesic effects produced by rTMS was related to the restoration of intracortical inhibition.

A limited number of studies have investigated the use of transcranial Direct Current Stimulation (tDCS) in chronic pain. tDCS is a non-invasive brain stimulation technique that delivers low intensity electrical currents to modulate neuronal activity (Nitsche et al., 2008). In therapy-resistant chronic pain syndromes (post-stroke pain, back pain, fibromyalgia), intracortical inhibition was reduced in the motor cortex compared to healthy controls (Antal et al., 2010). Anodal-tDCS (a-tDCS) over the motor cortex improved intracortical inhibition and decreased pain ratings (Antal et al., 2010). Moreover, studies of fibromyalgia and spinal cord injury have reported decreased pain following five daily sessions of a-tDCS over the motor cortex (Fregni et al., 2006a; Fregni et al., 2006b). In healthy volunteers, a-tDCS over the motor cortex modulated pain perception and pain thresholds. This suggests that tDCS is

able to modulate pain pathways independent of pain-related neural activity (Boggio et al., 2008; Vaseghi et al., 2014).

In CLBP, a-tDCS over the motor cortex did not modulate motor cortex excitability (Schabrun et al., 2018). Luedtke et al. (2015) also reported that a-tDCS over the motor cortex had no therapeutic effect on CLBP. In comparison, Hazime et al. (2017) reported that a-tDCS over the motor cortex could induce an analgesic effect in CLBP, but only when combined with peripheral electrical stimulation. A systematic review concluded a Level A recommendation against the use of tDCS over the motor cortex in CLBP, as it was shown to be ineffective in managing pain (Baptista et al. 2019). A systematic review led to a Level A recommendation against using tDCS over the motor cortex in CLBP due to its ineffectiveness in managing pain (Baptista et al., 2019). This was further corroborated by another systematic review and meta-analysis, which affirmed that the recurrent application of non-invasive brain stimulation—primarily over the motor cortex—did not alleviate pain or disability in CLBP (Patricio et al., 2021). Subsequent research has turned its focus to investigate stimulation of other cortical areas in the salience matrix, such as the DLPFC (Brighina et al., 2004; O'Reardon et al., 2007; Sampson et al., 2006).

1.11.2 Brain Stimulation over DLPFC in Chronic Pain

1.11.2.1 Impact of Brain Stimulation over DLPFC on Short Interval Intracortical Inhibition and Intracortical Facilitation in Chronic Pain

Functional imaging studies have shown left DLPFC activation is associated with improved (decreased) pain (Lorenz et al., 2002; Lorenz et al., 2003). Decreased pain following rTMS over the DLPFC has also been reported in those with migraine and fibromyalgia (Brighina et al., 2004; O'Reardon et al., 2007; Sampson et al., 2006). It has been suggested that the reduction of chronic pain following rTMS over the DLPFC is related to changes in motor cortex excitability (Diamond, 2000; Miller & Cohen, 2001).

Studies investigating the impact of a-tDCS in chronic pain suggest that tDCS has a modulatory effect on exhibitory/inhibitory systems and pain relief (Antal et al., 2010; Fregni et al., 2006a; Fregni et al., 2006b). A-tDCS over DLPFC improves defective excitatory and inhibitory systems in the motor cortex (Vaseghi et al., 2015b). This is thought to be because tDCS changes neuronal excitability in the

DLPFC and connected areas such as the periaqueductal gray area (PAG) and motor cortex (Kandić et al., 2021; Tamura et al., 2004; Tracey & Mantyh, 2007). These areas play a key role in descending mechanisms that modulate spinal nociceptive activity (Kandić et al., 2021; Tamura et al., 2004; Tracey & Mantyh, 2007).

A study in fibromyalgia reported decreased pain levels following five daily sessions of a-TDCS over DLPFC (Fregni et al., 2006b). Pain levels were lower following a-tDCS over DLPFC compared to sham-tDCS (Fregni et al., 2006b). Decreased pain levels following DLPFC stimulation were still present at three-week follow-up (Fregni et al., 2006b). A case study in chronic neuropathic pain reported a reduction in pain following ten sessions (on alternate weekdays) of a-tDCS over DLPFC (Arul-Anandam et al., 2009). After five sessions of a-tDCS, participants' pain ratings dropped from seven to four (1= no pain, 10= worst pain). In this case, improvements were maintained at one-month follow-up (Arul-Anandam et al., 2009). In chronic migraine, pain intensity was reduced following 12 sessions of a-tDCS over DLPFC. Addittionally, the reduction in pain intensity was greater for the a-tDCS over DLPFC group, compared to a-tDCS over the motor cortex (Andrade et al., 2017). Taken together, these findings indicate that stimulation over DLPFC can reduce pain and modulate motor cortex excitability in chronic pain.

1.11.2.2 Impact of Brain Stimulation over DLPFC on Cognitive Function in Chronic Pain

A-tDCS over left-DLPFC improves cognitive function in numerous conditions, such as neurodegenerative disease, and healthy ageing (Boggio et al., 2006; Boggio et al., 2009; Coffman et al., 2014). Participants who experience problems with their memory show improved cognitive functioning following a-tDCS over DLPFC (Hansen, 2012). Research in neurodegenerative diseases has also reported improvements in cognitive functioning following a-tDCS over DLPFC (Boggio et al., 2006; Boggio et al., 2009; Hansen, 2012). Participants with Parkinson's disease improved on a working memory task following a single session of a-tDCS over DLPFC (Boggio et al., 2006). Participants with Alzheimer's improved on a visual recognition memory task following a single session of a-tDCS over DLPFC (Boggio et al., 2009). While there is substantial evidence for the use of tDCS over left-DLPFC to improve cognition in clinical and healthy ageing

populations, few studies have investigated the impact of tDCS on cognitive functioning in chronic pain.

Limited studies have shown tDCS over DLPFC improves cognitive functioning in certain chronic pain conditions (Fregni et al., 2006b; Silva et al., 2017). A-tDCS over DLPFC reduces pain levels in some forms of chronic pain (Brietzke et al., 2020; To et al., 2017). Research in fibromyalgia indicated a trend towards improvement in global cognition following five daily sessions of a-tDCS over DLPFC (Fregni et al., 2006b). Improvements were also shown on an attention and working memory task, and simple reaction time task (Fregni et al., 2006b). Silva et al. (2017) reported improvements in selective attention (orientating and executive) in people with fibromyalgia following a single session of a-tDCS over DLPFC. It is believed that a-tDCS induces long-term potentiation-like plasticity mediated by upregulating N-methyl-d-aspartate (NMDA) and GABA receptor activity. These receptors play a key role in maintaining optimal cognitive function (Seminowicz et al., 2019). In chronic pain, a-tDCS over left-DLPFC is thought to inhibit the allocation of maladaptive cognitive and attentional resources to pain, such that people disengage their attention from their pain and assign those resources to other cognitive functions (Berryman et al., 2013; Smith & Ayres, 2014). For those with chronic pain, the inhibition of maladaptive cognitive evaluations of pain may help to alleviate the pain and improve cognitive functioning. However, the impact of tDCS over DLPFC on cognition has not yet been examined in CLBP.

1.12 Mechanisms by which tDCS over DLPFC may Modify the Pain Experience

The underlying mechanisms by which tDCS over DLPFC elicits an analgesic effect are not yet fully understood. However, there is initial evidence that tDCS has the potential to change chronic pain by acting upon the endogenous opioid system, changing the cognitive-attentional appraisal of pain, and altering the pain signal via descending pathways (DosSantos et al., 2012; Garcia-Larrea & Peyron 2007). tDCS likely acts upon the endogenous opioid system via interconnections between the DLPFC and the PAG and rostral ventromedial medulla (RVM; DosSantos et al., 2012; Taylor et al., 2012). The PAG and RVM are key components of the supraspinal opioidergic circuit (Hadjipavlou et al., 2006; Taylor et al., 2012). Research suggests that tDCS induces changes in this system by activating μ-opioid

receptors, which creates an analgesic effect (DosSantos et al., 2012; Taylor et al., 2012). The PAG and RVM also play a key role in descending mechanisms that modulate spinal nociceptive activity (Kandić et al., 2021; Tamura et al., 2004; Tracey & Mantyh, 2007). Research has shown neurons in the RVM project to the spinal and medullary dorsal horns, which modulates nociception and, therefore, the pain experience (Fields et al., 2005).

In addition to the analgesic effect, the potential for tDCS over DLPFC to change chronic pain may be due to its influence on cognitive-attentional mechanisms. It is believed that a-tDCS induces long-term potentiation-like plasticity mediated by upregulating N-methyl-d-aspartate (NMDA) and GABA receptor activity. These receptors play a key role in maintaining optimal DLPFC function (Seminowicz et al., 2019). tDCS over DLPFC has been shown to modify attention to threat (Clarke et al., 2014), suggesting that tDCS over DLPFC may modify cognitive and attentional aspects of pain (Pacheco-Barrios et al., 2020). Cognitive-attentional mechanisms that contribute to pain intensity and chronicity include, pain catastrophising, anxiety, and depression (de Heer et al., 2014; Peters et al., 2005). It has been suggested that tDCS over DLPFC in chronic pain induces an inhibitory effect on these maladaptive cognitive-attentional mechanisms, which leads to a reduction in pain (Pacheco-Barrios et al., 2020).

1.13 General purpose and outline.

The overall aim of this thesis is to explore motor cortex excitability and cognitive function in people with CLBP, and to examine the impact of a-tDCS over left-DLPFC on motor cortex excitability and cognitive function in people with CLBP. The purpose for this is:

1. There is conflicting evidence whether people with CLBP exhibit altered motor cortex excitability, and if this is associated with pain experience.
2. The cognitive profile in people with CLBP is currently unknown. It is also unknown if deficits in cognitive function reach levels consistent with mild cognitive impairment.
3. A-tDCS over left-DLPFC can modulate motor cortex excitability and cognitive function in some chronic pain conditions, neurodegenerative disease, and healthy ageing. However, it is currently unknown if a-tDCS

over left-DLPFC can modulate motor cortex excitability and cognitive function in people with CLBP. The impact of a-tDCS over left-DLPFC on pain experience, mood, and quality of life is also unknown.

This thesis comprises six chapters. The first chapter provides a summary of CLBP, motor cortex excitability, and cognitive function. Chapter one also provides a summary of the impact of tDCS on motor cortex excitability and cognition in chronic pain, as well as the theoretical approach underlying the present research. Chapter two examines motor cortex excitability in people with CLBP compared to age- and gender-matched controls. In this chapter, an exploratory analysis is proposed to explore the relationship between excitation/inhibition balance and pain intensity. Chapter three examines cognitive functioning in people with CLBP compared to age- and gender-matched controls. In this chapter, I examine the cognitive profile of individuals with CLBP by examining cognitive performance over five cognitive domains. I also examine whether the pattern of performance identifies membership to the CLBP group. Finally, I identify whether cognitive performance in people with CLBP is consistent with mild cognitive impairment criteria. Chapter four examines the effect of a-tDCS over left-DLPFC on motor cortex excitability in people with CLBP. Chapter four also examines the effect of a-tDCS over left-DLPFC on pain intensity, disability, and pain catastrophising. Chapter five examines the effect of a-tDCS over left-DLPFC on cognitive functioning in people with CLBP. Chapter five also examines the effect of a-tDCS over left-DLPFC on pain experience, mood, and quality of life. Finally, in chapter six, I summarise the main findings of this thesis and provide future research directions.

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CHAPTER TWO: MOTOR CORTEX EXCITABILITY IN CHRONIC LOWER BACK PAIN

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2.0 Abstract

Chronic pain is associated with dysfunctional cortical excitability. Research has identified altered intracortical motor cortex excitability in Chronic Lower Back Pain (CLBP). However, research identifying the specific intracortical changes underlying CLBP has been met with inconsistent findings. In the present case–control study, we examined intracortical excitability of the primary motor cortex using transcranial magnetic stimulation (TMS) in individuals with CLBP. Twenty participants with CLBP (M_{age} = 54.45 years, SD_{age} = 15.89 years) and 18 age- and gender-matched, pain-free controls (M = 53.83, SD = 16.72) were included in this study. TMS was applied to the hand motor area of the right hemisphere and motor evoked potentials (MEPs) were recorded from the first dorsal interosseous muscle of the contralateral hand. Resting motor threshold (rMT) and MEP amplitude were measured using single-pulse stimulation. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were assessed using paired-pulse stimulation. Individuals with CLBP had significantly higher rMT (decreased corticospinal excitability) and lower ICF compared to controls. No significant differences were found in MEP amplitude and SICI. These findings add to the growing body of evidence that CLBP is associated with deficits in intracortical modulation involving glutamatergic mechanisms.

2.1 Introduction

Chronic pain is associated with altered excitability in the motor cortex (Moseley & Flor, 2012; Parker et al., 2016). Motor control dysfunction is common across many chronic pain conditions, including Chronic Lower Back Pain (CLBP). There is increasing support that these deficits are associated with pain-related plasticity (altered intracortical and corticospinal excitability; Massé-Alarie & Schneider, 2016; Parker et al., 2016). Those with CLBP and fibromyalgia demonstrate overall reductions in corticospinal excitability (Strutton et al., 2005; Mhalla et al., 2010). However, the dearth of research in this field means that the specific mechanisms underlying altered excitability in CLBP remain unclear (Schabrun & Hodges, 2012).

Evidence for altered motor cortex excitability in CLBP is inconclusive (Chang et al., 2018). Strutton et al. (2005) reported that people with CLBP demonstrated significantly higher motor thresholds (decreased cortical excitability) compared to controls. Conversely, Massé-Alarie et al. (2012; 2017) reported no significant difference in motor threshold and MEP amplitude between CLBP and controls. Tsao et al. (2008) also reported no significant difference in motor threshold between people with recurrent LBP and controls. The lack of consistent findings in global excitability in CLBP has led to investigating if specific intracortical mechanisms may underlie changes in excitability in CLBP.

Short interval intracortical inhibition (SICI) and facilitation (ICF) are the main mechanisms underlying cortical plasticity (Lotze & Moseley, 2007). Studies in induced pain have reported changes in SICI and ICF during pain and after the removal of pain, suggesting that modulation of intracortical excitability is affected by pain perception (Brighina et al., 2011; Farina et al., 2001; Fierro et al., 2010). Farina et al. (2001) and Fierro et al (2010) reported that changes in intracortical excitability occurred simultaneously with the onset of pain and continued as pain intensity progressed. This suggests SICI and ICF may be the key mechanisms associated with the maintenance of pain (Schabrun & Hodges, 2012).

Studies examining excitability in CLBP are limited. One study reported a decrease in corticospinal excitability in CLBP but did not examine intracortical mechanisms, SICI and ICF (Strutton et al., 2005). Massé-Alarie et al. (2016) reported reduced SICI in people with CLBP compared to controls. There were, however, no

significant differences between short ICF or cortical silent period (Massé-Alarie et al., 2016). Massé-Alarie et al. (2017) reported no difference in SICI and short ICF between people with CLBP and controls. In comparison, decreased SICI has been reported in those with chronic hand pain (Lefaucheur et al., 2006), and fibromyalgia, where both SICI and ICF levels are reduced compared to controls (Mhalla et al., 2010). Although the pattern of change in these studies differs, altered motor cortex excitability is the common element of chronic pain.

Several factors have been identified as potential contributors to impaired motor cortex excitability in individuals with chronic pain. Sensory feedback disruption may contribute to chronic pain, whereby pain may alter sensory signals, and as a result, the sensorimotor areas of the brain may not be able to accurately interpret and respond to the information (Tsay et al., 2015). Similarly, changes in motor cortex excitability may also be caused by altered muscle activation patterns in response to pain (i.e., using different movement strategies as a compensation to avoid using painful muscles; Schabrun et al., 2016). This may also be explained by inhibitory mechanisms, whereby the brain may limit activity within certain muscles to reduce painful movement (Juottonen et al., 2002; Lefaucheur et al., 2006). While such changes in the motor cortex may initially be aimed at avoiding pain, these may lead to maladaptive changes in plasticity (Schabrun et al., 2016; Thapa et al., 2018). In healthy brains, motor cortex excitability fluctuates between inhibitory and excitatory mechanisms to maintain healthy functioning (e.g., a shift from long-term potentiation to long-term depression in response to high motor cortex excitability to maintain a healthy inhibitory/excitation balance; Murakami et al., 2012). Research suggests that the balance between inhibition and excitation is impaired in people with chronic pain and that such disruption may contribute to the persistence of chronic pain (Thapa et al., 2018).Predominantly studies have focused on affected muscles (primary location of pain); however, there is some evidence to suggest that changes in excitability may be more generalised (i.e., not restricted to the cortical representations of the affected muscle; Thapa et al., 2018). Tagliazucchi et al. (2010) reported that chronic back pain disrupts normal activity across many cortical areas, even in brain resting state, supporting the notion and no single cortical area is responsible for the processing and evaluation of pain. This suggests that altered concentration of GABA and glutamate may reflect more of a global alteration in

cortical excitability that is not purely restricted to the region representing the painful muscle (Parker et al., 2016). Thapa et al. (2018) measured excitability in the motor cortex from unaffected hand muscles (First Dorsal Interosseous muscle; FDI) in individuals with CLBP. Thapa et al (2018) reported that individuals with CLBP have impaired motor cortex excitability, and that such changes in cortical excitability in individuals with CLBP is not restricted to the representation of painful muscles Additionally, the FDI has previously been used in research to infer underlying cortical dynamics in diseases that do not primarily affect the motor system (Groppa et al., 2012; Rawji et al., 2020). It has been suggested that research should explore excitability in other muscles (Strutton et al., 2005).

A greater understanding of intracortical excitability in CLBP is required. It is unclear if people with CLBP have altered excitability and, if so, whether these effects are indicative of global changes, as indicated by responses to TMS of muscles that are not in close proximity to the site of pain (i.e., FDI). The present study sought to explore how intracortical mechanisms within the motor cortex may differ between people with CLBP and controls. The relationships between motor cortex excitability and pain-related measures were also examined.

2.2 Methods

2.2.1 Participants

Participants were recruited via convenience sampling to participate in a 5-week intervention study. The participants' assessments at baseline form the data for this study. This study was approved by Curtin University ethics committee and all research was conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent. Inclusion in the study required a formal diagnosis of CLBP by a qualified health professional (General Practitioner or Physiotherapist) of at least 6 months (see Table 2.1 for demographic information and pain related information). Individuals were screened against Transcranial Magnetic Stimulation (TMS) inclusion criteria (Rossi et al., 2011) and screened for cognitive status using the Telephone Interview for Cognitive Status – 30 (TICS-30; score ≥ 18 for inclusion). Thirty-one participants met the initial inclusion criteria for participation. Eleven participants were removed from subsequent TMS analysis. Four participants did not produce reliable MEPs. Six participants rMT was too high to

complete the recruitment curve. One participant was excluded due to ongoing muscle activation across multiple trials. Twenty participants were included in the final data set. Control participants were recruited based on age and gender-match to the CLBP participants (n = 18).

Table 2.1
Demographics, Pain Classification, and Treatment Engagement.

	Total		CLBP		Control	
	CLBP	Control	Males	Females	Males	Females
	(n = 20)	(n =18)	(n = 11)	(n = 9)	(n = 12)	(n = 6)
Age	54.45 (15.89)	53.83 (16.72)	59.73 (15.87)	48.00 (14.12)	58.17 (16.47)	45.17 (14.78)
Years of Education	12.47 (3.23)	14.06 (4.95)	12.05 (2.66)	12.99 (3.92)	11.95 (2.67)	13.58 (3.62)
rMT	49.8 (8.7)	42.6 (6.7)	47.8 (5.9)	52.0 (11.1)	41.2 (7.3)	38.5 (16.0)
Duration of Diagnosis (years)	13.94 (13.12)	-	18.98 (15.12)	8.33 (7.92)	-	-
VAS Pain Average	5.02 (2.07)	-	4.64 (2.27)	5.44 (1.87)	-	-
PCS	12.05 (5.33)	-	15.82 (9.88)	22.89 (12.61)	-	-
RMDQ	19.65 (11.65)	-	13.00 (6.10)	10.41 (4.29)	-	-
CLBP Classification						
Non-Specific	85%	-	82%	89%	-	-
Specific	15%	-	18%	11%	-	-
Percentage taking Pain Medication	75%	-	55%	100%	-	-
Anti-Inflammatory (Celebrex, Mobic, Ibuprofen)*	53% (n = 8)	-	67% (n = 4)	44% (n = 4)	-	-
Pain Killer (Over the counter and prescription[a])*	67% (n = 10)	-	50% (n = 3)	78% (n = 7)	-	-
Benzodiazepine (Valium, Norflex)*	27% (n = 4)	-	17% (n = 1)	33% (n = 3)	-	-
Anti-Depressants (Endep)*	13% (n =2)	-	17% (n = 1)	11% (n = 1)	-	-
Engaging in Physiotherapy	50%	-	36%	67%	-	-
Past Surgery	25%	-	27%	22%	-	-
Other Pain Management (Chiropractor)	75%	-	73%	78%	-	-
Depression and Anxiety Disorder	20% (n = 3)	17% (n = 3)	9% (n = 1)	22% (n = 2)	17% (n = 2)	17% (n = 1)
Anti-Anxiety Medication*	33% (n = 1)	67% (n = 2)	0%	50% (n = 1)	100% (n = 2)	0%

Note. rMT = resting motor threshold, CLBP Classification = classification of chronic lower back pain based on Koes et al (2001), Non-Specific = no radiographical injury at time of participation, Specific = Radiographical evidence, Pain Average = Average pain intensity one week prior to participation. Other = Acupuncture, Chiropractor, Massage). * = Percentage based on individuals taking medication.[a] = 5 participants were taking prescription medication; Tramadol, Tapentadol, Lyrica and/or Codeine.

2.2.2 Measures

Demographic and pain-related information were collected via self-report questionnaire. All CLBP participants completed TMS and clinical measures. Control participants only completed the TMS measures.

2.2.2.1 Motor Cortex Excitability Measures

EMG signals were recorded from the left FDI muscle using Ag – AgCl surface electrodes placed over the belly and tendon of the FDI. The stimulation procedures were conducted using TMS. TMS was applied using a figure-of-eight coil (90mm in diameter) that was connected to two Magstim 200 magnetic stimulators through a Bistim module (Magstim Company Limited, UK). The motor area corresponding to the left FDI muscle was located using the 10/20 International system for electrode placement (Trans Cranial Technologies, 2012). The coil was positioned over the optimal location to produce a MEP in the contralateral FDI at a 45-degree angle from the inter-hemispheric line, with the handle pointing towards the right-hand side, to stimulate current flow in a posterior to anterior direction.

To determine resting motor threshold (rMT), stimulation intensity started at 30% and was adjusted in 1% increments until the rMT was established. rMT was established as the lowest stimulus level that elicits MEPs greater than 50 μV in at least three of five trials, while the muscle was at rest. To determine the recruitment curve stimulation intensity, the stimulation intensity was adjusted in 1% increments, until a mean MEP of 1mV was produced in eight trials (Rossini et al., 2015). The recruitment curve consisted of stimulation at 90%, 100% (1mV), 110%, 120%, and 130% of the intensity required to produce the 1mV MEP. The order of administration was randomised. Eight pulses were delivered for each intensity level and were averaged to attain a mean MEP amplitude. The mean MEP amplitude for each intensity level was normalised against the participant's 1mV response.

SICI and ICF were measured using the paired-pulse protocol developed by Kujirai et al. (1993) SICI and ICF were assessed using a subthreshold conditioning pulse set to 80% of rMT, followed by a suprathreshold test pulse set at 120% of rMT. A moderate suprathreshold (110–120% rMT) yields the most reliable measure of SICI (Garry & Thomson 2009). The interstimulus interval was set to 3 ms for SICI

and 10 ms for ICF. Fifteen trials were recorded at each interstimulus interval, and fifteen single unconditioned test pulses were also recorded (set at 120% rMT), with an 8 s interval between each trial. The order of administration was randomised. The fifteen trials for each interstimulus interval were averaged to attain a mean MEP amplitude. The mean MEP amplitude for each interstimulus interval was normalised against the participant's mean unconditioned pulse (see Figure 2.1 for example MEPs).

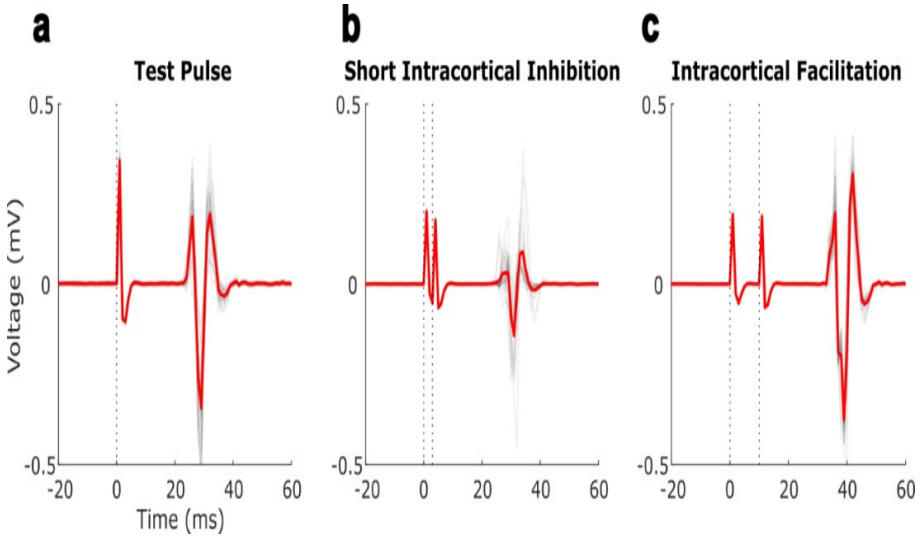

Figure 2.1. *Individual average waveforms (red) of an example control participant during test pulse (**a**), ICF (**b**), and SICI configuration (**c**).*
Note. Individual trials are denoted by the grey traces

2.2.2.2 Pain-related Measures

Pain Intensity. The Short-Form McGill Pain Questionnaire (SF-MPQ) contains a 10 cm Visual Analogue Scale (VAS) and was used to assess 7-day average pain intensity in CLBP (Melzack, 1987). Participants were required to mark the line at the spot they feel applied to their level of pain across the previous 7 days (Hawker et al., 2011).

Disability. The Roland-Morris Disability Questionnaire (RMDQ) assessed the level of disability in CLBP (Roland & Morris, 1983). The RMDQ consists of 24 items assessing the impact of CLBP across multiple domains (mobility, daily activities, sleeping, mood, and appetite).

Pain Catastrophising. The Pain Catastrophizing Scale (PCS) assessed the presence of pain catastrophising in individuals with CLBP (Sullivan et al., 1995). The PCS consists of 13 items assessing rumination, magnification, and helplessness.

