8-15-2024 2:00 PM

Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Corticosteroid Joint Injections (CJI) for the Treatment of Chronic Axial Pain (CAP): A Pilot Double-blinded Randomized-Controlled Trial

Anike A. Alarape Ms, *The University of Western Ontario*

Supervisor: Schabrun, Siobhan, *The University of Western Ontario*
Co-Supervisor: Loh, Eldon, *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

Abstract

Chronic axial pain (CAP) is a debilitating condition impacting millions globally, with traditional treatments providing only short-term relief. This pilot study explored the primary outcomes of feasibility, tolerability, and safety, as well as the secondary outcomes of pain intensity, disability, quality of life, and patients' perceived response to the combined intervention of repetitive transcranial magnetic stimulation (rTMS) and corticosteroid joint injections (CJI) as a novel approach to address CAP. Sixteen participants from St. Joseph's Healthcare Pain Clinic were randomized (1:1) to receive 11 active or sham rTMS sessions over 12 weeks, with follow-up until week 24 or their next CJI, whichever came first. Feasibility was assessed through dropout rates, session and assessment completeness, and screening-to-enrollment ratios. Tolerability was rated on a 1-5 scale, and safety was assessed based on reported adverse effects. Although secondary outcomes showed no significant differences between the treatment groups, the results support the feasibility, tolerability, and safety of combining rTMS with CJI, warranting a larger clinical trial to explore the question of clinical efficacy.

Keywords

Repetitive transcranial magnetic stimulation, non-invasive brain stimulation, chronic axial pain, pilot study, feasibility trial, corticosteroid joint injections

Summary for Lay Audience

Chronic axial pain (CAP), such as lower back and neck pain, is a serious issue affecting many people worldwide. It is one of the main reasons why people visit the emergency room,

placing a huge burden on the healthcare system. Even though several interventions are currently used to manage this condition, they are only effective for short-term pain relief and have some side effects. As this condition is very common, there is a need to provide a more lasting treatment with little to no side effects.

This thesis was conducted to assess a new form of intervention that combines two different approaches. The first approach is an existing treatment used in pain clinics to provide pain relief for patients with CAP. These patients received an injection containing steroids, which helped reduce swelling and pain in the joint. However, we know that this injection can help reduce pain for only a few weeks at a time. The second approach is to noninvasively stimulate the brain areas involved in processing how pain is experienced using magnetic energy. Evidence shows that the way the brain processes pain changes when people experience chronic pain. Even after the cause of pain is treated, the brain can still interpret body signals as painful. Although this approach has shown promise in reducing pain, there is no standard treatment protocol for its use in clinical practice.

We conducted 11 sessions of brain stimulation after the participants received regular steroid injections and monitored them for 24 weeks. We randomly chose participants to receive either real or fake brain stimulation to determine whether there was a true treatment effect without any bias. We found that this combined approach is generally tolerable and safe. We were unable to show that the combined intervention was better than injection alone. This was likely due to the small number of participants in the study. This study is important because we targeted pain at the source and from the brain, which is better than the available treatments that only focus on treating pain at its source.

Acknowledgments

This thesis would have been impossible without the guidance and support of several people.

- I appreciate my supervisor, Dr. Siobhan Schabrun, for taking me on as a graduate student in her lab. She saw my potential and gave me the opportunity to challenge myself and grow academically.
- I appreciate my co-supervisor Dr. Eldon Loh's contribution to this thesis. His support allowed me to access the clinical resources required to complete this research. His patients and clinical staff were amazing to work with.
- I appreciate my advisory committee members, Dr. Sue Peters, Dr. David Walton and Lindsay Nagamatsu, for their constructive feedback and suggestions in improving the quality of my research.
- I would also like to express my appreciation to my lab members Thivya Sivarajan, Nafisa Diya, and Phivos Phylactou. I worked alongside Thivya to develop the data collection questionnaires, ethics applications, patient recruitment, and data collection. Diya developed the randomization schedule and assisted with the rTMS coil switch during data collection sessions. Phivos assisted with data collection, reviewing, and providing feedback on this thesis, as well as in the analysis of the collected data. Thank you for taking the time to listen to my work and for providing feedback whenever needed.
- I would like to thank my family and friends for their encouragement, support, and prayer. My sister, who I lost during this program, was my motivation to pursue this degree. Although it was difficult to continue after her death, I had to find strength in knowing that she wanted me to continue to follow my dreams.
- Finally, I would like to thank God. All the glory belongs to him, and without him, this would have been impossible. I thank God for giving me strength, courage, wisdom, and knowledge to pursue my purpose.

Table of Contents

Abstract ii

Summary for Lay Audience ii

Acknowledgments iv

Table of Contents v

List of Tables viii

List of Figures ix

List of Abbreviations x

Chapter 1 1

1 Introduction 1

1.1 Chronic Axial Pain (CAP) 2

1.1.1 Overview of Chronic Axial Pain 2

1.1.2 Prevalence of Chronic Axial Pain 3

1.1.3 Overview of Chronic Axial Pain Mechanisms 4

1.1.4 The Role of Central Sensitization and Neuroplasticity 6

1.2 Existing Treatment Modalities 7

1.2.1 Pharmacological and Non-pharmacological Approaches 7

1.2.2 Invasive Interventional Approaches: Corticosteroid joint injections (CJI) 9

1.3 Brain Stimulation for Pain Management 11

1.3.1 Non-invasive Brain Stimulation (NIBS) 11

1.3.2 Repetitive Transcranial Magnetic Stimulation (rTMS) 13

1.4 Rationale for the Study 15

1.4.1 Potential of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Corticosteroid joint injections (CJI) 15

1.5 Research Objectives and Hypotheses 16

1.6 Conclusion 17

Chapter 2 18
2 Methodology 18
2.1 Study Design 18
2.1.1 Blinding and Allocation Concealment 20
2.2 Participants 21
2.2.1 Setting 21
2.2.2 Inclusion and Exclusion Criteria 21
2.2.3 Recruitment and Consent 22
2.3 Interventions 22
2.3.1 Corticosteroid joint injections (CJI) 22
2.3.2 Repetitive Transcranial Magnetic Stimulation Protocol 23
2.4 Primary Outcome Measures 25
2.4.1 Measure of Feasibility, Tolerability and Safety 25
2.5 Materials: Questionnaires 26
2.5.1 Intake Patient Health Questionnaire 26
2.5.2 Numerical Pain Rating Scale (NPRS) 26
2.5.3 Oswestry Disability Index (ODI) 27
2.5.4 12-Item Short Form Survey (SF-12) 27
2.5.5 Depression, Anxiety, and Stress Scales (DASS-21) 28
2.5.6 Brief-Pain Inventory Short Form (BPI-sf) 28
2.5.7 Global Rating of Change Scales (GRC) 29
2.6 Data Analysis 29
2.6.1 Statistical Methods 29
2.7 Ethical Considerations 30
Chapter 3 31
3 Results 31

3.1 Primary Outcomes 33

3.1.1 Measures of Feasibility 33

3.1.2 Measures of Tolerability 36

3.1.3 Measures of Safety 36

3.2 Secondary Outcomes 38

3.2.1 Measures of Pain Intensity, Severity, Disability, and Health-related Quality of Life 38

3.2.2 Measure of Patient's Perceived Response to Treatment 42

3.2.3 Conclusion 43

Chapter 4 45

4 Discussion 45

4.1 Strengths and Limitations 54

4.2 Future Directions 55

4.3 Conclusion 56

References 58

Curriculum Vitae 79

List of Tables

Table 2.1: Study Timeline with Scheduled Study Assessments. 19

Table 3.1: Demographic characteristics of participants. 32

Table 3.2: Participants' tolerability rating of active or sham rTMS on a 1-5 scale 36

Table 3.3: Results of the Repeated Measures ANOVA performed for NPRS, NPRS averages, DASS-21, BPI-sf, SF-12, and ODI scores 40

Table 3.4: Post Hoc Comparisons of Group and Time Point Differences with Bonferroni Adjustment on the MCS scores 41

List of Figures

Figure 1.1: Schematic Representation of the Facet Joint of the Lumbosacral Spine (Adopted from Princeton Spine & Joint Center, 2016) 5

Figure 1.2: Representation of a Lumbar Facet Joint Steroid Injection (Adopted from Aptiva Health, n.d.)..... 10

Figure 1.3: Transcranial magnetic stimulation (TMS) applied to the primary motor cortex (M1; Adopted from Zhu et al., 2022) 12

Figure 2.1: Diagram of the rTMS parameters used in this study.. 25

Figure 3.1: Consolidated Standards of Reporting Trials (CONSORT) flow chart of participants throughout the study. Notes. HQRoL: health-related quality of life; DASS-21: Depression Anxiety Stress Scale. 35

Figure 3.2: Side effects reported by participants in each treatment group. 38

Figure 3.3: Mean pain intensity (NPRS) scores reported weekly by participants in the sham and active rTMS groups. Note. W: week.. 42

Figure 3.4: A Likert Plot of the Proportion of Participants who reported perceived response to treatment in both groups. 43

List of Abbreviations

ANOVA	Analysis Of Variance
BPI-SF	Brief Pain Inventory Short Form
CAP	Chronic Axial Pain
CBT	Cognitive Behavioural Therapy
CJI	Corticosteroid Joint Injections
CLBP	Chronic Low Back Pain
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COX	Cyclooxygenase
CRC	Clinical Research Coordinator
CS	Central Sensitization
CT	Computed Tomography
DASS-21	Depression Anxiety and Stress Scale 21
DLPFC	Dorsolateral Prefrontal Cortex
EMG	Electromyography
FDI	First Dorsal Interosseous
FJI	Facet Joint Injections
FJSI	Facet Joint Steroid Injections
GBD	Global Burden of Disease

GH	General Health
GRC	Global Rating of Change
HF	High Frequency
HSREB	Health Sciences Research Ethics Board
IASP	International Association for the Study of Pain
IL	Interleukin
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
LBP	Low Back Pain
MCS	Mental Composite Summary
MEP	Motor Evoked Potential
MH	Mental Health
MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NIBS	Non-invasive Brain Stimulation
NP	Neck Pain
NPRS	Numerical Pain Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
ODI	Oswestry Disability Index
PCS	Physical Composite Summary
PEST	Parameter Estimation by Sequential Testing

PF	Physical Function
PGIC	Patient Global Impression of Change Scales
PHQ	Patient Health Questionnaire
PNE	Pain Neuroscience Education
RCT	Randomized Controlled Trial
RE	Role limitations due to emotional problems
RLS	Restless Leg Syndrome
RP	Role limitations due to physical issues
RTMS	Repetitive Transcranial Magnetic Stimulation
SE	Sling Exercise
SF	Social Function
SF-12	12-Item Short Form Survey
SIJ	Sacroiliac Joint
SIJI	Sacroiliac Joint Injection
SP	Spinal Pain
TACS	Transcranial Alternating Current Stimulation
TES	Transcranial Electrical Stimulation
TIDieR	Template For Intervention Description and Replication
TMS	Transcranial Magnetic Stimulation
US	United States

VAS	Visual Analogue Scale
VT	Vitality
WHO	World Health Organization

Chapter 1

1 Introduction

This thesis examines a widespread issue that affects individuals of all ages worldwide, significantly diminishing their quality of life. This issue is chronic axial pain (CAP), such as chronic neck pain and low back pain. In Canada, CAP affects between 4-25% of adults and is a primary concern for those under 60 years of age who seek medical assistance (Meucci et al., 2015). The societal burden associated with CAP is substantial, with estimated healthcare costs reaching $134.5 billion in the United States in 2016 (Dieleman et al., 2020).

Current interventions range from pharmacological to nonpharmacological approaches, but an effective treatment is yet to be found (Chou et al., 2017). Owing to the limitations of current interventions, researchers are investigating the use of noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), in chronic pain management. rTMS holds promise because of its ability to modulate cortical activity, which in turn can help manage chronic pain. High-frequency rTMS applied to the motor cortex contralateral to the side of the worst pain has been shown to be effective in inducing analgesia (pain relief) in various pain conditions including fibromyalgia, neuropathic pain, migraine, and chronic low back pain (CLBP). RTMS may be beneficial as an adjunct therapy for the management of CAP. This thesis presents a pilot, double-blind, randomized controlled trial of rTMS combined with an existing intervention, corticosteroid injections (CJI), as an adjunct therapy for patients with CAP.

Chapter one presents an overview of CAP, discussing its prevalence, mechanisms, and current interventions, including pharmacological and non-pharmacological treatments, invasive approaches, and non-invasive brain stimulation techniques. The section concludes by presenting the rationale for exploring an innovative approach to tackle this growing burden, stating the research question, feasibility, tolerability, safety, and potential effectiveness of the combined approach as well as the hypotheses.

Chapter two focuses on the methodology, which involved a two-week rTMS induction phase where participants received six sessions of rTMS followed by a maintenance phase of one rTMS session per week for five weeks (eleven sessions in total). Follow-up was either up to week 24 after the first rTMS session or the week of the participants' next scheduled CJI appointment, whichever came first. In addition to the intervention protocol, this chapter outlines the various outcome measures taken to evaluate the feasibility, tolerability, and safety of the pilot intervention, as well as to assess clinical factors such as pain severity, duration, disability, quality of life, and patients' perceived response to treatment. The data analysis methods and ethical considerations were also addressed.

The third chapter delves into the findings of the study and presents the results for each outcome measure. This thesis demonstrated the feasibility of the study protocol, as evidenced by the high intervention and follow-up assessment completion rates, low dropout rate, and successful participant and assessor blinding, however, the screening-to-enrollment rate was relatively low. In addition, the study intervention was well-tolerated and free of adverse effects.

Finally, chapter four explores the ramifications of these findings. This was accomplished by acknowledging the strengths and limitations of this thesis. One of the strengths of this thesis is the study design, which was a participant-assessor-blinded randomized controlled trial, mitigating the possibilities of placebo effects and bias in data collection and analysis. However, this study was limited by the sample size. Therefore, these findings should be cautiously interpreted. Finally, this thesis is clinically significant, as future research can apply the same methodologies with a sufficient sample size to power a full trial to determine the treatment effect of a combined rTMS and CJI intervention.

1.1 Chronic Axial Pain (CAP)

1.1.1 Overview of Chronic Axial Pain

Here, axial pain is used as an umbrella term referring to spinal pain (SP): pain or discomfort in the cervical (neck), thoracic (mid-back), and lumbosacral (lower back)

regions of the spine. CAP can be considered symptomatic pain lasting for more than 13 weeks (Giles & Müller, 2003). This study focused on axial pain secondary to facet joint arthropathy, which is typically managed in clinical practice using corticosteroid injections (MacMahon et al., 2009). CAP impacts a diverse range of individuals and places a significant burden on the individual, the healthcare system, and society. In the following subsection, the prevalence of CAP is discussed.

1.1.2 Prevalence of Chronic Axial Pain

CAP is a debilitating condition affecting millions of individuals worldwide (Hoy et al., 2014). The Global Burden of Disease report (2019) estimated that 30% of the global population is affected by Musculoskeletal Disorders (MSK), equating to approximately 1.71 billion individuals worldwide. This encompasses conditions such as lower back pain (LBP), neck pain (NP), fractures, osteoarthritis, and rheumatoid arthritis (de Luca et al., 2022). LBP, a form of CAP, is a major contributor to the MSK burden worldwide, representing 570 million cases and 7.4% of the global years lived with disability (YLDs). Following LBP, osteoarthritis is responsible for 528 million cases and 19 million YLDs worldwide (Global Burden of Disease 2023). CAP is more common in older adults (Edmond & Felson, 2000) and in females (Bailey, 2009). Given the projected substantial rise in older adults in the coming decades, MSK disorders require attention. It is estimated that by 2050, there will be a 32.5% increase (269 million cases) in neck pain, with a higher forecast in females (160 million) than in males, alongside an increase in global life expectancy (Wu et al., 2023).

CAP negatively affects the physical and psychological well-being of individuals. Psychologically, CAP is associated with anxiety, depression, and a decreased quality of life. Research has shown that persistent pain often results in feelings of helplessness, frustration, and loss of control, which can worsen psychological symptoms (Gatchel et al., 2007). Sufferers also experience disrupted sleep patterns that can lead to cognitive and emotional difficulties (Tang et al., 2008). This creates a cycle in which pain disrupts sleep, which, in turn, exacerbates pain perception. CAP also has a significant impact on social interactions and relationships, often leading to feelings of isolation and loneliness

(Finan et al., 2013). Individuals may withdraw from social activities because of pain or fear of exacerbating their symptoms, which further contributes to feelings of depression and anxiety.

Additionally, CAP poses a significant socioeconomic burden associated with indirect and direct costs to individuals and society, arising from healthcare utilization, time off work due to sickness and/or disability, and unemployment (Cimmino et al., 2011). In Canada, the economic burden of chronic pain, inclusive of both direct and indirect costs, is estimated to range from US $38.3 to US $40.4 billion annually, with MSK pain being the primary driver (Campbell et al., 2020). Despite its high prevalence and substantial burden, CAP remains poorly understood. This lack of understanding is reflected in the limited treatment options currently available, most of which provide only temporary symptomatic relief. Therefore, it is essential to gain a deeper understanding of the mechanisms underlying CAP, as discussed in the following subsection.

1.1.3 Overview of Chronic Axial Pain Mechanisms

Spinal symptoms often arise from non-emergent conditions, characterized by varying degrees of spinal degeneration. According to imaging studies, facet joint osteoarthritis has been identified as the primary cause of LBP in 59.6% of men and 66.7% of women (Kalichman et al., 2008). However, it is important to note that imaging abnormalities do not always align with the clinical symptoms. It is common to find individuals without symptoms who show significant abnormalities in imaging tests (Wiesel et al., 1984), while others with debilitating symptoms may have normal CT and MR findings (el-Khoury & Renfrew, 1991). Therefore, the connection between the symptoms and the imaging results is weak.

The facet joint (Figure 1.1), also known as the zygapophysial joint or intervertebral disc, is an anatomical unit of the spine that provides support and stabilizes the spine to prevent injury by limiting motion.

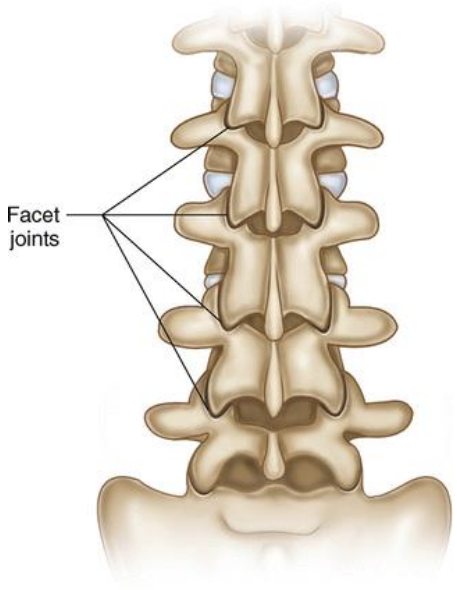


Figure 1.1: Schematic Representation of the Facet Joint of the Lumbosacral Spine (Adopted from Princeton Spine & Joint Center, 2016)

According to Manchikanti et al. (2004), facet joints are a common cause of CAP in patients with chronic LBP (CLBP), with a prevalence ranging from 15-45%. Additionally, they account for 48% of patients with thoracic pain and 54-67% of those with chronic NP. To determine if these joints are the source of pain, controlled diagnostic facet blocks are used, following the criteria established by the International Association for the Study of Pain (IASP; Merskey & Bogduk, 1994). Diagnostic spinal injections can help identify the source of pain and may be followed by therapeutic injections, if deemed appropriate. Pain relief confirms that the facet joint is the source of pain (Manchikanti et al., 2004). No other clinical features or diagnostic imaging methods can be used to diagnose CAP of the facet joint. However, despite modest management of pain originating from the facet joints with spinal corticosteroid injections, the pain remains refractory, and researchers are now considering the role of central nervous system mechanisms such as central sensitization (CS). The definition and mechanisms underlying CS, as well as the concept of neuroplasticity, are discussed in the following subsection.

