Unravelling the acute effects of exercise on pain in knee osteoarthritis: What can we learn to inform rehabilitation?

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Abstract

Knee OA (knee osteoarthritis) is a prevalent and disabling condition characterised by pain and functional limitations. Exercise is universally recommended as a first-line treatment for knee OA. However, the inter-individual variability in exercise induced hypoalgesia (EIH), may be important to consider in order to optimise adherence to, and the efficacy of, exercise based interventions in people with knee OA. This thesis explored sources of variability in EIH magnitude in people with knee OA and examined the potential utility of two different interventions to enhance EIH in people with the condition. The first study, a large cross-sectional observational study, aimed to identify which key clinical, psychological, and neurophysiological factors, were associated with EIH magnitude in people with knee OA, following an acute bout of exercise. The results showed significant variability in EIH responses, with age, anxiety and pain expectations associated with EIH magnitude across different models. However, together these variables accounted for <10% of the total variance in EIH, underscoring the need to explore additional factors, influencing EIH variability in people with knee OA. The second study, a parallel group, double blind randomised controlled trial, investigated the impact of positive pre-exercise education on EIH in individuals with knee OA, compared to a control condition. The study found that while positive pre-exercise education increased the belief that pain could be reduced from a single session of exercise, the magnitude of the EIH response was not different between groups. This suggests that short, positive educational interventions might not be sufficient to improve EIH in individuals with knee OA. The third study, a double-blind randomised crossover trial, examined whether a single session of 2mA anodal transcranial direct current stimulation (tDCS) over the primary motor cortex, could enhance EIH in individuals with knee OA compared to sham tDCS. The study found no significant differences in EIH responses between the active tDCS and sham tDCS sessions, suggesting that a single session of active tDCS may not be sufficient to enhance EIH, for several possible reasons. The findings underscore the importance of considering individual differences and the potential need for repeated or multi-session tDCS protocols. Overall, this thesis contributes to a deeper understanding of the factors influencing inter-individual variability in EIH

magnitude in people with knee OA and highlights several important areas for future research.

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Attestation of Authorship

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

Signature David Toomey Date 5/12/24

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Ethics Approval

Ethics approval for this research was granted by the Auckland University of Technology Ethics Committee (AUTEC) for two separate studies. Approval for the study presented in Chapter 4 was granted on August 17, 2021 for 21/241: Can a targeted pre-exercise education intervention enhance the exercise induced hypoalgesia (EIH) response in individuals with knee osteoarthritis (OA)? (Appendix C). Approval for the study presented in Chapter 5 was granted on August 17, 2021 for 21/242: Can a single session of 2mA active transcranial Direct Current Stimulation (tDCS) over the primary motor cortex enhance exercise induces hypoalgesia (EIH) compared to sham tDCS in individuals with knee Osteoarthritis (OA)? (Appendix D).

Abbreviations

ACR	American College of Rheumatology
ANCOVA	Analysis of covariance
ANS	Autonomic nervous system
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BFR	Blood flow restriction
BMI	Body mass index
BPI	Brief Pain Inventory
CBT	Cognitive behavioural therapy
CCK	Cholecystokinin
CFS	Chronic fatigue syndrome
CNS	Central nervous system
CPM	Conditioned pain modulation
CI	Confidence intervals
CRP	C-reactive protein
DALYs	Disability-adjusted life years
DNIC	Diffuse noxious inhibitory control
EIH	Exercise-induced hypoalgesia
EPM	Evoked pain model
FM	Fibromyalgia
HADS	Hospital Anxiety and Depression Scale

HRR	Heart rate reserve
HOA	Hip osteoarthritis
ICC	Intraclass correlation coefficient
IL-6	Interleukin-6
IQR	Interquartile range
KOA	Knee osteoarthritis
KOAKS	Knee Osteoarthritis Knowledge Scale
LLTQ	Lower Limb Task Questionnaire
M1	Primary motor cortex
MOAI	Monoamine oxidase inhibitor
mTS	Mechanical temporal summation
MVC	Maximal voluntary contraction
MVIC	Maximal voluntary isometric contraction
NICE	The National Institute for Health and Care Excellence
NRS	Numerical rating scale
NPRS	Numerical pain rating scale
NSAIDS	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OffA	Offset analgesia
PAG	Periaqueductal gray
PCS	Pain catastrophising scale
PNS	Parasympathetic nervous system