2.3 Statistical Analysis

All analyses were conducted using R software (v3.5.1; R Foundation for Statistical Computing, Vienna, Austria). All trials were visually inspected and peak to peak MEP amplitudes were manually marked. Trials were excluded from analysis if visual inspection indicated noise, artifacts, or voluntary contraction, which obscured the detection of MEP amplitude, was present in the EMG signal. Trials with muscle activation were also excluded from analysis. Robust ANOVAs and independent samples T-tests were conducted using WRS2 package (Mair & Wilcox, 2020). Recruitment curve data was analysed using robust two-way ANOVA with intensity (5 levels, 90-130%) and group (2 levels, CLBP and control), pbad2way function. Group differences in rMT, SICI, ICF, and were analysed using Yuen-Welch robust t-test with bootstrapping, yuenbt function (nboot = 10,000). Spearman correlations between motor cortex excitability measures (ICF and SICI) and clinical measures (pain intensity, disability, and pain catastrophising) were analysed using robust correlation, pbcor (percentage bend correlation coefficient) function.

As cortical excitability reflects the balance between excitation and inhibition, post hoc analysis was conducted to determine if the balance between SICI and ICF was related to pain. To determine the difference score between SICI and ICF, SICI MEP amplitudes were subtracted from ICF MEP amplitudes ([MEPICF/MEPcontrol] - [MEPSICI/MEPcontrol). Correlations between ICF-SICI and clinical measures (pain intensity, disability, and pain catastrophising) were analysed using robust correlation, pbcor function (see Mair and Wilcox (2020) for further details).

2.4 Results

2.4.1 Group comparison of rMT, recruitment curves, SICI and ICF

Analysis of rMT revealed a statistically significant difference between the CLBP and the control group (T_{pb} = -3.00 [-12.16, -2.75], p = .004*, trimmed mean difference = -7.56; see Figure 2.2a), such that the CLBP group had a higher rMT compared to the control group. Analysis of the recruitment curve data using robust ANOVA revealed a statistically significant main effect of Intensity (p < .001*), where MEP ratios increased with Intensity. However, the main effect of Group (p = .132) and the two-way interaction were not statistically significant (p = .816; see

Figure 2.2d). With respect to ICF and SICI, ICF was significantly reduced in the pain group (T_{pb} = 2.61 [0.09, 0.61], p = .016*, trimmed mean difference = 0.35; see Figure 2.2b). However, there was no significant difference in SICI between groups (T_{pb} = 0.47 [-0.10, 0.16], p = .632, trimmed mean difference = 0.03; see Figure 2.2c).

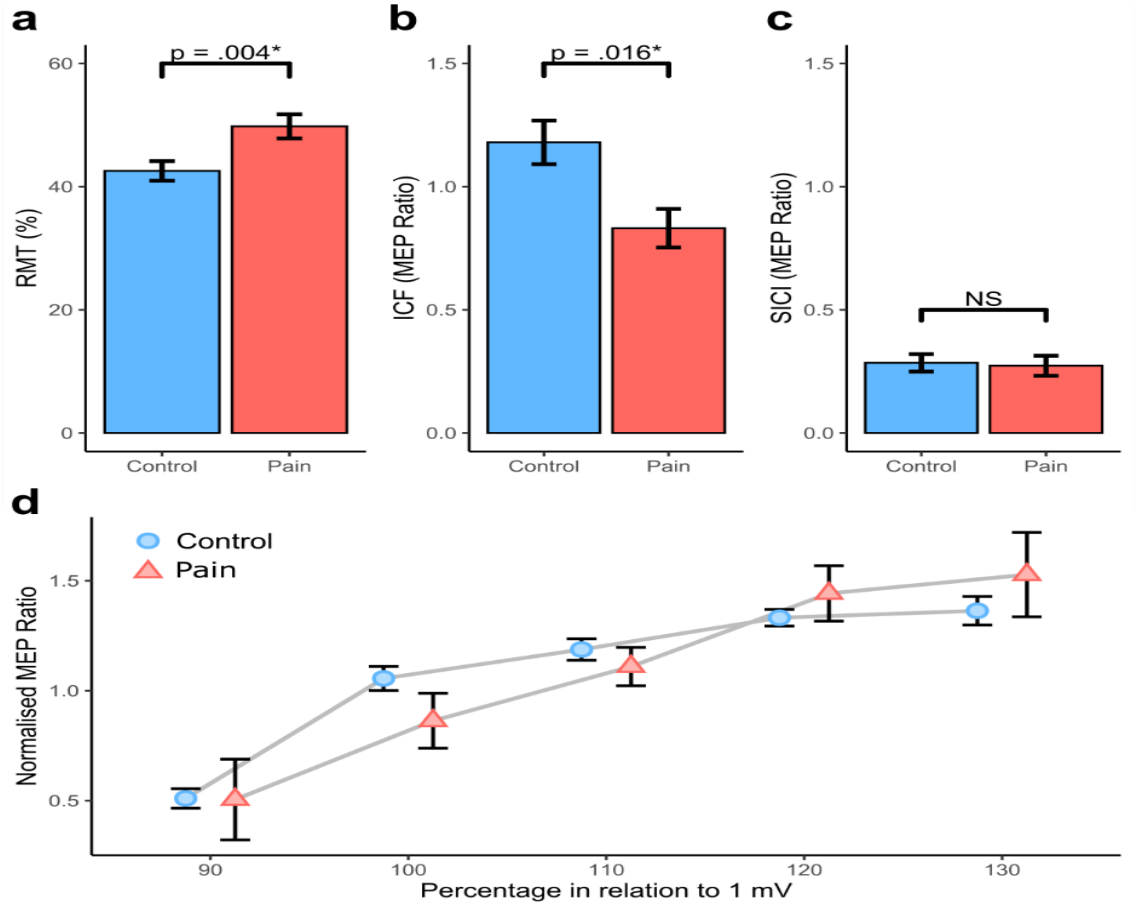

Figure 2.2. *Average rMT (**a**), ICF (**b**) and SICI (**c**) MEP Ratio for CLBP and Control Group. (**d**) Recruitment Curve with Normalised MEP Ratio at 90 – 130% Stimulation for CLBP and Control Group.*

Note. rMT = resting motor threshold, ICF = intracortical facilitation, SICI = short interval intracortical inhibition, MEP = motor evoked potential, MEP ratio = normalised MEP amplitude, mV = millivolt.

2.4.2 Association between rMT, SICI, ICF and Pain

There was no significant correlation between pain intensity and rMT (r_{pb} = 0.03, T_{pb} = 0.14, p = .891). For ICF, correlations with pain intensity (r_{pb} = 0.21, T_{pb} = 0.90, p = .379), PCS total, (r_{pb} = 0.04, T_{pb} = 0.20, p = .846) and RMDQ total (r_{pb} = -0.04, T_{pb} = -0.18, p = .856) were not statistically significant. For SICI, correlations with pain intensity (r_{pb} = -0.04, T_{pb} = -0.15, p = .884), PCS total (r_{pb} = -0.17, T_{pb} = -

0.74, p = .468) and RMDQ total (r_{pb} = -0.005, T_{pb} = -0.02, p = .985) were not statistically significant.

To explore whether pain may be explained by the balance between inhibitory and excitatory systems a correlation between pain intensity and ICF-SICI difference was conducted, and the result approached statistical significance (r_{pb} = 0.44, T_{pb} = 2.10, p = .050*; See Figure 2.3a). However, correlations between ICF-SICI difference and other pain measures (PCS total, r_{pb} = 0.09, T_{pb} = 0.36, p = .720, and RMDQ total, r_{pb} = 0.02, T_{pb} = 0.07, p = .946) were non-significant.

To further examine the likelihood of the association between ICF-SICI difference and pain intensity, a Bayesian general linear model was conducted. The resulting posterior distribution (See Figure 2.3b) indicated a positive association between ICF-SICI difference and pain intensity (Estimate median = 0.06 ICF-SICI difference per unit increase in pain intensity; 95% CI: [0.00, 0.12]), with a positive directional probability of 97.02%, an 86% probability of significance, and a 22.27% of being large (ICF-SICI difference > 0.08).

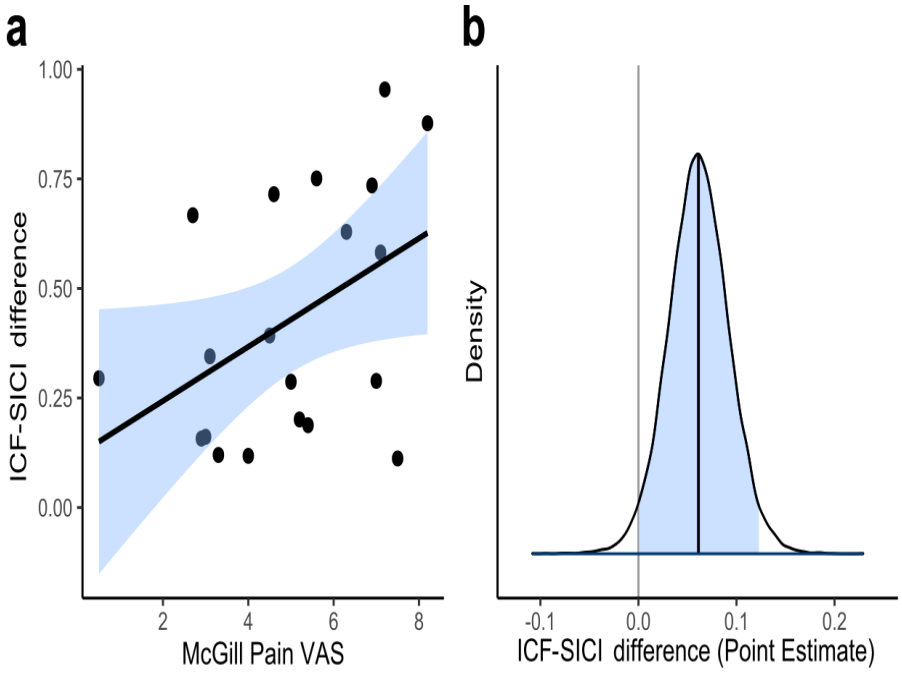

Figure 2.3. *(**a**) Correlation between pain intensity (McGill VAS) and ICF-SICI difference (positive = inhibition). (**b**) Bayesian posterior distribution of ICF-SICI difference for each unit increase in pain intensity (McGill VAS; 95% CI).*

2.5 Discussion

The present study explored motor cortex excitability in people with CLBP, compared to pain-free, age, and gender-matched controls. The present study revealed that CLBP is associated with changes in motor cortical excitability. The CLBP group demonstrated higher rMT and reduced ICF compared to controls, but there were no differences in SICI between the two groups. Individual differences in rMT, ICF and SICI were not associated with pain intensity, duration, pain sensation, use of medication, or disability in those with CLBP. Although further analysis revealed the balance between SICI and ICF (ICF-SICI difference) was associated with pain intensity.

2.5.1 Resting Motor Threshold

Previous evidence for change in motor cortex excitability in CLBP is mixed (Chang et al., 2018). Strutton et al. (2005) reported that individuals with CLBP had a significantly higher motor threshold, which is typically indicative of decreased global excitability (Mhalla et al., 2010; Schoenen et al., 2008). Conversely, Massé-Alarie et al. (2012) reported no significant difference in motor threshold between people with CLBP and controls. The present finding of higher rMT in CLBP is consistent with Strutton et al. (2005) and with research in fibromyalgia (Mhalla et al., 2010). An increase in rMT is thought to indicate a global hypoexcitability of the corticospinal tract (Mhalla et al., 2010; Perez & Cohen, 2009; Schoenen et al., 2008), which may suggest that the cortical system is less excitable in the CLBP group, compared to controls. However, the lack of a significant difference on MEP amplitude in the recruitment curve suggests that the pattern of corticospinal excitability at-rest may not differ between CLBP and the control group. This inconsistency may be due to the use of the 1 mV response as the baseline to generate the recruitment curve, and as such, only reflects the upper portion of a recruitment curve. Future research could utilise rMT as the baseline to generate recruitment curve to establish whether differences in MEP amplitude may be evident at lower stimulation intensities. If reduced MEP amplitude in CLBP is established in the lower portion of the recruitment curve, this may support a global hypoexcitability of the corticospinal tract in CLBP.

2.5.2 Intracortical Facilitation and Inhibition

The present study found that ICF was significantly decreased in CLBP compared to controls, a finding consistent with fibromyalgia research (Mhalla et al., 2010; Salerno et al., 2000). ICF involves excitatory glutamatergic interneurons, and reduced ICF is indicative of hypoexcitability of motor circuity (Powers et al., 2014). This is the first study to show decreased ICF in people with CLBP compared to pain-free controls. Two motor cortex mapping studies reported smaller map volumes in the motor cortex in people with CLBP. Tsao et al (2011) and Schabrun et al. (2017) reported that the smaller map volumes were indicative of reduced corticomotor excitability (Massé-Alarie & Schneider, 2016; Wassermann et al., 1992) and was therefore consistent with previous research that reported reduced corticospinal excitability in CLBP (Strutton et al., 2005). Although non-significant, Massé-Alarie et al. (2017) reported an overall reduced level of facilitation in people with CLBP compared to pain-free controls. Neurochemical N-Acetylaspartate, which acts on excitatory glutamate receptors, has also been shown to be reduced in CLBP compared to pain-free controls (Sharma et al., 2012). Sharma et al. (2012) suggested that a reduction in N-Acetylaspartate may underlie functional motor cortex changes in CLBP. This provides further support for the hypoexcitability of the motor cortex in CLBP. In comparison to other CLBP studies, the present findings did not indicate any changes in inhibition (SICI). Strutton et al. (2005) reported decreased GABA inhibition in people with CLBP, as measured by the cortical silent period, but did not investigate any changes in SICI or ICF. Conversely, Massé-Alarie et al. (2016) reported no difference in $GABA_B$ inhibition in people with CLBP but did report a decrease in $GABA_A$ SICI. This discrepancy may be related to the target muscle examined (e.g., lumbar multifidus muscles vs FDI). One possibility is that there may be distinct local and global effects on corticospinal excitability. Local effects may represent mixed effects of peripheral (occurs at the level of nociceptors) and central sensitisation (occurs in the central nervous system), while global effects may indicate persistent and maladaptive central sensitisation . Future research should compare the target muscle for stimulation (e.g., site of pain vs. muscles that are not in close proximity to the site of pain) to determine whether there are distinct local and global effects on corticospinal excitability in CLBP.

Hypoexcitability has been reported for other forms of chronic pain, including arthritis (Salerno et al., 2000) and fibromyalgia (Mhalla et al., 2010; Salerno et al., 2000). Although hypoexcitability may result from both spinal and supraspinal mechanisms, Mhalla et al. (2010) and Schoenen et al. (2008) suggested that hypoexcitability (as indicated by higher motor threshold) involves supraspinal mechanisms, as opposed to spinal mechanisms (Mhalla et al., 2010; Schoenen et al., 2008). The involvement of supraspinal mechanisms was supported by a lack of change in the H-reflex and dysfunctional motor control in fibromyalgia (Mhalla et al., 2010; Schoenen et al., 2008). Given the similar findings in the present study and frequently reported motor dysfunction in previous CLBP studies, it seems reasonable to suggest that hypoexcitability in people with CLBP may also involve supraspinal mechanisms. Establishing the involvement of supraspinal mechanisms in hypoexcitability in CLBP may be of clinical importance as there is evidence that cortical disruption contributes to, and/or maintains, chronic pain (Meier et al., 2019; Moseley & Flor, 2012; Thapa et al., 2018).

2.5.3 Association between Intracortical Mechanisms and Pain

It is known that clinical dysfunction in chronic pain and CLBP, including increased disability (Strutton et al., 2005), fatigue (Schabrun et al., 2017), depression, and catastrophising (Mhalla et al., 2010). It has been reported that the intensity of fatigue in fibromyalgia was correlated with decreased ICF, while depression and catastrophising was associated with decreased SICI (Mhalla et al., 2010). Furthermore, chronic pain studies have reported the restoration of normal SICI and ICF levels when pain was removed (Antal et al., 2010; Fregni et al., 2006a).

While the present study did not reveal significant relationships between pain intensity, disability, catastrophising, and specific measures of cortical excitability, exploratory analysis revealed a relationship between the balance of facilitation and inhibition with pain intensity. Results showed that a bias towards inhibition was associated with increased pain intensity. These results suggest that the relationship between cortical excitability and pain cannot be simply explained by a gross or singular measure (such as ICF) in isolation but may be the result of the interaction between multiple mechanisms. While the finding that increased pain is associated

with SICI appears incongruent with the overall finding of decreased ICF, it is possible that reduced excitability may be regulated by an increase in inhibition to keep the nervous system within a functional, dynamic range (Filmer et al., 2019; Thapa et al., 2018). As a result, pain might be a by-product of neural dysfunction when excitation/inhibition mechanisms are not balanced. This may be an important consideration for the use of neuromodulation techniques as a potential treatment for chronic pain. Thapa et al. (2018) reported that 68% of their CLBP sample exhibited impaired homestatic excitability, whereby participants did not show the expected increase in excitability following tDCS over the motor cortex. This suggests that establishing an imbalance in excitation may be beneficial in determing who may (or may not) respond to neuromodulation techniques.

2.5.4 Limitations

There are a few limitations that must be acknowledged. The use of analgesic medications can influence cortical excitability. Benzodiazepines are reported to significantly increase SICI, as benzodiazepines increase $GABA_A$ inhibitory transmission (Di Lazzaro et al., 2006). In contrast, ICF is decreased by $GABA_A$ receptor agonists (such as benzodiazepines), and N-methyl-D-aspartate receptor agonists (synthetic opioids; Schwenkreis et al., 1999). While medication use was recorded in the present study, frequency of use and dosage was not documented. Although a limitation, correlations revealed that there was no relationship between medication use (use of anti-inflammatories, over-the-counter medication, prescription pain killers, benzodiazepines, or anti-depressants for pain management) and MEP amplitude. Given this, and as analgesics were not associated with changes in cortical excitability and modulation in fibromyalgia (Mhalla et al., 2010), medication use is not thought to underlie the findings of the present study. Additionally, the present study did not examine motor control in CLBP. Given the involvement of motor cortical structures in movement planning and execution (Schabrun et al., 2017), it is likely that changes in motor cortex excitability may be associated with decreased motor control in people with CLBP. Future research should examine the relationship between corticospinal excitability and motor control to determine if reduced facilitation is associated with reduced motor control in CLBP.

2.5.5 Conclusion

These findings add to the growing body of evidence that CLBP is associated with changes in intracortical excitability. While it appears changes in ICF may contribute to the pathophysiology of CLBP, future studies should examine if these changes are directly responsible for CLBP symptoms, or an indirect result of the interaction between multiple mechanisms. Nonetheless, these results may have direct clinical applications in terms of the use of neuromodulation techniques for the treatment of CLBP. Previous research has suggested that functional improvements in chronic pain are related to the restoration of altered intracortical excitability (Lefaucheur et al., 2006; Mhalla et al., 2010). Given the present findings show that altered intracortical excitability occurs in CLBP, the use of neuromodulation techniques may be of clinical significance for rehabilitation and treatment of people with CLBP.

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CHAPTER THREE: COGNITIVE PROFILE AND MILD COGNITIVE IMPAIRMENT IN PEOPLE WITH CHRONIC LOWER BACK PAIN

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3.0 Abstract

A growing body of evidence suggests Chronic Lower Back Pain (CLBP) is associated with cognitive dysfunction. Little is known, however, about the extent of cognitive impairment in CLBP. The present study explored the cognitive profile of people with CLBP and sought to determine the extent of Mild Cognitive Impairment (MCI) according to the DSM-5 and the Movement Disorders Society criteria for MCI. Thirty-one participants with CLBP and 27 age and gender matched healthy controls completed a full neuropsychological battery, consisting of two tasks for each of the five cognitive domains (Executive Function, Attention/Working Memory, Memory, Language, and Visuospatial). Participants with CLBP performed worse, compared to controls, on measures of Attention/Working Memory, Memory, Language, and Visuospatial performance. Cognitive performance in CLBP was also compared to equivalent normative data to determine cognitive impairment. Sixteen CLBP participants were impaired on at least one cognitive measure, with 5 participants meeting criteria for MCI. MCI was not associated with pain-related experience, or psychological health. The present study supports and extends previous findings that CLBP is associated with cognitive dysfunction and some people with CLBP meet criteria for MCI. These findings support that rehabilitation in people with CLBP requires a multidisciplinary approach.

3.1 Introduction

Chronic Lower Back Pain (CLBP) is a leading cause of disability worldwide (Hoy et al., 2014). It is increasingly acknowledged that CLBP involves both physiological and cognitive changes. Pain is a conscious experience, as the pain response is produced by both actual and perceived danger to body tissues. Cognitive processing of pain information therefore underlies much of the pain experience (Melzack, 2001; Moseley & Flor, 2012). The prefrontal cortex plays a key role in pain modulation (Lorenz et al., 2003) and the cognitive evaluation of pain (Melzack, 2001; Mylius et al., 2006). The cognitive evaluation of pain involves the appraisal of the pain sensation and the emotional response to the pain sensation (Kong et al., 2006). Cognitive evaluative mechanisms contribute to pain chronicity, as these mechanisms increase the perceived threat of pain and activity in the salience matrix (Moseley, 2003). Functional imaging studies reveal that the Dorsolateral Prefrontal Cortex (DLPFC) is involved in pain modulation (Brighina et al., 2011), and is key to the cognitive processing of pain (Moseley, 2003).

There are several theories about why cognition may be impaired in chronic pain, one of which suggests that the processing of nociceptors engages a significant amount of resources in the DLPFC (Seminowicz & Moayedi, 2017). Consequently, there are fewer resources available for the typical cognitive functions of the DLPFC, such as executive functions, planning skills, and working memory (Berryman et al., 2013; Seminowicz & Davis, 2007). Another theory suggests that decreased cortical inhibition extends the duration of activation in the DLPFC during pain processing. As a result, the DLPFC is unable to shift attention away from the pain to 'free up' resources for normal cognitive functioning (Berryman et al., 2013). Pain processing renders any other typical DLPFC cognitive function a dual-task scenario. Although the underlying mechanisms may vary, both theories suggest that chronic pain is cognitively demanding and diverts resources away from normal cognitive functioning (Smith & Ayres, 2014).

While it is acknowledged that increased attention to pain is cognitively demanding, few studies have investigated the impact of CLBP on the different cognitive domains simultaneously. A Movement Disorder Society (MDS) taskforce suggested there are 5 key domains of cognition, including (i) Executive Function, (ii) Attention and Working memory, (iii) Language, (iv) Memory, and (v) Visuospatial.

Studies of different forms of chronic pain have examined multiple cognitive domains, but these studies do not provide information on the nature of cognition in individual chronic pain conditions such as CLBP. It is currently unknown if the nature of cognition, and potential impairments, varies across different forms of chronic pain (Moriarty et al*.,* 2011). It is important to profile the specific nature of cognition in CLBP, as deficits in cognitive function have the potential to hinder rehabilitation and contribute to pain chronicity.

People with chronic pain perform poorly on measures of global cognition compared to healthy controls (Moriarty et al*.,* 2011), and the prevalence of global cognitive impairment is higher in people with chronic pain compared to the general population (Povedano et al*.,* 2007; Rodriguez-Andreu et al., 2009). Studies in chronic pain have reported impaired cognitive functioning across many different cognitive domains, including memory and executive function (Moriarty et al., 2011; Berryman et al., 2013). A systematic review by Berryman et al. (2013) found that people with chronic pain performed poorly on measures of verbal working memory, non-verbal working memory and attention, and working memory compared to healthy controls (Berryman et al., 2013). Deficits have also been reported for verbal, visual, and spatial memory in people with CLBP compared to normative data (Jorge et al*.,* 2009). Ling et al. (2007) reported that people with CLBP were more likely to report problems with their everyday memory compared to those without chronic pain. It has been suggested that the cognitive demands of chronic pain uses resources that would have otherwise been allocated to working memory, resulting in working memory impairment (Smith & Ayres, 2014). As working memory is important for learning, people with chronic pain demonstrate poor retention of new information (Smith & Ayres, 2014). Such cognitive impairments may hinder rehabilitation and activities of daily living in people with chronic pain.

Deficits in executive functioning have also been identified in CLBP. A systematic review by Moriarty et al. (2011) found that tasks involving more complex executive-type function and attention switching were more likely to be affected by chronic pain compared to less complex, automatic tasks. In CLBP, performance on emotional decision-making tasks, which involve higher-level executive functioning, is typically impaired (Apkarian et al., 2004a; Moriarty et al., 2011; Verhoeven et al., 2011). Impairments in decision-making and planning are associated with

disengagement from everyday activities and poor quality of life (QOL) in people with chronic pain (Hoy et al., 2014; Roth et al*.,* 2005).

Most studies in CLBP have investigated cognitive domains independently of one another and provide only a snapshot into cognitive functioning (Apkarian et al., 2004a). In comparison, some studies in chronic pain (varying forms of chronic pain, including CLBP) have examined all cognitive domains simultaneously. This has allowed for the identification of typical cognitive impairment in chronic pain (Higgins et al., 2018). However, these studies are unable to identify the nature and extent of impairment in specific chronic pain conditions, and it is unknown which cognitive impairments are more likely to be impacted by CLBP.

To properly identify cognitive impairment in CLBP, the DSM–5 suggests participants must demonstrate modest impairment in at least *one or more* cognitive domains. To meet criteria for Mild Cognitive Impairment (MCI) according to the DSM-5, participants must score 1 – 2 standard deviations (*SD)* below the appropriate mean in one or more cognitive domains (American Psychiatric Association, 2013; Litvan et al., 2012). However, the DSM-5 provides few recommendations for the measures that should be used, or the number of tests required per domain to determine MCI. The Movement Disorders Society Taskforce criteria (MDS; https://www.movementdisorders.org/) recommends the use of two neuropsychological tests for each of the five cognitive domains, suggesting the use of *at least ten tests* for the comprehensive assessment of MCI (Litvan et al., 2012). According to the MDS criteria, if a participant demonstrates impairment on *at least 2 of the 10 tests*, they meet the criteria for MCI. As CLBP shares similar motor characteristics and motor impairments (e.g., bradykinesia, rigidity, poor balance; Jacobs *et al.,* 2018) as movement disorders such as Parkinson's Disease, for which pain can be very impactful in their everyday activities, and given the vague recommendations from the DSM-5, the MDS criteria may be more appropriate for the identification of MCI in CLBP.

Cognitive impairment in CLBP is associated with disengagement from everyday activities and poor quality of life (Hoy et al., 2014; Smith & Ayres, 2014). A greater understanding of the cognition-pain relationship may highlight avenues to improve engagement and quality of life in those with CLBP. The present study examined the nature of cognition in CLBP compared to age and gender matched controls. It was hypothesised that when compared to gender and age matched healthy

controls, those with CLBP would perform significantly worse on all measures of cognitive function. The present study also explored MCI in CLBP using both the MDS and DMS-V criteria. As cognitive function may be impacted by pain-related factors, the present study also examined pain experience, medication use, psychological health, and disability.