1.1.4 The Role of Central Sensitization and Neuroplasticity

CAP is a complex condition involving changes in both the peripheral and central nervous systems (CNS), resulting in increased pain sensitivity and persistent discomfort. It is widely believed that chronic pain can lead to central sensitization (CS), a phenomenon in which the CNS becomes hypersensitive to afferent information, thereby amplifying the intensity and duration of pain (Xiong et al., 2024). In the clinical manifestation of CS, there is a notable reduction in the pain threshold, accompanied by heightened sensitivity to non-mechanical stimuli such as sound, odor, and stress (Xiong et al., 2024). CS involves various pathophysiological changes including aberrant sensory processing (Staud et al., 2007) and defective descending inhibition (McPhee & Graven-Nielsen, 2019). Furthermore, there is an escalation in the efficacy with which nociceptive signals are processed and increased activity within pain facilitatory pathways in the brain (Staud et al., 2007). Research indicates that patients with CAP experience enhanced brain activity when exposed to painful stimuli, including activation of brain areas that are not typically associated with pain perception (Seifert & Maihöfner, 2009). This suggests the involvement of CS processes in the development and maintenance of chronic pain.

Additionally, chronic pain can induce maladaptive neuroplasticity, a pathological form of plasticity resulting from sustained nociceptive input from injured tissues. This plasticity contributes to pain maintenance and impedes recovery. Studies have used neurophysiological and neuroimaging techniques to demonstrate dysfunctional nervous system activity, including structural remodeling, in individuals with chronic MSK pain such as chronic axial pain (Malfliet et al., 2017). Evidence indicates that the primary somatosensory cortex undergoes reorganization in individuals with CLBP (Flor et al., 1997), and there is a smudging of corticospinal excitability in specific muscles among those who experience persistence or recurrence of LBP compared with healthy controls (Schabrun et al., 2017). Neuroimaging studies have also revealed alterations in brain regions involved in emotion and cognitive processes, such as the medial prefrontal cortex, amygdala, and hippocampus, in individuals with chronic MSK pain (Bushnell et al., 2013).

There is evidence of brain atrophy in patients with CLBP, specifically a decrease in gray matter volume and density. This loss of gray matter volume, which is seen in specific brain regions, such as the dorsolateral prefrontal cortex, thalamus, brain stem, and somatosensory cortex, is strongly correlated with both pain duration and intensity (Apkarian et al., 2004). Studies examining the impact of surgical interventions have shown that the observed gray matter abnormalities in patients with pain are normalized when pain is alleviated (Obermann et al., 2009). Therefore, it is believed that gray matter changes in patients with CAP are not indicative of brain damage but rather a result of chronic pain that can be reversed with pain treatment. This emphasizes the importance of adopting a comprehensive approach to pain management, with treatments that target both the peripheral and central mechanisms of pain. In the following section, I will discuss some current treatment modalities, such as pharmacological and non-pharmacological approaches, used to address CAP.

1.2 Existing Treatment Modalities

1.2.1 Pharmacological and Non-pharmacological Approaches

CAP remains challenging to manage, primarily because few treatment modalities have demonstrated substantial efficacy. This issue is compounded by limited evidence supporting the effectiveness of commonly used treatment approaches and their associated side effects. The mainstay of CAP treatment involves pharmacological intervention. Given their limited effectiveness and considerable side effects, several non-pharmacological approaches have been used along with medications to manage CAP.

Medications such as antidepressants, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids are commonly used but often fail to provide long-lasting relief for CAP. Antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, are effective in managing conditions, such as tension headaches, migraines, and fibromyalgia syndrome (Salerno et al., 2002). However, there is limited evidence to support their use in the treatment of CAP. Anticonvulsants, which are effective in treating neuropathic pain, may

not effectively target CAP (Hepner et al., 2013). NSAIDs, while managing inflammation, carry risks associated with prolonged use (Moore et al., 2005). Despite their strength, opioids cause significant side effects and potential dependence and risk of overdose, limiting their usefulness in the long term (Pati et al., 2017).

Exercise, cognitive behavioral therapy (CBT), and pain neuroscience education (PNE) offer alternative approaches, but also have limitations. Numerous studies have emphasized how exercise can reduce pain severity, enhance physical function, and improve psychological well-being and quality of life (Paley and Johnson 2016, Thompson et al., 2023, Park et al., 2015). For example, a systematic review by Busch et al. (2007) showed that aerobic exercise reduced pain by 1.3 (on a scale of 0 – 10) points in patients with fibromyalgia. However, exercise requires consistency and motivation, which makes long-term pain relief challenging. Ample evidence indicates that catastrophic thoughts and behaviors are predictive of both the onset and persistence of chronic pain, making interventions that target these aspects highly impactful (Smeets et al., 2009). CBT addresses the emotional aspects of pain but has yielded mixed results in CAP management, showing minimal clinical improvement in some studies. Rutledge et al. (2018) and Schemer et al. (2018) found no significant clinical improvements in chronic back pain after 8 and 14-week CBT sessions, respectively. Monticone et al. (2018) observed a decrease in kinesiophobia (a debilitating fear of movement), but no change in neck disability index following a 6-week CBT program for chronic NP. PNE has the potential to influence the structural and functional connectivity of specific brain regions involved in pain processing, such as the frontal, cingulate, and insular cortices, by alleviating pain catastrophizing and kinesiophobia, thus freeing up cognitive resources (Moseley 2005). While PNE is effective in reducing pain catastrophizing (Meeus et al., 2010), it does not consistently reduce pain perception or disability associated with CAP (Malfliet et al., 2018). Studies using PNE alone found it to have small effects on pain, but when combined with other interventions, such as physical therapy, there was a significant reduction in pain. A systematic review and meta-analysis assessed the effectiveness of using PNE against no PNE and in conjunction with physical therapy for reducing short-term pain and disability. The results indicated that combining PNE with physical therapy led to a greater reduction in pain (1.32/10) and disability (3.94/10) than using PNE alone,

which showed a smaller weighted mean difference of 0.73/10 for pain and 0.42/10 for disability ($p < .00001$; Wood & Hendrick, 2019).

In addition, individuals with chronic pain often contend with feelings of anxiety and depression, conditions for which meditation has demonstrated efficacy. Among the various meditation techniques used in chronic pain management, mindfulness-based meditation stands out. This practice involves cultivating a non-judgmental awareness of the present moment, allowing individuals to observe pain without criticism, and to foster self-acceptance (Abbott and Lavretsky, 2013). A meta-analysis of randomized controlled trials investigating mindfulness-based approaches to chronic pain management revealed significant reductions in pain intensity, pain interference, and mental distress associated with chronic pain (Hilton et al., 2017). However, non-pharmacological approaches have only modest and short-term effects, making them insufficient by themselves.

The combined limitations of pharmacological and non-pharmacological approaches highlight the complexity and inadequacy of effective management of CAP. None of these methods individually or collectively effectively address the multifaceted nature of CAP, leaving patients with limited options. In the following subsection, I discuss a more targeted approach to CAP through minimally invasive interventions, specifically, corticosteroid joint injections.

1.2.2 Invasive Interventional Approaches: Corticosteroid joint injections (CJI)

CJI are widely used for pain management in CAP conditions (Chang & Lee, 2018). They involve the direct injection of a combination of corticosteroids and local anesthetics into the affected joints to alleviate joint pain (Lim et al., 2017). However, there is an ongoing debate regarding their effectiveness.

Facet joint steroid injections (FJSIs; Figure 1.2) can provide pain relief for 6–8 weeks. After this period, a repeat FJSI is performed (Peh, 2011). Sacroiliac joint (SIJ) injections (SIJIs), such as FJSIs, contain local anesthetics and corticosteroids (Polly et al., 2016). They are administered if the source of the pain originates from the sacroiliac joint.

Research has indicated that SIJ pain is responsible for 10-27% of mechanical LBP cases (Hansen et al., 2007; Navani et al., 2019). A study by Scholten et al. (2015), examining a population of patients with SIJ dysfunction due to spondyloarthropathy, found that SIJIs containing triamcinolone effectively alleviated pain for more than six weeks in approximately 66.7% of the participants, with an average duration of pain relief of approximately 36.8 (± 9.9) weeks.

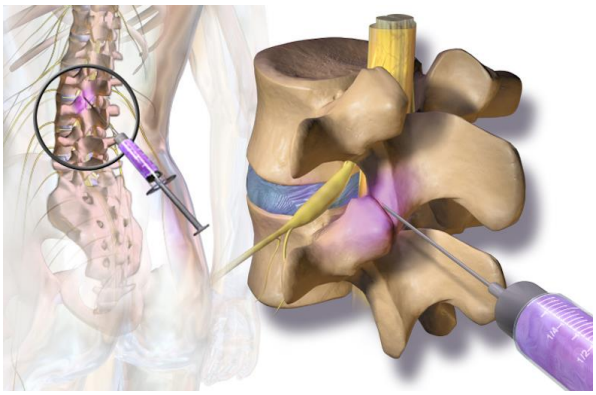


Figure 1.2: Representation of a Lumbar Facet Joint Steroid Injection (Adopted from Aptiva Health, n.d.)

Although observational studies have shown that CJI for LBP provide immediate pain relief that is sustained for a certain amount of time (Carrera, 1980; Lippitt, 1984), randomized controlled trials (RCTs) have not been able to confirm this finding (Lilius et al., 1989; Marks et al., 1992). RCTs have suggested that the pain relief seen from CJI could be due to the lack of use of controlled blocks in observational studies, meaning that the results could be due to placebo effects. Additionally, using local anesthetics could confound the benefits of corticosteroids by only numbing the pain for a period, masking the benefit or lack of benefit of the CJI (Bogduk, 2005).

The debate on the benefits of CJI for CAP is ongoing. However, their use in clinical settings is increasing. It is clear that CJI should not be the only form of intervention provided for pain relief and, like other forms of pain management, is insufficient when applied in isolation. It is also worth noting that certain risks are associated with the frequent and prolonged use of corticosteroids due to the secretion of adrenocortical

hormones, resulting in elevated blood sugar levels, blood pressure, osteoporosis (Lim et al., 2017), and risk of infection at the site of the injection (Bogduk, 2005). As a result, researchers are exploring the impact of persistent pain on the CNS and seeking ways to address it through non-invasive brain stimulation. The following section discusses the current non-invasive brain stimulation approaches being explored for managing chronic pain.

1.3 Brain Stimulation for Pain Management

1.3.1 Non-invasive Brain Stimulation (NIBS)

In the past decade, non-invasive brain stimulation (NIBS) has emerged as a tool to harness electrical signals of the brain to modulate pain. NIBS have been shown to have beneficial effects on pain (Xiong et al., 2022), regulation of neuronal function (Kim & Park, 2024), cognition (Hahn & Paik, 2015), and behavior (Pezzetta et al., 2024). Some commonly used NIBS techniques in clinical settings include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES; Toth et al., 2024). TMS encompasses single-pulse TMS and repetitive TMS (rTMS), whereas tES includes transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS; Toth et al., 2024).

TMS operates based on the principle of electromagnetic induction by utilizing a magnetic field generated by a high-voltage current in a coil that passes through the scalp (Mathew & Danion, 2018). This induces currents that modulate the excitability of neuronal cells in the stimulated region as well as connected neural networks. A single TMS pulse to the motor cortex (Figure 1.3) depolarizes neurons, resulting in measurable motor-evoked potentials that serve as indicators of neural pathway excitability (Mathew & Danion, 2018).

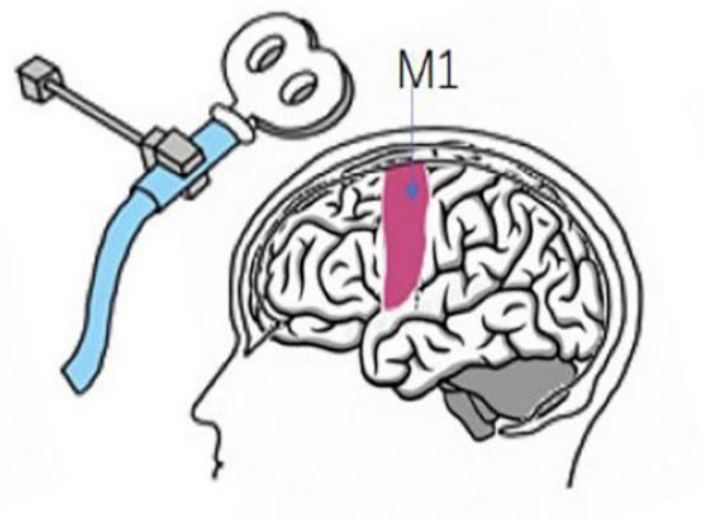


Figure 1.3: Transcranial magnetic stimulation (TMS) applied to the primary motor cortex (M1; Adopted from Zhu et al., 2022)

In contrast, TES is a noninvasive technique that alters brain activity by passing an electrical current through the brain cortex using two or more electrodes applied to the scalp. Although most currents are conducted through soft tissue and the skull, a portion penetrates the scalp and alters neuronal excitability (Vöröslakos et al., 2018). TACS and tDCS are different techniques of tES, and while they both use scalp electrodes, they differ in their electrical stimulation patterns, resulting in variations in behavioral and neuronal outcomes. It is important to note that, unlike TMS, the electrical current used in tES is not strong enough to initiate an action potential but is maintained at subthreshold levels to solely affect cortical excitability (Radman et al., 2009).

Research indicates that high-frequency (HF) rTMS applied to the primary motor cortex (M1) contralateral to the painful area can reduce pain (Yang & Chang, 2020). Numerous studies have demonstrated that HF-rTMS of the M1 is superior to sham rTMS in reducing pain scores by more than 30% in some chronic pain conditions (Galhardoni et al., 2015; Hirayama et al., 2006; Lawson et al., 2018). The analgesic effects of rTMS are enhanced by precise brain targeting and by repeated sessions. However, the optimal parameters for stimulation, such as frequency, duration, and intensity, vary among studies, and there is

currently no standardized treatment protocol. The following subsection delves further into a form of TMS called repetitive transcranial magnetic stimulation (rTMS).

1.3.2 Repetitive Transcranial Magnetic Stimulation (rTMS)

RTMS is a non-invasive procedure that has been shown to be safe (Malone & Sun, 2019). It involves delivering repeated single-pulse stimuli at specific frequencies, intensities, and durations to modulate the activity of specific brain areas (Galletta et al., 2011). This procedure has an immediate effect on cortical excitability, modulating cortical and subcortical activity by either increasing (excitatory, high-frequency ≥ 5 Hz) or decreasing (inhibitory, low-frequency ≤ 1 Hz) cortical excitability (Hoogendam et al., 2010). HF-rTMS of M1 has been found to be more effective than low-frequency rTMS in providing pain relief in chronic pain conditions (Lefaucheur, 2016). M1 is a key driver of motor output and may contribute to movement dysfunction in pain, making it a potential therapeutic target (Arle & Shils, 2008). Asci et al. (2023) conducted a neurophysiological study on patients with chronic pain to investigate M1 plasticity and found evidence of abnormal pain-motor integration processes, shedding light on the potential of M1-rTMS stimulation as a symptomatic treatment for chronic pain.

The exact mechanism by which rTMS relieves pain is unknown, however, it is believed to involve excitatory-inhibitory mechanisms in the corticospinal system. These mechanisms have been linked to pain severity and dysfunctional pain control in chronic pain (Passard et al., 2007). HF-rTMS enhances the excitability of the corticospinal system, modulates the central pain regulation system, and activates structures involved in processing pain bilaterally, resulting in long-term pain relief (Rossi et al., 2009). Additionally, a mechanism of action of rTMS is its effect on microglia, which reduces the inflammatory response by inducing synaptic plasticity, enhancing the production of the anti-inflammatory factor IL-10, and inhibiting the secretion of proinflammatory factors (Luo et al., 2022). RTMS can also regulate gene expression in astrocytes involved in proinflammatory and anti-inflammatory processes (Hong et al., 2020). It alters the membrane potential and cell function of astrocytes (Ruohonen & Karhu, 2012), resulting in the production of anti-inflammatory mediators that promote neuroprotective effects and reduce the inflammatory response (Liddlelow et al., 2017). RTMS also promotes

Nrf2 nuclear metastasis, which protects cells from inflammatory conditions and inhibits the expression of the signal channels that trigger inflammation (Tian et al., 2020).

Over the past two decades, rTMS has been studied as a treatment for different chronic pain conditions, such as fibromyalgia (Forogh et al., 2021), neuropathic pain (Galhardoni et al., 2019), migraine headaches (Schading et al., 2021), and CLBP (Johnson et al., 2006; Ambritz-Tututi et al., 2016), by targeting the M1 contralateral to the side of pain or left M1 in the case of bilateral pain. However, due to the limited sample size, study design, and varying stimulation parameters, rTMS use in chronic pain management requires further exploration. Johnson et al. (2006) examined the impact of a single 20 Hz M1-rTMS session on individuals with CLBP. Participants who received the active TMS reported a statistically significant reduction in the brief pain inventory (BPI) ratings from 4.4/10 (± 2.37) pre-treatment to 3.1/10 (± 2.55; $p < .0001$) post treatment. This study provides a foundation for determining the long-term effects of multiple sessions of M1-rTMS, which was conducted by Ambritz-Tututi et al. in 2016. That study also reported a statistically significant reduction in the visual analog scale (VAS) pain scores of 80% from the baseline score by the third week of treatment. They noted that the analgesic effects of rTMS persisted for up to 9 months with maintenance sessions. The results of this study should be interpreted with caution because of the open-label crossover design, which increases the risk of bias and placebo effects. Moreover, the study did not provide the mean VAS pain scores before and after the treatment session but rather an estimate of the change. Although there is limited evidence of the analgesic effects of HF-rTMS of the M1 contralateral to the side of pain, the optimal rTMS parameters to alleviate pain, specifically in CAP secondary to facet joint arthropathy, remain unclear. To determine whether rTMS has the potential to manage CAP, it is necessary to conduct high-quality randomized controlled trials.

1.4 Rationale for the Study

1.4.1 Potential of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Corticosteroid joint injections (CJI)

Current research on the use of rTMS for treating chronic pain has yielded encouraging results, although there is limited evidence regarding the long-term effectiveness of rTMS applied to the M1 region of the brain contralateral to the painful side in individuals with CAP. The complex nature of CAP necessitates exploration of a novel approach that employs a multimodal strategy targeting both the peripheral and central mechanisms involved in CAP. RTMS can influence the central mechanisms involved in pain processing through top-down control of the pain pathways, whereas CJI can target pain peripherally by reducing inflammation in the affected joint. By combining these two interventions, it is possible to address CAP holistically.

To date, the potential of combining rTMS with CJI as an adjunct therapy has not been explored. This combination has the potential to provide more comprehensive and long-lasting pain relief for individuals with CAP by addressing both the central and peripheral pain mechanisms. Frequent and long-term use of CJI can lead to serious adverse effects, such as joint damage, osteoporosis, and systemic effects, such as adrenal suppression (Kavanaugh et al., 2016). By combining it with rTMS, it may be possible to prolong analgesic effects and reduce the need for frequent injections and their associated risks. In addition to its analgesic effects, rTMS can enhance motor learning and rehabilitation outcomes (Ameli et al., 2009). Therefore, combining rTMS and CJI may provide more effective pain relief, allowing patients with CAP to participate in physical therapy or other rehabilitation programs, leading to improved functional outcomes and quality of life. As CAP poses a significant healthcare and economic burden, by combining these interventions, it may be possible to effectively minimize the long-term healthcare costs associated with frequent steroid use.