PPT	Pressure pain threshold
PPTol	Pressure pain tolerance
QST	Quantitative sensory testing
RA	Rheumatoid arthritis
RPE	Rating of perceived exertion
RVM	Rostroventromedial medulla
SD	Standard deviation
SO	Supraorbital area
SPA	Sensitivity to physical activity
StEPP	Staircase Evoked Pain Procedure
TDCS	Transcranial direct current stimulation
THR	Total hip replacement
TJR	Total joint replacement
TS	Temporal summation
TKR	Total knee replacement
VIF	Variance inflation factor
VAS	Visual analogue scale
WAD	Whiplash associated disorders
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
TUG	Timed up and go
6MWT	6-minute walk test

Chapter 1 Introduction

1.1 Knee osteoarthritis

Osteoarthritis (OA) is a pathological condition characterised by widespread changes affecting the entire joint, including cartilage degradation, synovial inflammation, bone remodelling, osteophyte formation, and alterations in the joint capsule and periarticular muscles (1, 2). OA is the most prevalent type of arthritis, affecting almost half of individuals aged over 65 (3, 4). OA poses a significant and growing health burden, with substantial associated socioeconomic costs and ramifications for affected individuals and healthcare systems (2). OA remains a pressing global issue, being the 12th highest contributor to disability globally and the 16th highest in New Zealand (5). In New Zealand, there are currently > 400,000 people living with OA, with a projected 50% increase in numbers by 2040, while the direct and indirect costs of OA are estimated to be over $4 billion per year and expected to increase by over 65% by 2040 (6, 7).

The primary risk factor associated with OA is age, with prevalence increasing from approximately 7% of adults aged 18-44 years to 50% in those aged over 65 (8), with females being more frequently affected (9). Globally, 85% of the burden of osteoarthritis is estimated to be caused by knee OA (2). The lifetime risk of developing symptomatic knee OA rises over 50% in those with risk factors such as increased age, history of knee injury, or obesity (10). Additionally, sex is a risk factor, with females being more frequently affected than males(9).

Knee OA typically presents clinically with joint pain and stiffness (11, 12). There are many additional clinical problems associated with the condition, such as peri-articular muscle weakness (13), reduced range of motion (14), functional limitations (15), problems sleeping (16), psychological distress (17), fear of movement (18), reduced quality of life (19) and increased risk of all-cause mortality (20). Currently, there is no convincing disease-modifying treatment available for knee OA (12, 21). Total knee replacement (TKR) is regarded as an effective treatment for advanced knee OA (22, 23). However, as with any surgery, TKR carries associated risks including post-operative complications, surgical

revision, and ongoing moderate to severe pain in approximately 10-20% of people (24, 25). Moreover, total TKR is a costly procedure, and its demand is expected to increase, placing additional strain on already overburdened healthcare systems (6). Therefore, current management strategies primarily aim to reduce symptoms and increase functional capacity in people with knee OA (26-29). Such approaches may act to significantly delay and potentially avoid the need for TKR (30).

Evidence-based guidelines for managing knee OA typically recommend a combination of non-pharmacological and pharmacological interventions (28, 31-35). Pharmacological interventions, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), intraarticular therapies (such as corticosteroids), and, in some cases, opioids or duloxetine can relieve pain (33, 35). However, these interventions can have limited efficacy and carry risks of significant potential harms, such as gastrointestinal and cardiovascular side effects (26, 33, 36-38), liver function abnormalities (39, 40), accelerated joint degeneration (41), and risk of dependence or addiction (34, 42, 43).