3.2 Methods

3.2.1 Participants

Participants were recruited via convenience sampling to participate in a 5-week intervention study. The participants' assessments at baseline form the data for the present study. This study was approved by Curtin University human research ethics committee (HR17/2015) and all research was conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent. Inclusion in the study required a formal diagnosis of CLBP by a qualified health professional (General Practitioner or Physiotherapist) of at least 6 months (see Table 3.1 for demographic information and pain related information). Individuals were screened for cognitive status using the Telephone Interview for Cognitive Status – 30 (TICS-30; score ≥ 18 for inclusion). Thirty-one participants met the inclusion criteria for participation. Control participants (n = 27, M = 56.70, SD = 3.34) were recruited based on age and gender-match to the CLBP participants. There were no significant demographic differences between the CLBP and control group.

3.2.2 Power Analysis

Sample size for this study was driven by the statistical power required for the over-arching intervention study. Power calculations using g-Power revealed thirty participants with CLBP in the intervention study would provide sufficient power to detect a very large multivariate interaction (f(V) = .63) at an alpha-level of .05. A posteriori power calculation revealed the current study has an appropriate number of participants, with an 80% chance of detecting moderate effects (f(V) = .25) at an alpha-level of .05.

Table 3.1

Baseline profile for CLBP participants

	Total (n = 31)	Males (n = 19)	Females (n = 12)
Age	56.90 (14.62)	61.11 (13.61)	50.25 (14.18)
Years of Education	12.58 (3.12)	11.95 (2.67)	13.58 (3.62)
Duration of Diagnosis (years)	16.38 (13.69)	19.65 (14.98)	11.21 (9.82)
VAS Pain Average	5.05 (1.98)	4.71 (2.10)	5.58 (1.73)
CLBP Classification			
Non-Specific	84%	84%	83%
Specific	13%	16%	8%
Neurological	3%	-	8%
Percentage taking Pain Medication	61%	53%	75%
Anti-Inflammatory (Celebrex)*	47%	50%	44%
Pain Killer (Tremadol)*	79%	70%	89%
Benzodiazepine (Valium)*	21%	10%	33%
Anti-Depressants (Endep)*	16%	20%	9%
Engaging in Physiotherapy	45%	37%	58%
Past Surgery	19%	21%	17%
Other Pain Management (Chiropractor)	74%	79%	67%
Depression and Anxiety Disorder	19%	16%	25%
Anti-Anxiety Medication*	33%	33%	33%

Note. CLBP Classification = classification of chronic lower back pain based on Koes *et al* (2001), Non-Specific = no radiographical injury at time of participation, Specific = Radiographical evidence, Neurological = related to change in the Central Nervous System. Pain Average = Average pain intensity one week prior to participation. Other = Acupuncture, Chiropractor, Massage. * = Percentage based on individuals taking pain medication

3.2.3 General Procedure

Participants were mailed a questionnaire pack before undertaking a neuropsychological assessment at the Curtin University. Assessments took approximately 2.5 hours to complete. All participants were asked to continue their normal medication routine.

3.2.4 Measures

Age, sex, employment status, marital status, level of education, age at diagnosis, diagnosis duration, and medication use were collected via self-report questionnaire. All participants completed the neuropsychological and clinical assessment. In accordance with DSM-5 and MDS criteria recommendations for MCI, two measures were administered for each of the five cognitive domains.

3.2.4.1 Neuropsychological Assessment

Executive Function. The Cambridge Neuropsychological Test Automated Battery (CANTAB™) *Stockings of Cambridge* (SOC) subtest involves participants being presented with two horizontal images on a computer screen of balls sitting in stockings (one image above the other). Participants are asked to move the balls in the bottom image to match the configuration of the balls in the top image. The *Controlled Oral Word Association Task* (COWAT; Benton *et al.,* 1994a) involves participants being given 60 seconds to say as many words as possible beginning with the letter F, then A, and S (FAS).

Attention and Working Memory. The *Letter-Number Sequencing* subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008) requires participants to listen to a list of alternating letters and numbers and then repeat the list in ascending order, numbers first (e.g., 6-F-2-B). The *Stroop (Colour-Word) Test* (Stroop 1935; Jensen & Rohwer, 1966) involves a set of 100 words (20 words x 5 columns) presented to participants. Participants were required to say what colour each word was printed in as they read through each column. The words are 'RED', 'GREEN', and 'BLUE' and were printed in an incongruent colour.

Memory. The *Hopkins Verbal Learning Test-Revised* (HVLT; Brandt, 1991) requires participants to listen a list of 12 words relating to animals, dwellings, and precious stones and were then required to recall as many of the words as possible (Brandt & Benedict, 2001). The *Paragraph Recall* subtest of the Rivermead Behavioural Memory Test (RBMT; Wilson *et al.,* 1989) involves a short passage being read to participants and then they were immediately asked to recall as many 'ideas' as possible.

Language. The *Boston Naming Test* (BNT; Kaplan et al., 2001) involves showing 60 ink drawings of common objects (e.g., pencil, tree). Participants were

required to describe what the drawings represent (Lezak et al., 2004). The *Similarities* subtest of the WAIS-IV (Wechsler, 2008) involved participants being read two words (e.g., yellow and green) and asked to explain how the words are similar (Wechsler, 2008).

Visuospatial. The *Judgement of Line Orientation* (JLO; Benton et al*.,* 1994b) required participants to estimate the angular orientation of two lines presented on a card. A referenced set of angled lines were provided for comparison. The *Hooper Visual Organisation Test* (HVOT; Hooper, 1983) involves showing 30 pictures of everyday objects that have been cut into pieces and asking participants to name the objects (Lopez et al*.,* 2003).

3.2.4.2 Clinical and Pain-related measures

Pain Experience. The *Short-Form McGill Pain Questionnaire* (SF-MPQ) contains a 10 cm Visual Analogue Scale (VAS) used to assess average pain intensity in CLBP (Melzack, 1975). The VAS is a unidimensional measure of pain intensity and participants were required to mark the line at the spot they felt represented their level of pain (Hawker et al*.,* 2011).

Disability. The *Roland-Morris Disability Questionnaire* (RMDQ) assessed the level of disability in CLBP (Roland & Morris, 1983). The RMDQ consists of 24 items assessing the impact of CLBP across multiple domains (mobility, daily activities, sleeping, mood, and appetite).

Depression. The *Depression, Anxiety, and Stress Scale-21* (DASS-21) assessed the presence of depression, anxiety, and stress in CLBP (Lovibond & Lovibond, 1995). The DASS-21 consists of three subscales; depression, anxiety, and stress.

Fatigue. Fatigue was assessed using the Energy/Fatigue subscale from The *MOS 36-Item Short-Form Health Survey* (SF-36; Ware & Sherbourne, 1992). The Energy/Fatigue subscale consists of 4 items assessing levels of energy and fatigue during the past 4 weeks.

3.3 Statistical Analysis

All Analyses were conducted using SPSS version 26. Analyses were conducted in 4 stages. Stage one identified possible covariates. Demographic

variables were assessed using a One-Way ANOVA. As cognitive performance can be influenced by depression, stress, anxiety, and fatigue, a One-Way MANOVA was also conducted to identify potential additional covariates. Following significant main-effects, univariate ANOVAs were conducted to identify which variables significantly differed between the CLBP and control group. If significant differences between the CLBP and control group were identified, bivariate correlations were conducted to assess the relationship between the covariates and cognitive variables. If the covariates were not significantly different between the groups, or were not significantly correlated with the cognitive variables, they were excluded from the main analysis.

In stage two, a One-Way MANCOVA was performed to assess whether the CLBP group and the controls differed significantly on the omnibus cognitive variables. Following a significant MANCOVA finding, univariate ANOVAs were conducted to identify the specific cognitive measures that demonstrated significant differences between the groups. Significant MANCOVA was followed by logistic regression to ascertain whether cognitive scores could identify membership to the CLBP or control group.

In stage three, cognitive performance was compared to normative data. The CLBP group was allocated to the No Impairment, Single Task Impairment and Multiple Domain MCI groups according to cognitive performance. Analysis to determine group differences between the mild cognitive impairment groups followed the same procedure as for the aforementioned stages one and two of analysis. Pain catastrophising and disability (in addition to depression, stress, anxiety, and fatigue) were assessed using a One-Way MANOVA to identify possible covariates. If no significant between-group differences were identified for a given variable (i.e. did not meet criteria for inclusion as a covariate), the variable was excluded from further analysis.

In stage four, a One-Way MANOVA assessed whether the No Impairment group, the Single Impairment group, and Multiple Domain MCI group differed on the omnibus cognitive variables. Following a significant MANOVA, univariate ANOVAs were conducted to identify the specific cognitive measure(s) that demonstrated significant between-group differences. Significant MANOVA was then followed by discriminant analysis to ascertain whether performance in the individual

cognitive domains could determine membership in the different mild cognitive impairment groups.

3.4 Results

A One-Way MANOVA showed that the CLBP group and the controls differed significantly on the combined measures of depression, stress, anxiety, and fatigue, $F(4, 53) = 5.38$, $p = .001$, Wilks' $\Lambda = .711$, partial $\eta 2 = .29$. Univariate ANOVAs revealed no significant differences between the CLBP and control groups for depression, stress, and anxiety. These measures were therefore omitted from future analysis. The Univariate ANOVA revealed a significant difference between the CLBP ($M = 40.16$, $SD = 19.77$) and control group ($M = 60.93$, $SD = 17.43$) for fatigue, $F(1, 56) = 17.75$, $p < .001$, partial $\eta 2 = .24$, whereby the CLBP group reported greater fatigue than the control group. However, correlations between fatigue and cognitive variables revealed that fatigue was not associated with the cognitive variables, and so was omitted from further analysis. As education was strongly correlated with the cognitive variables, it was included as a covariate in the analysis. There was a significant effect of education on the omnibus cognitive variables, $F(13, 43) = 2.72$, $p = .007$; Wilks' $\Lambda = .550$, partial $\eta^2 = .45$. After controlling for education, the CLBP group and the controls differed significantly on the omnibus cognitive variables (i.e. the combination of all cognitive variables), $F(13, 43) = 2.45$, $p = .014$; Wilks' $\Lambda = .574$, partial $\eta^2 = .43$. There was a significant difference between groups on the Attention/Working Memory task (LNS), Memory tasks (Paragraph Recall and Paragraph Delayed Recall), Language tasks (Similarities and BNT), and Visuospatial task (JLO). Effect sizes are presented in Table 3.2.

The significant MANCOVA was followed by logistic regression, to determine the effects of cognition on the likelihood that participants had CLBP. The logistic regression model was statistically significant, $\chi^2(12) = 39.60$, $p < .001$. The model explained 66.1% (Nagelkerke R^2) of the variance in CLBP and correctly classified 85% of cases (CLBP = 84%, controls = 85%). The Attention/Working Memory task (LNS) was the only measure that significantly predicted group membership, Wald's $\chi^2(1) = 4.63$, $p = .03$.

Table 3.2

Means, Standard Deviations, and Analysis of Variance (ANOVA) of Cognitive Scores for CLBP and Control Group

	Total Scores					
	CLBP (*n*=31)	Control (*n* =27)	*MS*	*F*	*DF*	η2
TICS – 30	24.55 (1.96)	25.67 (1.62)	3.34	1.27	1, 55	.02
Executive Function						
COWA - FAS	39.00 (13.79)	48.62 (12.07)	604.89	3.83	1, 55	.07
SOC Total	8.81 (1.80)	8.96 (2.23)	1.95	0.56	1, 55	.01
Memory						
HVLT Total	25.94 (3.15)	27.41 (3.32)	5.84	0.62	1, 55	.01
HVLT Delayed	9.26 (2.14)	9.85 (1.35)	1.88	0.57	1, 55	.01
Paragraph Recall	7.35 (3.09)	9.51 (2.30)	28.81	4.21*	1, 55	.07[a]
Paragraph Delayed	6.05 (3.09)	8.39 (2.26)	46.35	6.38*	1, 55	.10[b]
Language						
Similarities	22.90 (4.09)	26.96 (2.52)	134.91	12.44*	1, 55	.18[b]
BNT Total	55.32 (3.95)	58.74 (1.51)	121.53	12.99*	1, 55	.19[b]
Attention/Working Memory						
LNS	19.74 (2.56)	22.85 (2.28)	76.27	14.74**	1, 55	.21[b]
STROOP	38 (10.26)	43.59 (6.70)	202.42	2.75	1, 55	0.05
Visuospatial						
HVOT	25.44 (2.95)	26.96 (1.62)	20.92	3.56	1, 55	0.06
JLO Total	25.16 (4.16)	28.67 (2.27)	85.76	7.24*	1, 55	0.12[b]

Note. TICS- 30 = Telephone Interview for Cognitive Status – 30, HVLT = Hopkins Verbal Learning Test, JLO= Judgement of Line Orientation, BNT = Boston Naming Test, LNS = Letter Number Sequencing, COWA – FAS = Controlled Oral Word Association – FAS, HVOT = Hooper's Visual Organisation Test, SOC Total = Stockings of Cambridge, solved in minimum moves.
** = $p < .001$, * = $p < .05$. [a] = small effect, [b] = medium effect

3.4.1 MCI Classification in CLBP

According to the MDS and DSM-5, an individual test score is considered abnormal (i.e. meets criteria for MCI classification) if it is 1 -1.5 SD below the age/gender/education appropriate normative value (Litvan et al., 2012; APS, 2013). A test score is meets criteria for Major Cognitive Impairment if it is 2 or more SD below the appropriate normative value (see Table 3.3 for frequency of participants with scores 1, 1.5, and 2 SD below the appropriate normative value). For the current study, an individual test score was deemed abnormal if it was 1.5 SD or more below the age/gender/education appropriate normative mean (except error values, where 1.5 SD or more above the normative error was deemed abnormal). Participants were classified in accord with MDS criteria for MCI. Participants who demonstrated no deficit test scores were classified as "No Impairment". Participants who demonstrated one deficit test score in only one cognitive domain were classified as "Single Impairment". Participants who demonstrated at least one abnormal test score in two or more domains were classified as "Multiple-Domain MCI". Demographics and pain related information for each MCI group are presented in Table 3.4. Mean and standard deviations for each cognitive task for MCI group are presented in Table 3.5. Clinical and functional scores for each MCI group are presented in Table 3.6. At 1 SD, two control participants met the criteria for MCI and two control participants had a Single Impairment. At 1.5 SD, no control participants met the criteria for MCI, however, two participants had a Single Impairment.

Table 3.3

Frequency of Impairment in the CLBP group at 1, 1.5, and 2 SD

	1 SD		1.5 SD		2 SD	
	Single Impairment	Multiple Impairment	Single Impairment	Multiple Impairment	Single Impairment	Multiple Impairment
TICS – 30	-	-	-	-	-	-
Executive Function						
COWA - FAS	1	7	-	4	1	1
SOC Total	1	2	-	1	-	-
Memory						
HVLT Total	1	5	3	2	2	1
HVLT Delayed	1	4	1	3	1	1
Paragraph Recall	2	9	1	3	-	-
Paragraph Delayed	4	6	1	2	1	-
Language						
Similarities	-	5	1	3	1	1
BNT Total	-	5	2	1	2	1
Attention/Working Memory						
LNS	-	-	-	-	-	-
STROOP	-	3	-	1	-	1
Visuospatial						
HVOT	-	-	-	-	-	-
JLO Total	1	3	1	1	-	1

Note. TICS- 30 = Telephone Interview for Cognitive Status, HVLT = Hopkins Verbal Learning Test, JLO= Judgement of Line Orientation, BNT = Boston Naming Test, LNS = Letter Number Sequencing, COWA – FAS = Controlled Oral Word Association – FAS, HVOT = Hooper's Visual Organisation Test, SOC Total = Stockings of Cambridge, solved in minimum moves.

Table 3.4

Frequencies and demographics (mean, standard deviation) for each MCI group

n = 31	No Impairment	Single Impaired Task	Multiple Domain MCI
n	15	11	5
Males (% of subtype)	60%	55%	80%
Age	57.93 (12.03)	58.64 (17.52)	50.00 (16.05)
Years of Education	13.4 (3.58)	12.26 (2.52)	10.8 (2.37)
Duration of Diagnosis (years)	19.06 (15.68)	12.54 (9.53)	16.83 (15.86)
VAS Pain Average	4.95 (2.25)	4.57 (1.34)	6.38 (2.08)
Married (% of subtype)	73%	64%	80%
Employed (% of subtype)	67%	55%	60%
CLBP Classification			
Non-Specific	87%	73%	100%
Specific	13%	18%	-
Neurological	-	9%	-
Percentage taking Medication	67%	82%	20%
Anti-Inflammatory (Celebrex)*	60%	20%	100%
Analgesics (Tremadol, Paracetamol)*	70%	88%	100%
Benzodiazepine (Valium)*	30%	13%	-
Anti-Depressants (Endep)*	10%	25%	-
Engaging in Physiotherapy	54%	46%	20%
Past Surgery	20%	27%	-
Other Pain Management	80%	73%	60%

Note. Other Pain Management = Chiropractor, Massage, Acupuncture, Transcutaneous Electrical Nerve Stimulation (TENS), Cortisone.

*Percentage based on individuals taking medication.

A One-Way MANOVA revealed no significant demographic differences between the No Impairment, Single Impairment, and Multiple-Domain MCI groups.

No significant differences were observed between length of diagnosis, pain intensity, pain catastrophising, and disability. These variables were therefore omitted from further analysis.

There was a significant difference between MCI groups on the omnibus cognitive variables, $F(26, 32) = 2.20$, $p = .018$; Wilks' $\Lambda = 0.13$, partial $\eta^2 = .64$. There was also a significant difference between groups on the COWA-FAS (executive function) tasks, LNS (attention/working memory) task, and Paragraph Recall and Paragraph Delayed (memory) tasks (see Table 6). The significant MANOVA was followed by discriminant analysis, which revealed two discriminant functions. The first explained 83.1% of the variance, canonical $R^2 = .86$, and the second explained 16.9%, canonical $R^2 = .60$. In combination, these discriminant functions significantly differentiated the MCI groups, $\Lambda = .170$, $\chi^2(24) = 39.86$, $p = .022$. However, removing the first function indicated that the second function did not significantly differentiate the MCI groups, $\Lambda = .640$, $\chi^2(11) = 10.03$, $p = .528$. The correlations between cognition and the discriminant function revealed that the COWA and SOC (executive function) tasks, HVLT and HVLT Delayed (memory)tasks, Similarities (language) task, and JLO (visuospatial) task loaded most highly onto the first function (see Table 6). The Paragraph Recall and Delayed Paragraph Recall (memory) tasks, BNT (language), LNS and Stroop (attention/working memory) tasks, and HVOT (visuospatial) task loaded onto the second function (see Table 3.6). The discriminant function plot showed that the first function significantly discriminated the 'Multiple Domain' MCI group from the 'Single Task' MCI, and 'No Impairment' MCI groups (see Figure 3.1). The discriminant analysis also revealed that 84% of cases were correctly classified. Three cases that were classified as No Impairment using the MDS criteria were classified as single impairment by the discriminant analysis. Two cases that were classified as Single Impairment using the MDS criteria were classified as No Impairment by the discriminant analysis.

Table 3.5

Means, Standard Deviations, and Analysis of Variance (ANOVA) for each cognitive task by MCI group and number of participants impaired on each task

	No Impairment	Single Impairment	Multiple Domain	*MS*	*F*	*DF*	n2	Impaired Tasks	
								Single Task	Multiple Domain
TICS – 30	24.87 (2.23)	24.27 (1.74)	24.20 (1.79)	1.48	0.37	2, 27	.03	-	-
Executive Function									
COWA - FAS	45.67 (11.27)	38.82 (11.49)	19.4 (2.30)	1293.92	11.62**	2, 27	.45[c]	-	4
SOC Total	9.13 (1.73)	8.91 (1.64)	7.6 (2.19)	4.50	1.43	2,27	.09	-	1
Memory									
HVLT Total	26.73 (2.71)	25.73 (3.80)	24.00 (2.35)	14.38	1.50	2, 27	.10	3	2
HVLT Delayed	9.87 (2.00)	9.18 (1.72)	7.6 (2.97)	9.68	2.29	2, 27	.14	1	3
Paragraph Recall	9.13 (2.68)	6.00 (2.16)	5.00 (3.28)	47.68	7.02*	2, 27	.33[c]	1	3
Paragraph Delayed	7.77 (2.83)	4.45 (2.53)	4.40 (2.43)	42.91	6.00*	2, 27	.30[c]	2	1
Language									
Similarities	24.07 (2.55)	23.18 (4.53)	18.80 (4.97)	52.67	3.73*	2, 27	.21[b]	1	3
BNT Total	57.07 (2.15)	54.27 (4.43)	52.40 (5.13)	50.23	3.84*	2, 27	.22[b]	2	1
Attention/Working Memory									
LNS	21.07 (2.71)	18.91 (1.70)	17.60 (1.34)	28.45	5.73*	2, 27	.29[c]	-	-
STROOP	41.80 (11.25)	35.73 (3.29)	31.60 (14.12)	239.12	2.50	2, 27	.15	-	1
Visuospatial									
HVOT	25.23 (2.40)	24.82 (3.68)	27.40 (2.33)	12.05	1.42	2, 27	.09	-	-
JLO Total	25.93 (3.58)	25.45 (4.03)	22.20 (5.54)	26.87	1.62	2, 27	.10	1	1

Note. TICS- 30 = Telephone Interview for Cognitive Status, HVLT = Hopkins Verbal Learning Test, JLO= Judgement of Line Orientation, BNT = Boston Naming Test, LNS = Letter Number Sequencing, COWA – FAS = Controlled Oral Word Association – FAS, HVOT = Hooper's Visual Organisation Test, SOC Total = Stockings of Cambridge, solved in minimum moves. ** = p <.005, * = p<.001. [b] = medium effect, [c] = large effect.

Table 3.6

Pooled within-groups correlations between cognitive tasks and discriminant functions.

	Function 1	Function 2
Executive Function		
COWA - FAS	.547*	.081
SOC Total	.192*	-.038
Memory		
HVLT Total	.192*	.092
HVLT Delayed	.241*	.067
Paragraph Recall	.336	.581*
Paragraph Delayed	.262	.652*
Language		
Similarities	.310*	-.041
BNT Total	.276	.335*
Attention/Working Memory		
LNS	.333	.428*
STROOP	.224	.268*
Visuospatial		
HVOT	-.169	.202*
JLO Total	.203*	-.052

Note. HVLT = Hopkins Verbal Learning Test, JLO= Judgement of Line Orientation, BNT = Boston Naming Test, LNS = Letter Number Sequencing, COWA – FAS = Controlled Oral Word Association – FAS, HVOT = Hooper's Visual Organisation Test, SOC Total = Stockings of Cambridge, solved in minimum moves.
*Largest absolute correlation between each variable and function.

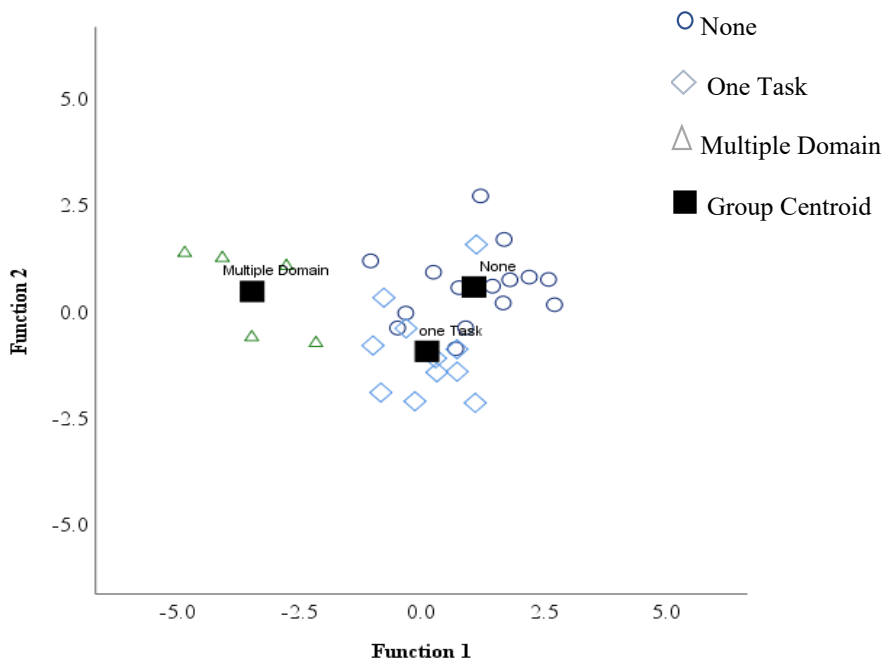

Figure 3.1. *Canonical Discriminant Functions of the No Impairment, Single Impairment, and Multiple Domain MCI groups.*

3.5 Discussion

The present study examined cognition in CLBP, compared to pain-free, age, and gender-matched controls. Previous research has focused on specific cognitive domains and has not provided a comprehensive picture of cognition in CLBP. The present study revealed that cognitive function was significantly worse in people with CLBP compared to matched controls. In particular, those with CLBP performed significantly worse on Memory, Language, Attention/Working Memory, and Visuospatial tasks. These deficits were not determined by depression, stress, anxiety, or fatigue. Logistic regression was used to examine whether cognition scores could be used to identify people with CLBP. The results of the logistic regression revealed that 84% of the CLBP sample could be correctly identified as having CLBP based on their cognitive performance, suggesting that the pattern of deficits in cognition present similarly in people with CLBP.

Previous research has identified deficits in individual cognitive domains in CLBP and chronic pain (Higgins et al., 2018), with reported deficits in attention/working memory, executive function, and visuospatial domains (Berryman et al., 2013; Higgins et al., 2018; Jorge et al., 2009; Verhoeven et al., 2011).

Consistent with such research, the present sample showed deficits in attention/working memory and visuospatial performance. Deficits in attention/working memory in chronic pain are considered to be associated with decreased cognitive resources available in the prefrontal cortex (Berryman *et al*., 2013; Borkum, 2010; Seminowicz & Davis, 2007). Very few studies have examined language in chronic pain. In the present study, CLBP participants performed significantly worse on both measures of language compared to age and gender matched controls. As the two language tasks required fast processing of semantic information and reasoning ability (Kaplan et al., 2001; Wechsler, 2008), a lack of prefrontal cognitive resources may explain the deficit in language ability. As pain processing itself is cognitively demanding, it may impact on a person's speed of processing such that words cannot be efficiently recalled (Schiltenwolf et al., 2014). Future research should examine the relationship between speed of processing and language in CLBP, to determine if deficits in language skills are related to a global reduction in processing speed or if they represent a specific language impairment.

The present study is the first to implement the MDS taskforce criteria for MCI, in conjunction with recommendations from the DSM-5, to determine the nature of cognitive impairment in CLBP. Using the MDS criteria, five participants were identified as meeting the criteria for multiple domain cognitive impairment. Of these five participants, three showed impairments across three cognitive domains; Executive Function, Language, and Memory. One participant showed impairments in Executive Function and Memory, and one participant showed impairments in Language and Memory. Eleven participants were impaired on a single task, and 15 participants were not impaired on any cognitive task. Over half the CLBP sample met standardised criteria for clinical MCI, compared to no MCI in their matched control group counterparts.