Consequently, utilizing a combination therapy approach may improve the overall treatment outcomes by addressing the multifactorial nature of CAP. Moreover, it is

necessary to evaluate the long-term benefits and risks of this novel approach for CAP, as well as its potential as a viable treatment option. Hence, the current thesis served as a pilot, double-blind, randomized controlled trial that functioned as a proof-of-concept to determine whether rTMS could be combined with CJI as an adjunct therapy for a more effective, safe, and long-term pain management approach to CAP.

1.5 Research Objectives and Hypotheses

The primary objective of this study was to determine the feasibility, tolerability, and safety of a combined intervention involving motor cortex (M1) repetitive transcranial magnetic stimulation (rTMS) and corticosteroid joint injections (CJI) as a novel approach for managing chronic axial pain (CAP). It was hypothesized that the combined M1-rTMS and CJI interventions would be:

Hypothesis 1: Feasible:

A. With a high screening-to-enrollment rate of >80% based on the estimated number of patients with CAP who are receiving CJI per week at the recruiting Pain Clinic.
B. With a study dropout rate of <20% (Chang et al., 2017).
C. With a high rTMS session completion rate of >80% (Ribeiro et al., 2017),
D. With a high follow-up assessment completion rate of >80% (Ribeiro et al., 2017),
E. With successful blinding of the group allocation, where no difference is observed between the treatment groups in correctly guessing their group allocation at the final follow-up assessment (Berlim et al., 2013).

Hypothesis 2: Tolerable:

A. With a median tolerability above 3 on a tolerability scale of 1 – 5, where 1 is not tolerable and 5 is very tolerable,
B. With fewer pauses during the session due to the intolerability of the intervention.

Hypothesis 3: Safe:

A. With no major adverse effects reported in the group receiving active rTMS (one or more serious adverse effects were considered unsafe).

The secondary objective of this study was to evaluate whether this intervention would demonstrate a trend toward efficacy by assessing pain severity, duration of pain relief, disability, quality of life, and participants' perceived response to treatment.

Hypothesis 4: Active M1-rTMS and CJI will have a synergistic effect compared with sham M1-rTMS and CJI:

A. With reduced pain intensity compared to baseline,
B. With reduced pain severity and interference,
C. With reduced disability,
D. With an improved health-related quality of life,
E. With a more positive perceived response to treatment.

1.6 Conclusion

This chapter introduces the chronic pain condition been addressed, CAP. CAP is a debilitating condition, with current pharmacological, non-pharmacological, and invasive approaches providing modest short-term relief. Combining rTMS with CJI provides an avenue for prolonging pain relief. The objectives of the study which are to assess feasibility, tolerability, safety and preliminary evidence of efficacy of the combined intervention were stated. The following chapter presents the methodological approach used in this thesis to examine the effects of the combined intervention.

Chapter 2

2 Methodology

2.1 Study Design

This study was a randomized, participant- and assessor-blinded pilot-controlled trial of active and sham rTMS in a population of individuals with chronic, moderate-to-severe axial pain who were receiving recurrent CJI through the St. Joseph's Healthcare Pain Clinic, London, Ontario. The rTMS intervention began 1-4 weeks after the most recent CJI and included a 2-week induction phase, with active or sham rTMS delivered three times each week. The maintenance phase followed, and in weeks 3, 4, 6, 8, and 12, participants received a single active or sham rTMS session. Details of the study design are shown in Table 2.1.

The average pain severity was assessed weekly using an electronic diary from the baseline (week of the first rTMS session) to week 24. Disability and quality of life were assessed at baseline and weeks 4, 8, 12, 18, and 24. The trial was reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacological treatment and the template for intervention description and replication (TIDieR) checklist and guide.

Table 2.1: Study Timeline with Scheduled Study Assessments.

Table 1 SPIRIT diagram of enrolment, interventions and assessments for the rTMS + CJI trial																
	Enrolment		Baseline\First treatment	Post first treatment												
Timepoint	−t2	−t1	w1	w2	w3	w4	w5	w6	w7	w8	wk9-11	w12	w13-17	w18	w19-23	w24
Enrolment																
Initial screening	x															
Eligibility assessment	x															
Informed consent	x															
Treatment allocation			x													
Interventions																
CJI		x														
Active rTMS			xxx	xxx	x	x		x		x		x				
Sham rTMS			xxx	xxx	x	x		x		x		x				
Assessments																
NPRS			x	x	x	x	x	x	x	x	x	x	x	x	x	x
ODI			x			x				x		x				x
SF-12			x			x						x				x
DASS-21			x			x						x				x
BPI-sf			x			x				x		x				x
GRC						x						x				x

Notes. BPI-SF, Brief Pain Inventory Short Form; DASS-21, Depression Anxiety and Stress Scale 21; CJI, Corticosteroid joint injections; GRC, Global Rating of Change; ODI, Oswestry Disability Index; NPRS, Numerical Pain Rating Scale; rTMS, Repetitive Transcranial Magnetic Stimulation; SF-12, 12-Item Short Form Survey

2.1.1 Blinding and Allocation Concealment

Interested participants were notified that there would be two groups: one group would receive active rTMS treatment and the other group would receive sham rTMS treatment. The sham rTMS group served as the control group to determine the effect of rTMS by minimizing the placebo effects. Participants were randomly assigned to one of the two groups.

The randomization schedule was developed by an independent investigator who was not involved in trial recruitment, data collection, and analysis. This investigator switched the rTMS coil based on participants' group allocation during the rTMS session, while the assessor/administrator of the rTMS stepped out of the room. During the rTMS coil switch, the participants were asked to maintain a forward-looking position to ensure that they could not see the switch. This ensured the blinding of both the participant and assessor during the session.

The success of assessor blinding was measured at the completion of the follow-up assessment through a 'yes or no' response to the question, 'Were you aware which intervention group participants were assigned to before the follow-up assessment was completed?'. If the assessor answered yes to this question, they were asked how the information was disclosed. The success of participant blinding was measured at the completion of the follow-up assessment through a 'yes or no' response to the question: "Do you feel you received the real or sham brain stimulation?" "How do you know it was a real/sham intervention you received?". Emergency unblinding was to occur only in the event of a major adverse reaction, or if the treating physician needed to know the group allocation for safety reasons. Emergency unblinding did not occur during this trial.

2.2 Participants

2.2.1 Setting

Participants were recruited from the Pain Clinic at St. Joseph's Healthcare located in London, Ontario, Canada. The clinic is an inter-professional program that provides chronic pain management services to this population. The rTMS facility was located at the Department of the Gray Centre for Mobility and Activity at the Parkwood Institute, London, Ontario.

2.2.2 Inclusion and Exclusion Criteria

Participants who met the inclusion criteria for this study were individuals aged ≥ 18 years who were undergoing recurrent CJI for the management of CAP at St. Joseph's Healthcare Pain Clinic in London, Ontario, Canada. These participants had experienced axial pain between the neck and low back region, with a minimum intensity of ≥4 out of 10 (on an 11-point scale, where 0 means no pain, and 10 means worst pain imaginable) in the week preceding their most recent CJI. Additionally, they had received at least two CJI within the past 12 months at regular intervals and had maintained a consistent medication regimen for the preceding three months.

Exclusion criteria encompassed individuals who were unable to read, understand, and speak English or provide informed consent. Patients with known or suspected serious spinal pathologies such as tumors, fractures, or dislocations, as well as those who underwent spinal surgery within the past 12 months, were also excluded. Further exclusion criteria included individuals with uncontrolled mental health conditions and those who met specific exclusion criteria related to rTMS, such as epilepsy, severe head trauma, hearing problems, pregnancy, presence of metal in the brain/skull (except titanium), cochlear implants, implanted neurostimulators (e.g., deep brain stimulator and vagus nerve stimulator), cardiac pacemakers or intracardiac lines, surgical procedures on the spinal cord, or prior adverse reactions to TMS.

2.2.3 Recruitment and Consent

We invited adults aged 18 years and older who had CAP and were referred to the Pain Clinic for image-guided CJI of the lumbar, cervical facet, and/or sacroiliac joint. Our goal was to recruit 40 patients, which was deemed achievable based on the number of patients (approximately three–five patients/week) with CLBP and/or NP seen by all four participating anesthesiologists and a recruitment timeline of 7 months.

Potential participants were assessed for eligibility based on the study's inclusion and exclusion criteria by accessing their electronic medical records using PowerChart (Oracle Cerner, North Kansis City). Anesthesiologists were then informed of the patients' eligibility. A registered nurse practitioner working with the anesthesiologists obtained consent from potential participants during their CJI appointment, allowing the research team to make further contact. After obtaining consent to participate in the study, eligible individuals were provided with a comprehensive Letter of Information at the clinic, which outlined the study's details. The individuals were screened for eligibility. Once their eligibility was confirmed, they were invited to participate in the study. Participants who expressed interest were enrolled in the study and underwent baseline assessments within a one- to four-week period following their most recent CJI.

Upon arrival at the research facility, participants were taken to a comfortable room. They were assisted in completing the screening checklist and reviewing and signing the consent form. Once the consent form was signed, the study procedure commenced.

2.3 Interventions

2.3.1 Corticosteroid joint injections (CJI)

Anesthesiologists at St. Joseph's Healthcare Pain Clinic administered CJI in the cervical, lumbar facet, and/or sacroiliac joint areas following standard clinical procedures which is to place a needle in the joint space (intra-articular) or the surrounding tissues (periarticular). The choice of steroid and needle types was left to the discretion of the physiatrist. The number of joints injected was determined by the treating physiatrist,

typically ranging from two to four joints, depending on the affected joints (see *Results*). For this study, the choice of needle placement, whether intra-articular and/or periarticular, was based on the previously determined care provided to patients.

2.3.2 Repetitive Transcranial Magnetic Stimulation Protocol

The enrolled patients underwent their first rTMS session within 1-4 weeks of their regular CJI appointment. A Brainsight neuronavigation system (Rogue Research Inc., Montreal) was used during the session. This system featured a pre-programmed MNI brain (a standard brain template based on MRI scans of a large series of healthy individuals) and was connected to a position sensor (optical camera) called Polaris. Polaris detected trackers placed on both the rTMS coil and the participant's head. Before the participants arrived, the rTMS coil was calibrated to ensure accurate detection.

Upon arrival, participants were asked to take a seat in a comfortable chair in front of the rTMS device and were provided a brief overview of the procedure. The administrator addressed any questions or concerns. Once the participant was seated, a headband with trackers was placed slightly above the eyebrows on their forehead, and the Polaris was adjusted until the participant was fully within view. To prepare the muscle of interest, the belly tendon of the first dorsal interosseous (FDI) muscle, an exfoliant, and an alcohol wipe were used. The participant was instructed to pinch their thumb and index finger to facilitate better localization of the belly tendon of the FDI muscle. After preparation and localization of the muscle, two electrodes were applied: one to the belly tendon (between the base of the index and thumb) and another to a reference point (on the side of the distal second metacarpal). In addition, a ground electrode was applied using a wriststrap. All three electrodes were connected to an electromyography (EMG) amplifier module that recorded the activity of the FDI muscle during the rTMS session.

Once the setup was completed, the procedure began by identifying the stimulation site, also known as the "motor hotspot". To locate the motor hotspot, rTMS single pulses were administered three times along the possible corticomotor representation of the FDI muscle using a biphasic stimulator (DuoMag XT100; Deymed, Czech Republic) and a figure-of-eight coil placed contralateral to the side of the worst pain. In cases where the

participants experienced pain on both sides, the target was the left M1. The single pulses caused twitching of the FDI muscle, and an objective measure of the muscle response, known as the motor evoked potential (MEP), was recorded through EMG until a spot that consistently produced the highest MEP amplitude at the lowest stimulator intensity was identified as the hotspot. The MEP is also an indicator of corticospinal pathway excitability (Rossini et al. 2015).

Once the hotspot was located, the resting motor threshold (rMT) was determined. The rMT is the lowest intensity required to elicit an MEP of at least 50μV in 5 out of 10 trials over the FDI representation of the motor cortex (Rossini et al., 1994). To determine the rMT, a TMS motor threshold assessment application called Adaptive Parameter Estimation by Sequential Testing (PEST) was used. Throughout the process of finding the hotspot and determining the rMT, the coil was positioned tangentially to the scalp at a 45-degree angle to the midsagittal plane to generate a current that moved in a posterior-anterior direction toward the rTMS target. The hotspot and rMT values were saved using the Brainsight and Adaptive PEST applications, respectively.

At each intervention session, the hotspot and rMT were reviewed and adjusted to account for any changes that may have occurred between the sessions. The participants were asked to rate their pain level on a scale of 0 to 10 before starting the rTMS treatment protocol. A score of 0 indicated no pain, whereas a score of 10 represented the worst pain imaginable. After this assessment, the administrator/assessor paused to switch the rTMS coil to a treatment coil (active/sham coil).

During each rTMS treatment session, which lasted for 20 minutes, the participants received 2000 stimulations administered in 40 trains at a rate of 10 Hz. Each train consisted of 50 pulses delivered for 5 seconds, followed by a 25-second rest interval (intertrain; Figure 2.1). The stimulus intensity was set to 85% of the rMT of the FDI muscle, which is a subthreshold for preventing muscle twitching during treatment. This treatment protocol adhered to the guidelines for the safe use of rTMS outlined by Wasserman (1998) and Rossi et al. (2009).

Previous studies using this protocol for CLBP have demonstrated that a minimum of 1000 high-frequency rTMS pulses are necessary to achieve significant reductions in pain and disability measures among patients receiving rTMS treatment (Ambriz-Tututi et al., 2016). In the sham condition, the setup was identical, with the only difference being the utilization of a sham coil, specifically DuoMag 70BFP-LQC. The sham coil is similar to the standard active coil, 70BF-LQC, except that it is primarily designed to provide peripheral stimulation. However, it maintains auditory, mechanical, and peripheral electrical sensations (muscle and skin) associated with the active coil. The purpose of using the sham coil was to ensure that participants were unable to discern whether they were receiving active or sham stimulation, effectively blinding them to the treatment conditions.

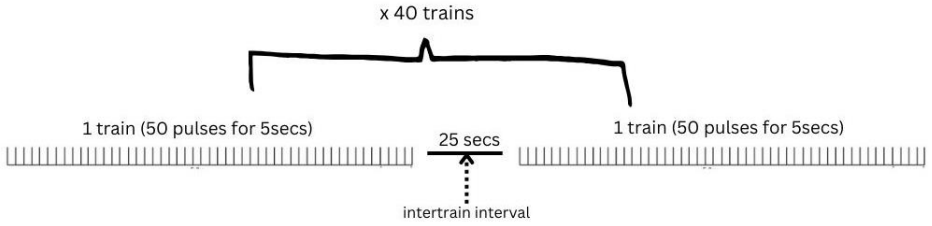


Figure 2.1: Diagram of the rTMS parameters used in this study.

2.4 Primary Outcome Measures

2.4.1 Measure of Feasibility, Tolerability and Safety

Feasibility of rTMS + CJI intervention was measured as: (1) the percentage of participants enrolled from the total number screened, (2) the percentage of participants who dropped out from the total number enrolled, (3) the percentage of completed rTMS sessions for each participant, (4) the percentage of completed follow-up assessments for each participant, and (5) the success of assessor and participant blinding

The tolerability of rTMS + CJI was measured quantitatively on a scale of 1-5 (where 1 is not tolerable and 5 is very tolerable) after each rTMS session. Tolerability was also

assessed qualitatively for any reason related to discomfort requiring the intervention to be paused during stimulation.

The safety of rTMS + CJI was measured as any adverse reaction, its severity, and the duration reported on verbal questioning during each session. The World Health Organization (WHO) characterizes an adverse reaction as a detrimental and unforeseen response to an intervention (rTMS) that typically occurs at regular therapeutic doses and is related to the intervention in question (Carlesso et al., 2010).

2.5 Materials: Questionnaires

2.5.1 Intake Patient Health Questionnaire

The intake patient health questionnaire contained patients' demographic information such as sex, gender, date of birth, ethnic ancestry, first language, highest level of education achieved, history of pain, medication list, and baseline measures of biopsychosocial factors such as the brief pain inventory short form (BPI-sf), depression, anxiety, and stress scale (DASS-21), Oswestry Disability Index (ODI), and 12-item Short Form Survey (SF-12).

2.5.2 Numerical Pain Rating Scale (NPRS)

The Numerical Pain Rating Scale (NPRS) is frequently employed as a unidimensional 11-point scale for individuals to self-report their pain level. Patients choose a whole number between 0 and 10, indicating the number that most accurately represents the intensity of their pain, with 0 indicating no pain, and 10 indicating the worst pain imaginable. Despite its categorization into various pain severity levels ranging from no pain (0) to severe pain (7-10), these categories do not fully capture patients' perception of change in pain intensity (Farrar et al., 2001). Therefore, other measures were used to fully capture patients' pain experiences.

The NPRS was administered electronically using REDCap (Vanderbilt, Tennessee) to assess the participants' pain severity on a weekly basis from baseline until follow-up at

week 24 or the participants' next scheduled CJI appointment. Pain severity was assessed as the average pain intensity over the preceding week with an 11-point pain numerical rating scale (NPRS; where a score of 0 = "no pain," and 10 = "worst pain imaginable").

2.5.3 Oswestry Disability Index (ODI)

The Oswestry Disability Index (ODI) is a self-reported measure of functional disability related to LBP. It encompasses ten domains: pain intensity, lifting ability, self-care, walking capability, sitting comfort, standing ability, sexual function, social engagement, sleep quality, and travel capacity. Within each domain, there are six statements representing varying levels of difficulty, and participants indicate the statement that best reflects their current situation. Each response is scored on a scale of 0 to 5, where 0 denotes no difficulty and 5 represents the highest level of difficulty (Fairbank & Pynsent, 2000).

Disability was assessed using the self-administered ODI V.2.1 for LBP (Fairbank et al., 1980) in a paper questionnaire form given to participants during their study visits at baseline, and at weeks 4, 8, 12, and at the final follow-up assessment.

2.5.4 12-Item Short Form Survey (SF-12)

The 12-Item Short Form Survey (SF-12) evaluates the impact of an intervention on health-related quality of life (HRQoL). This questionnaire comprised eight domains, each scored on a 100-point scale, covering physical function (PF), role limitations due to physical issues (RP), pain (BP), general health (GH), vitality/energy (VT), social function (SF), mental health/emotional well-being (MH), and role limitations due to emotional problems/mental health (RE). A higher score indicates a better perceived state of health. The PF, RP, BP, and GH domains are combined to form a physical composite summary (PCS), while the VT, SF, MH, and RE domains are combined to create a mental composite summary (MCS; Pagels et al., 2012).

SF-12 was administered in a paper questionnaire form to participants during their study visits at baseline, at weeks 4, 12 and at the final follow-up assessment.