Conversely, non-pharmacological interventions such as education, exercise and weight loss are associated with significantly fewer harmful effects and are typically considered first-line treatments for knee OA (44-50). Regular exercise has been shown to effectively reduce OA pain, improve physical function, and may also decrease the risk of a plethora of secondary health concerns such as cardiovascular, metabolic, neurodegenerative, skeletal and psychological conditions (51, 52). At a group level, exercise therapy has been shown to have a similar or, in some cases, larger effect size for pain relief compared to common pharmacological agents such as NSAIDs (33, 53, 54). As a result, exercise is universally recommended by international evidence-based guidelines as a first-line treatment for knee OA, regardless of disease stage, comorbid health conditions, pain severity or disability (32, 35, 38, 55-59).

However, despite the well-documented relationship between exercise interventions and positive therapeutic outcomes, exercise interventions for people with OA continue to be underutilised by clinicians and patients alike (60, 61).

Several key factors have been identified as barriers that influence uptake and adherence to exercise in people with knee OA, such as patient illness and treatment beliefs, variability in the long-term benefits of exercise, and exercise-induced flares in pain (62-66).

Negative patient illness and treatment beliefs regarding exercise have the potential to limit both adherence (67) and the effectiveness (68) of exercise therapy. In a large-scale survey of older adults with knee pain, Holden et al. (69) reported the common misconception that participation in physical activity and exercise, in the presence of OA, may cause further damage to the affected joint. Similarly, a review by Dobson et al (64) highlighted that people with knee OA often believe that exercise has limited effectiveness for OA and/or that exercise will result in negative consequences such as increased pain or other symptoms.

It is also important to note that the effects of exercise on knee OA pain are variable across individuals (70, 71). While underexplored, there is increasing evidence of individual variability in outcome, with not everyone achieving reduced symptoms and impairments from the same exercise programme (70, 72-74). For example, Lee et al. (65) identified several different pain trajectories in people with knee OA undertaking a 12 week knee exercise programme, consisting of strengthening, stretching and range of motion exercises. Importantly, ~25% of participants either had no improvement in pain or experienced delayed improvements that only began several weeks after starting the exercise programme (65). Additionally, Bennell et al. (75) found that only 59% of knee OA patients indicated that their condition was improved after 12 weeks of receiving a physiotherapy programme that included resistance exercises. Finally, in a large cohort study of more than 26,000 participants across three different countries, <50% of those with knee OA were classified as pain responders (≥2/10-point change on a numerical pain rating scale) following a structured 8 week programme involving 2-3 education sessions and 12 supervised exercise sessions (70) .

Finally, evidence suggests that for a proportion of those suffering from knee OA, exercise can be an antecedent for an intense, transient increase in joint pain, otherwise known as a flare (72). Flares in pain are more common at the beginning

of an exercise programme (71), and are known to disrupt daily life and negatively impact exercise adherence (66). A deeper understanding of the variable effects of exercise on pain in people with knee OA may help to overcome these barriers.

1.2 Exercise induced hypoalgesia

Exercise-induced hypoalgesia (EIH) refers to the acute pain-relieving effect of physical activity, characterised by a temporary reduction in pain perception or sensitivity following a single bout of exercise (76, 77).While this response is well-documented in healthy, pain-free individuals, producing pain relief lasting up to 30 minutes (76, 77), the EIH effect is notably more variable in populations with chronic pain, including knee OA (78). Indeed, people with knee OA, may have a normal EIH response (79-81), an impaired EIH response with no change in pain or pain sensitivity, or sometimes an increase in pain or pain sensitivity (hyperalgesia) (82-85). Notably, there appears to be an association between impaired EIH and exercise-induced pain flares (86, 87). Additionally, impaired EIH, measured at the start of an exercise programme, reduces the long-term effectiveness of exercise therapy in people with knee OA (88).

It is clear that high levels of variability in the EIH response exist within chronic pain populations, such as with knee OA. However, the factors explaining this variability are poorly understood and warrant further investigation. Furthermore, recent studies in healthy, pain-free, populations suggest that EIH can be enhanced through the use of targeted pre-exercise education (89) and transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation (90). However, there is a lack of research specifically targeting non-pharmacological interventions to enhance EIH in individuals with knee OA. If shown to be effective, such interventions could have important clinical benefits, reducing the risk of exercise induced flares in pain, (thereby helping to improve exercise adherence) and, potentially, enhancing the long-term pain-relieving effects of exercise. Importantly, even within knee OA populations, the magnitude and direction of EIH varies markedly between individuals, with some showing robust hypoalgesia and others no change or hyperalgesia, yet the clinical, psychological, and

neurophysiological factors that might explain this variability remain poorly understood (73, 78, 91).