The present study also examined how cognition differed between the three MCI groups (multiple, single, no impairment). There was a significant difference between all three MCI groups on cognitive performance, with the multiple domain MCI group performing worse in four of the five cognitive domains, compared to the single impairment and no impairment groups. The multiple domain MCI group had significantly lower scores on measures of Executive Function (COWA-FAS), Memory (Paragraph Recall and Paragraph Delayed), Language (BNT and

Similarities), and Attention/Working Memory (LNS). This suggests that cognitive impairment in CLBP may be present across more cognitive domains than previously reported.

A discriminant function analysis determined if cognition scores could predict membership to an MCI group. The results revealed that 84% of cases were classified to the correct MCI group. One hundred per cent of participants were correctly classified to the multiple domain MCI group. The discriminant analysis also revealed that the cognitive scores for the multiple domain MCI group could be significantly differentiated from the single and no impairment groups. This differentiation was primarily driven by Executive Function, with both tests of Executive Function loading onto the differentiating function. This indicates that individuals with CLBP who perform poorly on tasks of Executive Function are more likely to belong to the multiple MCI group, suggesting that those who demonstrate Executive Function dysfunction are also likely to be deficit in other cognitive domains. This finding suggests that cognitive impairment in CLBP is not limited to distinct cognitive domains and may be evident across all aspects of cognition. Due to the lack of relationships between fatigue and cognitive performance, the deficit in cognition does not appear to be driven by fatigue. These findings support the use of the MDS criteria for determining cognitive impairment in CLBP, as it allows for cognition to be assessed across multiple domains and provides a more comprehensive indication of the nature of cognitive dysfunction.

The cognitive findings in the present study are consistent with the theory that the processing of CLBP engages valuable resources in the prefrontal cortex. Furthermore, the impairment of timed tasks in the Language and Visuospatial domains supports the suggestion that individuals with CLBP have impaired speed of processing (Higgins et al., 2018; Schiltenwolf et al., 2014;). Schiltenwolf et al. (2014) suggested that individuals with CLBP may perform normally on simple tasks, but that performance worsens when tasks require fast, cognitive flexibility and when the cognitive demand of the task increases. This suggests that the prefrontal cortex may not have the available resources to cope with increased cognitive demand during pain processing and may lead to a loss of attention. This may have a significant impact on rehabilitation in CLBP. Weiner et al (2006) reported that cognitive performance on measures that require fast, cognitive flexibility were strongly

associated with physical performance. Weiner et al (2006) suggested that some physical disability in CLBP may result from deteriorating cognition. If this is the case, rehabilitation and treatment of CLBP should take a multidisciplinary approach that focuses on improving cognition as well as physical performance and pain.

The use of MCI diagnostic criteria is typically applied to those with degenerative neurological conditions, such as Alzheimer's and Parkinson's disease (Litvan et al., 2012; Petersen, 2004). Recent research suggests there are underlying brain changes in chronic pain that are consistent with neurodegeneration (Fritz et al., 2016; Jongsma et al., 2011; Seminowicz & Moayedi, 2017). In light of this, the use of the MDS criteria for identification of MCI in CLBP may be more suitable than other identification methods. Prevalence rates in healthy ageing suggest that 3 -15% of the ageing population (over 65 years of age) meet the criteria for MCI (Petersen et al., 2009). In midlife adults (50 – 60 years of age), the prevalence of Multiple domain MCI is between 2 and 6% (Kremen et al., 2013). In the present study, 16% of CLBP participants met the criteria for Multiple Domain MCI, suggesting that those with CLBP are more likely to meet MCI criteria than the general population. This is important, as those with MCI are more likely (than those without) to rapidly progress to dementia (Kremen et al., 2013; Petersen et al., 2009). As this is the first study to identify MCI in CLBP, the prevalence statistics on progression to dementia in CLBP are unknown. Future research should adopt a longitudinal approach to identify if MCI is associated with dementia in CLBP. While the Single Impairment Group did not meet the criteria for MCI in the present study, they did score worse on all cognitive measures compared to the No Impairment group. Future research should investigate if people with single impairments go on to develop MCI. If this is identified in future research, cognitive intervention at an early stage of CLBP may be beneficial in slowing down cognitive impairment in CLBP.

Previous research has identified domain-specific cognitive deficits in CLBP (Higgins et al., 2018), but this is the first study to examine and identify deficits across all five cognitive domains. Studies in chronic pain have attempted to profile cognitive functioning, but have yielded unclear results (Berryman et al., 2013; Higgins et al., 2018; Moriarty et al., 2011). Several studies have reported that cognitive impairments, particularly in attention, may only be present in individuals who exhibit fear of pain, worry of injury, and high pain catastrophising (Apkarian et

al., 2004a; Grisart & Van der Linden., 2001; Pincus & Morley., 2001). These results suggest that fear of pain, worry of injury, and pain catastrophising cause interference between the cognitive resources required for pain processing and the resources that are allocated to cognitive performance. In contrast, Grisart and Van der Linden (2001) and Dick et al. (2002), reported that deficits in attention were not related to pain intensity, depression, or anxiety. Consistent with this, the present study found no significant difference in depression, stress and anxiety between the CLBP group and controls. Furthermore, no significant differences were observed between pain intensity, duration of pain, pain catastrophising, and disability between the CLBP MCI groups. This suggests that pain-related experiences do not fully account for the cognitive deficits in CLBP, and that deficits may be associated with other factors that place strain on valuable prefrontal cognitive resources.

The use of medication in the CLBP group was correlated with some of the cognitive measures, however, the groups did not differ in their use (or not) of medication despite differences in cognition. While medication use was recorded in the present study, frequency of use and dosage was not documented. Although this is a limitation of the current study, previous research has provided conflicting results about the impact of opioid medication on cognitive performance in chronic pain (Higgins et al., 2018). Schiltenwolf et al. (2014) reported that the use of opioid medication contributes to cognitive impairment in chronic pain. However, Sjøgren et al. (2005) reported that there were no significant relationships between morphine dosage, pain duration, or type of analgesic and cognitive performance in chronic pain. Jamison et al. (2003) reported that long-term use of opioids improved cognitive performance in low back pain. Future research should examine type of medication, frequency of use, and dosage on cognitive performance to determine if pain medication impacts cognitive performance in chronic pain.

3.5.1 Limitations

There are a number of limitations that must be acknowledged. The data in the current study forms the baseline assessment of a larger 5-week intervention study. Due to the nature of the intervention and the extensive inclusion criteria, the participant sample is smaller than ideal. Additionally, no p-value corrections were applied to adjust for multiple comparisons. While this may increase the risk of type I

errors in the present study, research suggests that the use of p-value corrections increases the chance of type II errors and important differences may be deemed non-significant (Feise, 2002; Perneger, 1998). While significant differences were reported in this study, it is also important to examine these differences in terms of effect size. Most of the significant differences reported in the present study have medium – large effects, suggesting these results are unlikely to be due to chance (Feise, 2002). However, these results should still be interpreted with caution. Future research should access a larger sample size to determine if the effect sizes reported here remain the same. Future research should also consider the use of composite scores for cognitive functioning to reduce multiple comparisons (Feise, 2002). Furthermore, despite a significant difference in fatigue between the CLBP and control group, fatigue was not generally correlated with cognitive performance. The lack of relationship between fatigue and cognitive performance may be due to the measurement of fatigue in the present study. Fatigue was measured over the 4 weeks prior to completing the cognitive assessment. It may be that generalised fatigue cannot adequately capture the level of fatigue a person is experiencing on the day of, and/or during cognitive assessment. Future research should consider the use of a fatigue measure that captures fatigue on the day of testing, and/or during cognitive assessment, to determine if fatigue may be influencing cognitive performance in individuals with CLBP.

3.5.2 Conclusion

In conclusion, the present study found that individuals with CLBP perform significantly worse on cognitive tasks compared to age-gender matched controls. This study also identified that some individuals with CLBP met the criteria for MCI. The present study adds to our understanding of the effect of pain on the brain, with emphasis on the engagement of resources in the prefrontal cortex. As cognitive impairment hinders engagement in rehabilitation and activities of daily living, the development of cognitive interventions in CLBP may assist in improving rehabilitation outcomes and reduce the burden of CLBP on the individual, their family, and the health care system.

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CHAPTER FOUR: ANODAL-TDCS OVER DLPFC MODULATES MOTOR CORTEX EXCITABILITY IN CHRONIC LOWER BACK PAIN

This is the extended version of the peer reviewed article:

Corti, E.J., Nguyen, A.T., Marinovic, W., Gasson, N., & Loftus, A.M. (2022). Anodal-tDCS over left-DLPFC modulates motor cortex excitability in people with chronic lower back pain. *Brain Sciences, 12*, 1654. https://doi.org/10.3390/brainsci12121654

4.0 Abstract

Chronic pain is associated with abnormal cortical excitability and increased pain intensity. Research investigating the potential for transcranial direct current stimulation (tDCS) to modulate motor cortex excitability and reduce pain in individuals with chronic lower back pain (CLBP) yield mixed results. The present randomised, placebo-controlled study examined the impact of anodal-tDCS over left-dorsolateral prefrontal cortex (left-DLPFC) on motor cortex excitability and pain in those with CLBP. Nineteen participants with CLBP (Mage = 53.16 years, SDage = 14.80 years) received 20-minutes of sham or anodal tDCS, twice weekly, for 4 weeks. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were assessed using paired-pulse Transcranial Magnetic Stimulation prior to and immediately following the tDCS intervention. Linear Mixed Models revealed no significant effect of tDCS group or time, on SICI or ICF. The interactions between tDCS group and time on SICI and ICF only approached significance. Bayesian analyses revealed the anodal-tDCS group demonstrated higher ICF and SICI following the intervention compared to the sham-tDCS group. The anodal-tDCS group also demonstrated a reduction in pain intensity and self-reported disability compared to the sham-tDCS group. These findings provide preliminary support for anodal-tDCS over left-DLPFC to modulate cortical excitability and reduce pain in CLBP.

4.1 Introduction

Chronic Lower Back Pain (CLBP) is a leading cause of disability worldwide and is the most common job-related disability and cause of work absence (Hoy et al., 2014). Despite affecting half a billion people world-wide, little is understood about the cause of CLBP, and commonly prescribed treatments (including opioids) are often ineffective for the long-term management of CLBP (Chou et al., 2017a; Chou et al., 2017b). Research has recently begun to consider the potential for nonpharmacological management of CLBP.

Research suggests that cortical adaptations to pain may contribute to its persistence (Massé-Alarie & Schneider, 2016; Moseley & Flor, 2012; Parker et al., 2016). A number of studies indicate decreased activation in areas of the pain 'Neuromatrix', which includes the motor cortex and prefrontal cortex (Apkarian et al., 2009; Baliki et al., 2006; 2011; Konno & Sekiguchi 2018; Tracey & Bushnell 2009). Chronic pain, including CLBP, is associated with altered excitability in the motor cortex (Chiang et al., 2022; Moseley & Flor, 2012; Parker et al., 2016). Research in experimentally induced and chronic pain have suggested that short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) may be the key mechanisms associated with the maintenance of pain (Schabrun & Hodges, 2012), whereby an imbalance between inhibition ($GABA_A$; indicated by SICI) and excitation (glutamate; indicated by ICF) may be associated with increased pain intensity (Chiang et al., 2022; Li et al., 2019; Moseley & Flor, 2012). CLBP imaging studies also report reduced cortical grey matter density in the dorsolateral prefrontal cortex (DLPFC; Apkarian et al., 2004; Ivo et al., 2013). In light of these findings, emerging research has sort to establish whether chronic pain can be managed using non-invasive brain stimulation to modulate activity in the brain areas involved in pain processing (Luedtke et al., 2012; O'Connell et al., 2018).

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that delivers low intensity electrical currents to modulate neural activity (Nitsche et al., 2008). tDCS has the potential to change chronic pain by acting upon the endogenous opioid system, changing the emotional appraisal of pain, and altering the pain signal via descending pathways (DosSantos et al., 2012; Garcia-Larrea & Peyron 2007). Most studies examining tDCS in chronic pain have focused on stimulation of the motor cortex. In therapy-resistant chronic pain

syndromes, such as post-stroke pain, back pain, and fibromyalgia, anodal-tDCS (a-tDCS) over the motor cortex increased intracortical excitability and decreased pain ratings (Antal et al., 2010). Studies of fibromyalgia and spinal cord injury also indicate that pain is reduced following five daily sessions of a-tDCS over the motor cortex (Fregni et al., 2006a; Fregni et al., 2006b).

A number of CLBP studies have investigated the impact of tDCS over the motor cortex. Schabrun et al. (2018) reported that a-tDCS over the motor cortex did not change motor cortex excitability in individuals with CLBP. Luedtke et al. (2015) also reported that a-tDCS over the motor cortex had no therapeutic effect on CLBP. Hazime et al. (2017) reported that a-tDCS over the motor cortex can induce a short-term and long-term analgesic effect in CLBP, but only when combined with peripheral electrical stimulation. A systematic review exploring the use of tDCS in CLBP concluded a Level A recommendation against the use of tDCS over the motor cortex, as it was shown to be ineffective in managing pain (Baptista et al. 2019). Subsequent research has turned its focus to investigate stimulation of other cortical areas involved in pain processing, such as the DLPFC (Brighina et al., 2004; O'Reardon et al., 2007; Sampson et al., 2006).

The prefrontal cortex plays a key role in pain modulation synergistically through descending inhibition and cognitive-attentional mechanisms (Brighina et al., 2011; Lorenz et al., 2003). Functional imaging studies reveal that the DLPFC is involved in pain modulation (Lorenz et al., 2002; Lorenz et al., 2003). Cao et al. (2018) reported that stimulation of the DLPFC in healthy individuals can modulate motor cortex excitability via inhibitory and facilitatory connections. Imaging studies indicate that increased left-DLPFC activation is associated with reduced pain (Lorenz et al., 2002; Lorenz et al., 2003). Further, repetitive transcranial magnetic stimulation (rTMS) over left-DLPFC is associated with reduced pain in those with migraine and fibromyalgia (Brighina et al., 2004; Lefaucheur et al., 2020; O'Reardon et al., 2007; Sampson et al., 2006). It has been suggested that such reductions in pain is associated with changes in motor cortex excitability (Fierro et al., 2010). Fierro et al. (2010) reported that rTMS of the left-DLPFC in capsaicin-induced pain had an analgesic effect and reverted motor cortex excitability changes induced by the capsaicin pain stimulus. Vaseghi et al (2015) examined the impact of a-tDCS over left-DLPFC on motor cortex excitability in healthy individuals and found that a-

tDCS increased the pressure-pain threshold and sensory threshold. These findings support the theory that the left-DLPFC and motor cortex play a key role in pain modulation and indicate that non-invasive brain stimulation to these areas might lead to changes that modify the pain experience. However, the impact of a-tDCS over left-DLPFC on motor cortex excitability in CLBP remains unclear and this in an area of increasing interest.

Individuals with chronic pain exhibit abnormal motor cortex excitability, and this abnormality is associated with increased pain levels (Lefaucheur et al., 2006; Schwenkreis et al., 1999). A-tDCS over DLPFC restores normal inhibitory and excitatory systems and reduces pain levels in some forms of chronic pain (Fierro et al., 2010; Sampson et al., 2006). It is unclear whether a-tDCS over DLPFC can modulate excitability in the motor cortex in people with CLBP and, if so, whether there is a corresponding reduction in pain. For the present study, the primary proposal was that 2 weekly, 1.5mA a-tDCS over left DLPFC for 4 weeks would modulate excitability in people with CLBP, whereby participants in the a-tDCS group would demonstrate an increase in ICF and SICI, compared to the sham-tDCS (s-tDCS) group. It was secondarily proposed that the a-tDCS group would demonstrate a reduction in pain-related outcomes (pain intensity, disability, and pain catastrophising), compared to the s-tDCS group.

4.2 Method

4.2.1 Participants

Participants took part in a 5-week randomised controlled trial approved by Curtin University Human Research Ethics Committee (approval number: HR17/2015; ACTRN12615000110583). Participants were recruited via convenience sampling between 2015-2018. All research was conducted in accordance with the Declaration of Helsinki and all participants provided written, informed consent. Study inclusion required a formal diagnosis of CLBP of at least 6 months duration by a qualified health professional (General Practitioner or Physiotherapist), a Transcranial Magnetic Stimulation (TMS) screening questionnaire (Rossi et al., 2009), and a cognitive status assessment using the Telephone Interview for Cognitive Status – 30 (score ≥ 18 for inclusion) was conducted to determine participant eligibility. Thirty-one participants met the inclusion criteria. Participants were

randomised to the a-tDCS (anodal) or s-tDCS (sham) group. Of the 31 participants, four participants did not produce reliable MEPs and six participants had very high resting motor thresholds (rMT) that prevented completion of recruitment curves. As such they were subsequently excluded from the TMS measures analysed here. One participant was excluded due to ongoing muscle activation across multiple trials. One participant left the study prior to the intervention. Twelve participants (of the 31 who met inclusion criteria) were not included in the final TMS analysis presented here.

4.2.2 Measures

Demographic and pain-related information were collected via self-report questionnaire. Motor cortex excitability measures and pain-related measures were completed at baseline and immediately (~1 hour) following the 4-week intervention.

4.2.2.1 Motor Cortex Excitability Measures

EMG signals were recorded using Ag – AgCl surface electrodes placed over the belly and tendon of the left First Dorsal Interosseous (FDI) muscle. The EMG signal was sampled at 1000 Hz with a Power-1401 A/D board (Cambridge Electronic Design [CED], Cambridge, UK) and band-pass filtered at 5-500 Hz. The stimulation procedures were conducted using TMS. TMS was applied using a figure-of-eight coil (90mm in diameter) connected to two Magstim 200 magnetic stimulators through a Bistim module (Magstim Company Limited, UK). The 10/20 International system for electrode placement was used to locate the motor area corresponding to the left FDI muscle (Trans Cranial Technologies, 2012). The coil was positioned over the optimal location to produce a MEP in the contralateral FDI. The coil was placed at a 45-degree angle from the inter-hemispheric line (handle pointing towards the right), to stimulate current flow in a posterior to anterior direction. The FDI was chosen as the target area for stimulation as it has been reported that global alteration in cortical excitability can be reflected by responses to TMS of this muscle (Parker et al., 2016; Strutton et al., 2005).

TMS stimulation intensity started at 30% (adjusted in 1% increments) until the resting motor threshold (rMT) was established. rMT was defined as the lowest stimulation intensity that elicited MEPs ≥ 50μV in at least 3 of 5 trials while the muscle was a rest (Bouguetoch et al., 2020; Rossini et al., 2015). To determine the

recruitment curve stimulation intensity, the stimulation intensity was adjusted in 1% increments, until a mean MEP of 1mV was produced in eight trials (Rossini et al., 2015). The recruitment curve consisted of stimulation at 90%, 100% (1mV), 110%, 120%, and 130% of the intensity required to produce the 1mV MEP. The order of administration was randomised. Eight pulses were delivered for each intensity level and were averaged to attain a mean MEP amplitude. The mean MEP amplitude for each intensity level was normalised against the participant's 1mV response.

The paired-pulse protocol developed by Kujirai et al. (1993) was used to measure SICI and ICF. SICI and ICF were defined using a subthreshold conditioning pulse set to 80% of rMT, and a suprathreshold test pulse set at 120% of rMT. The interstimulus interval was set to 3ms and 10ms for SICI and ICF, respectively. Fifteen trials were recorded at each interstimulus interval. Fifteen single unconditioned test pulses (at 120% rMT) were also recorded. The order of administration was randomised. The fifteen trials for each interstimulus interval were averaged to attain a mean MEP amplitude. The mean MEP amplitude for SICI and ICF was normalised against the participant's mean unconditioned pulse.

4.2.2.2 Pain-related Measures

Pain Intensity. The Short-Form McGill Pain Questionnaire (SF-MPQ) contains a 10 cm Visual Analogue Scale (VAS). The VAS was used to assess average pain intensity (scored from 0 – 10) in CLBP (Melzack, 1987). Participants indicated their level of pain by placing a mark on the line (Hawker et al., 2011). Higher scores are indicative of greater pain intensity. The VAS has high test-retest reliability in people with pain (.97; Gallagher et al., 2002).

Disability. The Roland-Morris Disability Questionnaire (RMDQ) assessed the level of self-reported disability (Roland & Morris, 1983). The RMDQ assessing the impact of CLBP across multiple domains, including mobility, daily activities, sleeping, mood, and appetite. The 24 Items are summed for a total score (higher scores are indicative of greater self-reported disability). The RMDQ has high internal consistency in people with CLBP ($\alpha = .93$; Rocchi et al., 2005).

Pain Catastrophising. The Pain Catastrophizing Scale (PCS) assessed the presence of pain catastrophising (Sullivan et al., 1995). The PCS assesses rumination, magnification, and helplessness over 13 items, with higher scores

indicating greater pain catastrophising. The PCS has high internal consistency in people with CLBP (α = .92; Osman et al., 2000).

4.2.3 Brain Stimulation

Participants completed 8-sessions of tDCS stimulation over 4-weeks (2 sessions per week). tDCS was delivered using a constant current stimulator (Soterix®). Participants were randomly assigned (1:1 using block randomisation) to the anodal (a)-tDCS or sham (s)-tDCS group. The a-tDCS group received 20 minutes of constant 1.5 mA stimulation over left DLPFC every session. tDCS was delivered using two 35 cm2 sponge electrodes soaked in saline solution. According to the 10-20 international system for EEG electrode placement, the anode electrode was placed over F3 to stimulate the left DLPFC. The reference electrode was placed above the left eye, to ensure the current flowed through the prefrontal area. There was a ramp up period of 30 seconds at the beginning and 30 seconds ramp down at the end of the tDCS stimulation. Participants in the s-tDCS experienced the 30 second ramp up/down of tDCS (1.5 mA stimulation) at the commencement and end of the stimulation (20 minutes). The ramp up/down in the s-tDCS group at the beginning and end of the stimulation is designed to keep the participant blind to the stimulation group (Ambrus et al., 2012; Nitsche et al., 2008)

4.3 Statistical Analysis

R software (v4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all analyses. All trials were visually inspected and peak to peak MEP amplitudes were manually marked. The EMG signal was screened for noise, artifacts, and voluntary contraction. Trials that were identified as obscuring the detection of the MEP amplitude were excluded from analysis. Trials were also excluded from further analysis if repeated muscle activation was identified.

4.3.1 Motor Cortex Excitability Analysis

Recruitment curve data, ICF, and SICI were analysed using linear mixed models using lme function, nlme package (Pinheiro et al., 2022). For the recruitment curve model, tDCS group (2 levels, Active and Sham), time (2 levels, pre and post), intensity (5 levels, 90-130%), and their interactions were included as fixed effects

with the intercept of each participant modelled as a random effect. For the ICF and SICI models, tDCS group, time, and their interaction were included as fixed effects with the intercept of each participant modelled as a random effect. Given our relatively low numbers of participants and the fact that we expected that tDCS of the DLPFC would improve outcomes for the anodal stimulation group, ICF and SICI difference scores (Post MEP amplitude – Pre MEP amplitude) were also analysed using bootstrapped Welch two sample t-test, with the boot.t.test function from the MKinfer package (Kohl, 2020).

4.3.2 Pain-related Measures Analysis

Pain Intensity, RMDQ score, and Pain Catastrophising were analysed using linear mixed models. For all three models, tDCS group, time, and their interactions were included as fixed effects with the intercept of each participant modelled as a random effect. Pain Intensity, RMDQ score, and Pain Catastrophising difference scores (Post score – Pre score) were also analysed using a bootstrapped Welch two sample t-test, with the boot.t.test function from the Mkinfer package (Kohl, 2020).

4.3.3 Supplementary Analysis

Analyses were further supplemented with Bayesian linear mixed effects analyses using the rstanarm (Goodrich et al., 2022) and report (Makowski et al., 2021) packages. In line with the Sequential Effect eXistence and sIgnificance Testing framework (Makowski et al., 2019), the median of the posterior distribution, its 95% CI (Highest Density Interval), the probability of direction (*pd*), and the probability of significance are reported. Default weakly informative priors from the rstanarm package were used in analyses. The default Region of Practical Equivalence (ROPE) threshold, |0.05|, from the report package was used to assess the probability of significance. Values within this range are considered as practically equivalent to zero (Makowski et al., 2019).

4.4 Results

Nineteen participants (from the sample of n = 30) were included for analysis (see Figure 4.1). Participant demographic and pain-related information is provided in Table 4.1.