2.5.5 Depression, Anxiety, and Stress Scales (DASS-21)

The Depression Anxiety and Stress Scale 21 (DASS-21) comprises 21 items organized into three categories: depression, anxiety, and stress, with seven items allocated to each category (Nilges & Essau, 2015). Each item is rated on a scale of 0 to 3, where 0 represents "never," 1 indicates "sometimes," 2 denotes "often," and 3 signifies "almost always." The scores for each item within a category were summed, resulting in a total DASS score of 21 for each category. Severity ratings are provided separately for depression (ranging from 0 to 4 for normal, 5–6 for mild, 7–10 for moderate, 11–13 for severe, and >14 for extremely severe), anxiety (ranging from 0 to 3 for normal, 4–5 for mild, 6–7 for moderate, 8–9 for severe, and >10 for extremely severe), and stress (ranging from 0 to 7 for normal, 8–9 for mild, 10–12 for moderate, 13–16 for severe, and >17 for extremely severe; Lovibond & Lovibond, 1995).

The DASS-21 was used to evaluate the effects of rTMS treatment on three domains (depression, anxiety, and stress). DASS-21 was administered in a paper questionnaire form to participants during their study visits at baseline, at weeks 4, 12 and at the final follow-up assessment.

2.5.6 Brief-Pain Inventory Short Form (BPI-sf)

The Brief Pain Inventory short form (BPI-sf) was used to evaluate the severity of pain, its effect on daily activities, its location, pain medication usage, and the level of pain relief experienced within the previous 24 hours. Pain severity was determined by calculating the average of four severity-related items (i.e., pain at its worst, least, average, and current pain), whereas pain interference was assessed by computing the average of seven items (i.e., general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) pertaining to how pain affects daily functioning (Cleeland & Ryan, 1994).

Pain severity and impact of pain on the patients’ daily functioning were assessed using the 9-item self-administered BPI-sf in a printed paper questionnaire during the study visits at baseline, weeks 4, 8, 12, and at the final follow-up assessment.

2.5.7 Global Rating of Change Scales (GRC)

The Global Rating of Change scale (GRC), also known as the Patient Global Impression of Change Scale (PGIC), prompts patients to assess the degree of improvement or deterioration in their condition, typically following treatment (Schmitt & Abbott, 2015). Unlike assessments based on the dimensions of change defined by clinicians or researchers, GRC requires patients to reflect on their initial condition before treatment and compare it to their current health status (Kamper et al., 2009). The scale features a midpoint of 0 (indicating no change), negative values on the left (indicating worsening symptoms), and positive values on the right (indicating improvement in health status; Schmitt & Di Fabio, 2005). The GRC measure is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for use in chronic pain clinical trials (Dworkin et al., 2005).

A 15-point GRC (-7 = “a very great deal worse,” 0 = “about the same,” 7 = “a very great deal better”) was administered to assess participants’ perception of symptom improvement or worsening in response to treatment. GRC was administered in a paper questionnaire form to participants during their study visits on weeks 4 and 12 and at the final follow-up assessment.

2.6 Data Analysis

2.6.1 Statistical Methods

To examine feasibility (Hypothesis (H) 1A, B, C, D, E), tolerability (H2A, B), and safety (H3A), we used summary descriptive statistics, such as means, proportions, and standard deviations (*sd*). Descriptive statistics were done using Microsoft Excel and JASP (Version 0.18.3). A Wilcoxon signed-rank test was performed against the value of 80% session and assessment completion rate, followed by a Mann-Whitney U test to detect any statistical significance between groups.

To assess the trends of effectiveness, scores of secondary outcome measures (H4A-E, i.e., pain intensity, severity, interference, disability, quality of life, and patients' perceived

response to treatment) were analyzed according to the intention-to-treat principle using analysis of variance (ANOVA) to assess changes within groups and differences between groups over time. All data were assessed for normality (data distribution) using the Shapiro-Wilk test. Normally distributed data were assessed using two-way repeated measures ANOVA with two levels for intervention (active rTMS/sham rTMS) and five levels for time (baseline, week 4, week 8, week 12, and week 24) as separate factors. Significant ANOVAs were followed with Bonferroni corrected post hoc tests to determine where the significance lay. The outcomes (NPRS, ODI, BPI-sf, SF-12, and DASS-21 scores) of each measurement were dependent variables. Data that violated normality were assessed using the Mann-Whitney U test on change in scores between groups. Results are presented as mean ± standard deviation (SD) unless otherwise stated.

2.7 Ethical Considerations

Ethical approval was received from the Health Sciences Research Ethics Board (HSREB) at Western University (HSREB file number 122486) and the Lawson Ethics Board at Lawson Health Research Institute (ReDA file number 13218; LORA file number R-23-283). As an intervention study examining the combined intervention of rTMS and CJI, this study was registered on ClinicalTrials.gov (ID: NCT05840354).

Chapter 3

3 Results

The demographic characteristics of all the participants are summarized in Table 3.1. There were five participants in the sham rTMS group and seven in the active rTMS group. Among those in the sham rTMS group, 80% were male and 20% were female, whereas the active rTMS group comprised 42.9% males and 57.1% females. The average age of participants in the sham and active rTMS groups was 60.6 years (±5.9) and 68.4 years (±9.3), respectively. Most participants reported experiencing pain symptoms for more than five years, with 60% in the sham rTMS group and 100% in the active rTMS group.

Participants in both groups received CJI treatment for pain, including facet joint injections (FJI), sacroiliac joint injections (SIJI), or both. In the sham rTMS group, 80% of the participants received only FJI, while 20% received only SIJI. In the active rTMS group, 57.1% received only FJI, 28.6% received only SIJI, and 14.3% received both FJI and SIJI. Low back pain (LBP) was common in both groups, affecting 60% of the participants in the sham rTMS group and 71.4% in the active rTMS group. Neck pain (NP) was reported by 40% of the participants in the sham rTMS group, but none in the active rTMS group, however, 28.6% of the participants in the active rTMS group experienced both LBP and NP. Intra-articular needle placement for corticosteroid delivery was the most common method used in both groups. In the sham rTMS group, 60% of the participants had their left M1 stimulated, whereas 40% had their right M1 stimulated. Conversely, in the active rTMS group, the left M1 was stimulated in 57.1% of participants and the right M1 in 42.9% of participants.

Table 3.1: Demographic characteristics of participants.

Number of Participants, N	Sham rTMS (N = 5)			Active rTMS (N = 7)
Gender	**n**	**%**	**n**	**%**
Male	4	80%	3	42.9%
Female	1	20%	4	57.1%
Ethnicity				
Caucasian	2	40%	2	28.6%
British	1	20%	0	0%
Chinese	0	0%	1	14.3%
Dutch	0	0%	1	14.3%
English	0	0%	1	14.3%
European	1	20%	0	0%
German	1	20%	0	0%
Latino	0	0%	1	14.3%
Ukrainian	0	0%	1	14.3%
Age	**Mean (SD)**		**Mean (SD)**	
	60.6 (±5.9)		68.4 (±9.3)	
Education				
Post-graduate degree	0		1	14.3%
Bachelors	2	40%	2	28.6%
Certificate/Diploma	1	20%	2	28.6%
Trade Qualification	0	0%	1	14.3%
Secondary School	1	20%	1	14.3%
Some secondary school	1	20%	0	0%
Location of Pain				
Low Back	3	60%	5	71.4%
Neck	2	40%	0	0%
Low back & Neck pain	0	0%	2	28.6%
Duration of Pain				
12 mths - 2 years	1	20%	0	0%
2 - 5 years	1	20%	0	0%
> 5 years	3	60%	7	100%
Type of Corticosteriod Joint Injections				
Facet Joint Injection (FJI)	4	80%	4	57.1%
Sacroiliac Joint Injection (SIJI)	1	20%	2	28.6%
FJI + SIJI	0	0%	1	14.3%
Site of Injections				
cervical joint	2	40%	0	0%
lumbar joint	2	40%	3	42.9%
sacroiliac joint	1	20%	2	28.6%
cervical + lumbar joint	0	0%	1	14.3%
sacroiliac + lumbar joint	0	0%	1	14.3%
sacroiliac + cervical joint	0	0%	0	0%
Injection Placements				
Intra-articular	4	80%	4	57.1%
Peri-articular	0	0%	1	14.3%
intra & peri-articular	1	20%	2	28.6%
rTMS stimulation site				
left M1	3	60%	4	57.1%
right M1	2	40%	3	42.9%

3.1 Primary Outcomes

3.1.1 Measures of Feasibility

The recruitment period was from July 2023 to February 2024, during which 316 patients were screened for eligibility. Of these, 181 (57.3%) were deemed ineligible, 135 (42.7%) were eligible, and of those, 118 (37.3%) were not enrolled. Of those not enrolled, 83 (26.3%) declined to participate and cited reasons such as time commitments (*n* = 17; 5.4%), distance to the research location (*n* = 11; 3.5%), going out of the country (*n* = 3; 1.0%), enrollment in another research study (*n* = 1; 0.3%), did not think they would benefit from added intervention (*n* = 2; 0.6%), not wanting to be randomized (*n* = 1; 0.3%), and having no reliable means of transportation to the research location (*n* = 1; 0.3%). Forty-six patients (14.6%) did not provide consent to be approached for research purposes. Additionally, 22 (7.0%) were not approached due to cancelled appointments or unavailability of the recruiter, 13 (4.1%) were lost to follow-up, and one (0.3%) was unable to join because of financial limitations.

Of those who were eligible in the pre-screening stage, only 17 (5.4%) were assessed for eligibility. Of these 17 patients, one was excluded because of contraindications to rTMS (metal in the neck). Sixteen (5.1%) patients who met the inclusion criteria consented and were randomized to receive either sham rTMS (n = 6; 1.9%) or active rTMS (n = 10; 3.2%). The screening-to-enrollment rate was 5%, compared with the anticipated rate of > 80% (H1A).

Of the remaining 15 enrolled participants, three (20%; 6.7% in sham rTMS and 13.3% in active rTMS) withdrew (H1B). The participant in the sham rTMS group withdrew at week 6 because of unblinding of their treatment group allocation. One participant in the active rTMS group withdrew due to personal reasons after the first week of rTMS, and another withdrew at week 3 because of worsening restless leg syndrome (RLS) symptoms. Twelve participants (n = 5; 41.7% received sham rTMS and n = 7; 58.3% received active rTMS) completed the treatment and post-intervention assessments (see Figure 3.1).

The overall completion rate of the rTMS sessions by each participant (H1C) was high at 97% (±4.5%). A Wilcoxon signed-rank test indicated that the median number of sessions completed was significantly higher than 80% *(V* = 78, *p* = .002), which was the minimum anticipated completion rate of the rTMS sessions. The individual group session completion rate was also high, at 96.4% (±4.9%) in the sham rTMS group and 97.4% (±4.4%) in the active rTMS group. A Mann-Whitney U test suggested no significant difference in the completion rate between the two groups (*W = 15.5, p = .77*). The overall follow-up assessment completion rate for each participant (H1D) was 99.4% (±2.1%). The Wilcoxon signed-rank test suggested that the median number of completed assessments was significantly higher than the anticipated minimum completion rate of 80% (V = 78, p < .001). It was not possible to conduct a Mann-Whitney U test to compare group differences because all participants in the sham rTMS group completed 100% of the assessments. Thus, there was no variance in the data, allowing for statistical testing. The follow-up completion rate for active rTMS was 99% (±2.7%).

Participants and assessor blinding was successful with no statistically significant difference (participants: $\chi^2_{(1,11)} = 0.11$, $p = .74$, assessor: $\chi^2_{(1,12)} = 0.069$, $p = .793$) between the treatment groups in correctly guessing group allocation (H1E). The assessor/administrator was unblinded to one participant due to a scratch on the sham coil that was concealed with a covering in subsequent sessions.

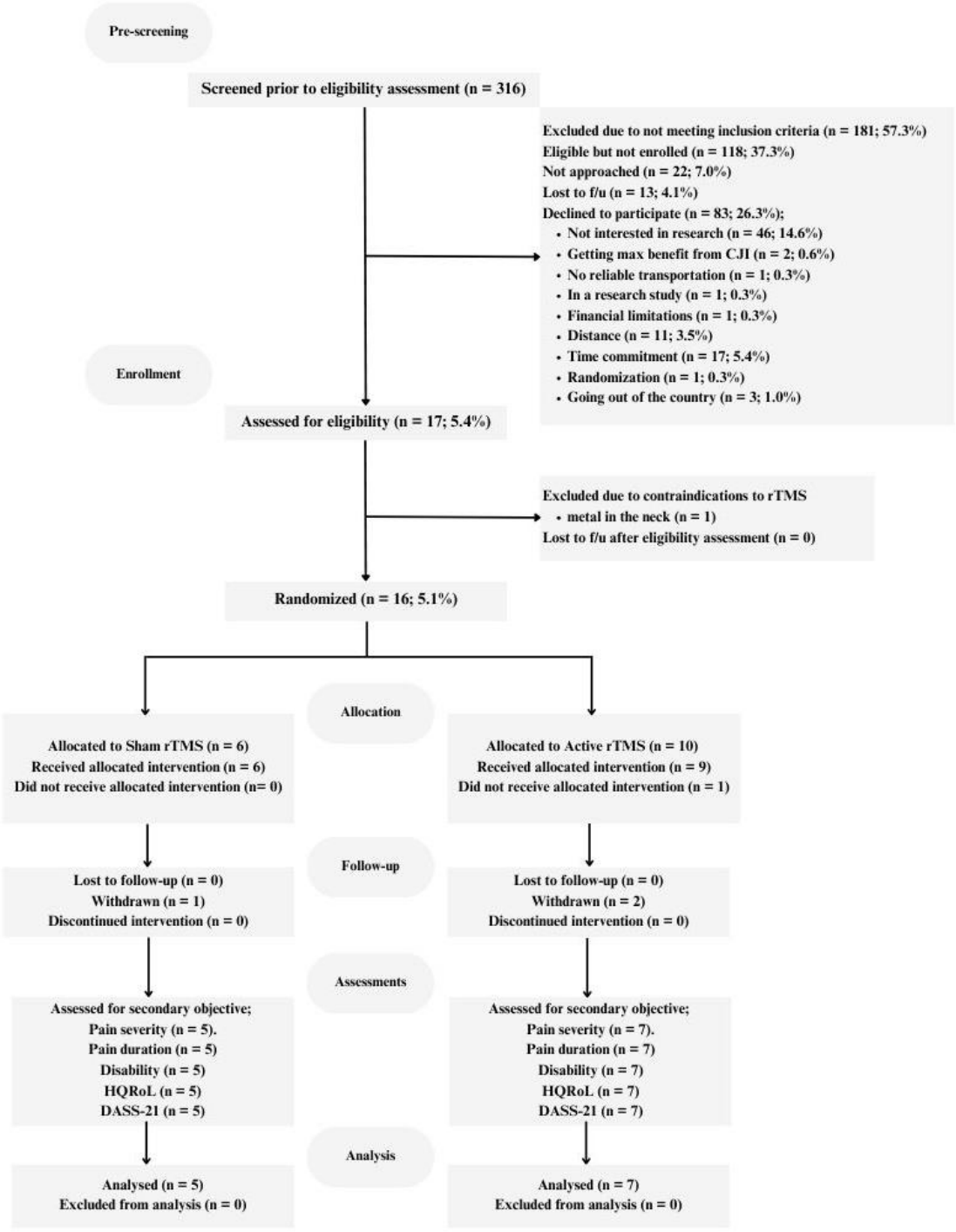


Figure 3.1: Consolidated Standards of Reporting Trials (CONSORT) flow chart of participants throughout the study. Notes. HQRoL: health-related quality of life; DASS-21: Depression Anxiety Stress Scale.

3.1.2 Measures of Tolerability

It was expected that participants in both treatment groups would tolerate the intervention well, with a median rating of >3 (H*2A*) on a scale of 1-5 (1: not tolerable and 5: very tolerable). Participants in both treatment groups reported high tolerability (median = 5, [min = 3, max =5]), as shown in Table 3.2. As for the qualitative assessment of tolerability (H*2B*), one participant in the active rTMS group reported neck soreness in the fifth and tenth sessions and requested that the session be paused for positional adjustment. Participants were willing to continue the session after adjustment.

Table 3.2: Participants' tolerability rating of active or sham rTMS on a 1-5 scale

Participants	Median	Min	Max
Sham rTMS			
1	5	5	5
7	5	5	5
8	5	5	5
13	5	5	5
14	5	5	5
Active rTMS			
2	5	5	5
3	5	5	5
5	5	5	5
6	5	3	5
9	5	5	5
10	5	5	5
11	5	5	5

Note: 1 indicates not tolerable and 5 indicates very tolerable.

3.1.3 Measures of Safety

It was predicted that the combination of M1-rTMS and CJI would be safe, with no major adverse effects reported by the participants receiving active rTMS (H3A). No major adverse effects were reported; however, the participants reported mild transient side

effects due to rTMS (Figure 3.2). Most side effects were reported during stimulation and ceased after stimulation ended.

In the sham rTMS group, one individual reported two side effects: jaw discomfort and facial tingling. Additionally, two other individuals reported three side effects, one of whom experienced jaw discomfort, facial tingling, and neck soreness, while the other experienced nasal tingling in conjunction with jaw discomfort and facial tingling. It is worth noting that jaw vibration and facial tingling were the prevalent side effects among the five participants in the sham rTMS group. Notably, two participants in the sham rTMS group did not report any adverse reactions. In the active rTMS group, one participant reported a single side effect of nasal tingling. Another participant documented both scalp discomfort and neck soreness, while one individual reported two side effects: jaw discomfort and irritation from surface EMG electrodes on the skin. One participant reported three side effects: light headedness, scalp discomfort, and neck soreness. Another participant reported three side effects: jaw discomfort, scalp discomfort, and heightened emotional state. Finally, two participants in the active rTMS group did not report any adverse reactions.

In summary, participants in the sham rTMS group reported jaw discomfort (3 cases), face tingling (3 cases), nose tingling, and neck soreness (1 case), whereas those in the active rTMS group experienced scalp discomfort (3 cases), neck soreness (2 cases), jaw discomfort (2 cases), and various other side effects, including light-headedness (1 case), nose tingling (1 case), skin irritation from the electrode (1 case), and heightened emotional state (1 case). Overall, all reported reactions are anticipated and are common in rTMS (Rossi et al., 2009). No major adverse effects were reported in either treatment groups.