1.3 Statement of the problem

Exercise is a key component of effective knee OA management and remains a first-line treatment in evidence-based guidelines (92). The efficacy of exercise as a long-term pain-relieving intervention in people with knee OA is variable across individuals, with exercise-induced flares in pain, presenting a significant barrier to maintaining exercise adherence. Impaired EIH has been linked to flares in pain (73, 93, 94), reduced long term effectiveness of exercise (88), and is, itself, highly variable in chronic pain populations, including people with knee OA (91). The factors that impair and facilitate EIH in individuals with knee OA are poorly understood and warrant further investigation. Moreover, it remains unknown whether pre-exercise interventions such as positive education and tDCS can enhance EIH in people with knee OA. These are important gaps in our understanding that this PhD thesis will help to address.

1.4 Aims and hypotheses

The overarching aims of this thesis were to 1) explore factors associated with individual differences in EIH in people with knee OA, and 2) to determine whether selected interventions can be used to enhance EIH in people with knee OA. To address these aims, three experimental studies were designed and undertaken with the specific questions outlined below.

Study 1 A cross-sectional observational study that aimed to determine which key clinical, psychological and neurophysiological factors were associated with the magnitude of EIH in individuals with knee OA, and to what extent the observed variables contributed to the overall variance in EIH? (Chapter Three).

Hypothesis: A range of the investigated variables will be associated with greater exercise-induced hypoalgesia magnitude at both the symptomatic knee and a remote site.

Study 2 A double-blind, randomised controlled trial with two parallel groups that aimed to determine whether a targeted pre-exercise education intervention can enhance EIH in individuals with knee OA, compared to a control education intervention? (Chapter Four)

Hypothesis: Participants receiving targeted pre-exercise education will demonstrate a greater increase in EIH (larger pre- to post-exercise increases in PPT at the symptomatic knee and a remote site) compared to those receiving control education.

Study 3 A double-blind, randomised controlled crossover trial that aimed to determine whether a single session of 2 mA active tDCS over the primary motor cortex can enhance EIH in individuals with knee OA, compared to sham tDCS? (Chapter Five)

Hypothesis: Active tDCS will result in a greater increase in EIH (larger pre- to post-exercise increases in PPT at the symptomatic knee and a remote site) compared to sham tDCS.

1.5 Structure of the thesis

Following this chapter (Introduction), Chapter 2 (Literature review) delves into OA, the role of exercise in managing it, and EIH. The following three experimental chapters address the proposed research questions by examining the clinical, psychological, and neurophysiological factors that are associated with EIH magnitude in people with knee OA (Chapter 3), as well as potential interventions to enhance EIH through positive pre-exercise education (Chapter 4) and anodal tDCS of the primary motor cortex (Chapter 5). Each chapter presents detailed methods, results, and discussion of the study. The sixth chapter (Summary/Conclusion) provides a synthesis of the main findings of the experimental studies and discusses their clinical implications, along with recommendations for future research.

1.6 Significance of the research

The proposed series of studies will comprehensively examine EIH as it relates to the experience of knee OA. The findings from this thesis have significance for health professionals involved in the rehabilitation of individuals with knee OA. By enhancing our understanding of the underlying mechanisms of EIH and identifying key factors that influence its variability, this research can help optimise exercise interventions in people with knee OA. In turn, this may enhance the pain-relieving effects of exercise and improve adherence, helping to improve long term treatment outcomes for people with knee OA. Additionally, optimising exercise interventions could delay or reduce the need for TKR, which is not only a costly procedure but also carries associated risks, such as post-operative complications and, in a proportion of people, persistent pain. By reducing the reliance on surgical interventions, this research may help lower healthcare costs and improve the quality of life for individuals with knee OA.