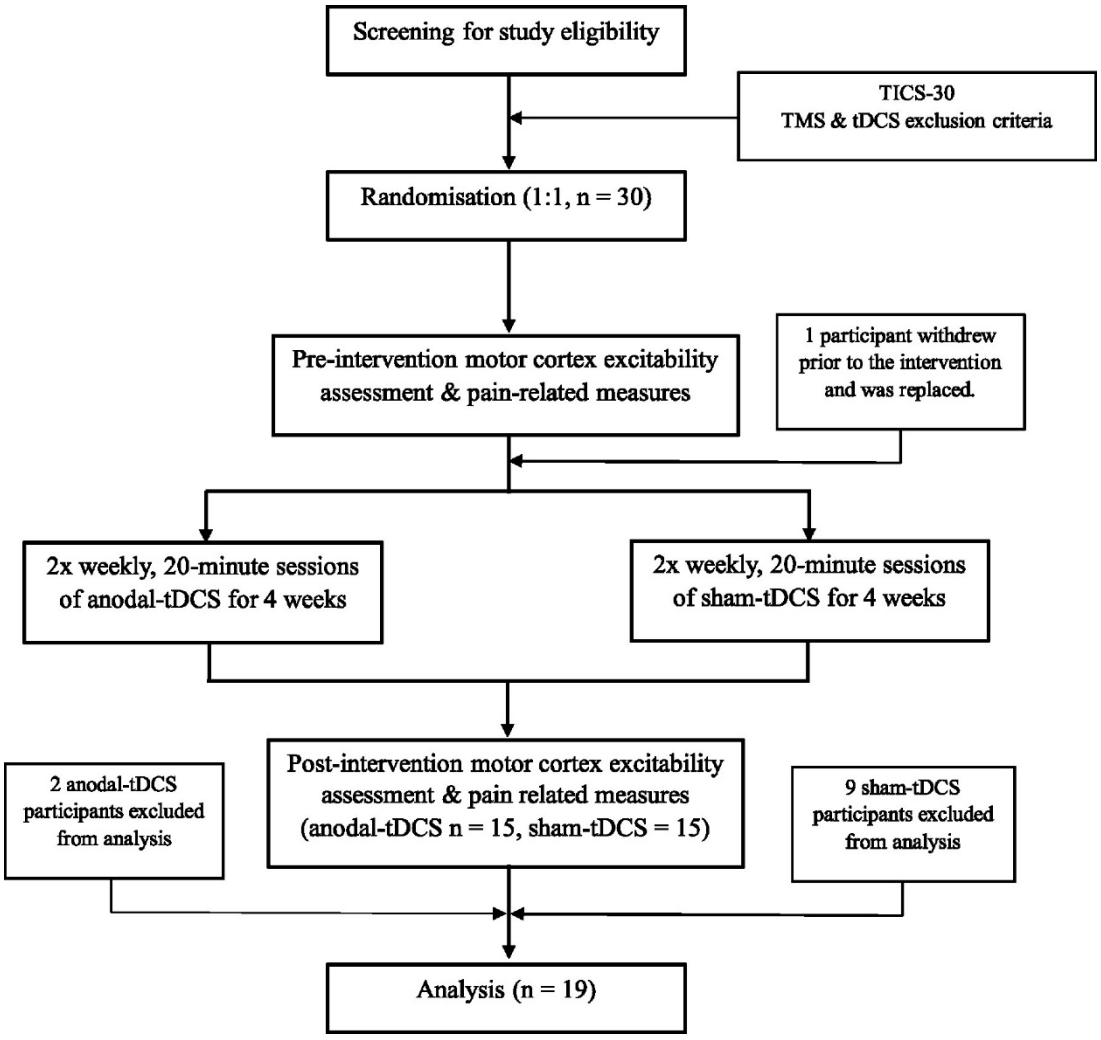

Figure 4.1. *Flow diagram of the progress of the trial for anodal and sham transcranial direct current stimulation (tDCS) groups.*

Table 4.1

Participant Demographics, CLBP Classification, and Treatment Engagement

	Total (n = 19)	Males (n = 10)	Females (n = 9)	Anodal-tDCS (n = 13)	Sham-tDCS (n = 6)
Age	53.16 (14.80)	57.80 (14.52)	48.00 (13.32)	49.69 (14.34)	60.67 (12.87)
Years of Education	12.65 (3.48)	12.55 (3.25)	12.77 (3.72)	12.53 (3.59)	12.92 (3.22)
Duration of Diagnosis (years)	13.38 (12.41)	17.93 (14.11)	8.33 (7.47)	12.31 (9.50)	15.71 (16.87)
Resting Motor Threshold	49.79 (8.75)	47.80 (5.90)	52.00 (11.07)	49.31 (9.12)	50.83 (8.59)
CLBP Classification					
Non-Specific	84%	80%	89%	85%	83%
Specific	16%	20%	11%	15%	17%
Percentage taking Pain Medication	74%	50%	100%	69%	83%
Anti-Inflammatory (Celebrex)[a]	42%	40%	44%	54%	17%
Pain Killer (Tremadol)[a]	53%	20%	89%	46%	67%
Benzodiazepine (Valium)[a]	21%	10%	33%	23%	17%
Anti-Depressants (Endep)[a]	5%	10%	-	8%	-
Engaging in Physiotherapy	47%	30%	67%	54%	33%
Past Surgery	21%	20%	22%	77%	17%
Other Pain Management	79%	80%	78%	15%	67%
Depression and Anxiety Disorder	16%	10%	22%	15%	17%
Anti-Anxiety Medication[a]	33%	-	50%	50%	-

Note. CLBP Classification = classification of chronic lower back pain based on Koes et al. (2001), Non-Specific = no radiographical injury at time of participation, Specific = Radiographical evidence, Other = Acupuncture, Chiropractor, Massage. [a] = Percentage based on individuals taking medication.

4.4.1 Recruitment Curve

The linear mixed model revealed a significant main effect of TMS intensity, $F(4,153) = 18.49$, $p < .001$, (MEP amplitude increased with TMS intensity) and Group, $F(1,17) = 8.63$, $p = .010$ (MEP amplitude smaller for Active group [est.mean = 1.02mV, SE = .06] versus Sham group [est.mean = 1.33mV, SE = .89]; see Figure 4.2 for MEP amplitude). Further inspection of the plots suggests the group effect may be partly driven by reduced MEP amplitudes at 110-130% intensity post-intervention. There was no statistically significant main effect of Time ($p = .779$) or Interaction (all interactions $p > .05$).

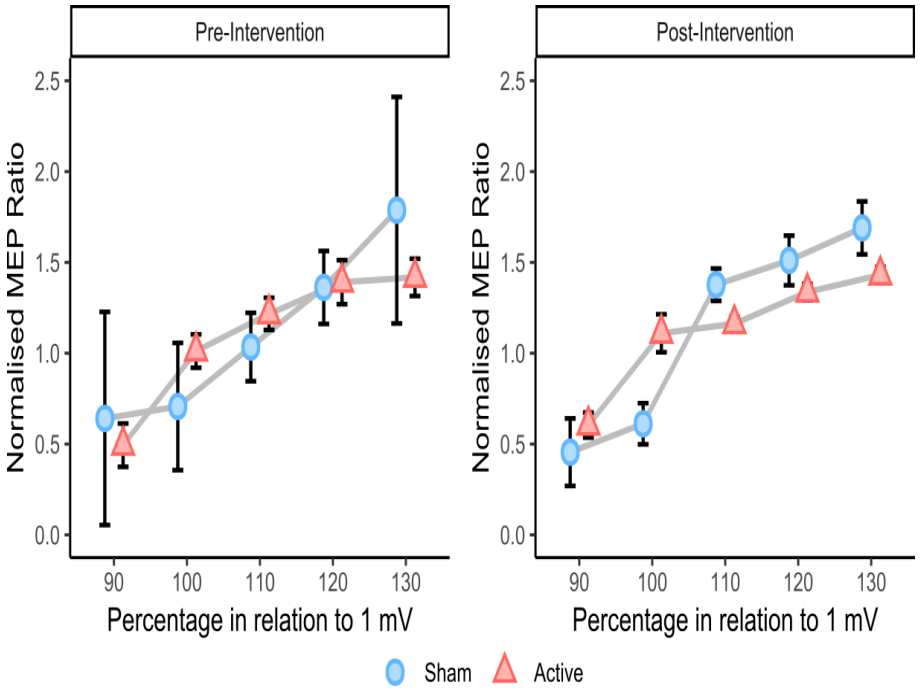

Figure 4.2. *Recruitment Curve with Normalised MEP Ratio at 90 – 130% Stimulation at baseline and post 4-weeks tDCS intervention.*

4.4.2 Test Pulse

Bootstrapped paired t-tests revealed no significant difference in pre- and post-test pulse MEP amplitude in the a-tDCS group and s-tDCS group, p = .527 and p =. 708, respectively.

4.4.3 ICF

The linear mixed model revealed there was no significant main effect of Group (p = .428) and Time (p = .291). The interaction between Group and Time approached significance, $F(1, 17) = 4.07$, p =.059). Further inspection of the plots suggests this interaction was driven by an increase in MEP amplitude in the a-tDCS group (see figure 4.3a). At the suggestion of a reviewer, pain intensity was included in the model as a covariate. With the inclusion of pain intensity as a covariate, the Group and Time interaction became significant, $F(1, 13.63) = 6.02$, p = .028.

To follow-up the interaction effect, a bootstrapped Welch two sample t-test compared pre- and post-intervention ICF MEP amplitude. There was a significant difference in pre-post MEP amplitude between the a-tDCS and s-tDCS group (bootstrapped p = .040, one-sided), such that the active group showed increased ICF MEP amplitude compared to the sham group (see figure 4.3b).

A Bayesian linear mixed effects analysis of the same model supported these findings. The effect of tDCS group (anodal) had a probability of 96.79% [*pd*] of being positive (median = 0.47, 95% CI [-0.04, 0.96]), 96.16% of being significant, and 90.18% of being large (>.15).

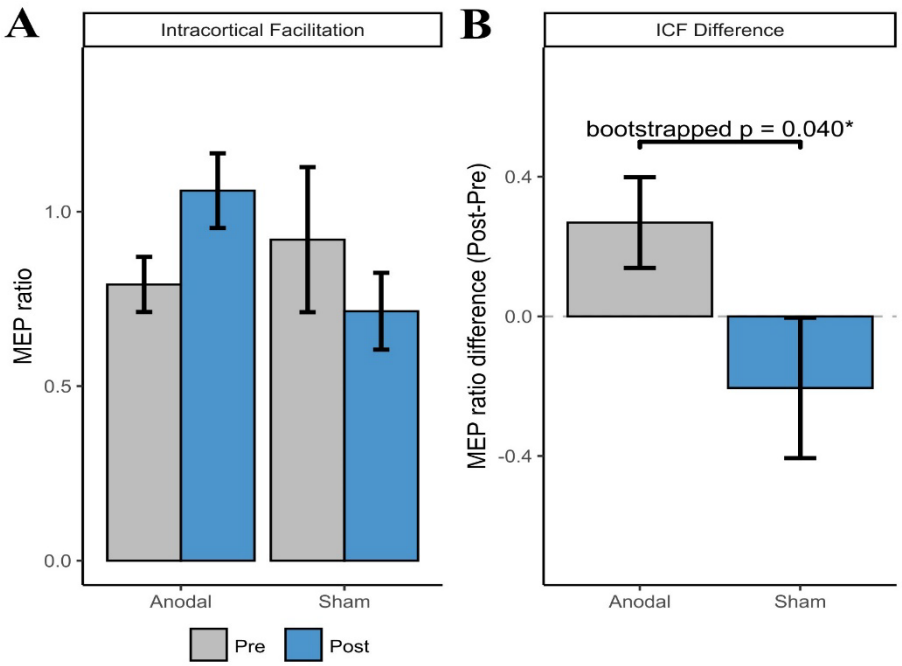

Figure 4.3. *(A) Intracortical facilitation (ICF) motor evoked potential (MEP) amplitude (with standard error of the mean error bars) at pre- and post-intervention*

*by group. (**B**) ICF difference score (Post ICF MEP amplitude – Pre ICF MEP amplitude; with standard error of the mean error bars) by group.*

4.4.4 SICI

There was no significant main effect of Group (p = .272) or Time (p = .139). The interaction between Group and Time approached significance, $F(1,17) = 3.76$, p =.069. Further inspection of the plots suggests this interaction was driven by an increase in MEP amplitude in the a-tDCS group (see figure 4.4a). At the suggestion of the reviewer, pain intensity was included in the model as a covariate. The Group and Time interaction remained nonsignificant, $F(1,16.00) = 4.28$, p = .055.

To follow-up the interaction effect, a bootstrapped Welch two sample t-test compared pre- and post-intervention SICI MEP amplitude. The t-test revealed a significant difference in pre-post MEP amplitude between the a-tDCS and s-tDCS group (bootstrapped p = .023, one-sided), whereby the a-tDCS group showed increased SICI MEP amplitude compared to the s-tDCS group (see figure 4.4b).

A Bayesian linear mixed effects analysis of the same model supported these findings. The effect of tDCS group (anodal) had a probability of 96.60% [*pd*] of being positive (median = 0.20, 95% CI [-0.02, 0.43]), 95.73% of being significant, and 88.82% of being large (>.07).

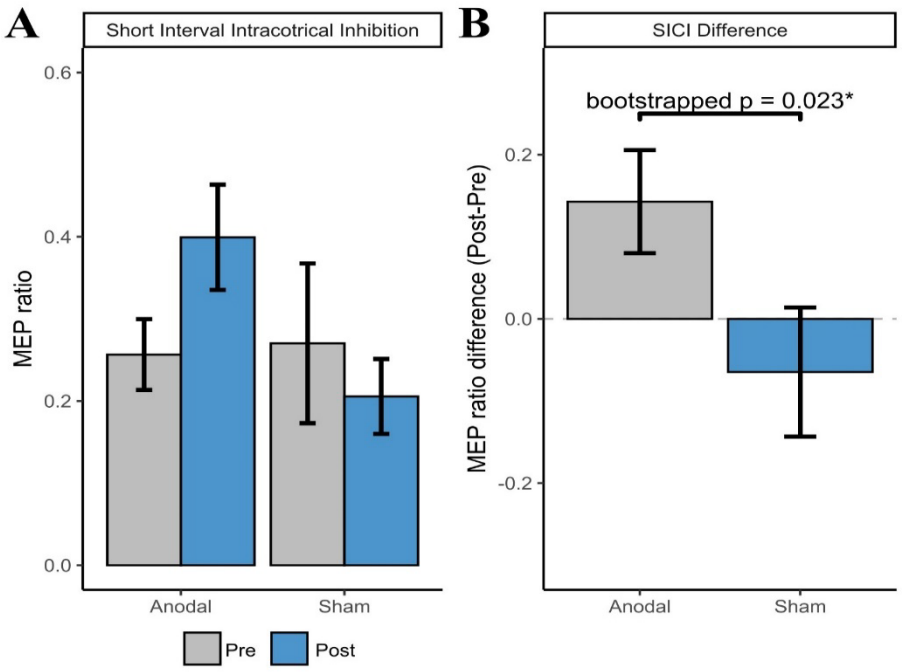

Figure 4.4. *(**A**) Short interval intracortical inhibition (SICI) motor evoked potential (MEP) amplitude (with standard error of the mean error bars) at pre- and post-*

*intervention by group. (**B**) SICI difference score (Post SICI MEP amplitude – Pre SICI MEP amplitude; with standard error of the mean error bars) by group.*

4.4.5 Pain-related Outcomes

Pain Intensity. The linear mixed model revealed no significant main effect of Group (p = .675). There was a significant main effect of Time, $F(1,16) = 7.74$, p = .013). The interaction between Group and Time was not significant $F(1,16) = 3.13$), p = .096. Although the interaction effect did not cross the statistical threshold, inspection of mean values in the plot suggests that the effect of pain before and after the intervention was driven by the active group, as pain scores in the sham group were largely similar over time (see figure 4.5a).

To investigate this, a bootstrapped Welch two sample t-test compared pre-post pain intensity. The t-test revealed a significant pre-post difference in pain intensity between the a-tDCS and s-tDCS group (bootstrapped p = .047, one-sided), whereby the a-tDCS group had a greater reduction in pain intensity compared to the s-tDCS group (see figure 4.6a and table 4.2).

A Bayesian linear mixed effects analysis of the same model supported these findings. The effect of tDCS group (anodal) had a probability of 94.96% [*pd*] of being negative (median = -1.38, 95% CI [-3.13, 0.32]), 93.92% of being significant, and 85.56% of being large (>.51).

Disability (RMDQ). The linear mixed model revealed no significant main effect of Group (p = .637) or Group and Time Interaction (p =.130). There was a significant main effect of Time, $F(1,17) = 5.61$, p = .03. Further inspection of the plots suggests this effect was driven by a decrease in RMDQ score in the a-tDCS group (see figure 4.5b).

To investigate this, a bootstrapped Welch two sample t-test compared pre and post intervention disability. The t-test revealed a significant difference in disability between the a-tDCS and s-tDCS group (bootstrapped p =.033, one-sided), whereby that the a-tDCS group had a greater reduction in disability compared to the s-tDCS group (see figure 4.6b and table 4.2).

A Bayesian linear mixed effects analysis of the same model supported these findings. The effect of tDCS group (anodal) had a probability of 93.66% [*pd*] of

being negative (median = -3.22, 95% CI [-7.53, 0.98]), 92.41% of being significant, and 82.14% of being large (>1.30).

Pain Catastrophising. The linear mixed model revealed no significant main effect of Group (p = .178) or Group and Time Interaction (p =.355). There was a significant main effect of Time, $F(1,17) = 17.39$, p <.001. Further inspection of the plots suggests pain catastrophising was reduced in both a-tDCS and s-tDCSgroup at post-intervention (see figure 4.5c).

A bootstrapped Welch two sample t-test compared pre and post intervention catastrophising. The t-test revealed a non-significant pre-post difference in catastrophising between the a-tDCS and s-tDCS group (bootstrapped p =.820, one-sided), whereby catastrophising was reduced in both the a-tDCS and s-tDCS group (see figure 4.6c and table 4.2).

A Bayesian linear mixed effects analysis of the same model supported these findings. The effect of tDCS group (anodal) had a probability of 81.87% [*pd*] of being positive (median = 3.18, 95% CI [-3.90, 10.59]), 78.89% of being significant, and 61.26% of being large (>2.11).

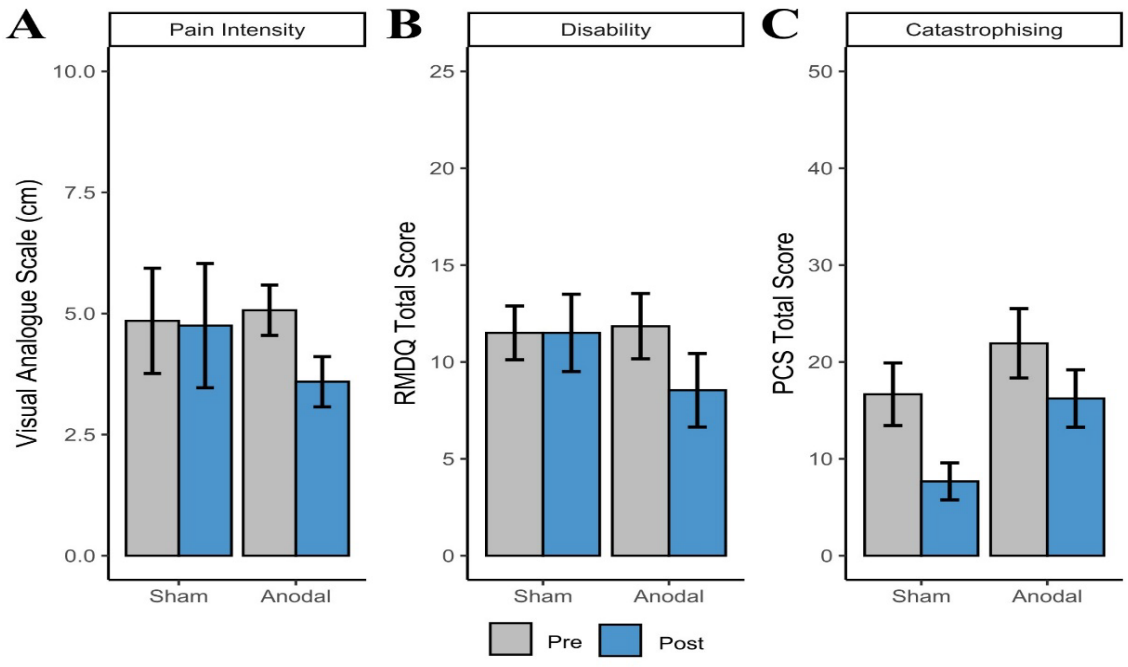

Figure 4.5. *(**A**) Pain intensity, (**B**) Roland Morris Disability Questionnaire (RMDQ), and (**C**) Pain Catastrophising Scale (PCS) total scores (with standard error of the mean error bars) at pre- and post-intervention by group.*

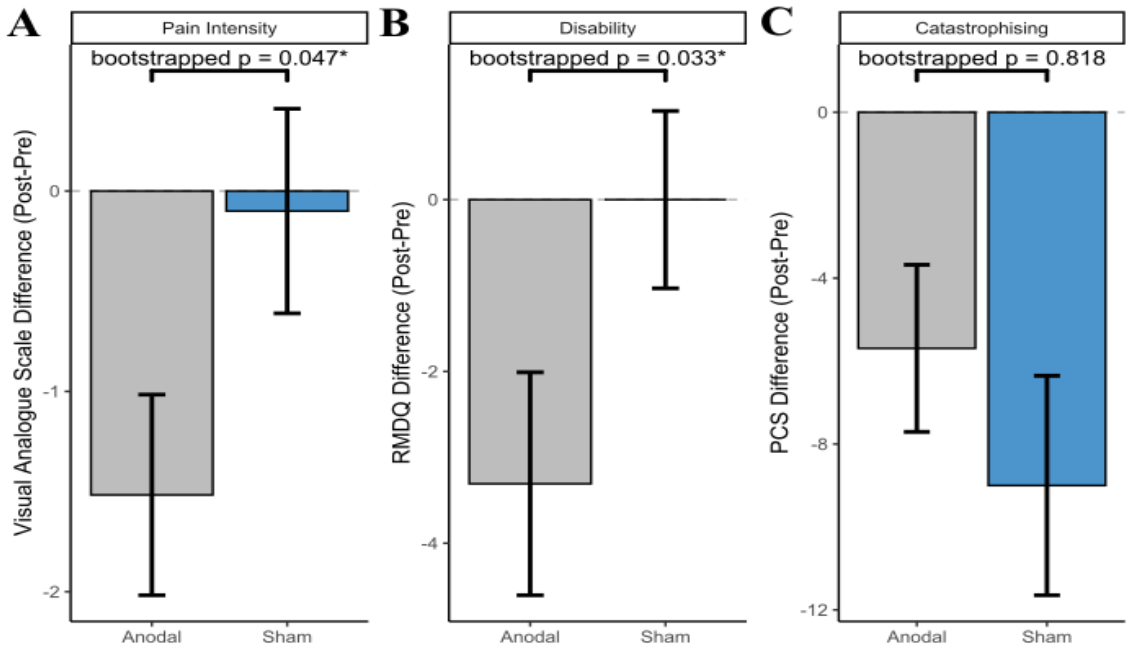

Figure 4.6. *(**A**) Pain intensity, (**B**) Roland Morris Disability Questionnaire (RMDQ), and (**C**) Pain Catastrophising Scale (PCS) difference scores (Post score – pre score; with standard error of the mean error bars) by group.*

Table 4.2

Mean and standard deviation for Pain intensity, disability, and pain catastrophising pre- and post-intervention.

	Anodal-tDCS		Sham-tDCS	
	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention
VAS	5.07 (1.87)	3.59 (1.72)[a]	4.85 (2.66)	4.75 (3.14)
RMDQ	11.85 (6.08)	8.54 (6.84)[b]	11.50 (3.39)	11.50 (4.89)
PCS	21.92 (12.93)	16.23 (10.67)[c]	16.67 (7.94)	7.67 (4.68)

Note. VAS = Visual Analogue Scale (pain intensity), RMDQ = Roland Morris Disability Questionnaire (disability), PCS = Pain Catastrophising Scale (catastrophising). [a] = borderline minimal detectable change (< 1.5; Kovacs et al., 2007), [b] = reached minimal detectable change (≥ 2.5; Kovacs et al, 2007), [c] = did not reach minimally clinically important difference (< 6.71; Suzuki et al., 2020).

4.5 Discussion

The present study examined if 8 sessions (twice weekly) of 1.5mA a-tDCS over left-DLPFC modulated motor cortical excitability and self-reported measures of pain and disability in those with CLBP. The recruitment curve data indicated no significant difference in global cortical excitability between the anodal and sham group. The interaction between tDCS group and time was not significant for both ICF and SICI, suggesting a-tDCS over left-DLPFC did not modulate motor cortex excitability. However, the interactions between tDCS group and time approached significance. Follow-up Bayesian analyses indicated that 8 sessions of a-tDCS over left-DLPFC may modulate ICF and SICI in those with CLBP. These interactions appear to be driven by, 1) an increase in ICF and SICI MEP amplitude in the a-tDCS group, and 2) a decrease in ICF and SICI MEP amplitude in the s-tDCS group. For self-reported measures, tDCS group did not impact upon pain intensity, disability, and catastrophising. However, tDCS impacted upon each measure independently. The changes in pain intensity and disability before and after the intervention may be driven by a reduction in the a-tDCS group. These results are consistent with the theoretical framework that restoration of abnormal motor cortical excitability in CLBP may be associated with decreased pain and disability.

The present findings that a-tDCS over DLPFC may modulate motor cortex excitability extends on those of Vaseghi et al. (2015). Vaseghi et al (2015) used a-tDCS over DLPFC in motor excitability to explore the role of the DLPFC in pain in healthy adults. They reported increased MEP amplitude following 20-minute a-tDCS, which was evident both immediately following the stimulation and thirty minutes later. a-tDCS also increased the pressure-pain threshold and sensory threshold, suggesting that the DLPFC and the motor cortex play an important role in pain modulation. However, as Vaseghi et al (2015) examined motor cortical excitability using a single-pulse paradigm, the specific mechanisms underlying this cortico-pain relationship could not be determined. The present study extends on Vaseghi et al's (2015) findings by specifically examining the impact of a-tDCS over DLPFC on ICF and SICI in CLBP.

ICF and SICI provide a measure of glutamatergic (excitatory) and gamma-aminobutyric acid (GABA; inhibitory) neurotransmitters (Cash et al., 2017). Glutamate and GABA are critical in maintaining and regulating many physiological

functions and are reported to underlie altered excitability in varying chronic pain conditions (Cash et al., 2017; Peek et al., 2020). The potential for tDCS over DLPFC to modulate ICF and SICI in chronic pain may be due to interconnections between the DLPFC and the periaqueductal gray area and motor cortex (Kandić et al., 2021; Tamura et al., 2004; Tracey & Mantyh, 2007). These areas play a key role in descending mechanisms that modulate spinal nociceptive activity (Kandić et al., 2021; Tamura et al., 2004; Tracey & Mantyh, 2007). A recent meta-analysis reported that while the balance of glutamate and GABA differed between chronic pain conditions, glutamate and GABA are vital to the pathophysiology of pain processing and modulation (Peek et al., 2020). This is supported in the present findings with increased ICF and SICI in the a-tDCS group corresponding with decreased pain and decreased perceived disability. Modulation of glutamatergic and GABAa via DLPFC stimulation may therefore play an important role in the relationship between corticospinal excitability and pain perception in CLBP.

In the present study, the reduction in pain intensity was greater for the a-tDCS group than for sham. To the best of our knowledge, no studies have investigated the use of a-tDCS over DLPFC to reduce pain in CLBP. Studies using another form of non-invasive brain stimulation (rTMS) yielded conflicting results. While the mechanisms between tDCS and rTMS may differ, both techniques may lead to similar changes in cortical activity and, as such, have a similar effect on chronic pain (Antal et al., 2010). Freigang et al (2021) reported that, compared to motor cortex stimulation and sham, rTMS over left-DLPFC significantly reduced pain intensity in CLBP. In line with this, the present findings suggest that multi-session a-tDCS of left-DLPFC has an analgesic effect on CLBP. Perceived disability was also significantly reduced in the a-tDCS group compared to the s-tDCS group in the present study. Although no previous studies have examined the impact of left-DLPFC a-tDCS on perceived disability in CLBP, the present findings reflect those of Freigang et al. (2021), who found that tDCS over DLPFC improved perceived health-related quality of life - physical functioning in those with CLBP. Taken together, these findings suggest that a-tDCS over DLPFC may modulate the cognitive and emotional appraisal of pain, which may be evidenced as a reduction in the pain experience for those with CLBP.

The present findings did not indicate that a-tDCS (compared to sham) was associated with reduced pain catastrophising. Both the anodal and the sham groups reported a reduction in pain catastrophising following tDCS, but this was not statistically significant. One potential explanation for the reduction in catastrophising in both groups may be the placebo effect. Engaging in the intervention may have had a positive impact on psychological health and wellbeing, such that catastrophising was reduced for both groups (Price et al., 2008). The pre-stimulation sensation ('ramp-up') in the sham group may have generated treatment expectancy effect, whereby participants in the sham group believed they were receiving anodal tDCS. However, the placebo effect does not account for the reduced pain and disability in the a-tDCS group only. It is also possible that participants experienced higher levels of pain-related anxiety before undertaking brain stimulation for the first time.