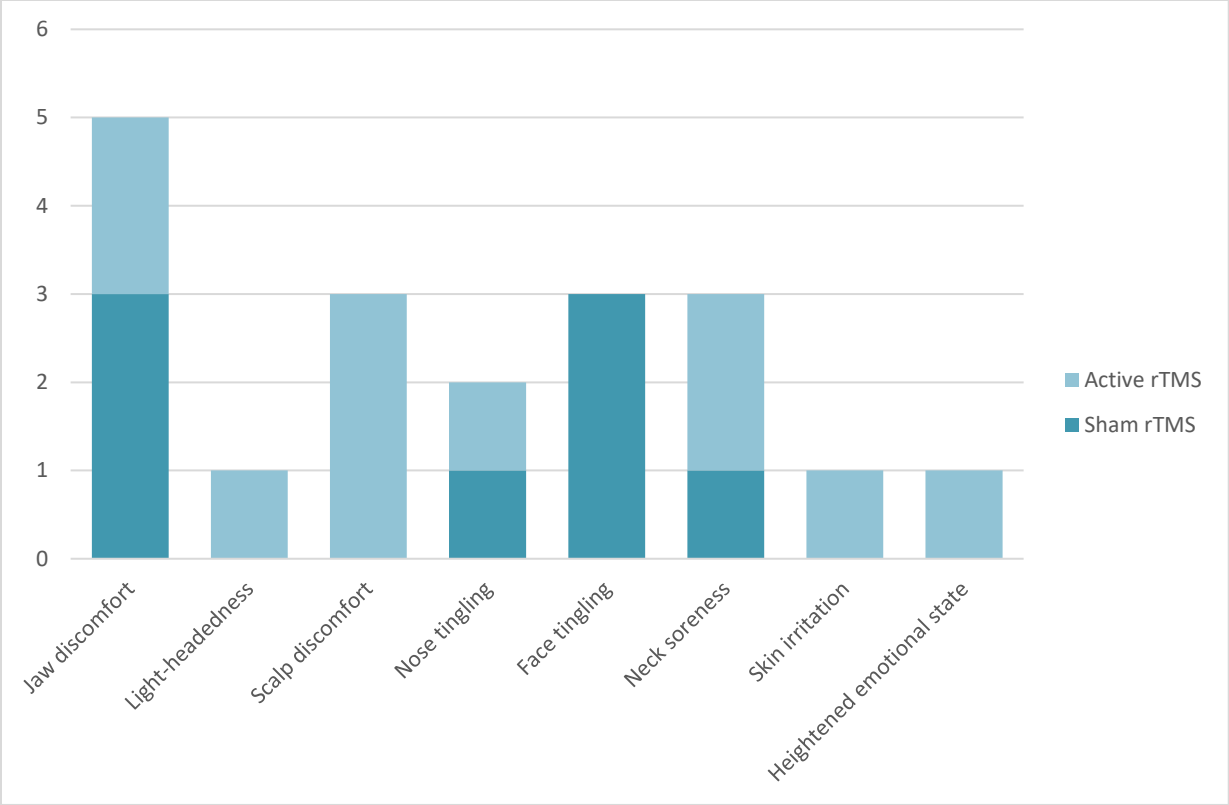


Figure 3.2: Side effects reported by participants in each treatment group.

3.2 Secondary Outcomes

3.2.1 Measures of Pain Intensity, Severity, Disability, and Health-related Quality of Life

The secondary outcome measures (H4A-E), including the NPRS, BPI-sf, ODI, DASS-21, and SF-12, were assessed using repeated-measures ANOVA. Specifically, the effects of four time points (baseline, weeks 4, 12, and final week) were determined for the DASS-21, BPI-sf, and NPRS, and the effects of five time points (baseline, weeks 4, 8, 12, and final week) were assessed for the SF-12 and ODI. Additionally, the interaction between the group and time was evaluated. The results are presented in Table 3.3. The Last Observation Carried Forward approach was employed as an imputation technique to address missing values in the statistical analysis.

The assumption of sphericity was assessed using Mauchly's test, which indicated that the assumption of sphericity was violated for anxiety score ($\chi^2_{(5)} = 13.07$, $p = .02$), depression score ($\chi^2_{(5)} = 15.58$, $p = .01$), pain severity score ($\chi^2_{(9)} = 36.70$, $p < .001$), and disability score ($\chi^2_{(9)} = 22.83$, $p = .01$). Therefore, a Greenhouse-Geisser correction was applied to adjust the degrees of freedom (Greenhouse & Geisser, 1959). The ANOVA results showed that there were no statistically significant differences in anxiety, depression, and pain severity scores across the four time points and treatment groups (anxiety: $F_{(1.6, 17.6)} = 0.67$, $p = .49$, $\eta 2 = .02$; depression: $F_{(1.5, 17.1)} = 1$, $p = .37$, $\eta^2 = .02$; pain severity: $F_{(1.7, 18.2)} = 0.31$, $p = .71$, $\eta^2 = .02$), and disability ($F_{(2.2, 23.5)} = 0.15$, $p = .88$, $\eta^2 = .01$).

Maulchy's test for stress ($\chi^2_{(5)} = 6.82$, $p = .24$), PCS ($\chi^2_{(5)} = 9.24$, $p = .102$), MCS ($\chi^2_{(5)} = 3.87$, $p = 0.57$), and pain interference ($\chi^2_{(9)} = 15.43$, $p = .09$) scores met the assumption of sphericity. The ANOVA results showed no statistically significant differences in stress ($F_{(3, 33)} = 1.57$, $p = .22$, $\eta^2 = .04$) and pain interference ($F_{(4, 44)} = 0.11$, $p = .98$, $\eta^2 = .003$) scores across all time points and between the treatment groups. However, the group-time interaction had a statistically significant effect on PCS ($F_{(3, 33)} = 2.95$, $p = .05$, $\eta^2 = .01$) and MCS ($F_{(3, 33)} = 3.48$, $p = .03$, $\eta^2 = .08$) scores. Time also had a significant effect on MCS scores ($F_{(3, 33)} = 3.07$, $p = .05$, $\eta^2 = .07$). The Bonferroni-corrected post-hoc test (Table 3.4) indicated a significantly higher MCS score at week 4 (p = .018) compared to baseline, with a mean difference of 13.8 in the sham rTMS group but not in the active rTMS group.

A repeated measures ANOVA was also performed to assess the effects of time, group, and group-time interaction on pain intensity (NPRS) scores. Two separate tests were performed. For the first test, the baseline score and the average scores between weeks 2 to 6 and weeks 7 to 12 were taken to represent the intervention phase, and weeks 13 to 18 and weeks 19 to 24 were taken to represent the follow-up phase for all participants. The ANOVA results showed no statistically significant differences in pain intensity scores ($F_{(4, 44)} = 0.71$, $p = .59$, $\eta^2 = .04$). For the second test, the reported scores at the time points other outcome measures were collected; that is, baseline, week 4, 8, 12, and end point (final week) for each participant were used. The results also showed no statistically significant difference in pain intensity scores ($F_{(4, 44)} = 0.87$, $p = .49$, $\eta^2 = .034$) across all

time points and between the groups. The mean NPRS scores across weeks and in the treatment group are shown in Figure 3.3.

Table 3.3: Results of the Repeated Measures ANOVA performed for NPRS, NPRS averages, DASS-21, BPI-sf, SF-12, and ODI scores

	Sphericity correction	Sum of Squares	df	Mean Sqaure	F-Value	p	η^2
DASS (stress) score							
Time		54.4	3	18.1	0.57	0.64	0.01
Groups		34.9	1	34.9	0.13	0.73	0.01
Time x Groups		151	3	50.3	1.57	0.22	0.04
DASS (anxiety) score							
Time	Greenhouse-Geisser	53.4	1.6	33.7	0.75	0.46	0.03
Groups		73.8	1	73.8	0.65	0.44	0.04
Time x Groups	Greenhouse-Geisser	47.8	1.6	30.1	0.67	0.49	0.02
DASS (depression) score							
Time	Greenhouse-Geisser	13.8	1.5	9.2	0.2	0.76	0.004
Groups		0.1	1	0.1	3.99×10-4	0.98	3.17×10-5
Time x Groups	Greenhouse-Geisser	66.5	1.5	44.1	1	0.37	0.02
SF-12 (PCS) score							
Time		81.5	3	27.2	1.13	0.36	0.02
Groups		28.7	1	28.7	0.08	0.79	0.05
Time x Groups		214.1	3	71.4	2.95	0.05	0.01
SF-12 (MCS) score							
Time		297.2	3	99.1	3.07	0.045	0.07
Groups		292.3	1	292.3	1.09	0.32	0.07
Time x Groups		336	3	112	3.48	0.03	0.08
BPI-sf (Pain severity)							
Time	Greenhouse-Geisser	3.4	1.7	1.97	0.46	0.62	0.02
Groups		0.1	1	0.14	0.01	0.92	9.58×10-4
Time x Groups	Greenhouse-Geisser	2.4	1.7	1.35	0.31	0.71	0.02
BPI-sf (Pain interference)							
Time		5.6	4	1.4	0.88	0.49	0.03
Groups		1.6	1	1.6	0.07	0.8	0.01
Time x Groups		0.7	4	0.2	0.11	0.98	0.003
ODI (Disability)							
Time	Greenhouse-Geisser	565.1	2.2	259.6	1.14	0.34	0.05
Groups		0.1	1	0.1	1.78×10-4	1	9.78×10-6
Time x Groups	Greenhouse-Geisser	72	2.2	33.1	0.15	0.88	0.01
NPRS scores (b, wk 4, 8, 12, end point)							
Time		9.6	4	2.4	1.25	0.31	0.05
Groups		0.5	1	0.5	0.03	0.86	0.002
Time x Groups		6.6	4	1.7	0.87	0.49	0.03
NPRS Average scores (b, wk 2-6, 7-12, 13-18, 19-24)							
Time		3.2	4	0.8	0.56	0.69	0.03
Groups		0.6	1	0.6	0.04	0.84	0.01
Time x Groups		4.1	4	1.01	0.71	0.59	0.04

Notes. b = baseline, wk = weeks, PCS = physical composite score, MCS = mental composite score, NPRS = numerical pain rating scale, DASS = depression, anxiety, stress scale, BPI-sf = brief pain inventory short form, ODI = Oswestry disability index, df = degree of freedom, η^2 = eta squared

Table 3.4: Post Hoc Comparisons of Group and Time Point Differences with Bonferroni Adjustment on the MCS scores.

		Mean Difference	SE	t	p_{bonf}
sham, Baseline	active, Baseline	3.737	5.788	0.646	1.000
	sham, Week 4	13.820	3.591	3.849	0.018
	active, Week 4	2.320	5.788	0.401	1.000
	sham, Week 12	9.100	3.591	2.534	0.486
	active, Week 12	3.087	5.788	0.533	1.000
	sham, Final week	11.900	3.591	3.314	0.073
	active, Final week	4.970	5.788	0.859	1.000
active, Baseline	sham, Week 4	10.083	5.788	1.742	1.000
	active, Week 4	−1.417	3.278	−0.432	1.000
	sham, Week 12	5.363	5.788	0.927	1.000
	active, Week 12	−0.650	3.278	−0.198	1.000
	sham, Final week	8.163	5.788	1.410	1.000
	active, Final week	1.233	3.278	0.376	1.000
sham, Week 4	active, Week 4	−11.500	5.788	−1.987	1.000
	sham, Week 12	−4.720	3.591	−1.315	1.000
	active, Week 12	−10.733	5.788	−1.854	1.000
	sham, Final week	−1.920	3.591	−0.535	1.000
	active, Final week	−8.850	5.788	−1.529	1.000
active, Week 4	sham, Week 12	6.780	5.788	1.171	1.000
	active, Week 12	0.767	3.278	0.234	1.000
	sham, Final week	9.580	5.788	1.655	1.000
	active, Final week	2.650	3.278	0.808	1.000
sham, Week 12	active, Week 12	−6.013	5.788	−1.039	1.000
	sham, Final week	2.800	3.591	0.780	1.000
	active, Final week	−4.130	5.788	−0.714	1.000
active, Week 12	sham, Final week	8.813	5.788	1.523	1.000
	active, Final week	1.883	3.278	0.575	1.000
sham, Final week	active, Final week	−6.930	5.788	−1.197	1.000

Note. P-value adjusted for comparing a family of 28

Note: SE = standard errors, t = t-statistics, pbonf = Bonferroni-adjusted p-values

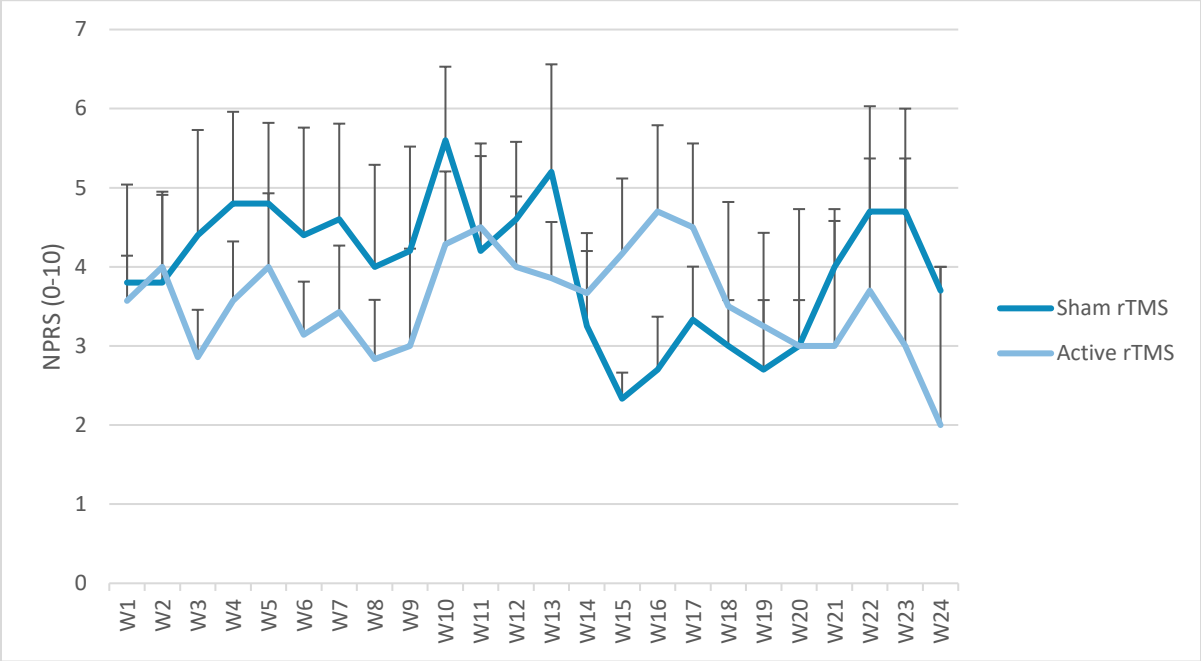
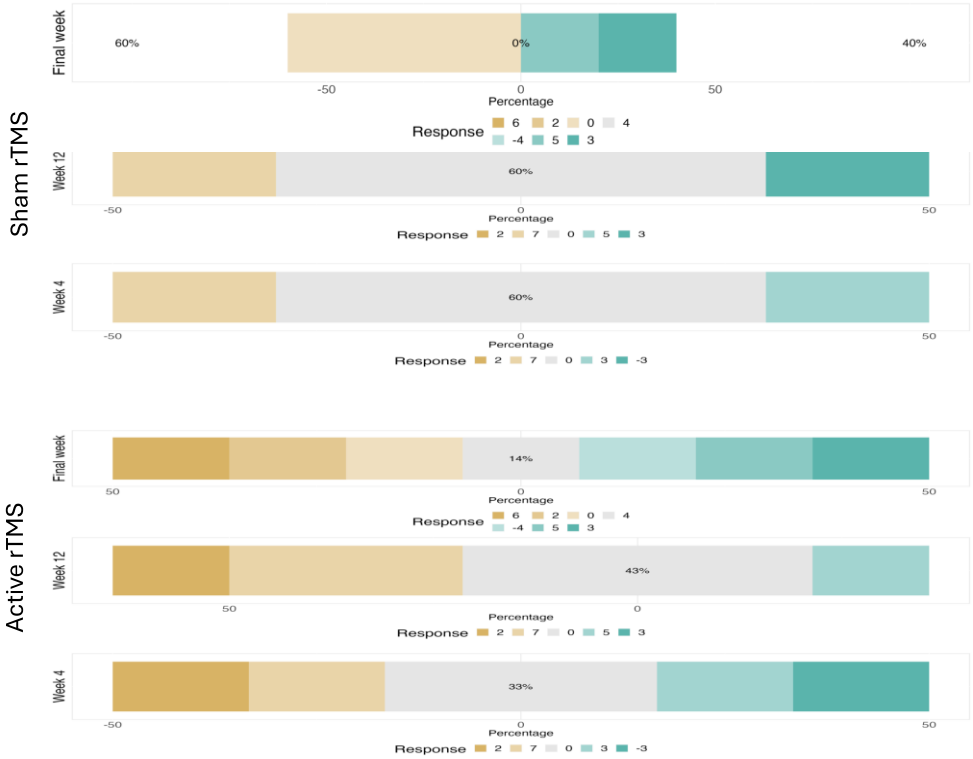


Figure 3.3: Mean pain intensity (NPRS) scores reported weekly by participants in the sham and active rTMS groups. Note. W: week.

3.2.2 Measure of Patient's Perceived Response to Treatment

The evaluation of the patients' perceived response to treatment was conducted using descriptive statistics, and the findings are shown using a Likert plot (Figure 3.4). Participants in the sham rTMS group exhibited a relatively stable pattern, with certain individuals reporting feeling a great deal better initially (at week 4); however, the overall perception of improvement did not increase over time. Three participants in this group reported feeling "About the same" (60% in week 4, 12, and the final week). Other ratings of improvement by participants receiving sham rTMS included feelings of "A very great deal better" (n = 1; 20% in week 4 and 12) and "Somewhat better" (n = 1; 20% in weeks 4 and 12 and the final week). At the final week, only one (20%) participant in sham rTMS group reported feeling "Quite a bit better." Participants receiving active rTMS displayed greater variability in their responses, with some experiencing varying levels of improvement and others reporting worsening conditions over time. In week 4, two (33%) participants reported feeling "About the same," three (43%) in week 12, and only one

(14%) in the final week. All seven participants (14.3% per responses) in active rTMS group reported a range of responses from feeling "A great deal better" to "Moderately worse" in the final week. To summarize, there was no consistent trend in the patient-reported improvement or worsening of symptoms in this study.



Responses	Description
-7	A very great deal worse
-6	A great deal worse
-5	Quite a bit worse
-4	Moderately worse
-3	Somewhat worse
-2	A little bit worse
-1	A tiny bit worse (almost the same)
7	A very great deal better
6	A great deal better
5	Quite a bit better
4	Moderately better
3	Somewhat better
2	A little bit better
1	A tiny bit better (almost the same)
0	About the same

Figure 3.4: A Likert Plot of the Proportion of Participants who reported perceived response to treatment in both groups.

3.2.3 Conclusion

Chapter 3 presents the qualitative and quantitative findings addressing the four research objectives (feasibility, tolerability, safety, and potential efficacy of combined active or sham M1-rTMS and CJI interventions) of this thesis. The study protocol was feasible, with a high rTMS session and follow-up assessment completion rate. However, the

recruitment rate was low, with a low screening-to-enrolment rate. The participants tolerated the intervention well and reported no major adverse effects. Participants in both treatment groups reported only mild and transient side effects. Finally, no statistically significant effect of group, time, or group-time interaction was observed for the secondary outcome measures of pain intensity, stress, anxiety, depression, disability, pain severity, or interference. A statistically significant effect of the group-time interaction was observed for the PCS and MCS scores, as well as a significant effect of time on the MCS score in the sham rTMS group. Chapter 4 presents the discussion, limitations, recommendations for future research directions, and conclusions.

Chapter 4

4 Discussion

This thesis examined the feasibility, tolerability, safety, and potential efficacy of combining rTMS as an adjunct therapy with CJI as a novel approach for managing CAP. A total of 11 sessions of active/sham M1-rTMS were conducted across 12 weeks with another 12-week follow-up period or until the participants' next scheduled CJI appointment was completed. As this was a feasibility study, it was important to determine the viability of the recruitment strategy, methodology, and data collection methods to inform the design of a future full-scale trial. Moreover, obtaining an estimate of the proportion of individuals that should be screened to successfully enroll one participant would enable us to estimate the time and resources required for optimal subject recruitment within a specified timeframe.