Chapter 2 Literature Review

2.1 Introduction

This chapter aims to provide the reader with a deeper understanding of OA, the role of exercise in its management, and our current knowledge of EIH, including in people with knee OA. In the first section, the mechanisms contributing to OA-related pain will be explored. Subsequently, the discussion navigates through the use of exercise therapy in knee OA management, highlighting the varying outcomes and some key challenges with implementation. Thereafter, EIH is discussed in detail, including its variance in chronic pain conditions, the purported mechanisms and factors that may influence its magnitude. Particular attention is then given to those studies that have focused on EIH in OA and studies that have explored interventions aimed at enhancing EIH effects, with a focus on pre-exercise education and tDCS.

2.2 Literature search

To perform this narrative review, an initial search of the literature was carried out using a range of sources, including books, experimental papers, review articles, and a general internet search. From this preliminary search, an extensive keyword list was developed which included: pain(ful), exercise, contraction, exercise-induced hypoalgesia, exercise-induced analgesia, exercise-induced hyperalgesia, flares, isometric, aerobic, resistance training, strength training, isotonic, osteo(arthritis)(arthrosis), OA, knee, psychosocial, psychological, expectation, education, adherence, compliance, overactivity, intervention, non-invasive brain stimulation, transcranial direct current stimulation, tDCS.

A keyword list comparison was made against several databases (AMED, CINAHL, MEDLINE, OVID, SPORTDiscus and Scopus) up to December 2022. Citation reference searches of previous review articles on EIH increased search results. Following this, additional keywords were combined to the existing keyword list and modifications were made where appropriate. Only peer-reviewed papers published in the English language were included in this review. While this review is narrative rather than systematic, the full search strategy, including databases,

search terms, and inclusion/exclusion criteria, is provided in Appendix A to ensure transparency.

2.3 Epidemiology and symptoms of OA

OA, a prevalent, debilitating chronic disease, increasingly burdens health systems globally and impacts individuals, organisations, and societies (95, 96). Worldwide, it affects an estimated 250 million people (2), contributes to nearly 19 million disability-adjusted life years (DALYs), and is the 12th leading cause of disability (6, 97). Within New Zealand, over 400,000 individuals currently live with OA, a number projected to rise by over 50% by 2040, representing over 15,000 DALYs and exceeding $5 billion in direct and indirect costs annually (6). The most common site of OA is the knee, which accounts for approximately 85% of the burden of the condition globally (2). The lifetime risk of developing symptomatic knee OA is reported to be ~45%, with the risk increasing to ~56% in those with a history of a knee injury and ~60% in those who are obese (10).

The contemporary understanding of knee OA is as a comprehensive, whole joint condition involving structural changes across several joint tissues and a process driven by mechanical, inflammatory, metabolic, and environmental factors that can lead to synovial joint destruction and failure (98-100). Thus, to truly grasp the intricacies of knee OA, it is essential to consider its effects on symptoms, structure, and function. Recognising OA as a complex syndrome rather than a singular disease is vital, as each risk factor may trigger distinct mechanistic pathways leading to OA (101).

Age is the most potent OA risk factor, with prevalence escalating significantly with advancing age (2). From a 7% occurrence in adults aged 18-44, it surges to 50% in those over 65 due to cumulative exposure to risk factors and age-related joint structure changes (8, 102). Additional risk factors include obesity, sex (with females having a higher risk), ethnicity (e.g. African Americans have a higher prevalence compared to Europeans), genetic predisposition, menopause, mechanical and occupational stresses, past joint trauma, and congenital and developmental diseases (100, 103).

The hallmark symptoms of knee OA are pain and joint stiffness, with pain being the primary symptom that motivates people with knee OA to seek medical attention (11, 12). In addition, knee OA is commonly associated with several problems that increase its clinical burden, including periarticular muscle weakness (13), reduced range of motion (14), functional limitations (15), problems sleeping (16), psychological distress (17), fear of movement (18), reduced quality of life (19) and increased risk of all-cause mortality (20).

People with knee OA may experience two primary types of pain: intermittent severe, sharp, stabbing pain associated with movement or joint loading, and constant, aching, throbbing background pain that is more prevalent at rest, including at night (104). The intermittent intense pain can have a significant impact on quality of life due to its unpredictable occurrence, causing greater distress when it becomes less predictable (105).