4.5.1 Limitations

There are a number of limitations that must be acknowledged. Due to the nature of the over-arching project, participants were not required to complete or have useable TMS data to be included in the main project. This resulted in small, unequal group sizes in the present study. To accommodate the small sample size, Bayesian linear mixed models were conducted. Bayesian linear mixed models are better suited to handle small and unbalanced sample sizes, providing better estimates of the effects (see Hsieh & Maier, [2009] and McNeish, [2016] for review). Additionally, the interpretation of Bayesian linear mixed model analyses does not depend on the significance of p-values. Rather, Bayesian linear mixed models provide multiple alternative indices for p-values, and gives probabilities based on the measured data. As such, the results from the Bayesian linear mixed models were interpreted in the present study. While the findings from the Bayesian analyses suggest that a-tDCS over left-DLPFC may modulate motor cortex excitability and reduce pain intensity and disability in CLBP, it must be acknowledged that the interpretation of p-values of the primary analysis provides less clear-cut results. As such, the present findings should be interpreted with caution. Future research should include a larger sample size to not only establish the current findings, but allow for more comprehensive examination of the relationships between motor cortex excitability, pain, disability, and pain catastrophising. This should also include follow-up testing to be able to

examine whether the effects of a-tDCS are acute or long lasting. A larger sample size would also allow for an intention-to-treat analysis and per-protocol analysis. The inclusion of both intention-to-treat and per-protocol would reduce the potential bias of excluding participants who do not produce useable TMS data and could provide important information as to the effect of being assigned to a treatment versus potential treatment effects (Smith et al., 2021).The use of analgesic medications (commonly prescribed for the management of CLBP) have been reported to influence cortical excitability. Benzodiazepines have been reported to significantly increase SICI and decrease ICF (Di Lazzaro et al., 2006), while synthetic opioids (N-methyl-D-aspartate receptor agonists) have also been reported to decrease ICF (Schwenkreis et al., 1999). Medication use was recorded in the present study, however, frequency of use and dosage was not documented. Future research should include a non-medicated sample to determine the influence of medication on the present findings, although given the chronic pain population sample, it may be difficult to find individuals who are not medicated.

The present study did not include measures of motor control. As motor cortical structures are involved in movement planning and execution (Schabrun et al., 2017), changes in motor cortex excitability and pain may be associated with changes in motor control in those with CLBP. Future research should include measures of motor control to examine if an increase in excitability and reduced pain intensity is associated with improved motor control in CLBP. This would most likely require a longitudinal study of changes in excitability, pain, and motor control.

The present study also included a combination of participants with non-specific or specific CLBP. As the aetiology behind these classifications differs, the combination of non-specific and specific CLBP participants may have influenced the findings. Future research should examine whether there are differences in global excitability between non-specific and specific CLBP. This would allow for a greater understanding of the impact of pain aetiology on global excitability.

4.5.2 Conclusion

The present findings add to our understanding of the use of neuromodulation techniques to alleviate chronic pain. The present findings provide some preliminary evidence that repeated application of a-tDCS over left-DLPFC may modulate motor

cortex excitability in CLBP. The present findings also provide preliminary evidence that a-tDCS over left-DLPFC may reduce pain and disability. While the findings of the present study should be interpreted with caution given the small sample size, the findings provide support for research to further investigate the potential of a-tDCS as a therapeutic tool in the management of CLBP. Future studies should examine if changes in motor cortex excitability underlie changes in CLBP symptoms and experience, and whether a-tDCS over left-DLPFC is a viable tool the management of CLBP.

4.6 References

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CHAPTER FIVE: A-tDCS over DLPFC is no more effective than placebo in improving cognition and pain-experience in chronic lower back pain

5.0 Abstract

Chronic pain is associated with deficits in cognitive functioning and increased pain intensity. Research investigating the potential for transcranial direct current stimulation (tDCS) to improve cognitive functioning, pain experience, and psychological health in individuals with chronic lower back pain (CLBP) yield mixed results. The present randomised, placebo-controlled study examined the impact of anodal-tDCS over left-dorsolateral prefrontal cortex (left-DLPFC) on cognitive functioning, pain experience, and psychological health in those with CLBP. Thirty participants with CLBP (Mage = 57.47 years, SDage = 14.28 years) received 20-minutes of sham or anodal tDCS, twice weekly, for 4 weeks. Cognitive functioning was assessed using two measures for each of the five cognitive domains; memory, attention and working memory, executive function, visuospatial, and language. Cognition, pain experience, and psychological health were assessed prior to and immediately following the tDCS intervention. Linear Mixed Models revealed a significant tDCS group and time interaction on an attention and working memory task, whereby participants in the a-tDCS showed a significant improvement on the letter number sequencing task at post-intervention. There was a significant main effect of time for both tDCS groups across the five cognitive domains. Both groups demonstrated a significant improvement on at least one measure for each of the five cognitive domains. Linear Mixed Models revealed there was a significant main effect of time for both tDCS groups on pain intensity, disability, catastrophising, anxiety, and stress, whereby both groups demonstrated a significant reduction on these outcome measures. There was a significant main effect of time for both tDCS groups on quality of life, whereby both groups demonstrated a significant improvement in quality of life. There was no significant main effect of tDCS group or interaction between tDCS group and time on pain intensity, disability, catastrophising, anxiety, stress, and quality of life. These findings suggest anodal-tDCS over left-DLPFC is no more effective than sham-tDCS in improving cognition, pain experience, and psychological health in those with CLBP.

5.1 Introduction

Chronic lower back pain (CLBP) is a multidimensional condition characterised by alterations in cognition, psychological health, and quality of life. However, current recommended treatments typically focus only on pain and physical symptoms of the condition. These treatments usually result in small to modest improvements in the short-term but are ineffective for long-term pain management (Chou et al., 2017). It has been suggested that management of CLBP should encompass a biopsychosocial approach that aims to improve not only pain experience, but also functionality (cognition and disability) and psychological wellbeing (mood and quality of life; Cuomo et al., 2021).

The prefrontal cortex plays a key role in pain modulation (Lorenz et al., 2003). Functional imaging studies have revealed that the dorsolateral prefrontal cortex (DLPFC) is involved in both pain modulation (Brighina et al., 2011) and the cognitive evaluation of pain (Melzack, 2001; Mylius et al., 2006). Research suggests that the processing of pain engages significant neural resources in the DLPFC. Consequently, there are fewer neural resources available for other cognitive functions of the DLPFC, such as planning and working memory (Berryman et al., 2013; Seminowicz & Davis, 2007). It has also been suggested that decreased cortical inhibition extends the duration of activation in the DLPFC during pain processing. During this time, the DLPFC is unable to shift attention away from the pain and reallocate those resources to other cognitive tasks (Berryman et al., 2013). Attending to pain is therefore highly cognitively demanding and leaves little resources available in the DLPFC for normal functioning (Moseley, 2003; Smith & Ayres, 2014)

Research has provided strong evidence of cognitive deficits in people with chronic pain (Higgins et al., 2018). However, there are discrepancies regarding which cognitive domains are affected and whether this differs between pain conditions. Compared to controls, people with chronic pain perform poorly on general measures of cognition (Oosterman et al., 2010; Weiner et al., 2006) and the prevalence of significant global deficit (≤ 24 on the Mini Mental State Examination) is higher in the chronic pain population compared to the general population (Povedano et al., 2007; Rodriguez-Andreu et al., 2009). Deficits in attention have been reported in multiple chronic pain conditions, including CLBP (Dick & Rashiq, 2007) and Fibromyalgia (Dick et al., 2002). A systematic and meta-analytic review

reported working memory deficits in multiple chronic pain conditions, including CLBP and non-specific CLBP (Berryman et al., 2013). Specific differences between people with chronic pain and healthy controls were reported in verbal working memory, non-verbal working memory, and attention (Berryman et al., 2013). However, no differences were identified in spatial working memory between people with chronic pain and healthy controls (Berryman et al., 2013). In comparison, a review by Moriarty et al. (2011) reported that people with chronic pain performed poorly on measures of verbal and spatial working memory. These findings were consistent with research in CLBP, that reported deficits in verbal, visual, and spatial memory when compared to pain-free controls (Jorge et al., 2009).

While the specific impairment may differ between pain conditions, cognitive impairment is a common feature of chronic pain that significantly impacts treatment outcomes. Cognitive impairment in people with chronic pain can impact upon a person's planning ability, mental flexibility, and decision making (Apkarian et al., 2004; Berryman et al., 2013; Moriarty et al., 2011), rendering cognitive-behavioural rehabilitation strategies ineffective (Smeets et al., 2006). Poor cognitive performance is associated with disengagement from daily activities, reduced treatment adherence, and poor quality of life in people with chronic pain (Hoy et al., 2014, Roth et al., 2005). As such, effective management of chronic pain needs to encompass strategies to improve cognitive function.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that delivers low intensity electrical currents to modulate neural activity (Nitsche et al., 2008). Anodal-tDCS (a-tDCS) over left-DLPFC improves cognitive function in numerous conditions, such as neurodegenerative disease, and healthy ageing (Boggio et al., 2006; Boggio et al., 2009; Coffman et al., 2014). Research in healthy individuals has found that tDCS over DLPFC improves cognitive functioning (Coffman et al., 2014). Participants who experience problems with their memory show improved cognitive functioning across multiple cognitive domains following a-tDCS over DLPFC (Hansen, 2012). Research in neurodegenerative diseases has also reported improvements in cognitive functioning following a-tDCS over DLPFC (Boggio et al., 2006; Boggio et al., 2009; Hansen, 2012). Participants with Parkinson's disease improved on a working memory task following a single session of a-tDCS over DLPFC (Boggio et al., 2006). Participants

with Alzheimer's improved on a visual recognition memory task following a single session of a-tDCS over DLPFC (Boggio et al., 2009). While there is substantial evidence for the use of tDCS over left-DLPFC to improve cognition in clinical and healthy ageing populations, few studies have investigated the impact of tDCS on cognitive functioning in chronic pain.

Research in fibromyalgia indicated a trend towards improvement in global cognition following five daily sessions of a-tDCS over DLPFC (Fregni et al., 2006). Improvements were also shown on an attention and working memory task, and simple reaction time task (Fregni et al., 2006). Silva et al. (2017) reported improvements in selective attention (orientating and executive) in people with fibromyalgia following a single session of a-tDCS over DLPFC. It is believed that a-tDCS induces long-term potentiation-like plasticity mediated by upregulating N-methyl-d-aspartate (NMDA) and GABA receptor activity. These receptors play a key role in maintaining optimal cognitive function (Seminowicz et al., 2019). In chronic pain, a-tDCS over left-DLPFC is thought to inhibit the allocation of maladaptive cognitive and attentional resources to pain, such that people disengage their attention from their pain and assign those resources to other cognitive functions (Berryman et al., 2013; Smith & Ayres, 2014). For those with chronic pain, the inhibition of maladaptive cognitive evaluations of pain may help to alleviate the pain and improve cognitive functioning. However, the impact of tDCS over DLPFC on cognition has not yet been examined in CLBP.

Limited studies have shown tDCS over DLPFC improves cognitive functioning in certain chronic pain conditions (Fregni et al., 2006; Silva et al., 2017). A-tDCS over DLPFC reduces pain levels in some forms of chronic pain (Brietzke et al., 2020; To et al., 2017). It is unclear whether a-tDCS over left-DLPFC can improve cognitive functioning in people with CLBP and, if so, whether there is a corresponding improvement in pain-related outcomes and psychological health. For the present study, it was proposed that 2x weekly, 1.5mA a-tDCS over left- DLPFC for 4 weeks would improve cognitive function in people with CLBP, whereby participants in the a-tDCS group would demonstrate an increase in cognitive performance compared to a sham-tDCS group (s-tDCS). It was also proposed that the a-tDCS group would demonstrate a reduction in pain-related outcomes (pain intensity, disability, and pain catastrophising), compared to the s-tDCS group.

Finally, it was proposed that the a-tDCS group would demonstrate an improvement in psychological outcomes (depression, stress, anxiety, and quality of life) compared to the s-tDCS group.

5.2 Methods

5.2.1 Participants

Participants were recruited to participate in a 5-week intervention study. This study was approved by Curtin University Human Research Ethics Committee (HR17/2015) and all research was conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent. Inclusion in the study required a formal diagnosis of CLBP by a qualified health professional (General Practitioner or Physiotherapist) of at least 6 months (see Table 5.1 for demographics and pain related information). Individuals' eligibility was assessed against a tDCS screening questionnaire (Nitsche et al., 2008) and individuals were screened for cognitive status using the Telephone Interview for Cognitive Status – 30 (TICS-30; score ≥ 18 for inclusion). Thirty-one participants met the inclusion criteria. One participant withdrew from the study prior to the first session of the intervention and was not included in the analysis. Thirty participants completed the intervention (see Figure 5.1).

Table 5.1

Baseline demographics and pain-related information by intervention group.

	Total (n = 30)	Anodal (n = 15)	Sham (n = 15)
Age	57.47 (14.28)	52.13 (15.26)	62.80 (11.95)
Years of Education	12.56 (3.17)	11.83 (3.19)	13.30 (3.09)
Duration of Diagnosis (years)	16.33 (13.69)	14.42 (12.67)	18.23 (15.28)
VAS Pain Average	4.96 (1.95)	5.05 (1.73)	4.86 (2.21)
CLBP Classification			
Non-Specific	84%	87%	80%
Specific	13%	13%	13%
Neurological	3%	-	7%
Percentage taking Pain Medication	64%	60%	67%
Anti-Inflammatory (Celebrex)*	30%	78%	20%
Pain Killer (Tremadol)*	79%	67%	90%
Benzodiazepine (Valium)*	21%	44%	10%
Anti-Depressants (Endep)*	16%	22%	10%
Engaging in Physiotherapy	47%	53%	40%
Past Surgery	20%	27%	13%
Other Pain Management (Chiropractor)	77%	87%	67%
Depression and Anxiety Disorder	20%	20%	20%
Anti-Anxiety Medication*	33%	67%	-

Note. CLBP Classification = classification of chronic lower back pain based on Koes *et al* (2001), Non-Specific = no radiographical injury at time of participation, Specific = Radiographical evidence, Neurological = related to change in the Central Nervous System. Pain Average = Average pain intensity one week prior to participation. Other = Acupuncture, Chiropractor, Massage. * = Percentage based on individuals taking pain medication

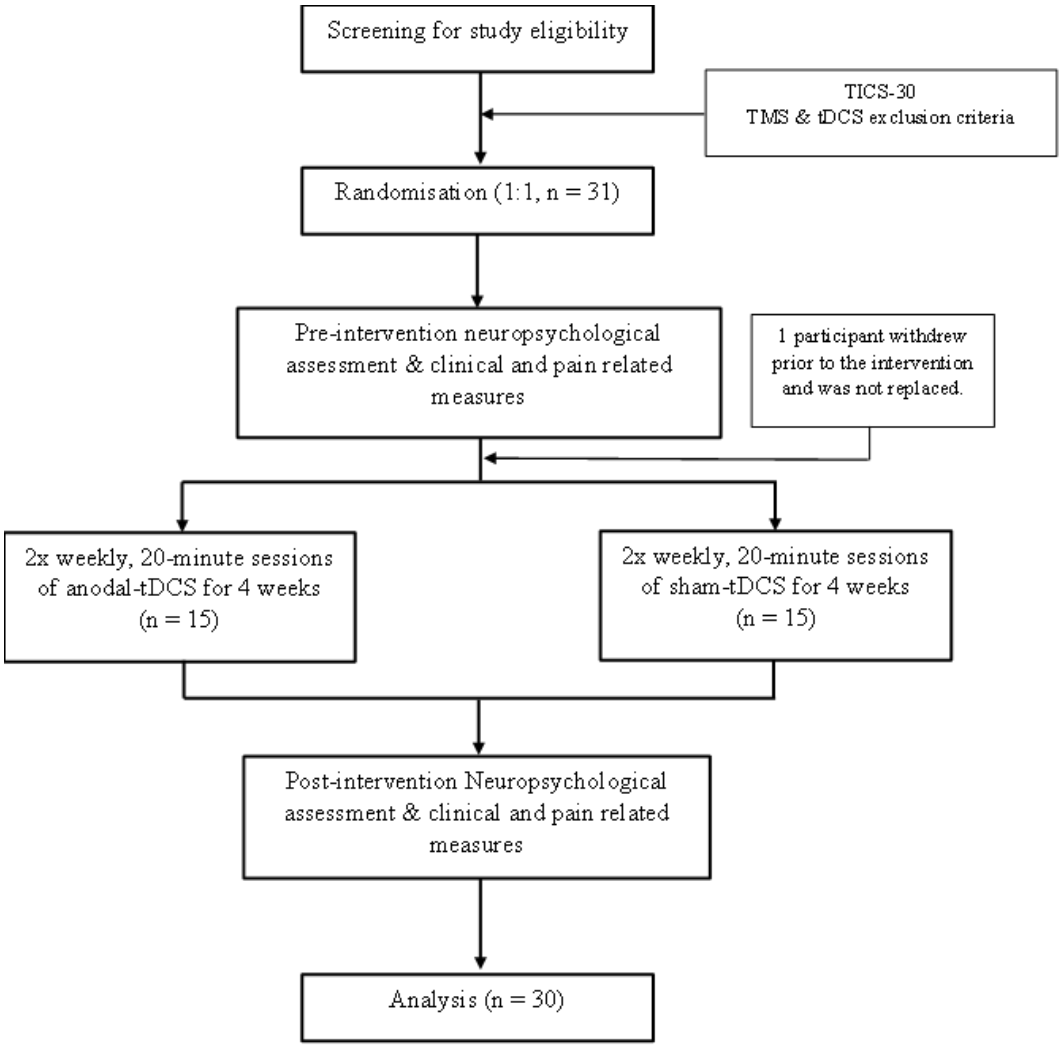

Figure 5.1. *Flow diagram of the progress of the trial for anodal and sham transcranial direct current stimulation (tDCS) groups.*

5.2.2 General Procedure

Demographic and pain-related information were collected via self-report questionnaire. All participants were asked to continue their normal medication routine. Neuropsychological and clinical measures were completed at baseline and immediately following the 4-week brain stimulation. Neuropsychological measures took approximately 2.5 hours to complete.

5.2.3 Measures

Age, sex, level of education, diagnosis duration, and medication use were collected via self-report questionnaire. All participants completed the neuropsychological and clinical assessment. In accordance with DSM-5, and

Movement Disorder Society criteria recommendations for mild cognitive impairment, two measures were administered for each of the five cognitive domains (American Psychiatric Association, 2013; Litvan et al., 2012).

5.2.3.1 Neuropsychological Assessment

The neuropsychological measures have been previously reported (see Corti et al., 2021).

5.2.3.2 Clinical and Pain-related Measures

Pain experience. The *Short-Form McGill Pain Questionnaire* (SF-MPQ) contains a 10 cm Visual Analogue Scale (VAS; scored 0 – 10) used to assess average pain intensity over the last week in CLBP (Melzack, 1975). The VAS is a unidimensional measure of pain intensity and participants were required to mark the line at the spot they felt represented their level of pain (Hawker et al*.,* 2011). An individual *VAS* was used to assess current pain intensity in those with CLBP (Price et al., 1983). Participants completed the individual VAS prior to each intervention session.

Disability. The *Roland-Morris Disability Questionnaire* (RMDQ) assessed the level of disability in CLBP (Roland & Morris, 1983). The RMDQ consists of 24 items assessing the impact of CLBP across multiple domains (mobility, daily activities, sleeping, mood, and appetite) with higher scores reflective of greater disability. The RMDQ has high internal consistency in people with CLBP ($\alpha = .93$; Rocchi et al., 2005).

Depression. The *Depression, Anxiety, and Stress Scale-21* (DASS-21) assessed the presence of depression, anxiety, and stress in CLBP (Lovibond & Lovibond, 1995). The DASS-21 consists of 21 items assessing depression, anxiety, and stress over the past seven days, with higher scores indicative of greater levels of depression, anxiety, and stress (Lovibond & Lovibond, 1995). The DASS subscales have high internal consistency in people with chronic pain, depression ($\alpha = .96$), anxiety ($\alpha = .89$), and stress ($\alpha = .95$; Taylor et al., 2005).

Quality of Life. The MOS 36-Item Short-Form Health Survey (SF-36) assessed QOL in individuals with CLBP (Ware & Sherbourne, 1992). The SF-36 consists of eight subscales (scored from 0 – 100; higher scores indicative of better

quality of life); physical functioning, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perceptions (McHorney, Ware & Raczek, 1993). The SF-36 has high internal consistency for the eight subscales in people with chronic pain; physical functioning (α = .92), role-physical (α = .90), bodily pain (α = .86), general health (α = .81), vitality (α =.77), social functioning (α= .64), role-emotional (α=.87), and metal health (α = .80; Picavet & Hoeymans, 2004).

5.2.4 Brain Stimulation

As reported in Corti et al. (2022), participants completed 8-sessions of tDCS stimulation over 4-weeks (2 sessions per week). tDCS was delivered using a constant current stimulator (Soterix®). Participants were randomly assigned (1:1 using block randomisation) to the anodal (a)-tDCS or sham (s)-tDCS group. Participants in the a-tDCS group received 20 minutes of constant 1.5 mA stimulation over left DLPFC every session. The stimulation was administered using two 35 cm2 sponge electrodes soaked in saline solution. The anode electrode was placed over F3 according to the 10-20 international system for EEG electrode placement, to stimulate the left DLPFC. The reference electrode was placed above the left eye, to ensure the current flowed through the prefrontal area. There was a period of 30 seconds at the beginning and end of the tDCS for ramp up/down. Participants in the s-tDCS experienced the 30 second ramp up/down of tDCS but the stimulation was ceased after the 30 seconds. The ramping up of the tDCS aims to provide participants with the initial experience of receiving active tDCS (Ambrus et al., 2012; Nitsche et al., 2008).

5.3 Statistical Analysis

All analyses were conducted using R software (v4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

5.3.1 Neuropsychological Analysis

Cognition data were analysed using linear mixed models using lme function, nlme package, with the nlme default covariance structure (variance components structure; Pinheiro et al., 2022). For all models, tDCS group (2 levels, Active and

Sham), time (2 levels, pre and post), and their interactions were included as fixed factors with the intercept of each participant modelled as a random effect.

5.3.2 Clinical and Pain-related Measures Analysis

Pain Intensity, RMDQ score, Pain Catastrophising, Depression, Stress, Anxiety, and Quality of Life subscales were analysed using linear mixed models (Pinheiro et al., 2022). For all models, tDCS group, time, and their interactions were included as fixed factors with the intercept of each participant modelled as a random effect.

5.4 Results

5.4.1 Memory

Hooper Verbal Language Test (HVLT) Total Recall. The linear mixed model revealed no significant main effect of Group ($p = .637$) or Group and Time Interaction ($p = .481$). There was a significant main effect of Time, $F(1,28) = 28.12$, $p < .001$. Further inspection of the plots suggests this was driven by an increase in total recall score at post-intervention for both groups (see figure 5.2a).

HVLT Delayed Recall. The linear mixed model revealed no significant main effect of Group ($p = .338$), Time ($p = .067$) or Group and Time Interaction ($p = .381$; see figure 5.2a).

Paragraph Total Recall. The linear mixed model revealed no significant main effect of Group ($p = .250$), Time ($p = .120$) or Group and Time Interaction ($p = .429$; see figure 5.2b).

Paragraph Delayed Recall. The linear mixed model revealed no significant main effect of Group ($p = .213$) or Group and Time Interaction ($p = .744$). There was a significant main effect of Time, $F(1,28) = 6.48$, $p = .017$. Further inspection of the plots suggests this was driven by an increase in total recall score at post-intervention for both groups (see figure 5.2b).

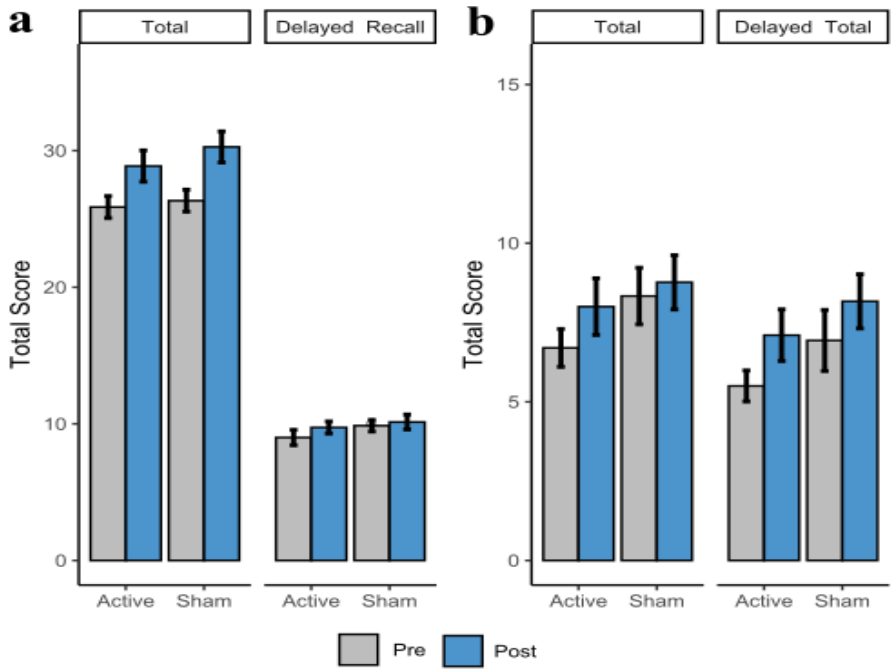

Figure 5.2. *(**A**) Total and delayed recall score on the Hooper Verbal Language Test pre- and post-intervention by group. (**B**) Total and delayed recall score on the Paragraph Recall task pre- and post-intervention by group.*

5.4.2 Attention and Working Memory

Letter Number Sequencing. The linear mixed model revealed there was no significant main effect of Group (p = .220). There was a significant main effect of time, $F(1, 28) = 18.04$, p <.001. There was a significant interaction between Group and Time, $F(1, 28) = 7.67$, p =.010, such that the total score on the LNS task significantly increased in the a-tDCS group at post-intervention see figure 5.3a).

Stroop. The linear mixed model revealed no significant main effect of Group (p = .970), Time (p = .209) or Group and Time Interaction (p = .081; see figure 5.3b).