The first objective of feasibility was assessed in terms of screening-to-enrollment rate, drop-out rate, rTMS session completion, follow-up assessment completion rate, success of participant, and assessor blinding. Initially, the study aimed to recruit 40 participants within a 7-month timeframe, however, the recruitment rate was below the threshold that was retrospectively deemed achievable within the study timeframe because many patients did not meet the eligibility criteria for the study or refused to participate. The low recruitment rate is consistent with findings from Dalton et al. (2018), who had a longer recruitment period of approximately two years, but still had to make changes to their intended sample size (from 44 to 30), as many of their potential population did not meet the inclusion criteria due to contraindications to rTMS. Those who were eligible but declined to participate provided reasons such as distance, time commitment, and financial limitations. It is noteworthy that many of those who showed interest in our study were above 50 years of age and either did not work full-time or were retired. Patients younger than 50 years often declined to participate for reasons such as conflict with work schedule, which is stated as time commitment. Distance to the research facility was also a deterrence, as many patients were attending the pain clinic outside of their residential cities.

Although the recruitment rate was low, the enrolled participants found the study protocol feasible with a low dropout rate of 20%. The dropout rate was consistent with that reported in other rTMS studies in CAP populations (Ambriz-Tututi et al., 2016; Freigang et al., 2021). Only one participant in the active rTMS group dropped out because of side effects associated with rTMS. The participant was unable to continue treatment as restless legs syndrome (RLS) worsened their sleep quality. This was unexpected since no other study has reported worsening of RLS with rTMS. Conversely, HF-rTMS has been shown to have a positive effect on RLS symptoms (Altunrende et al., 2014; Lin et al., 2015; Liu et al., 2015). However, it is important to note that these studies delivered fewer pulses (600 – 1000 pulses) and targeted the leg motor cortex, whereas this study targeted the hand motor cortex and delivered 2000 pulses. Altunrende et al. (2014) performed a total of ten sessions of rTMS once every three days, Liu et al. (2015) did daily sessions of rTMS for 14 consecutive days, and Lin et al. (2015) performed a total of 14 sessions (daily for 5 consecutive, paused for 2 days, daily sessions for 4 days, paused for another 2 days and then a final round of daily sessions for 4 days). Despite differing protocols, none of these studies reported adverse effects of rTMS. A possible explanation for the worsening of RLS symptoms could be the longer pulses delivered (2000 pulses) and the different stimulation targets (FDI) in this study. Despite this, worsening of RLS symptoms could have occurred as a result of something unrelated to rTMS, therefore, further research is needed to explore this finding.

Adherence to the intervention and assessments was high, with over 90% of the sessions and assessments completed in both groups. A small number of sessions were missed by participants owing to having a prior scheduled trip and/or conflict with a public holiday, while those that missed the weekly assessments preferred contact by phone rather than going through the generated data collection link. Other feasibility studies have also reported high adherence rates to rTMS interventions (Pick et al., 2020). Pick et al. (2020) reported a high rate of outcome assessments completion between 90-100%. Although this study assessed the completion rate for only one outcome measure (NPRS), they assessed the completion rate for all the outcome measures (12 in total) used in the study. The decision to only assess the completion of one outcome measure was to determine barriers to participants' completion of the assessment when not in the research facility.

The final feasibility indicator was the success of participant blinding, which was found to be successful as there was no statistically significant difference between the groups in correctly identifying their group allocation. Those who guessed that they received active treatment and were accurate attributed it to experiencing improvement in their pain either because they needed a reduced medication regimen or felt that their pain was generally better. One participant, who correctly guessed that they were in the sham group, commented that they did not experience any benefit. About 42% of the participants reported not being sure which treatment group they had been assigned to, as their condition did not necessarily improve or worsen. However, one participant dropped out of the study because they were unblinded to their treatment allocation. This was an oversight of the research team, and not because of the failure of the blinding protocol. Measures were implemented following the event to avoid recurrence. Assessor blinding was also successful as the assessor was unable to tell which participants were receiving the active or sham treatment because the sham coil did not feel or look different from the active coil. In addition, having an independent party switch the coil, while the administrator/assessor stepped out of the room, made blinding effective. Dalton et al. (2018) applied a similar protocol of using a sham coil that produced the same sound and feels exactly like the active coil, however no active stimulations were delivered. Although they did not assess the success of blinding in their feasibility trial, there were no dropouts owing to unblinding. In this study, unblinding of the administrator occurred for the first participant because the sham coil had a scratch on it, which made it easy to distinguish between the coils. A decision was made to conceal this scratch with paper taped to both the active and sham coils before beginning the rTMS treatment. The blinding protocol used in this study was effective as it allowed simultaneous blinding of the administrator, who also assessed and analyzed the data collected. Often, rTMS studies have had to use an administrator not involved in data analysis to ensure the blinding of assessors (Freigang et al., 2021; Ambriz-Tututi et al., 2016).

The second objective was to assess the tolerability of the combined intervention. This was done by asking the participants to rate the tolerability of the treatment after each session. The number of times the participants requested to pause the intervention due to discomfort was also noted as a measure of intolerability. Ninety-two percent of the

participants in both treatment groups found the treatment tolerable (5/5) and did not need to pause or discontinue the intervention. One participant in the active rTMS group experienced neck soreness in the fourth and tenth rTMS sessions, and rated tolerability as 4/5 and 3/5, respectively. The ratings were still above the threshold (median of 3/5) for the predicted tolerability indicators. rTMS to the hand motor cortex has been demonstrated to be well tolerated and safe when used within safety guidelines (Rossi et al., 2009). The absence of major adverse effects is often considered evidence of tolerability. For instance, a review of the literature by Galhardoni et al. (2015) of double-blinded, controlled studies supports the tolerability of rTMS, which produces significant pain relief without any major adverse effects. Notably, this is the first study assessing tolerability on a scale from 1 to 5, where a rating of three is considered neutral, balancing negative and positive experiences. Participants were also informed that they might experience some discomfort, but they were usually manageable. This realistic expectation can enhance participants' adherence and satisfaction, as they are less likely to be caught off guard or discouraged by minor discomfort.

The third objective was safety, which was assessed by the number, severity, and duration of adverse effects reported. The participants were also asked before every session to report any adverse effects that occurred following their previous session in order to monitor the progression of side effects. No major adverse effects were observed in this study. Sufficient evidence supports the safe use of rTMS. Some minor side effects are expected with rTMS use, such as transient headaches or local pain around the stimulation site (Rossi et al., 2009). Studies using active rTMS in patients with CAP have not reported major adverse effects, with the exception of some common mild side effects. For instance, one study reported acute headaches in the active rTMS group (Ambriz-Tututi et al., 2016). Interestingly, a participant in the sham rTMS group, who frequently suffered from headaches, consistently reported feeling relief from headaches after every treatment session. However, this effect was transient. In addition, as observed in this study, scalp discomfort was reported by participants in the active rTMS group during stimulation. A systematic review on the safety of rTMS in depression found that headache and pain at the stimulation site were most common, possibly due to scalp or upper facial muscle contractions by rTMS (Loo et al., 2008). The side effect of jaw discomfort is consistent

with that found by Säisänen et al. (2022) using combined 10 and 20 Hz rTMS protocols targeting the face motor area in patients with chronic facial pain. They found the 10 Hz rTMS protocol to be more tolerable, resulting in fewer side effects than the 20 Hz protocol. In contrast, they utilized the lower face hotspot and a higher stimulation intensity (90% of rMT), which could have accounted for discomfort in the jaw. A possible explanation for the jaw discomfort reported in this study could be the unintentional activation of sensory nerve fibers innervating the facial muscles during stimulation. Moreover, one participant reported signs of heightened emotional state after the first week of rTMS treatment. This participant reported experiencing negative experiences due to personal reasons during this time and reported feeling more emotional than usual and associated this with the rTMS. There is evidence that patients undergoing treatment for depression with rTMS have also exhibited acute mania and hypomania, but it is uncertain whether these psychiatric changes are attributed to rTMS or are a result of their existing psychiatric conditions (Xia et al., 2008). Although the participant did not mention these side effects explicitly, it is uncertain whether the cause of the heightened emotions was related to the use of rTMS, as it was only reported by a single participant who was receiving active rTMS. Furthermore, a study by Mhalla et al. (2011) reported transient dizziness in one participant in an active rTMS group. This is consistent with our observation of light-headedness reported by one participant in the active rTMS group. Although the exact mechanisms causing light-headedness are unclear, it is possible that the influence of M1-rTMS on neuronal activity could potentially interfere with brain areas involved in balance regulation and spatial orientation, leading to light-headedness (Thut & Pascual-Leone, 2020). Neck soreness was also reported by the participants in both treatment groups (one in the sham rTMS group and two in the active rTMS group). This was attributed to the weight of the coil and pressure applied by the administrator. To manage this discomfort during stimulation, the participants were informed that they could take breaks during the session to stretch and adjust as needed. Finally, one participant reported experiencing a slight rash due to the surface electrodes used, which was temporary and resolved by the next session. The participant reacted to the adhesive residue of the electrode, after which the adhesive residue from the electrode was completely wiped at the end of each session. Overall, many reported side effects were

mild and transient, mostly during stimulation. In this study, rTMS safety screening was utilized to mitigate any serious adverse events, as recommended for studies using rTMS (Rossi et al., 2009).

The effectiveness of the combined intervention was explored as a secondary focus of this study, and all reported effects are preliminary due to the limited sample size, resulting in underpowered analyses. The results of the repeated-measures ANOVA revealed no statistically significant differences in the assessed outcomes (pain intensity, stress, anxiety, depression, pain severity, interference, and disability) across the measured time points and between the active and sham rTMS groups. However, there was a significant effect of time and group-time interaction on the MCS scores in the sham rTMS group only at week 4. This improvement in the sham group could be attributed to the placebo effect. Participants receiving sham treatment might have experienced psychological benefits from simply believing they were receiving the active intervention, leading to reported improvements in their mental health status.

While the pain-relieving effects of M1-rTMS in chronic pain conditions have been demonstrated, evidence for its benefits in CAP is limited. Three studies explored the use of rTMS in patients with CAP (Ambritz-Tututi et al., 2016; Freigang et al., 2021; Johnson et al., 2006). Johnson et al. (2006) demonstrated foundational insights into the mechanistic aspects of rTMS through its effects on sensory processing and pain threshold in patients with LBP. The ability of rTMS to modulate sensory processing and pain perception has laid the groundwork for the potential benefits of rTMS in CAP. They found that a single session of rTMS reduced brief pain scores by 1.23 points (from 4.35/10 pre-treatment to 3.12/10 post-treatment; $p < 0.001$). However, they did not investigate the duration of pain relief or the effects of multiple sessions in this population. Ambriz-Tututi et al. (2016) assessed the effect of repeated sessions of rTMS over an extended period using the same rTMS parameters and found that one week of 20 Hz rTMS applied to the left M1 hand area can decrease pain perception. The group that received active rTMS experienced significant reduction in the visual analogue scale of 80% from the baseline score by the third week, and the Short Form McGill pain scores (23.2 ± 2.5 before treatment to 8.3 ± 1.5 after treatment, $p < 0.05$) by the fourth week of

treatment. However, no reduction was observed in the sham group. This finding suggests that rTMS could be used as a therapeutic option for CAP, however caution should be exercised when interpreting the results. Participants knew that they were receiving active rTMS, and the positive findings could be attributed to treatment expectancy (placebo) effects. Patients receiving pain therapy are prone to placebo effects, especially in brain stimulation research, where the attention-drawing clicking sound of the TMS coil could take participants' focus off their pain, resulting in alterations in their subjective pain assessments (Colloca, 2019). In addition, patients' beliefs and expectations about treatment can trigger real physiological changes in the brain, mimicking the effects of an actual treatment (Benedetti et al., 2003).

Freigang et al. (2021) expanded the understanding of target specificity in rTMS treatment for CLBP, emphasizing the comparative effectiveness of DLPFC to M1 stimulation. Using the same parameters as Ambriz-Tututi et al. (2016), they conducted a 36-week long study comparing the effects of 13 sessions of 20 Hz M1-rTMS and 5 Hz DLPFC-rTMS in patients with non-specific CLBP. Their findings revealed that the DLPFC group experienced a more cumulative analgesic effect with repeated sessions than the M1-group. Although there was a reduction in the NPRS score in both groups, the M1-group failed to show a lasting effect and the pain relief was limited to the within-session period. The DLPFC group continued to show a reduction in their NPRS score, even at later sessions, suggesting a cumulative analgesic effect of DLPFC-rTMS stimulation. It is worth noting that in the study by Ambriz-Tututi et al. (2016), the sample size was larger (n = 28), while this study had a smaller sample size (n = 11) in the M1-rTMS group. The lack of similar findings can also be attributed to this. Additionally, the DLPFC group experienced improved health-related quality of life (from moderate at baseline to normal by the 4th and 36th week of stimulation), and their mental composite scores (MCS) were higher than the M1-group (MCS score increase to 49.12 in the DLPFC group and 39.46 in the M1-group). These results suggest that targeting the DLPFC may be more effective than targeting the M1 in reducing pain perception and improving health-related quality of life. Further studies are necessary to confirm these findings.

This study utilized rTMS parameters different from those employed in previous research in the CAP population. In contrast to the aforementioned studies, which used 20 Hz rTMS, this study utilized 10 Hz rTMS and a lower intensity of 85% of rMT. Originally, the study protocol used an intensity of 95% of rMT, however, during pilot testing on healthy individuals, some experienced discomfort due to facial twitching at this intensity. Since tolerability is an objective of this study, the intensity was reduced to a more tolerable level of 85% of rMT prior to administering the treatment to the participants. The 10 Hz frequency was selected based on prior research in neuropathic and other chronic pain conditions, such as fibromyalgia and migraine, which demonstrated a significant reduction in pain perception (Mhalla et al., 2011). A systematic review of rTMS use in various neuropathic pain conditions found that the most effective stimulation parameters for inducing analgesia were frequencies between 10-20 Hz, intensities of 80-120% of rMT, 1000-2000 pulses, and 5-10 sessions while targeting M1 (K.L. Zhang et al., 2021). Currently, there is no consensus on the optimal rTMS parameters required to achieve long-lasting analgesic effects in CAP. This study was unable to demonstrate that multiple sessions of active M1-rTMS significantly reduced pain perception, severity, interference, and disability, as there were no statistically significant effects of group (active vs. sham rTMS), time (sessions), or group-time interaction on these secondary outcome measures. It is not possible to draw a definitive conclusion regarding the effectiveness of this combined intervention, as the sample size was insufficient to determine the true treatment effect. One must also consider the possibility that the absence of clinical improvement following rTMS treatment may be attributed to the fact that these patients primarily experience peripheral pain drivers rather than central drivers or sensitization. In other words, pain originating from facet-mediated sources may possess a substantial peripheral component that is not directly influenced by rTMS stimulation of the hand motor hotspot, resulting in the absence of therapeutic benefits.

In addition, rTMS alone is insufficient as an intervention for CAP. Li et al. (2024) compared the effect of a combined intervention of rTMS and sling exercise (SE) to rTMS alone and SE alone on pain intensity (NPRS) and disability (ODI) in patients with CLBP by stimulating the trunk muscles. They found that the combined intervention showed significant effects of time on pain intensity ($p = 0.000$) and disability ($p = 0.002$) scores

compared with rTMS alone. However, this did not demonstrate superiority over SE alone. Although our findings are not consistent with theirs, the combined intervention of rTMS and CJI is a potentially more beneficial approach than CJI alone and rTMS alone for CAP. Combining interventions allows for the optimization of treatment strategies. CJI induces motor cortical plasticity through a bottom-up pathway through the production of inflammatory mediators, resulting in a reduction of inflammation in the joints (Lee et al., 2016), whereas rTMS induces motor cortical plasticity through a top-down pathway by modulating cortical excitability and remote impact on brain areas involved in pain perception (Massé-Alarie et al., 2018). It has been proposed that one intervention would have a priming effect, thereby enhancing the sensitivity of the brain to subsequent interventions (Li et al., 2024; Schabrun & Chipchase, 2012). For the priming effect, there is no evidence to suggest which order of intervention is more favorable for clinical outcomes. It is unclear whether rTMS before CJI is more beneficial than if it is performed first. In a study by Li et al. (2024), participants underwent sling exercises immediately followed by rTMS in the first week and alternated it in the second week. Future studies should investigate the order of intervention that is most beneficial.

Furthermore, as indicators of the preliminary effectiveness of the combined intervention, participants' global perceived response to treatment was assessed using a 15-point Global Rating of Change (GRC) scale. Stratford et al., (1994) claimed that an important improvement in the 15-point GRC is a score of 5 (quite a bit better), while a score of -5 (quite a bit worse) is deterioration. Clinically, patients with lower scores tend to seek more treatment. The results of the GRC suggest that the participants in the sham rTMS group perceived their condition to be more stable, whereas those in the active rTMS group perceived their condition to be more variable, with some experiencing improvements (71.4%) and others experiencing worsening (14.2%) over time. It was anticipated that those that would benefit from the combined interventions would need to move their next CJI appointment further back, indicating a longer duration of pain relief. However, participants in the active rTMS group reported varying levels of improvement (71.4%) and went on to get their next scheduled CJI before the final follow-up assessment (week 24). Interestingly, one participant in the active rTMS group who completed follow-up at week 22 reported not receiving steroids at their CJI appointment

but instead was informed by the physician that only a local anesthetic should be administered. This participant reported feeling “A great deal better” at this time point. It is noteworthy that only this participant provided this feedback, and no other participant was interviewed or contacted after the completion of the CJI appointment. It might be necessary for future studies to conduct a final interview session even after the participants receive their next scheduled CJI.

4.1 Strengths and Limitations

This thesis explores an innovative treatment paradigm that combines rTMS with standard treatments. The study design was a double-blind randomized controlled trial in which placebo effects were controlled. Neuronavigated rTMS was used in this study to accurately localize the stimulation target and easily reposition the coil during sessions. Outcome measures were also used to detect important clinical effects, such as the impact of treatment on disability, health-related quality of life, and emotional dimensions of pain.

One limitation of this study was the small sample size, with only 16 participants being recruited. This may limit the amount of data collected and the ability to determine a statistically significant difference between treatment groups. Therefore, the findings of this study should be considered as preliminary. Additionally, there were administrative delays with ethics approval and the clinic, which shortened the recruitment period. Furthermore, this feasibility study was part of a larger study, which narrowed the inclusion criteria and number of potential participants for this specific study. Moreover, recruitment was only performed from one pain clinic in London, Ontario, and patients from outside London were less likely to consent for the study.

Second, there were limitations to the rTMS protocol and outcome measures utilized. No qualitative interviews were conducted to assess the tolerability. Although participants were asked to report tolerability on a scale of 1-5, there was no standard follow-up interview to determine what participants considered intolerable. Additionally, there was no stratification in randomization based on the duration and location of pain, injection

type, site of injection, age, and gender. These confounding variables may introduce inconsistencies in treatment effects. Furthermore, only one specific set of rTMS parameters and stimulation targets was used in this study. These findings cannot be generalized to other rTMS parameters that have not yet been explored. Finally, the administration of rTMS may impose an additional burden on participants, particularly those who work full time or have familial obligations, thus hindering their ability to participate in the study. It is important to note that studies employing rTMS for pain management typically recommend multiple consecutive sessions during the initial two weeks to optimize the analgesic effects of rTMS, which are then maintained through subsequent maintenance sessions.

4.2 Future Directions

Future research can use similar methodologies adopted in this thesis to further explore the potential effectiveness of combined rTMS and CJI interventions. A larger sample size is required to determine the statistical significance between the treatment groups. In addition, researchers can explore the mechanism behind how approaching CAP from both a central and peripheral perspective can produce synergistic effects and, in turn, long-term pain relief.