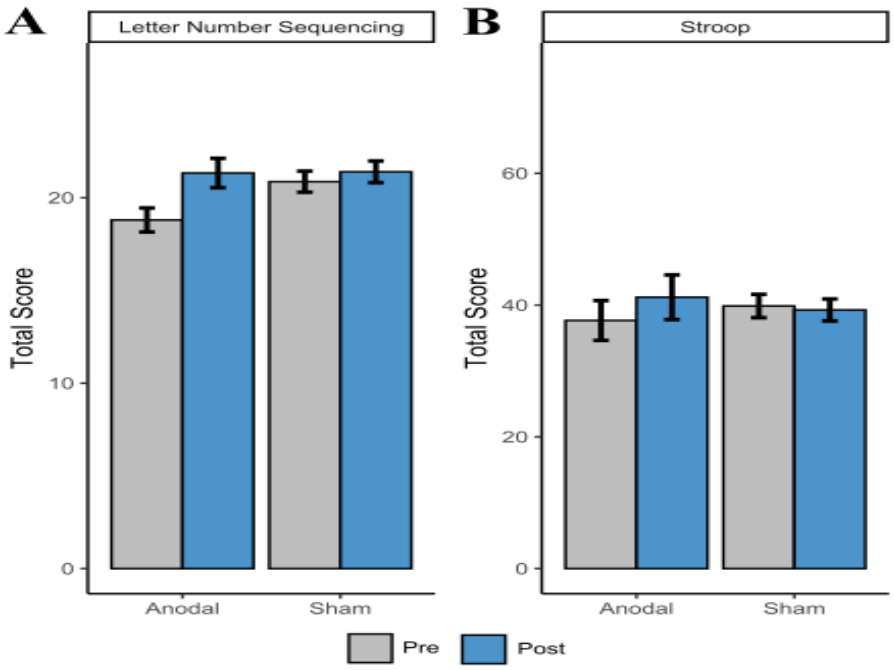

Figure 5.3. *(**A**) Total score on the Letter Number Sequencing pre- and post-intervention by group. (**B**) Total score on the Stroop task pre- and post-intervention by group.*

5.4.3 Executive Function

Controlled Oral Word Association Task. The linear mixed model revealed no significant main effect of Group (p = .621) or Group and Time Interaction (p = .177). There was a significant main effect of Time, $F(1, 28) = 5.54$, p = .026. Further inspection of the plots suggests this was driven by an increase in total score at post-intervention for both groups (see figure 5.4a).

Stockings of Cambridge. The linear mixed model revealed no significant main effect of Group (p = .115), Time (p = .926) or Group and Time Interaction (p = .926; see figure 5.4b).

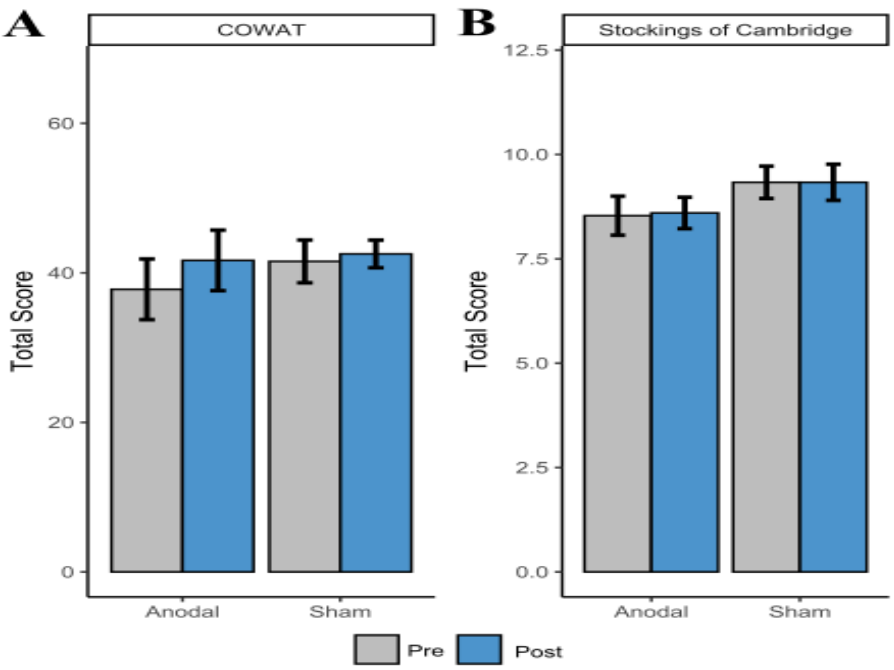

Figure 5.4. *(A) Total score on the Controlled Oral Word Association Task (COWAT) pre- and post-intervention by group. (**B**) Total score on the Stockings of Cambridge pre- and post-intervention by group.*

5.4.4 Visuospatial

Judgement of Line Orientation. The linear mixed model revealed no significant main effect of Group (p = .805) or Group and Time Interaction (p = .791). There was a significant main effect of Time, $F(1, 28) = 4.36$, p = .046. Further inspection of the plots suggests this was driven by an increase in total score at post-intervention for both groups (see figure 5.5a).

Hooper Visual Organisation Test. The linear mixed model revealed no significant main effect of Group (p = .848) or Group and Time Interaction (p = .725). There was a significant main effect of Time, $F(1, 28) = 18.60$, p = .< .001. Further inspection of the plots suggests this was driven by an increase in total score at post-intervention for both groups (see figure 5.5b).

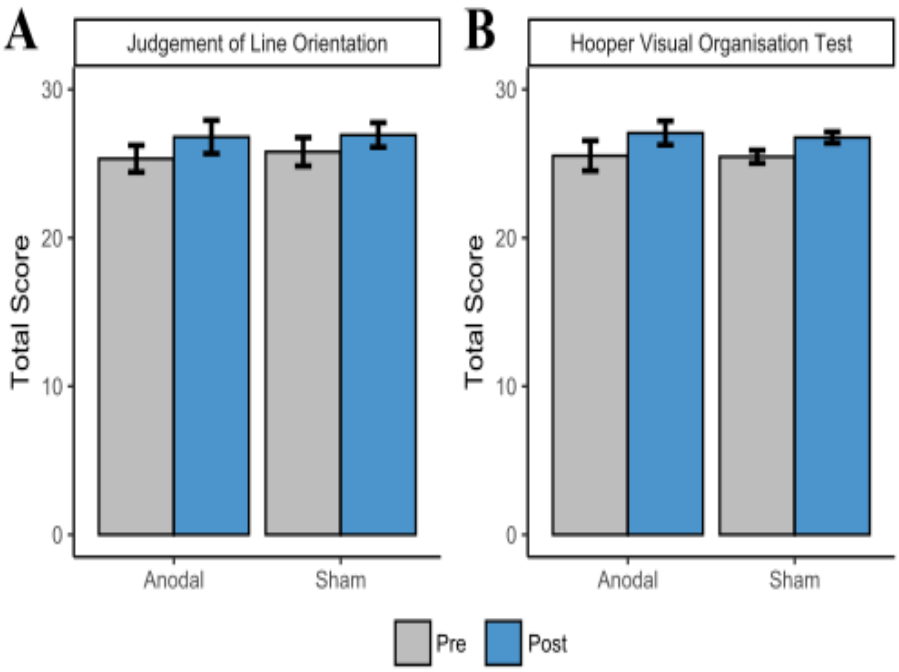

Figure 5.5. *(**A**) Total score on the Judgement of Line Orientation task pre- and post-intervention by group. (**B**) Total score on the Hooper Visual Organisation Test pre- and post-intervention by group.*

5.4.5 Language

Boston Naming Test. The linear mixed model revealed no significant main effect of Group (p = .056) or Group and Time Interaction (p = .516). There was a significant main effect of Time, $F(1, 28) = 17.85$, p = <.001. Further inspection of the plots suggests this was driven by an increase in total score at post-intervention for both groups (see figure 5.6a).

Similarities. The linear mixed model revealed no significant main effect of Group (p = .280) or Group and Time Interaction (p = .128). There was a significant main effect of Time, $F(1, 28) = 23.40$, p = <.001. Further inspection of the plots suggests this was driven by an increase in total score at post-intervention for both groups (see figure 5.6b).

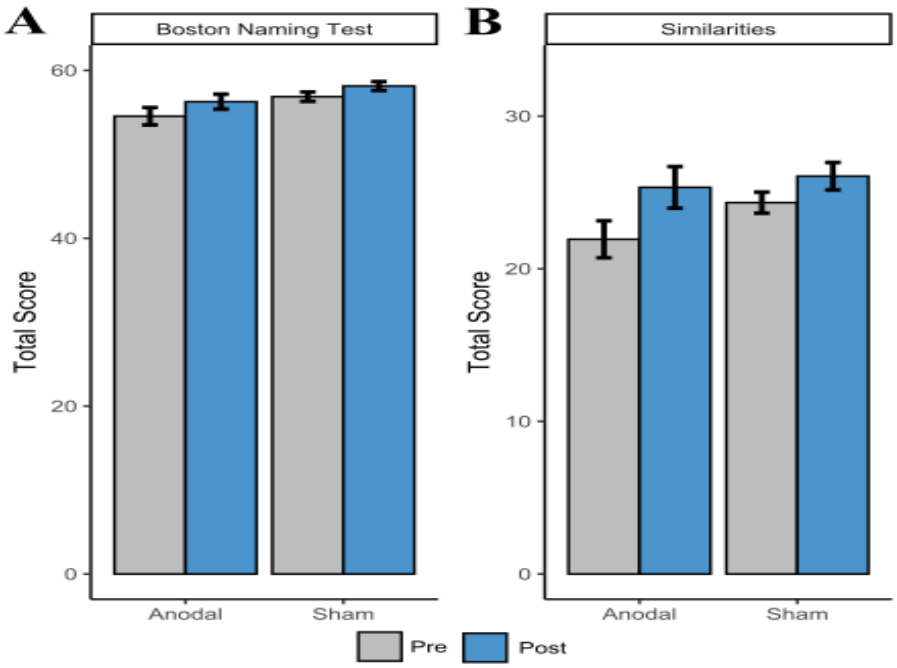

Figure 5.6. *(**A**) Total score on the Boston Naming Test pre- and post-intervention by group. (**B**) Total score on the Similarities task pre- and post-intervention by group.*

5.4.6 Pain-related Outcomes

Pain Intensity. The linear mixed model revealed no significant main effect of Group (p = .570) or Group and Session Interaction (p = .865). There was a significant main effect of Session, $F(1, 28) = 2.94$, p = .002. Further inspection of the plots suggests this was driven by an overall decrease in pain across the intervention sessions for both groups (see figure 5.7a).

The linear mixed model revealed no significant main effect of Group (p = .744) or Group and Time (pre-post) Interaction (p = .247). There was a significant main effect of Time, $F(1, 28) = 2.94$, p = .006. Further inspection of the plots suggests this was driven by an overall decrease in pain at post-intervention for both groups (see figure 5.7b).

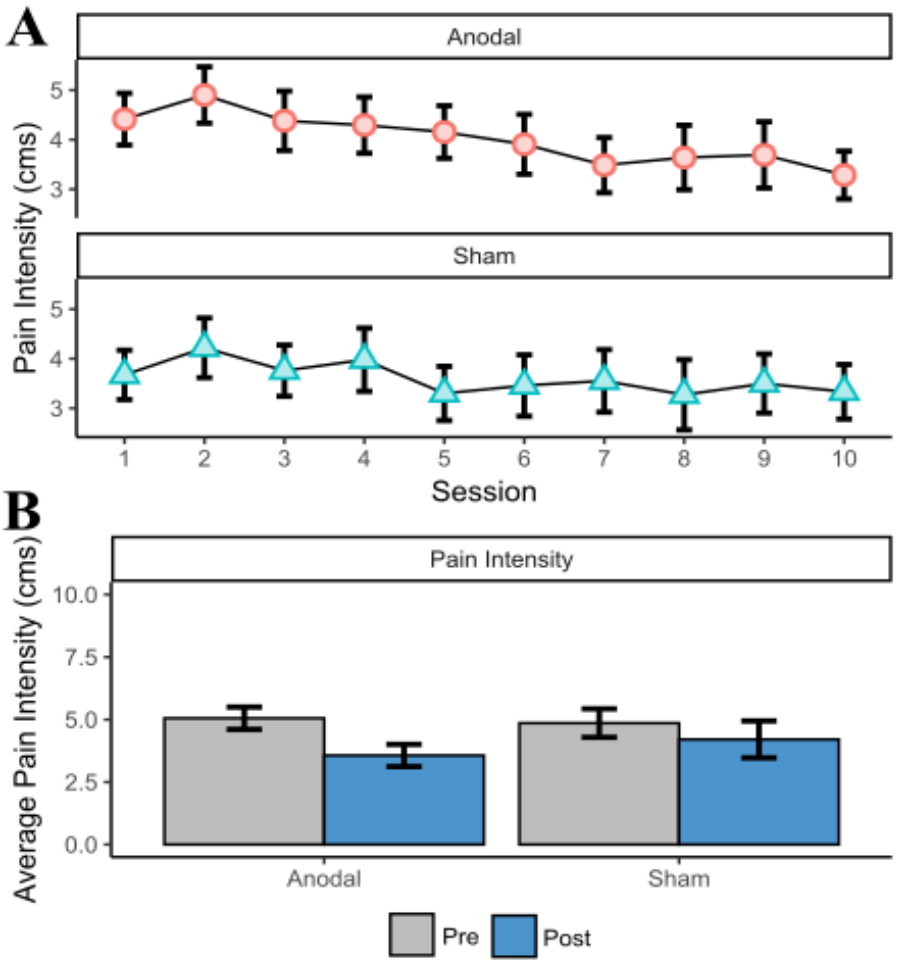

Figure 5.7. *(**A**) Current Pain intensity recorded at baseline, intervention sessions, and post-intervention by group. (**B**) Average pain intensity pre- and post-intervention by group.*

Disability (RMDQ). The linear mixed model revealed no significant main effect of Group (p = .851) or Group and Time Interaction (p =.234). There was a significant main effect of Time, $F(1, 28) = 4.40$, p = .045. Further inspection of the plots suggests this effect was driven by a decrease in RMDQ total score at post-intervention for both groups (see figure 5.8a).

Pain Catastrophising. The linear mixed model revealed no significant main effect of Group (p = .075) or Group and Time Interaction (p =.981). There was a significant main effect of Time, $F(1, 28) = 10.48$, p =.003. Further inspection of the plots suggests pain catastrophising was reduced in both groups at post-intervention (see figure 5.8b).

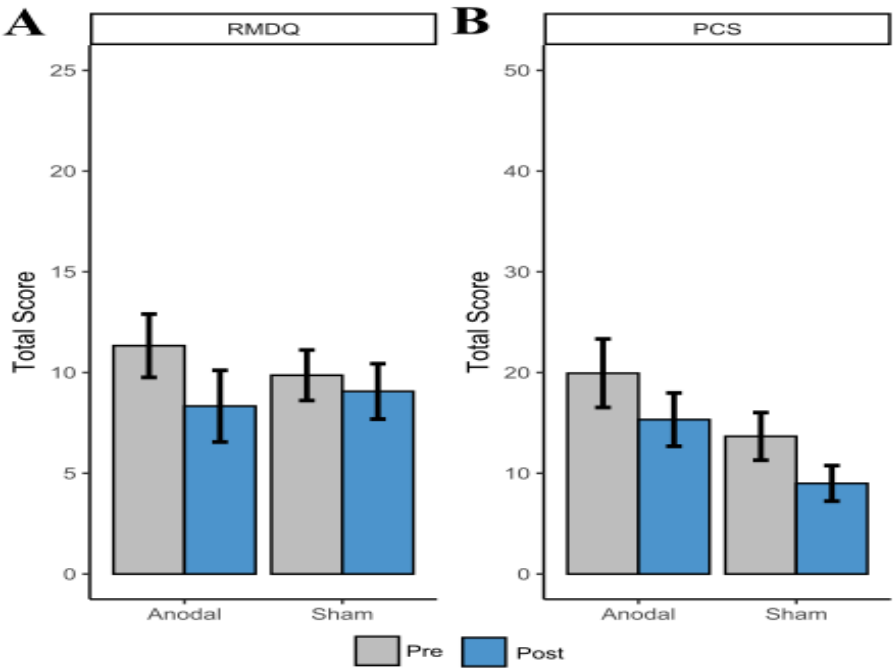

Figure 5.8. *(**A**) Total score on the Roland Morris Disability Questionnaire (higher scores = greater level of disability) pre- and post-intervention by group. (**B**) Total score on the Pain Catastrophising scale (higher scores = greater level of catastrophising) pre- and post-intervention by group.*

5.4.7 Clinical Outcomes

Anxiety. The linear mixed model revealed no significant main effect of Group (p = .425) or Group and Time Interaction (p =.421). There was a significant main effect of Time, $F(1, 28) = 5.50$, p = .026. Further inspection of the plots suggests anxiety was reduced for both groups at post-intervention (see figure 5.9).

Depression. The linear mixed model revealed no significant main effect of Group (p = .343), Time (p = .086) or Group and Time Interaction (p =.588; see figure 5.9).

Stress. The linear mixed model revealed no significant main effect of Group (p = .158) or Group and Time Interaction (p =.126). There was a significant main effect of Time, $F(1, 28) = 28.72$, p <.001. Further inspection of the plots suggests stress was reduced for both groups at post-intervention (see figure 5.9).

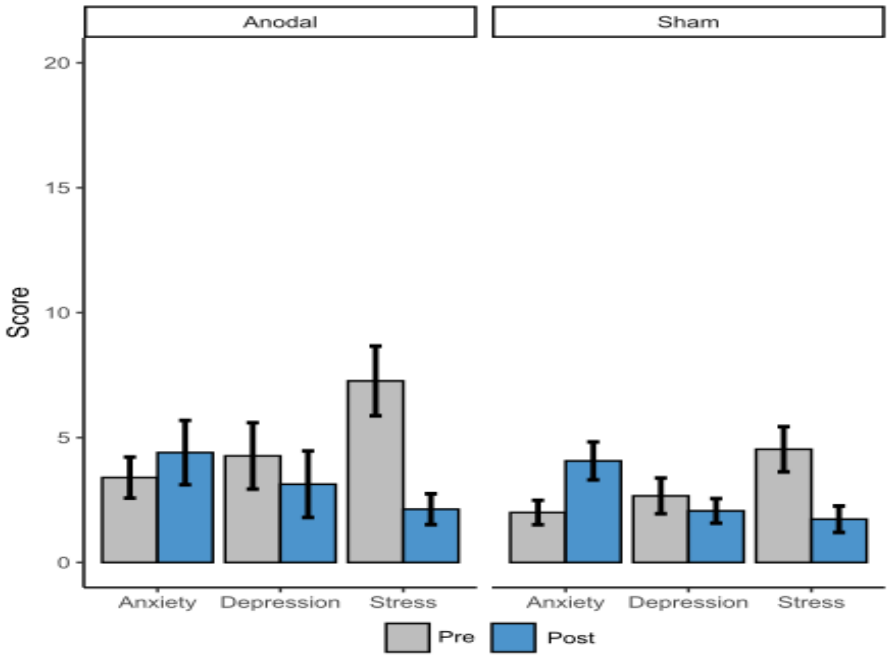

Figure 5.9. *Total score on each subscale of the Depression Anxiety and Stress Scale – 21 pre- and post-intervention by group.*

Quality of Life. *Physical Functioning*. The linear mixed model revealed no significant main effect of Group (p = .177) or Group and Time Interaction (p =.762). There was a significant main effect of Time, $F(1, 28) = 5.63$, p =.025. Further inspection of the plots suggests *Physical Functioning* score increased (improved) for both groups at post-intervention (see figure 5.10).

Physical Health Limitations. The linear mixed model revealed no significant main effect of Group (p = .444) or Group and Time Interaction (p =.881). There was a significant main effect of Time, $F(1,28) = 21.91$, p <.001. Further inspection of the plots suggests *Physical Health Limitations* score increased (improved) for both groups at post-intervention (see figure 5.10).

Emotional Health Limitations. The linear mixed model revealed no significant main effect of Group (p = .308) or Group and Time Interaction (p = .223). There was a significant main effect of Time, $F(1, 28) = 5.54$, p = .026. Further inspection of the plots suggests *Emotional Health Limitations* score increased (improved) for both groups at post-intervention (see figure 5.10).

Fatigue. The linear mixed model revealed no significant main effect of Group (p = .365) or Group and Time Interaction (p =.373). There was a significant main effect of Time, $F(1, 28) = 15.57$, p <.001. Further inspection of the plots suggests

Fatigue score increased (improved) for both groups at post-intervention (see figure 5.10).

Emotional Well-being. The linear mixed model revealed no significant main effect of Group (p = .232) or Group and Time Interaction (p =.820). There was a significant main effect of Time, $F(1, 28)$ =9.57, p = .004. Further inspection of the plots suggests *Emotional Well-being* score increased (improved) for both groups at post-intervention (see figure 5.10).

Social Functioning. The linear mixed model revealed no significant main effect of Group (p = .188), Time (p = .331) or Group and Time Interaction (p =.137; see figure 5.10).

Pain. The linear mixed model revealed no significant main effect of Group (p = .970) or Group and Time Interaction (p =.090). There was a significant main effect of Time, $F(1, 28) = 16.68$, p <.001. Further inspection of the plots suggests pain related quality of life was increased (improved) for both groups at post-intervention (see figure 5.10).

General Health. The linear mixed model revealed no significant main effect of Group (p = .541) or Group and Time Interaction (p =.438). There was a significant main effect of Time, $F(1, 28) = 7.40$, p = .011. Further inspection of the plots suggests general health related quality of life was increased (improved) for both groups at post-intervention (see figure 5.10).

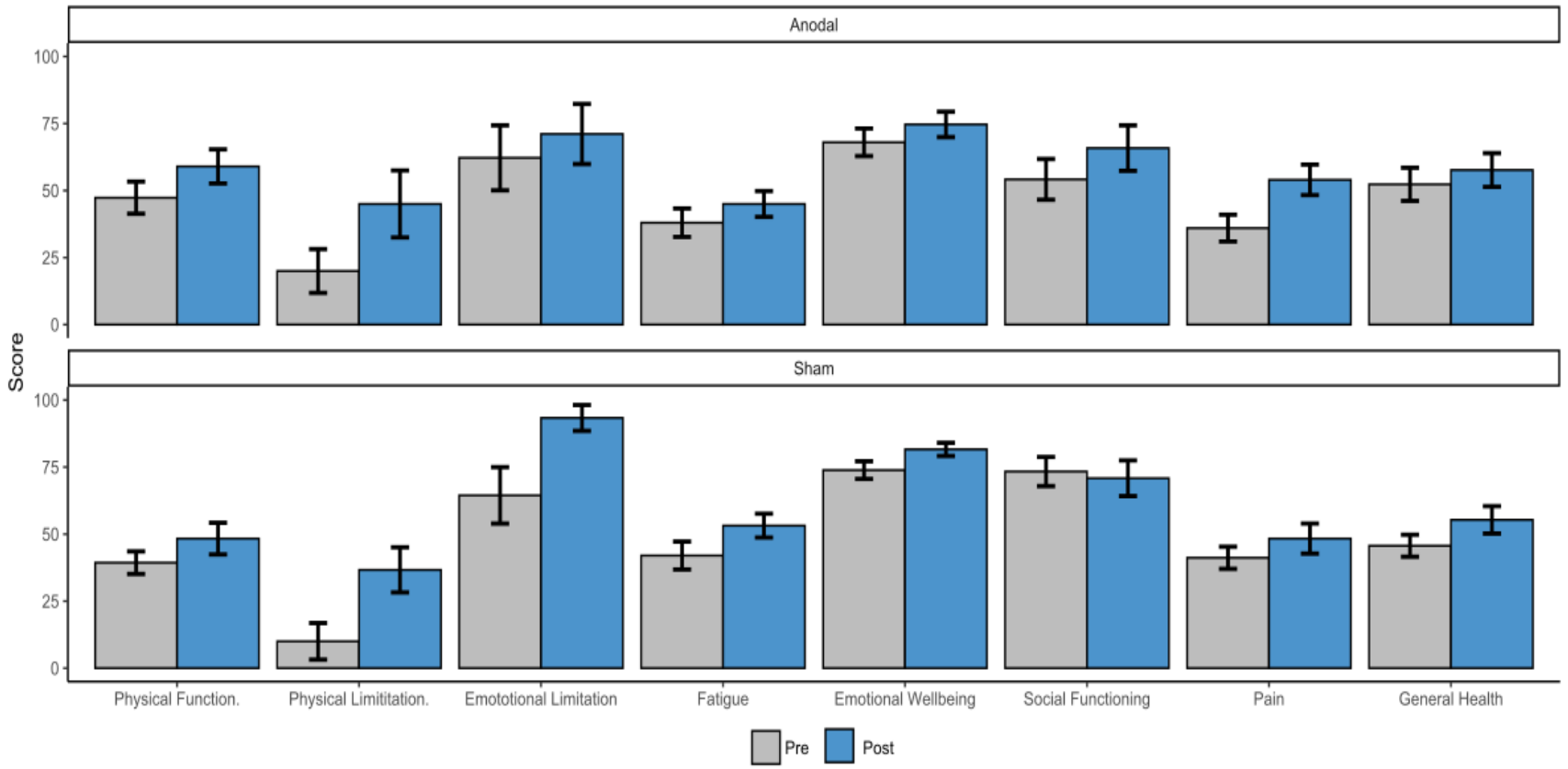

Figure 5.10. *Total score for each subscale of the Medical Outcomes Study 36-Item Short-Form Health Survey (higher scores = greater health-related quality of life) pre- and post-intervention by group.*

5.5 Discussion

The present study examined if twice weekly, 1.5mA a-tDCS over left-DLPFC improved cognitive functioning, self-reported measures of pain and disability, and quality of life in people with CLBP. The findings indicate an increase in performance in the Attention/Working memory task, letter number sequencing, for the a-tDCS group. For both tDCS groups, there was a pre-post intervention improvement in the following cognitive domains; memory (immediate and delayed), executive function, visuospatial, and language. The findings also indicate reduced pain intensity, disability, and pain catastrophising for both a-tDCS and s-tDCS groups. Anxiety and stress were also reduced for both groups. For quality of life, there was an improvement in seven of the eight domains (physical functioning, physical health limitations, emotional health limitations, fatigue, emotional wellbeing, pain, and general health) for both groups. No significant differences were found between the a-tDCS and s-TDCS groups on the aforementioned measures at post-intervention, suggesting that twice weekly, 1.5mA a-tDCS over left-DLPFC is no better than s-tDCS for improving cognition, pain-related experience, or quality of life in those with CLBP.

Attention and working memory performance have been shown to be reduced in individuals with chronic pain (including CLBP) when compared to healthy controls (Berryman et al., 2013; Corti et al., 2021; Moore et al., 2019). A-tDCS over left-DLPFC has been shown to improve working memory performance in several populations, including healthy ageing, neurological, and acute and chronic pain conditions. In line with this, the present findings support the use of a-tDCS over left-DLPFC to improve attention and working memory performance in those with CLBP, without having a direct effect on pain-related processes. As pain intensity was reduced in both the a-tDCS group and s-tDCS, the improvement in attention/working memory in the a-tDCS group cannot be solely attributed to a reduction in pain. These findings are in line with previous research that suggests a-tDCS over left-DLPFC improves attention/working memory performance in people with pain through top-down processes via increased activation of the DLPFC and an improved allocation of attentional resources. Improved attention/working memory may lead to an indirect

top-down inhibition of nociceptive activity without affecting pain perception (Deldar et al., 2018; Deldar et al., 2019).

In the present study, both a-tDCS and s-tDCS groups improved on memory (immediate and delayed), visuospatial, executive function, and language tasks following the intervention. These findings indicate that a-tDCS over left left-DLPFC does not improve cognitive function any more than sham tDCS. The improvements for both tDCS groups may be attributed to the placebo effect. It seems reasonable to suggest that the participants in the sham condition, who received 30-seconds of ramp-up stimulation, believed they were in the experimental (anodal) tDCS group. In this case, participants' expectation of the tDCS to improve cognitive functioning may have affected task performance (Bin Dawood et al., 2020). This is in line with previous research suggesting that tDCS has a strong placebo effect, such that it can influence participant behaviour and performance (Bin Dawood et al., 2020; Rabipour et al., 2018). Future studies should consider the use of a no-stimulation group to further explore the placebo effect of tDCS on cognition in CLBP, as s-tDCS alone cannot provide an accurate estimation of the overall influence of a potential placebo effect (Aslaksen et al., 2014; Benedetti et al., 2003). By including a no-stimulation group, the size of the placebo effect in the s-tDCS group can be determined by comparing the effect with the no-intervention group. Additionally, the inclusion of the three groups (a-tDCS, s-tDCS, and no-stimulation group) will inform on the specific effect of tDCS on pain as well as the placebo effect. Another potential explanation for the improvements observed for both groups is a practice effect. Although 5 weeks (the length of the intervention) has been used in previous research (Falleti et al., 2006), it is possible that participants may have recalled some of the tasks at post-intervention. Future studies should consider a longer timeframe between pre and post assessments to reduce the possibility of practice effects and should consider the use of alternate assessment forms (e.g., different, but comparable, word lists at pre and post intervention) to eliminate potential practice effects. Another alternate explanation for the observed improvements may be regression to the mean. Pain can be unpredictable and can fluctuate due to multiple reasons (e.g., acute injury, psychological factors). Additionally, the measurement of pain is subjective and is therefore prone to random variation. As such, regression to the mean cannot be ruled out in the present study.

Pain-related outcomes (intensity, disability, and catastrophising) and psychological outcomes (anxiety, stress, and health-related quality of life) also improved for both groups. This suggests that a-tDCS does not reduce the pain experience or improve psychological outcomes in CLBP any more than can be attributed to the placebo effect. The present findings are in line with research indicating that tDCS-induced placebo reduced and stabilised pain intensity in neuropathic pain for 3 months following stimulation (Tuttle et al., 2015). It has been suggested that the widely observed placebo effect following tDCS is due to positive participant expectations of the treatment. Benedetti et al. (2014) suggested that when analgesia associated with the placebo effect aligns with a participant's expectations of the treatment, an analgesic feedback loop is created, which subsequently maintains the reduction in pain. Given the reduction in pain across both groups, it is not surprising that self-reported disability and quality of life were also improved across both groups. These findings are consistent with previous tDCS and fibromyalgia research that reported improvements in quality of life in both a-tDCS and s-tDCS groups following tDCS over DLPFC (Fregni et al., 2006; Samartin-Veiga et al., 2022), and that improvements in quality of life were maintained at 6-month follow up (Samartin-Veiga et al., 2022).

The present findings support the growing body of research that suggests the placebo effect can improve chronic pain outcomes, including in CLBP (Chaparro et al., 2014; Henschke et al., 2010; Kleine-Borgmann et al., 2019). Research has reported that placebo treatment has led to improvements in pain-related disability and reduction in pain intensity in people with CLBP (Carvalho et al., 2016; Kleine-Borgmann et al., 2019). This is consistent with the present findings, whereby both a-tDCS and s-tDCS groups reported reduced pain and pain-related disability. The present study also suggests that the placebo effect may be associated with improvements in cognitive functioning and quality of life in people with CLBP. Although the present findings are unable to determine whether these improvements are directly caused by the placebo effect, or a natural consequence of improved pain outcomes, it does suggest that the placebo effect may be therapeutically beneficial not only for pain-related outcomes, but also to improve cognition and psychological wellbeing in people with CLBP. While the use of blinded placebo treatments can raise ethical concerns, this can be avoided by using open-label placebos (Kaptchuk & Miller, 2018). Research investigating the potential therapeutic benefit of the placebo

effect in CLBP, found that participants reported clinically significant improvement in pain outcomes, even when participants were aware they were receiving a placebo treatment (open-label placebo; Carvalho et al., 2016; Kleine-Borgmann et al., 2019). Future open-label placebo, randomised controlled trials should examine whether tDCS-induced placebo effect may be of therapeutic benefit for people with CLBP.

5.5.1 Limitations

The present findings should be considered in line with a number of limitations. In accordance with DSM-5 and MDS criteria for identifying mild cognitive impairment, the present study included 10 cognitive tests. The inclusion of so many tests may have inflated the Type I error rate, such that the significant effect of a-tDCS on the attention and working memory task is a natural consequence of the number of tasks used (Loftus et al., 2015). Given the effect of time was also significant, indicating that both the a-tDCS and s-tDCS group improved on the task, it is reasonable to suggest that the improvement in the a-tDCS group on the attention and working memory tasks may be a combination of the placebo effect and Type I error. Hence, this finding may be a natural consequence of the design of the study. Future research should consider reducing the overall number of tasks, or consider the use of a composite score for each cognitive domain, to reduce the potential for Type I errors (Feise, 2002).

The use of analgesic medications can influence cognitive functioning, pain, and psychological outcomes. While medication use was recorded in the present study, frequency of use and dosage was not documented. It is unknown if medication use was similar, reduced, or increased between pre- and post-intervention. We cannot rule out if changes in analgesic medication use may play some role in the observed improvements in pain-related and psychological outcomes. Previous research has produced conflicting results as to whether the use of analgesic medication hinders or improves cognitive future (Higgins et al., 2018). Future research should consider the inclusion of non-medicated participants to reduce any potential influence of medication on cognitive function. However, this may be difficult to achieve given that chronic pain is usually managed through medication.

The design of the study makes it difficult to differentiate between the effect of tDCS and the effect of engaging in the intervention. Previous research has

reported trial characteristics (e.g., the number of visits) were significantly associated with increased placebo response (Tuttle et al., 2015; Vase et al., 2015). Participants in the present study attended 9 appointments over a 5-week period, and it is possible that this may have impacted on both physical and emotional health. Attending the appointments may have increased participants movement and physical functioning and may have increased perceived social support (from the researchers). Research has reported that perceived social support is associated with pain intensity and depression in chronic pain, such that higher levels of perceived social support is associated with reduced pain and depression (López-Martínez et al., 2008). Although the present study did not collect information on perceived social support, it is reasonable to suggest that attending appointments twice weekly to discuss the participants' pain experience, may have increased their level of perceived social support. Future studies should consider modifying the study design to reduce the potential confounding impact of study-related effects of the intervention (e.g., reduce face-to-face appointments, or utilise home appointments). Future research should also consider including a no-intervention group, who receive the same level of social support as the intervention group, to examine if improvements in pain-related outcomes may be associated with an increase in perceived social support.

5.5.2 Conclusion

The present findings suggest that a-tDCS does not improve cognitive function in people with CLBP any more than s-TDCS. Both tDCS groups improved on measures of cognitive functioning, pain-related outcomes, and psychological outcomes, and this is most likely reflective of a strong placebo effect for tDCS. The present findings raise an interesting question as to the potential therapeutic benefit of the placebo effect in CLBP. Not only do current treatment options (pharmacological and surgical interventions) carry significant side-effects, but they are also typically ineffective for long-term pain management. As tDCS is safe and relatively inexpensive, the tDCS-induced placebo effect may be a beneficial approach in the management of CLBP. Further investigation of the potential clinical benefit of tDCS, even if such benefit is the result of placebo, in CLBP is required.

5.6 References

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CHAPTER SIX: GENERAL DISCUSSION

6.0 Overall Summary

The work presented in this thesis examined motor cortex excitability and cognition in people with Chronic Lower Back Pain (CLBP). Additionally, this thesis examined the impact of transcranial Direct Current Stimulation (tDCS) over left-Dorsolateral Prefrontal Cortex (DLPFC) on motor cortex excitability and cognition in people with CLBP. As a secondary outcome, this thesis also examined the impact of tDCS over left-DLPFC on the pain experience (intensity, disability, and catastrophising), mood, and quality of life. This thesis comprises six chapters. Chapter one summarised CLBP, motor cortex excitability, and cognitive function. Chapter one also summarised the impact of tDCS on motor cortex excitability and cognition in chronic pain, as well as the theoretical approach taken during this research.

In chapter two, motor cortex excitability was examined in participants with CLBP and age- and gender-matched healthy controls, to determine if intracortical mechanisms within the motor cortex may differ between people with CLBP and controls. Our analysis revealed that the CLBP group demonstrated higher resting motor threshold (rMT) and reduced intracortical facilitation (ICF) compared to controls. There were no differences in motor-evoked potential (MEP) amplitude (in the recruitment curve) and short interval intracortical inhibition (SICI) between the two groups. These findings seem to support that CLBP is associated with changes in intracortical excitability. We also examine the relationship between motor cortex excitability and pain-related outcomes in people with CLBP. Individual differences in rMT, ICF and SICI were not associated with pain intensity, duration, pain sensation, use of medication, or disability. However, we conducted an exploratory analysis to determine if the balance between inhibition and excitation was associated with pain intensity. This analysis revealed that the balance between inhibition and excitation was associated with pain intensity, such that increased net inhibition was associated with greater pain intensity.

In chapter three, participants with CLBP and age- and gender-matched healthy controls completed a neuropsychological assessment battery to determine whether cognitive function differed between the two groups. Our analysis revealed that, on average, people in the CLBP group performed worse on the cognition tasks across the five cognitive domains. Additionally, our analysis also revealed the

cognitive performance could correctly identify 84% of people with CLBP, suggesting the pattern of deficits in cognition present similarly in people with CLBP. Given the significant difference in cognitive performance between the two groups, we further explored whether the performance in the CLBP group met criteria for mild cognitive impairment (MCI). Using the Movement Disorders Society (https://www.movementdisorders.org/) and Diagnostic Statistical Manual-5 criteria for cognitive impairment, the CLBP group were then classified into three groups: no impairment, single-domain impairment, and multiple-domain impairment. Approximately 16% of the CLBP group met the criteria for MCI, and over 50% of the CLBP group were impaired on at least one cognitive task.

In chapter four, we examined the impact of anodal-tDCS (a-tDCS) over left-dorsolateral prefrontal cortex (left-DLPFC) on motor cortex excitability and pain-related outcomes in individuals with CLBP. CLBP participants that took part in chapter 2 were randomised to receive either 1.5mA a-tDCS or sham-tDCS (s-tDCS) twice per week for four weeks. Our analysis revealed no significant difference in motor cortex excitability (MEP amplitude, ICF, and SICI) between the a-tDCS and s-tDCS group. There was also no significant main effect of tDCS group on pain-related outcomes (intensity, disability, and catastrophising). However, follow-up analysis revealed the a-tDCS group demonstrated higher ICF and SICI following the intervention compared to the s-tDCS group. The a-tDCS group also demonstrated a reduction in pain intensity and self-reported disability compared to the s-tDCS group. These findings, while preliminary, suggest that 8 sessions of a-tDCS over left-Dorsolateral Prefrontal Cortex (left-DLPFC) may modulate motor cortex excitability in people with CLBP. Additionally, these findings support the theoretical framework that restoration of abnormal motor cortical excitability in CLBP may be associated with decreased pain and disability.

In the final experimental chapter, we examined the impact of a-tDCS over left-DLPFC on cognitive functioning, pain-related outcomes, and psychological health in individuals with CLBP. CLBP participants that took part in chapter 3 were randomised to receive either 1.5mA a-tDCS or s-tDCS twice per week for four weeks. Our analysis revealed a significant difference in the attention and working memory task, letter number sequencing, in the a-tDCS group. For both a-tDCS and s-tDCS groups, there was a significant improvement in four of the cognitive domains: memory, executive function, visuospatial, and language at post-intervention. The

findings also indicate improvement (reduced) pain intensity, disability, and pain catastrophising in both a-tDCS and s-tDCS groups. Anxiety and stress were also reduced at post-intervention in both groups. For quality of life, there was an improvement in seven of the eight domains (Physical functioning, physical health limitations, emotional health limitations, fatigue, emotional wellbeing, pain, and general health) in both groups. There were no significant differences between the a-tDCS and s-tDCS groups on any of the above outcomes. Our findings suggest that twice weekly, 1.5mA a-tDCS over left-DLPFC is not better than s-tDCS for improving cognition, pain-related experience, or psychological health in those with CLBP.

6.1 Motor Cortex Excitability in CLBP

The findings of this thesis add to our understanding of the mechanisms that underline changes in motor cortex excitability in CLBP. While previous studies have provided inconclusive evidence for change in excitability in CLBP (Chang et al., 2018), our analysis in chapter two suggests CLBP is associated with deficits in intracortical modulation involving glutamatergic mechanisms. Furthermore, by investigating motor cortex excitability via the First Dorsal Interosseous muscle as opposed to a muscle at the site of pain, we have provided evidence for a global change in excitability that is not specific to the area of pain. This extends on Strutton et al (2005) who proposed the need for research to investigate corticospinal excitability via responses to TMS of muscles that are not in close proximity to the site of pain. Our findings suggest that changes in motor cortex excitability involving glutamatergic mechanisms may be more generalised than previously thought. To further explore this, future research needs to compare motor cortex excitability via the muscle at the site of pain vs a muscle that is not in close proximity to the site of pain. This would provide a greater understanding of the changes in motor cortex excitability associated with chronic pain, and will help to clarify whether there is a global alteration in motor cortex excitability, or whether changes in excitability are site specific to the brain region corresponding to the area of pain. It may also provide insight into whether changes in motor cortex excitability occur both in the region associated with pain, as well as globally. This may inform on a more targeted approach for non-invasive brain stimulation as a potential modulator of motor cortex

excitability. It may be that the determination for optimal stimulation site is dependent on whether we are attempting to modulate site-specific excitability versus global excitability.

Our exploratory analysis of the balance between inhibition and excitation has also provided support for an association between motor cortex excitability and pain intensity, such that increased net inhibition was associated with increased pain intensity. We have shown that the relationship between cortical excitability and pain may not be simply explained by a singular measure in isolation but may be the result of an imbalance between excitation and inhibition. As a result, pain might be a by-product of neural dysfunction when these mechanisms are not balanced. Few studies using TMS have investigated the relationship between excitation/inhibition balance and pain (Andrews et al., 2020). However, Magnetic resonance spectroscopy studies provide initial support for examining the excitation/inhibition balance. Magnetic resonance spectroscopy studies have examined the excitation/inhibition balance through the measurement of neurochemicals indicative of excitation (glutamate) and inhibition (GABA) as an indicator of cortical excitability (Filmer et al., 2019; Mullins et al., 2014). As ICF and SICI provide an indication of glutamate and GABA, respectively, we suggest that TMS can be used to assess the excitation/inhibition balance (Cuypers & Marsman, 2021). As the findings from this thesis suggest that pain intensity is associated with the excitation/inhibition balance, but not the individual systems, future research should explore the use of TMS to assess the excitation/inhibition balance and to establish whether this balance is associated with the pain experience. If this relationship were to be established, it would indicate that chronic pain treatment needs to be aimed at restoring the balance between the two systems, rather than targeting each system individually.

Given altered motor cortex excitability was established in chapter two, the study described in chapter four aimed to modulate motor cortex excitability using non-invasive brain stimulation. The findings from chapter four provide preliminary evidence that tDCS over left-DLPFC may modulate motor cortex excitability in people with CLBP. Additionally, tDCS over left-DLPFC reduces pain and self-reported disability in people with CLBP. The present findings add to our understanding of the use of neuromodulation techniques to alleviate pain in people with CLBP, and provides preliminary support for the theoretical framework that restoration of abnormal motor cortex excitability co-occurs with improved pain-

related outcomes (Fierro et al., 2010; Vaseghi et al., 2015). It is, however, important to note that the trend for pain reduction in only the a-tDCS group identified in chapter 4 was not present in chapter 5 (pain was reduced in both tDCS groups). As such, the findings of the present study should be considered preliminary, and future research is required to confirm whether restoration of abnormal motor cortex excitability co-occurs with improved pain-related outcomes.

While the present findings support the theory that stimulation of the DLPFC may modulate motor cortex excitability, it is not possible to rule out the influence of surrounding structures. As tDCS is not hyper-localised, it is possible surrounding areas of the DLPFC may have also been influenced by the stimulation and may have played a role in modulating motor cortex excitability (Morya et al., 2019). Future research should consider the use of more focal stimulation techniques, such as HD-tDCS and rTMS. If similar results are found following more focal stimulation modalities, this would provide greater support for the role of the DLPFC in modulating motor cortex excitability.

The present study did not examine whether changes in motor cortex excitability mechanisms, or the excitation/inhibition balance, were directly associated with changes in pain intensity and self-reported disability. Furthermore, we did not include measures of motor control, and as such, we do not know whether tDCS-induced changes in motor cortex excitability are associated with changes in motor function. Future research should examine if changes in motor cortex excitability are directly responsible for changes in the pain experience (pain, disability, motor function). This should include examining whether changes in specific mechanisms (i.e., ICF or SICI) are directly responsible for changes in the pain experience, or whether changes in the pain experience are associated with the interaction between multiple mechanisms (i.e., excitation/inhibition balance). This will allow for a greater understanding about the cortical mechanisms underlying CLBP symptoms and, consequently, the development of interventions targeted at restoring motor cortex excitability to improve functional outcomes in people with CLBP.

6.2 Cognitive Function in CLBP

The findings of this thesis add to our understanding of effect of chronic pain on the brain, with emphasis on the engagement of cognitive resources in the prefrontal cortex. While previous studies have provided some evidence of cognitive deficits in specific cognitive domains in CLBP (Higgins et al., 2018; Jorge et al., 2009; Ling et al. 2007), we examined cognitive functioning across five cognitive domains. Our analysis in chapter three suggests that the pattern of cognitive deficits is similar in people with CLBP. This has important implications for early intervention in CLBP. Knowing the likely pattern of cognitive deficits a person with CLBP may experience, may allow for interventions aimed at targeting those specific cognitive domains early in the condition. Early cognitive intervention may also reduce the number of people with CLBP who meet criteria for mild cognitive impairment (Fernández-Blázquez et al., 2016). This thesis was the first to use the Movement Disorder Society (Litvan et al., 2012) and Diagnostic Statistical Manual-5 (American Psychiatric Association, 2013) criteria for determining mild cognitive impairment (MCI) in people with CLBP. Our analysis identified that 16% of our sample met criteria for mild cognitive impairment, and over 50% of the sample were impaired on at least one cognitive task. Given MCI is a significant predictor of progression to dementia (Kremen et al., 2014; Petersen et al., 2009), the level of impairment identified in the present thesis is of great concern. Future research needs to examine whether people with CLBP who meet the criteria for MCI are more likely (than those without MCI) to progress to dementia. This should also include individuals who do not meet criteria for MCI, but are impaired on at least one cognitive task. This will provide insights into whether individuals impaired on one task are more likely (than those with no impairments) to progress to MCI. It would also provide strong support for the development of early cognitive intervention for people with CLBP. Also of interest is the decreasing years of education with increasing levels of impairment identified in the present sample. Although the no impairment, single impairment, and MCI group did not significantly differ in years of education, the reduction in the years of education may suggest that those with lower levels of education may be more likely to progress to mild cognitive impairment. Conversely, it could suggest that higher levels of education may serve as a protective factor against cognitive decline. Future research should examine the role

of education in the progression to MCI in individuals with CLBP. This may provide insights into individuals who may be more likely to progress to MCI based on years of education and support for the development of early cognitive intervention. Given cognitive impairment is associated with disengagement from treatment and poor quality of life (Hoy et al., 2014; Roth et al*.,* 2005), identifying whether people with CLBP may be more likely to experience significant cognitive impairment is vital for early intervention (Chandler et al., 2016). Early cognitive intervention may assist in reducing the burden of cognitive impairment in CLBP on the individual, their family, and the health care system.

Given deficits in cognitive performance were established in chapter three, chapter five examined the impact of a-tDCS over left-DLPFC on cognitive function in people with CLBP. Research in multiple conditions associated with cognitive deficits has shown that tDCS delivered over the left-DLPFC can improve cognitive functioning (Boggio et al., 2006; Boggio et al., 2009; Coffman et al., 2014; Silva et al., 2017). However, our analysis in chapter five revealed that both the anodal and the s-tDCS group improved across all five cognitive domains. This suggests that a-tDCS over left-DLPFC is no more effective than sham in improving cognitive function in people with CLBP. We also examined the impact of a-tDCS over left-DLPFC on pain experience (intensity, disability, and catastrophising), and psychological wellbeing (mood, and quality of life). In line with the improvements in cognitive functioning, both the anodal and sham-tDCS group showed reduced pain intensity, disability, and catastrophising, and improved anxiety, stress, and quality of life. Again, this suggests that a-tDCS over left-DLPFC is no more effective than sham in improving pain-related outcomes in people with CLBP. Although the results of the present study, suggest a-tDCS is no more effective than sham, it is possible that a-tDCS over l-DLPFC may have had an effect on cognitive functioning, however the small sample size makes this difficult to ascertain. It is possible that such effect may be so small and diffuse that a larger sample size may be required to be able to detect any effect. In conjunction with the inclusion of a no-stimulation group, future research should ensure an adequate sample size to be able to tease apart such effects.

The improvements in cognition and pain-related outcomes in the present thesis may be due to the placebo effect, expectancy effect, and/or social interaction. While these results were unexpected, they do raise an interesting question about the

potential therapeutic benefit of the placebo effect in CLBP. The placebo effect observed in this study may be due to treatment-expectation effects (Bin Dawood et al., 2020; Rabipour et al., 2019). Research has suggested that when analgesia associated with the placebo effect aligns with a participant's expectations of the treatment, an analgesic feedback loop is created. This loop then maintains the reduction in pain (Medoff & Colloca, 2015). This feedback loop is likely due to placebo activation of the endogenous opioid system (Zubieta et al., 2005). Brain imaging studies have shown that placebo administration is associated with activation in the DLPFC, periaqueductal gray area (PAG) and rostral ventromedial medulla (RVM). Activation of the endogenous opioid system then alters the pain signal via descending inhibitory pathways (Eippert et al., 2009; Kandić et al., 2021). Interestingly, support for tDCS over DLPFC to elicit an analgesic effect in chronic pain has also been suggested to be due to activation of this system (DosSantos et al., 2012; Taylor et al., 2012). Future research should include a no-stimulation group to determine the size of the placebo effect in the s-tDCS group. This may provide insights as to if the placebo effect entirely accounts for the improvements in the a-tDCS group. If this is established, it could support the use of a tDCS-induced placebo effect as a therapeutic tool in the management of CLBP. It is also reasonable to suggest that the intensive schedule of the research (i.e., 9 visits over a 5-week period) may have impacted on participants' physical and psychological health. It is possible that the requirement to attend appointments outside of the home may have increased physical activity. An increase in movement may have had a positive influence on pain and physical functioning. Additionnaly, the collaborative relationship between participants and researchers may have increased perceived social support. Research in chronic pain has reported that higher levels of perceived social support are associated with reduced pain and depression (López-Martínez et al., 2008). As such, it is reasonable to suggest that the reduction in pain and clinical outcomes in the present study may be due, even partly, to the participant-researcher relationship. Establishing whether such a relationship improves pain outcomes can have important implications for the treatment of CLBP. In psychotherapy research, the therapeutic alliance (relationship between client and therapist) has been reported to improve psychotherapy outcomes in people with mental health disorders (Baier et al., 2020). The therapeutic alliance is typically built on shared treatment goals and the development of a positive, emotional relationship (Baier et al., 2020). As such, the

establishment of a therapeutic alliance between CLBP patient and healthcare provider, may contribute to improved outcomes for people with CLBP. While the findings in chapter five may be due to placebo rather than the effect of tDCS, the findings do support the role of the DLPFC in the cognitive appraisal of pain in CLBP. Our analysis showed improvements in cognitive function in both tDCS groups also corresponded with improvements in pain-related outcomes and psychological wellbeing. It is reasonable to suggest that as pain was reduced (regardless of whether that reduction was attributed to the placebo effect), less cognitive resources in the DLPFC were consumed by pain processing. This would allow for cognitive resources to be available for normal cognitive functioning (Berryman et al., 2013; Smith & Ayres, 2014), and may explain the improvements seen in both groups in the present study. This may also be true for the improvements seen in pain catastrophising, anxiety, and stress. As the DLPFC is key to the cognitive-attentional appraisal of pain, when pain is reduced, the appraisal and attention given to pain may also be reduced (Brighina et al., 2011; Lorenz et al., 2003). Given cognitive function and pain are key indicators for quality of life (Hadi et al., 2019), it is perhaps unsurprising that the improvements in cognitive function and pain-related outcomes also corresponded with improvements in quality of life in the present study. These findings add to our understanding of the role of the DLPFC in pain modulation in CLBP and lends support to research suggesting the DLPFC plays a key role in pain modulation synergistically through interconnections with the endogenous opioid system, descending inhibition, and cognitive-attentional mechanisms.

6.3 Future Directions

The findings of this thesis provide evidence for 1) alterations in motor cortex excitability via glutamatergic mechanisms in people with CLBP, 2) a pattern of cognitive dysfunction in people with CLBP, 3) some people with CLBP meet the criteria for MCI and that such impairment may increase the risk of progression to dementia, 4) a-tDCS over l-DLPFC may induce changes in motor cortex excitability in CLBP, and such changes may be associated with reduced pain, and 5) improvements in cognitive function is associated with improvements in pain outcomes. Future studies should expand on the current findings and examine whether

alterations in motor cortex excitability via glutamatergic mechanisms are directly responsible for changes in the pain experience. Establishing such a relationship will allow for the development of targeted treatment approaches, including the use of non-invasive brain stimulation, aimed at modulating glutamatergic mechanisms as a potential therapeutic treatment for CLBP. Additionally, future studies should adopt a longitudinal approach to determine if MCI in individuals with CLBP increases the risk of dementia, and whether level of education may serve as a protective factor against cognitive decline in individuals with CLBP. Given the present findings establish a pattern of cognitive dysfunction in individuals with CLBP, future research should examine whether targeted (i.e., impairment specific) versus general (i.e., global cognition) cognitive interventions may be better suited at improving cognitive function in individuals with CLBP. Establishing the right approach for improving cognitive function is vital for the development of early intervention treatments. As the present findings suggest improvement in cognitive function is associated with improvement in pain-related outcomes (i.e., reduced pain, disability, catastrophising, and improved quality of life), early cognitive interventions may assist in improving rehabilitation outcomes and reduce the burden of CLBP on the individual, their family, and the health care system.

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