Future research can address some of the limitations of this thesis, such as barriers to recruitment. I recommend recruitment from more than one pain clinic and extending the recruitment period to ensure adequate time for recruitment. Since the study protocol is extensive, I recommend that most of the recruitment be done in the warmer months, as more patients will be more willing to take part in the study. Additionally, I recommend having a dedicated clinical research coordinator (CRC) to recruit patients in the clinic. This person will have fewer commitments and will be able to be at the clinic all day to approach patients. Also, it is important to have a standard protocol of involving patients in research. The pain clinic can work alongside researchers to design a consent form for all patients, and those who are interested in research will give consent to be contacted, and those who decline to sign will be opted out. Having this consent form will allow the CRC to build a database of patients who are more likely to participate in the research.

This will also save resources, as the recruiter will not need to go to the clinic on days when all patients have opted out of participating in the research. Moreover, educating and incentivizing healthcare professionals on the importance of research will allow them to be more willing to advise their patients to consider ongoing clinical trials.

Furthermore, future research could explore different orders of combining interventions. In this thesis, participants received their CJI as scheduled and were then recruited to participate in the study within 1-4 weeks of their injection. It would be worthwhile to explore administering rTMS on the same day as the CJI, either before or after the CJI. Also, it will be worthwhile to have the rTMS device at the same site as the CJI is being done. Some patients might be interested in participating in the research but are not willing to make a trip to a different location to get the rTMS.

4.3 Conclusion

In conclusion, this thesis aimed to examine the feasibility, tolerability, safety, and preliminary efficacy of integrating rTMS with CJI in treating CAP. This was a pioneering attempt to reshape the therapeutic strategies for this persistent ailment. Based on this research study, I can confidently state that this combined intervention appears to be safe and well-tolerated, with high session and assessment completion rates. The results showed no major adverse effects and patients reported no significant discomfort during the treatment process. Despite these positive findings, the study faced challenges with a low screening-to-enrollment rate, suggesting barriers to participation. Various factors, including distance, time commitment, recruiter availability, recruitment during cold weather months, and prolonged ethics approval process, contributed to this low recruitment rate. Additionally, although no statistical significance was found in most of the secondary outcome measures between the treatment groups, this may largely be attributed to an insufficient sample size rather than the ineffectiveness of the intervention itself. It is imperative for subsequent research to increase the number of participants and possibly extend follow-up durations to better evaluate the potential clinical efficacy and long-term benefits of this combined therapy approach. The potential clinical implications of this combined approach are numerous and complex, as it can offer improved pain

relief by targeting both central and peripheral mechanisms of CAP. With more effective long-term pain relief, patients can expect better mobility, less disability, and higher quality of life. This approach can also lead to lower healthcare costs for CAP patients, as they will no longer require as many CJI procedures, thus reducing the strain on the healthcare system. This study, with a sufficient sample size, can also add to the body of evidence on the efficacy of the rTMS protocol employed in this research in reducing CAP. Additionally, with proper stratification in the randomization process, it may be possible to identify those individuals who will respond better to the combined intervention.

References

Abbott, R., & Lavretsky, H. (2013). Tai chi and qigong for the treatment and prevention of mental disorders. Psychiatric Clinics of North America, 36, 109-119.

Ambriz-Tututi, M., Alvarado-Reynoso, B., & Drucker-Colín, R. (2016). Analgesic effect of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic low back pain. Bioelectromagnetics, 37(8), 527–535.

Ameli, M., Grefkes, C., Kemper, F., Riecker, A., Kiebel, S., Huber, W., ... & Nowak, D. A. (2009). Repetitive transcranial magnetic stimulation for rehabilitation of central motor disorders. Clinical Neurophysiology, 120(7), 1401-1413.

Altunrende, B., Yildiz, S., Cevik, A., & Yildiz, N. (2014). Repetitive transcranial magnetic stimulation in restless legs syndrome: preliminary results. *Neurological Sciences*, *35*(7), 1083-1088.

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., & Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. The Journal of Neuroscience, 24(46), 10410–10415.

Aptiva Health. (n.d.). Facet joint injections. Retrieved from https://www.aptivahealth.com/facet-joint-injections

Arle, J. E., & Shils, J. L. (2008). Motor cortex stimulation for pain and movement disorders. Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics, 5(1), 37–49.

Asci, F., Di Stefano, G., Di Santo, A., Bianchini, E., Leone, C., La Cesa, S., Zampogna, A., Cruccu, G., & Suppa, A. (2023). Pain-motor integration in chronic pain: A neurophysiological study. *Clinical Neurophysiology*, *154*, 107-115.

Bailey, A. (2009). Risk factors for low back pain in women: Still more questions to be answered. Menopause, 16(3-4).

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *23*(10), 4315–4323.

Bender, T., Nagy, G., Barna, I., Tefner, I., Kádas, E., & Géher, P. (2007). The effect of physical therapy on beta-endorphin levels. European Journal of Applied Physiology, 100, 371–382.

Berlim, M. T., Broadbent, H. J., & Van den Eynde, F. (2013). Blinding integrity in randomized sham-controlled trials of repetitive transcranial magnetic stimulation for major depression: a systematic review and meta-analysis. The international journal of neuropsychopharmacology, 16(5), 1173–1181.

Bogduk, N. (2005). A narrative review of intra-articular corticosteroid injections for low back pain. Pain Medicine, 6(4), 287–296.

Busch, A. J., Barber, K. A., Overend, T. J., Peloso, P. M. J., & Schachter, C. L. (2007). Exercise for treating fibromyalgia syndrome. Cochrane Database of Systematic Reviews, (4), CD003786.

Bushnell, M. C., Čeko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*, *14*(7), 502-511.

Campbell, F., Hudspith, M., Choinière, M., El-Gabalawy, H., Laliberté, J., Sangster, M. (2020). Working together to better understand, prevent, and manage chronic pain: What we heard. A report by the Canadian Pain Task Force. Ottawa.

Carlesso, L. C., Macdermid, J. C., & Santaguida, L. P. (2010). Standardization of adverse event terminology and reporting in orthopaedic physical therapy: application to the cervical spine. The Journal of orthopaedic and sports physical therapy, 40(8), 455–463.

Carrera, G. F. (1980). Lumbar facet joint injection in low back pain and sciatica: preliminary results. Radiology, 137(3), 665–667.

Chang, M. C., & Lee, D. G. (2018). Outcome of transforaminal epidural steroid injection according to the severity of lumbar foraminal spinal stenosis. Pain Physician, 21, 67–72.

Chang, W.-J., Bennell, K. L., Hodges, P. W., Hinman, R. S., Young, C. L., Buscemi, V., Liston, M. B., & Schabrun, S. M. (2017). Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: A pilot randomised controlled trial. *PLOS ONE, 12*(6), e0180328.

Cherkin, D. C., Wheeler, K. J., Barlow, W., & Deyo, R. A. (1998). Medication use for low back pain in primary care. Spine, 23(5), 607–614.

Chou, R., Deyo, R., Friedly, J., Skelly, A., Hashimoto, R., Weimer, M., & Fu, R. (2017). Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine, 166(7), 493-505.

Cimmino, M. A., Ferrone, C., & Cutolo, M. (2011). Epidemiology of chronic musculoskeletal pain. Best Practice & Research Clinical Rheumatology, 25(2), 173–218.

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore, 23(2), 129-138.

Colloca, L. (2019). The placebo effect in pain therapies. Annual Review of Pharmacology and Toxicology, 59, 191–211.

Conforto, A. B., Amaro, E., Jr., Gonçalves, A. L., Mercante, J. P., Guendler, V. Z., Ferreira, J. R., Kirschner, C. C., & Peres, M. F. (2014). Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia, 34*(6), 464-472.

Dalton, B., Bartholdy, S., McClelland, J., Kekic, M., Rennalls, S. J., Werthmann, J., Carter, B., O'Daly, O. G., Campbell, I. C., David, A. S., Glennon, D., Kern, N., & Schmidt, U. (2018). Randomised controlled feasibility trial of real versus sham repetitive transcranial magnetic stimulation treatment in adults with severe and enduring anorexia nervosa: the TIARA study. BMJ Open, 8(7), e021531.

de Luca, K., Briggs, A. M., French, S. D., Ferreira, M. L., Cross, M., Blyth, F., & March, L. (2022). Disability burden due to musculoskeletal conditions and low back pain in Australia: findings from GBD 2019. *Chiropractic & manual therapies, 30*(1), 22.

Di Iorio, D. (2000). A Survey of Primary Care Physician Practice Patterns and Adherence to Acute Low Back Problem Guidelines. *Archives of Family Medicine, 9*(10), 1015-1021.

Dieleman, J. L., Cao, J., Chapin, A., Chen, C., Li, Z., Liu, A., Horst, C., Kaldjian, A., Matyasz, T., Scott, K. W., Bui, A. L., Campbell, M., Duber, H. C., Dunn, A. C., Flaxman, A. D., Fitzmaurice, C., Naghavi, M., Sadat, N., Shieh, P., Squires, E., … Murray, C. J. L. (2020). US Health Care Spending by Payer and Health Condition, 1996-2016. *JAMA, 323*(9), 863–884.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D.,

Manning, D. C., Martin, S., … IMMPACT (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 113(1-2), 9–19.

Edmond, S. L., & Felson, D. T. (2000). Prevalence of back symptoms in elders. Journal of Rheumatology, 27, 220–225.

el-Khoury, G. Y., & Renfrew, D. L. (1991). Percutaneous procedures for the diagnosis and treatment of lower back pain: Diskography, facet joint injection, and epidural injection. American Journal of Roentgenology, 157(4), 685–691.

Fairbank, J. C., Couper, J., Davies, J. B., & O'Brien, J. P. (1980). The Oswestry low back pain disability questionnaire. Physiotherapy, 66(8), 271–273.

Fairbank JCT & Pynsent, PB. (2000). The Oswestry Disability Index. Spine, 25(22), 2940–2953.

Farrar, J. T., Young, J. P., Jr, LaMoreaux, L., Werth, J. L., & Poole, M. R. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain, 94(2), 149–158.

Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. The Journal of Pain, 14(12), 1539–1552.

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neuroscience letters*, *224*(1), 5–8.

Forogh, B., Haqiqatshenas, H., Ahadi, T., Ebadi, S., Alishahi, V., & Sajadi, S. (2021). Repetitive transcranial magnetic stimulation (rTMS) versus transcranial direct current stimulation (tDCS) in the management of patients with fibromyalgia: A randomized controlled trial. Neurophysiologie clinique = Clinical neurophysiology, 51(4), 339–347.

Fransen, M., McConnell, S., Harmer, A. R., Van der Esch, M., Simic, M., & Bennell, K. L. (2015). Exercise for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews, 2015*(1).

Freigang, S., Lehner, C., Fresnoza, S. M., Mahdy Ali, K., Hlavka, E., Eitler, A., Szilagyi, I., Bornemann-Cimenti, H., Deutschmann, H., Reishofer, G., Berlec, A., Kurschel-Lackner, S., Valentin, A., Sutter, B., Zaar, K., & Mokry, M. (2021). Comparing the impact of multi-session left dorsolateral prefrontal and primary motor cortex neuronavigated repetitive transcranial magnetic stimulation (nrTMS) on chronic pain patients. Brain Sciences, 11(8), 961.

Galhardoni, R., Aparecida da Silva, V., García-Larrea, L., Dale, C., Baptista, A. F., Barbosa, L. M., Menezes, L. M. B., de Siqueira, S. R. D. T., Valério, F., Rosi, J., Jr., de Lima Rodrigues, A. L., Reis Mendes Fernandes, D. T., Lorencini Selingardi, P. M., Marcolin, M. A., Duran, F. L. de S., Ono, C. R., Lucato, L. T., Fernandes, A. M. B. L., da Silva, F. E. F., … Ciampi de Andrade, D. (2019). Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain.

Galhardoni, R., Correia, G. S., Araujo, H., Yeng, L. T., Fernandes, D. T., Kaziyama, H. H., Marcolin, M. A., Bouhassira, D., Teixeira, M. J., & de Andrade, D. C. (2015). Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. Archives of physical medicine and rehabilitation, 96(4 Suppl), S156–S172.

Galletta, E. E., Rao, P. R., Barrett, A. M. (2011) Transcranial magnetic stimulation (TMS): potential progress for language improvement in aphasia. Top Stroke Rehabil. 18(2):87.

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological bulletin, 133(4), 581–624.

GBD 2021 Other Musculoskeletal Disorders Collaborators (2023). Global, regional, and national burden of other musculoskeletal disorders, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *The Lancet. Rheumatology*, *5*(11), e670–e682.

Giles, L. G., & Muller, R. (2003). Chronic Spinal Pain: A Randomized Clinical Trial Comparing Medication, Acupuncture, and Spinal Manipulation. Spine, 28, 1490-1502.

Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. Psychometrika, 24, 95–112.

Hahn, S. J., & Paik, N. J. (2015). Application of Non-invasive Brain Stimulation for Neurorehabilitation: Cerebellar Stimulation. Brain Neurorehabil, 8(2), 90-95.

Hansen, H.C., McKenzie-Brown, A. M., Cohen, S. P., Swicegood, J. R., Colson, J. D., Manchikanti, L. (2007). Sacroiliac joint interventions: a systematic review. Pain Physician. Jan;10(1):165-84.

Hepner, S., & Claxton, R. (2013). Anti-epileptic drugs for pain #271. Journal of palliative medicine, 16(7), 799–800.

Hilton, L., Hempel, S., Ewing, B. A., Apaydin, E., Xenakis, L., Newberry, S., Colaiaco, B., Maher, A. R., Shanman, R. M., Sorbero, M. E., & Maglione, M. A. (2017). Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Annals of Behavioral Medicine, 51*(2), 199-213.

Hirayama, A., Saitoh, Y., Kishima, H., Shimokawa, T., Oshino, S., Hirata, M., Kato, A., & Yoshimine, T. (2006). Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. PAIN®, 122(1-2), 22-27.

Hong, Y., Liu, Q., Peng, M., Bai, M., Li, J., Sun, R., Guo, H., Xu, P., Xie, Y., Li, Y., Liu, L., Du, J., Liu, X., Yang, B., & Xu, G. (2020). High-frequency repetitive transcranial magnetic stimulation improves functional recovery by inhibiting neurotoxic polarization of astrocytes in ischemic rats. *Journal of neuroinflammation*, *17*(1), 150.

Hoogendam, J. M., Ramakers, G. M., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain stimulation, 3(2), 95–118.

Hoy, D., March, L., Brooks, P., Blyth, F., Woolf, A., Bain, C., Williams, G., Smith, E., Vos, T., Barendregt, J., Murray, C., Burstein, R., & Buchbinder, R. (2014). The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(6), 968-974.

Jamison, R. N., Raymond, S. A., Slawsby, E. A., Nedeljkovic, S. S., & Katz, N. P. (1998). Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine, 23(23), 2591–2600.

Johnson, S., Summers, J., & Pridmore, S. (2006). Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain, 123(1-2), 187–192.

Kalichman, L., Li, L., Kim, D. H., Guermazi, A., Berkin, V., O'Donnell, C. J., Hoffmann, U., Cole, R., & Hunter, D. J. (2008). Facet Joint Osteoarthritis and Low Back Pain in the Community-Based Population. *Spine*, *33*(23), 2560-2565.

Kamper, S. J., Maher, C. G., & Mackay, G. (2009). Global rating of change scales: a review of strengths and weaknesses and considerations for design. *The Journal of manual & manipulative therapy*, *17*(3), 163–170.

Kavanaugh, T. E., Werfel, T. A., Cho, H., Hasty, K. A., & Duvall, C. L. (2016). Particle-based technologies for osteoarthritis detection and therapy. *Drug delivery and translational research*, *6*(2), 132–147.

Kim, S., & Park, H. Y. (2024). Update on Non-invasive Brain Stimulation on Stroke Motor Impairment: A Narrative Review. Brain Neurorehabil, 17(1), e5.

Lawson McLean, A., Frank, S., Zafar, N., Waschke, A., Kalff, R., & Reichart, R. (2018). Time course of the response to navigated repetitive transcranial magnetic stimulation at 10 Hz in chronic neuropathic pain. *Neurological Research*, *40*(7), 566-574.

Lee, D. G., Ahn, S. H., & Lee, J. (2016). Comparative effectivenesses of pulsed radiofrequency and transforaminal steroid injection for radicular pain due to disc herniation: a prospective randomized trial. Journal of Korean Medical Science, 31(8), 1324–1330.

Lefaucheur, J. P. (2016). Cortical Neurostimulation for Neuropathic Pain: State of the Art and Perspectives. Pain, 157, S81–S89.

Li, X., Lu, S., Ge, L., Li, Z., Chen, R., Zu, Y., Fu, R., Li, L., & Wang, C. (2024). Repetitive transcranial magnetic stimulation combined with sling exercise modulates the motor cortex in patients with chronic low back pain. Neuroscience, 545, 196–206.

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W.-S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*(7638), 481-487.

Lilius, G., Laasonen, E. M., Myllynen, P., Harilainen, A., & Gronlund, G. (1989). Lumbar facet joint syndrome. A randomised clinical trial. The Journal of Bone & Joint Surgery British Volume, 71(4), 681-684.

Lim, J. W., Cho, Y. W., Lee, D. G., & Chang, M. C. (2017). Comparison of intraarticular pulsed radiofrequency and intraarticular corticosteroid injection for management of cervical facet joint pain. Pain Physician, 20, E435–E444.

Lin, Y.-C., Feng, Y., Zhan, S.-Q., Li, N., Ding, Y., Hou, Y., Wang, L., Lin, H., Sun, Y., Huang, Z.-Y., Xue, Q., Wang, Y.-P. (2015). Repetitive transcranial magnetic stimulation for the treatment of restless legs syndrome. Chinese Medical Journal, 128(13), 1728-1731.

Lippitt, A. B. (1984). The facet joint and its role in spine pain. Management with facet joint injections. Spine, 9(7), 746–750.

Liu, C., Dai, Z., Zhang, R., Zhang, M., Hou, Y., Qi, Z., Huang, Z., Lin, Y., Zhan, S., He, Y., & Wang, Y. (2015). Mapping intrinsic functional brain changes and repetitive transcranial magnetic stimulation neuromodulation in idiopathic restless legs syndrome: a resting-state functional magnetic resonance imaging study. *Sleep Medicine*, *16*(6), 785-791.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour Research and Therapy, 33, 335–343.

Luo, J., Feng, Y., Li, M., Yin, M., Qin, F., & Hu, X. (2022). Repetitive Transcranial Magnetic Stimulation Improves Neurological Function and Promotes the Anti-inflammatory Polarization of Microglia in Ischemic Rats. Frontiers in cellular neuroscience, 16, 878345.

Loo, C. K., McFarquhar, T. F., & Mitchell, P. B. (2008). A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. International Journal of Neuropsychopharmacology, 11, 131–147.

MacMahon, P. J., Eustace, S. J., & Kavanagh, E. C. (2009). Injectable corticosteroid and local anesthetic preparations: a review for radiologists. *Radiology, 252*(3), 647–661. https://doi.org/10.1148/radiol.2523081929

Massé-Alarie, H., Neige, C., Bouyer, L. J., & Mercier, C. (2018). Modulation of Corticospinal Excitability of Trunk Muscles in Preparation of Rapid Arm Movement. *Neuroscience*, *369*, 231–241.

Malone, L. A., & Sun, L. R. (2019). Transcranial Magnetic Stimulation for the Treatment of Pediatric Neurological Disorders. Curr Treat Options Neurol, 21, 58.

Malfliet, A., Coppieters, I., Van Wilgen, P., Kregel, J., De Pauw, R., Dolphens, M., & Ickmans, K. (2017). Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. *European journal of pain (London, England)*, *21*(5), 769–786.

Malfliet, A., Kregel, J., Meeus, M., Roussel, N., Danneels, L., Cagnie, B., Dolphens, M., & Nijs, J. (2018). Blended-Learning Pain Neuroscience Education for People with Chronic Spinal Pain: Randomized Controlled Multicenter Trial. Physical therapy, 98(5), 357–368.

Melzack, R., Wall, P. D., Steptoe, A., & Wardle, J. (1994). Pain mechanisms: A new theory. In Psychosocial processes and health: A reader (pp. 112-131).

Meeus, M., Nijs, J., Van Oosterwijck, J., Van Alsenoy, V., & Truijen, S. (2010). Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind

randomized controlled trial. Archives of physical medicine and rehabilitation, 91(8), 1153–1159.

Manchikanti, L., Boswell, M. V., Singh, V., Pampati, V., Damron, K. S., & Beyer, C. D. (2004). Prevalence of facet joint pain in chronic spinal pain of cervical, thoracic, and lumbar regions. BMC Musculoskeletal Disorders, 5, 15.

Marks, R. C., Houston, T., & Thulbourne, T. (1992). Facet joint injection and facet nerve block: a randomized comparison in 86 patients with chronic low back pain. Pain, 49(3), 325–328.

Mathew, J., & Danion, F. R. (2018). Ups and downs in catch-up saccades following single-pulse TMS-methodological considerations. *PloS one*, *13*(10), e0205208.

McCarron, R. F., Wimpee, M. W., Hudkins, P. G., & Laros, G. S. (1987). The inflammatory effect of nucleus pulposus: A possible element in the pathogenesis of low-back pain. Spine (Phila Pa 1976), 12(8), 760–764.

McPhee, M. E., & Graven-Nielsen, T. (2019). Recurrent low back pain patients demonstrate facilitated pronociceptive mechanisms when in pain, and impaired antinociceptive mechanisms with and without pain. *Pain*, *160*(12), 2866–2876.

Meeus, M., Nijs, J., Van Oosterwijck, J., Van Alsenoy, V., & Truijen, S. (2010). Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Archives of physical medicine and rehabilitation*, *91*(8), 1153–1159.

Merskey, H., & Bogduk, N. (1994). Classification of chronic pain. In H. Merskey & N. Bogduk (Eds.), Descriptions of Chronic Pain Syndromes and Definition of Pain Terms (2nd ed., pp. 180–181). Seattle: IASP Press.

Meucci, R. D., Fassa, A. G., & Faria, N. M. (2015). Prevalence of chronic low back pain: systematic review. *Revista de saude publica*, *49*, 1.

Mhalla, A., Baudic, S., de Andrade, D. C., Gautron, M., Perrot, S., Teixeira, M. J., Attal, N., & Bouhassira, D. (2011). Long-term maintenance of the analgesic effects of

Millan, M. J. (2002). Descending control of pain. Progress in Neurobiology, 66(6), 355–474.

Moore, R. A., Derry, S., Makinson, G. T., & McQuay, H. J. (2005). Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports. Arthritis Research & Therapy, 7(3), R644–R665.

Monticone, M., Ambrosini, E., Vernon, H., Rocca, B., Finco, G., Foti, C., & Ferrante, S. (2018). Efficacy of two brief cognitive-behavioral rehabilitation programs for chronic neck pain: Results of a randomized controlled pilot study. European Journal of Physical and Rehabilitation Medicine, 54(6), 890-899.

Moseley G. L. (2005). Widespread brain activity during an abdominal task markedly reduced after pain physiology education: fMRI evaluation of a single patient with chronic low back pain. *The Australian journal of physiotherapy*, *51*(1), 49–52.

Navani, A., Manchikanti L., Albers S.L., Latchaw R.E., Sanapati J., Kaye, A.D., Atluri, S., Jordan, S., Gupta, A., Cedeno, D., Vallejo, A., Fellows, B., Knezevic, N.N., Pappolla, M., KD, Bakshi S., Benyamin, R.M., Vallejo, R., Watanabe, A., Beall, D., Stitik, T.P., Foye, P.M., Helander, E.M., Hirsch, J.A. (2019). Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. Jan;22(1S): S1-S74.

Nilges, P., & Essau, C. (2015). Die Depressions-Angst-Stress-Skalen: Der DASS--ein Screeningverfahren nicht nur für Schmerzpatienten [Depression, anxiety and stress scales: DASS--A screening procedure not only for pain patients]. Schmerz (Berlin, Germany), 29(6), 649–657.

Obermann, M., Nebel, K., Schumann, C., Holle, D., Gizewski, E. R., Maschke, M., Goadsby, P. J., Diener, H. C., & Katsarava, Z. (2009). Gray matter changes related to chronic posttraumatic headache. Neurology, 73(12), 978–983.

Olmarker, K., Blomquist, J., Strömberg, J., Nannmark, U., Thomsen, P., & Rydevik, B. (1995). Inflammatogenic properties of nucleus pulposus. Spine (Phila Pa 1976), 20(6), 665–669.

Olmarker, K., & Rydevik, B. (1991). Pathophysiology of sciatica. Orthopedic Clinics of North America, 22(2), 223–234.

Pagels, A. A., Söderkvist, B. K., Medin, C., Hylander, B., & Heiwe, S. (2012). Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health and quality of life outcomes, 10, 71.

Paley, C. A., & Johnson, M. I. (2016). Physical activity to reduce systemic inflammation associated with chronic pain and obesity: A narrative review. The Clinical Journal of Pain, 32(4), 365-370.

Park, J., Engstrom, G., Tappen, R., & Ouslander, J. (2015). Health-Related Quality of Life and Pain Intensity Among Ethnically Diverse Community-Dwelling Older Adults. *Pain management nursing: official journal of the American Society of Pain Management Nurses*, *16*(5), 733–742

Passard, A., Attal, N., Benadhira, R., Brasseur, L., Saba, G., Sichere, P., Perrot, S., Januel, D., & Bouhassira, D. (2007). Effects of unilateral repetitive transcranial

magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain : a journal of neurology*, *130*(Pt 10), 2661–2670.

Pati, N., Gupta, V., Mayasa, V., Velivela, S., & Hussain, M. A. (2017). Rethinking Chronic Pain Treatment with Opioids. Indian Journal of Pharmaceutical Sciences, 79.

Peh, W. (2011). Image-guided facet joint injection. Biomed Imaging Interv J. Jan-Mar;7(1): e4.

Pezzetta, R., Gambarota, F., Tarantino, V., Devita, M., Cattaneo, Z., Arcara, G., Mapelli, D., & Masina, F. (2024). A meta-analysis of non-invasive brain stimulation (NIBS) effects on cerebellar-associated cognitive processes. Neuroscience and biobehavioral reviews, 157, 105509.

Pick, S., Hodsoll, J., Stanton, B., Eskander, A., Stavropoulos, I., Samra, K., Bottini, J., Ahmad, H., David, A. S., Purves, A., & Nicholson, T. R. (2020). Trial of neurostimulation in conversion symptoms (TONICS): a feasibility randomised controlled trial of transcranial magnetic stimulation for functional limb weakness. BMJ Open, 10(10), e037198.

Polly, D., Cher D, Whang PG, Frank C, Sembrano J. (2016). INSITE Study Group. Does Level of Response to SI Joint Block Predict Response to SI Joint Fusion? Int J Spine Surg.10:4.

Princeton Spine & Joint Center. (2016, September 22). Clinical anatomy of the lumbosacral spine. Neupsy Key. https://neupsykey.com/clinical-anatomy-of-the-lumbosacral-spine/

Radman, T., Ramos, R. L., Brumberg, J. C., & Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimulation, 2(4), 215–228.

Ribeiro, D. C., Milosavljevic, S., & Abbott, J. H. (2017). Effectiveness of a lumbopelvic monitor and feedback device to change postural behaviour: a protocol for the ELF cluster randomised controlled trial. BMJ open, 7(1), e015568.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology, 120, 2008–2039.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., Dimitrijević, M. R., Hallett, M., Katayama, Y., Lücking, C. H., Maertens de Noordhout, A. L., Marsden, C. D., Murray, N. M. F., Rothwell, J. C., Swash, M., & Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, *91*(2), 79-92.

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., Di Lazzaro, V., Ferreri, F., Fitzgerald, P. B., George, M. S., Hallett, M., Lefaucheur, J. P., Langguth, B., Matsumoto, H., Miniussi, C., Nitsche, M. A., Pascual-Leone, A., Paulus, W., Rossi, S., Rothwell, J. C., … Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *126*(6), 1071–1107.

Ruohonen, J., & Karhu, J. (2012). tDCS possibly stimulates glial cells. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *123*(10), 2006–2009.

Rutledge, T., Atkinson, J. H., Chircop-Rollick, T., D'Andrea, J., Garfin, S., Patel, S., Penzien, D. B., Wallace, M., Weickgenant, A. L., & Slater, M. (2018). Randomized controlled trial of telephone-delivered cognitive behavioral therapy versus supportive care for chronic back pain. The Clinical Journal of Pain, 34(4), 322.

Rydevik, B., Brown, M. D., & Lundborg, G. (1984). Pathoanatomy and pathophysiology of nerve root compression. Spine (Phila Pa 1976), 9(1), 7–15.

Saal, J. S., Franson, R. C., Dobrow, R., Saal, J. A., White, A. H., & Goldthwaite, N. (1990). High levels of inflammatory phospholipase A2 activity in lumbar disc herniations. Spine (Phila Pa 1976), 15(7), 674–678.

Säisänen, L., Huttunen, J., Hyppönen, J., Nissen, M., Kotiranta, U., Mervaala, E., & Fraunberg, M. V. U. Z. (2022). Efficacy and tolerability in patients with chronic facial pain of two consecutive treatment periods of rTMS applied over the facial motor cortex, using protocols differing in stimulation frequency, duration, and train pattern. Neurophysiologie Clinique = Clinical Neurophysiology, 52(2), 95–108.

Salerno, S. M., Browning, R., & Jackson, J. L. (2002). The effect of antidepressant treatment on chronic back pain: a meta-analysis. Archives of Internal Medicine, 162(1), 19–24.

Seifert, F., & Maihöfner, C. (2009). Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cellular and Molecular Life Sciences, 66(3), 375–390.

Schabrun, S. M., & Chipchase, L. S. (2012). Priming the brain to learn: the future of therapy? Manual Therapy, 17(2), 184–186.

Schabrun, S. M., Elgueta-Cancino, E. L., & Hodges, P. W. (2017). Smudging of the Motor Cortex Is Related to the Severity of Low Back Pain. *Spine*, *42*(15), 1172–1178.

Schading, S., Pohl, H., Gantenbein, A., Luechinger, R., Sandor, P., Riederer, F., Freund, P., & Michels, L. (2021). Tracking tDCS induced grey matter changes in episodic migraine: a randomized controlled trial. The journal of headache and pain, 22(1), 139.

Schemer, L., Schroeder, A., Ørnbøl, E., & Glombiewski, J. A. (2019). Exposure and cognitive-behavioural therapy for chronic back pain: An RCT on treatment processes. European journal of pain (London, England), 23(3), 526–538.

Schmitt, J., & Abbott, J. H. (2015). Global ratings of change do not accurately reflect functional change over time in clinical practice. The Journal of orthopaedic and sports physical therapy, 45(2), 106–D3.

Schmitt, J., & Di Fabio, R. P. (2005). The validity of prospective and retrospective global change criterion measures. Archives of physical medicine and rehabilitation, 86(12), 2270–2276.

Scholten, P. M., Patel, S. I., Christos, P. J., Singh, J. R. (2015). Short-term efficacy of sacroiliac joint corticosteroid injection based on arthrographic contrast patterns. PM R. Apr;7(4):385-91.

Shorr, R. I., Griffin, M. R., Daugherty, J. R., & Ray, W. A. (1992). Opioid analgesics and the risk of hip fracture in the elderly: Codeine and propoxyphene. Journal of Gerontology, 47, M111–M115.

Smeets, R. J., Maher, C. G., Nicholas, M. K., Refshauge, K. M., & Herbert, R. D. (2009). Do psychological characteristics predict response to exercise and advice for subacute low back pain?. *Arthritis and rheumatism*, *61*(9), 1202–1209.

Staud, R., Craggs, J. G., Robinson, M. E., Perlstein, W. M., & Price, D. D. (2007). Brain activity related to temporal summation of C-fiber evoked pain. Pain, 129(1-2), 130–142.

Stratford, P. W., Binkley, J., Solomon, P., Gill, C., & Finch, E. (1994). Assessing change over time in patients with low back pain. *Physical therapy*, *74*(6), 528–533.

Tang, N. K., Wright, K. J., & Salkovskis, P. M. (2008). Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. Journal of sleep research, 17(4), 411–417.

Takeuchi, N., Tada, T., Toshima, M., Chuma, T., Matsuo, Y., & Ikoma, K. (2008). Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. Journal of Rehabilitation Medicine, 40(4), 298–303.

Thompson, D., Rattu, S., Tower, J., Egerton, T., Francis, J., & Merolli, M. (2023). Mobile app use to support therapeutic exercise for musculoskeletal pain conditions may help improve pain intensity and self-reported physical function: a systematic review. *Journal of physiotherapy*, *69*(1), 23–34.

Thut, G., & Pascual-Leone, A. (2020). Repetitive transcranial magnetic stimulation. In TMS: A Clinical Guide. Retrieved from [https://www.taylorfrancis.com/chapters/edit/10.1201/9781003076421-13/repetitive-transcranial-magnetic-stimulation-gregor-thut-alvaro-pascual-leone]

Tian, L., Sun, S. S., Cui, L. B., Wang, S. Q., Peng, Z. W., Tan, Q. R., Hou, W. G., & Cai, M. (2020). Repetitive Transcranial Magnetic Stimulation Elicits Antidepressant- and Anxiolytic-like Effect via Nuclear Factor-E2-related Factor 2-mediated Anti-inflammation Mechanism in Rats. *Neuroscience*, *429*, 119–133.

Toth, J., Kurtin, D. L., Brosnan, M., & Arvaneh, M. (2024). Opportunities and obstacles in non-invasive brain stimulation. Frontiers in human neuroscience, 18, 1385427.

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z. T., Iványi, B., Buzsáki, G., & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*, *9*(1).

Wasserman, E. M. (1998). Risk and safety of repetitive trans- cranial magnetic stimulation: Report and suggested guidelines from the international workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, 1998. Electroencephalogr Clin Neurophysiol 108:1–16.

Whale, K., & Gooberman-Hill, R. (2022). The importance of sleep for people with chronic pain: Current insights and evidence. JBMR Plus, 6, e10658.

Wiesel, S. W., Tsourmas, N., Feffer, H. L., Citrin, C. M., & Patronas, N. (1984). A study of computer-assisted tomography. I. The incidence of positive CAT scans in an asymptomatic group of patients. Spine, 9(6), 549–551.

Wood, L., & Hendrick, P. A. (2019). A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: Short-and long-term outcomes of pain and disability. *European Journal of Pain*, *23*(2), 234-249.

Wu, A., Cross, M., Elliott, J., Culbreth, G., Haile, L., Steinmetz, J., Rhinehart, P., Kopec, J., Brooks, P., Woolf, A., Kopansky-Giles, D., Walton, D., Treleaven, J., Dreinhoefer, K., Ong, L., Vos, T., & March, L. (2023). Global, Regional, and National Burden of Neck Pain, 1990 to 2020 and Projections to 2050: A Systematic Analysis of the Global

Xia, G., Gajwani, P., Muzina, D. J., Kemp, D. E., Gao, K., Ganocy, S. J., & Calabrese, J. R. (2008). Treatment-emergent mania in unipolar and bipolar depression: focus

on repetitive transcranial magnetic stimulation. International Journal of Neuropsychopharmacology, 11, 119–130.

Xiong, H. Y., Zheng, J. J., & Wang, X. Q. (2022). Non-invasive Brain Stimulation for Chronic Pain: State of the Art and Future Directions. Frontiers in molecular neuroscience, 15, 888716.

Xiong, H.-Y., Hendrix J., Schabrun, S., Wyns, A., Campenhout, J. V., Nijs, J., Polli, A. (2024). The Role of the Brain-Derived Neurotrophic Factor in Chronic Pain: Links to Central Sensitization and Neuroinflammation. Biomolecules, 14(1), 71.

Yang, S., & Chang, M. C. (2020). Effect of repetitive transcranial magnetic stimulation on pain management: A systematic narrative review. Frontiers in Neurology, 11, 114.

Yildirim, K., Şışecıoğlu, M., Karatay, S., Erdal, A., Levent, A., Uğur, M., & Şenel, K. (2003). The effectiveness of gabapentin in patients with chronic radiculopathy. The Pain Clinic, 15(3), 213-218.

Zhang, K. L., Yuan, H., Wu, F. F., Pu, X. Y., Liu, B. Z., Li, Z., Li, K. F., Liu, H., Yang, Y., & Wang, Y. Y. (2021). Analgesic Effect of Noninvasive Brain Stimulation for Neuropathic Pain Patients: A Systematic Review. Pain and therapy, 10(1), 315–332.

Zhu, H. Q., Luo, J., Wang, X. Q., & Zhang, X. A. (2022). Non-invasive brain stimulation for osteoarthritis. *Frontiers in aging neuroscience*, *14*, 987732.

Curriculum Vitae

Name: Anike Alarape

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
2022 - Present M.Sc.

Oxford College
Mississauga, Ontario, Canada
2018 - 2019 Clinical Research Diploma

York University
North York, Ontario, Canada
2013 - 2017 B.Sc.

Honours and Awards: Data Blitz Presentation Award at Neuroscience Research Day, Valued at $200, 2024

Related Work Experience:

Graduate Teaching Assistant
The University of Western Ontario
Course Title: HS1111: Health and Wellness: Exploring the Evidence on How to Achieve a Balanced and Meaningful Life.
Winter 2023

Graduate Teaching Assistant
The University of Western Ontario
Course Title: HS1002: Social Determinant of Health
Fall 2023

Publications:

Poster Presentation: Feasibility, Tolerability and Safety of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Steroid Joint Injections (SJI) for Chronic Spinal Pain (CSP): A Pilot Double-Blinded Randomized Controlled Trial.
Authors: A. Alarape, T. Sivarajan, S. Schabrun, E. Loh
Parkwood Institute Research Day, May 16th, 2024

Poster Presentation: Determining the Feasibility, Tolerability and Safety of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Intra-articular Joint Injections (IAJI) for Chronic Spinal Pain (CSP): A Pilot Randomized Controlled Trial.
Authors: A. Alarape, T. Sivarajan, S. Schabrun, E. Loh
London Health Research Day, May 7th, 2024

Poster Presentation: Determining the Feasibility, Tolerability and Safety of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Intra-articular Joint Injections (IAJI) for Chronic Spinal Pain (CSP): A Pilot Randomized Controlled Trial.
Authors: A. Alarape, T. Sivarajan, S. Schabrun, E. Loh
Canadian Pain Society, 2024 Annual Scientific Meeting, April 28th, 2024

Data Blitz Oral Presentation: Feasibility, Tolerability and Safety of Combining Repetitive Transcranial Magnetic Stimulation (rTMS) with Steroid Joint Injections (SJI) for Chronic Spinal Pain.
Authors: A. Alarape, T. Sivarajan, S. Schabrun, E. Loh
Neuroscience Research Day, Western University, February 23rd, 2024

Oral and Poster Presentation: The Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients Receiving Facet Joint Injection (FJI) for Chronic Non-specific Low Back Pain; Pilot Randomized-controlled Trial.
Authors: A. Alarape, T. Sivarajan, S. Schabrun, E. Loh
Parkwood Institute Research Day, April 27th, 2023