Knee OA can be conceptualised as progressing through overlapping but recognisable stages. In the early stage, pain typically follows a mechanical pattern, presenting during activities that load the joint, such as walking, climbing stairs, or squatting. Structural changes may be minimal, but early cartilage degeneration and occasional inflammation can be present (104). In the middle stage, symptoms become more persistent, with pain often present at rest or during the night, alongside increasing stiffness, reduced range of motion, and functional limitations. Radiographic changes such as joint space narrowing and osteophyte formation are more common (104). In the advanced stage, structural joint damage is extensive, and people frequently experience constant pain punctuated by unpredictable episodes of severe pain. Severe loss of function, pronounced muscle weakness, and significant limitations in daily activities are typical (31). While these stages provide a useful framework, progression is not linear, and individuals may fluctuate between phases.

However, in large longitudinal cohort studies, pain trajectory is described as highly variable and fluctuating in intensity within and between days (106). Over time, the natural course of knee OA pain varies across individuals (107-109). A systematic review evaluating knee OA pain trajectories (110), found that 85% of participants

reported stable pain over the medium to long term (5-8 years of follow-up). For others, pain appears to worsen over time (6.7%), and a similar proportion belong to a trajectory of decreasing pain (7.9%) (110). Although OA has been considered a progressive condition, the evidence indicates that long-term pain worsening is far from inevitable (31).

2.4 Pain mechanisms in Knee OA

2.4.1 Introduction

Pain is a subjective experience and is best understood within a multifactorial, biopsychosocial framework (111). Pain experienced in knee OA is poorly to moderately correlated with structural changes related to the condition This section provides an overview of the mechanisms contributing to knee OA-related pain, including nociceptive mechanisms, neuropathic mechanisms and psychosocial factors. Knee OA-related pain involves the activation of nociceptors in the affected joint, transmission of nociceptive signals from peripheral to central nervous system (CNS) structures, perception of nociceptive signals in the brain, and modulation of all such signals peripherally, in the dorsal horn of the spinal cord, as well as in supraspinal areas such as the brainstem, sub-cortical and cortical structures. Additionally, this section highlights the distinction between nociception, (the neural process of encoding noxious stimuli) (112), and pain (an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage) (113). Furthermore, individual differences/pain phenotypes will be discussed. By examining these various processes and factors, this section aims to deepen our understanding of the complex nature of knee OA-related pain and their potential relevance to EIH.

2.4.2 Nociceptive mechanisms

Understanding the precise mechanisms of pain associated with knee OA remains a challenge, partly due to variance between individuals and the condition's distinct phases (104, 114). To begin, it is critical to note that the degeneration of articular cartilage associated with OA does not directly induce nociception. Cartilage is aneural and avascular, and hence lacks the capacity for nociception (115). Instead, nociception arises from the stimulation of nociceptors in structures

such as the subchondral bone, periosteum, ligaments, capsule, and synovium (104). Nociceptive pain in knee OA is typically localised to the affected joint and adjacent periarticular regions, and is most often described as dull, aching, or throbbing (115). In early stages, it follows a mechanical pattern, intensifying with activities that load the joint (e.g., walking, stair climbing, squatting) and easing with rest (12). As disease severity increases, pain may persist for longer periods, including at rest and during the night (116).

Pathological features of OA, such as bone marrow lesions, synovitis, and joint effusion are consistently associated with nociceptive pain (117). Although OA was historically classified as a non-inflammatory form of arthritis, there is growing evidence that synovitis frequently occurs in knee OA and contributes to peripheral sensitisation (118). In an active inflammatory process, like synovitis, the nociceptive system can become hyperexcitable through the sustained release of various cytokines (e.g. tumor necrosis factor) and mediators (pro-inflammatory interleukins, chemokines, nerve growth factor, leukotrienes, prostaglandins and matrix metalloproteinases) which activate and subsequently sensitise chemosensitive nociceptors within the joint, a phenomenon known as peripheral sensitisation (119). Peripheral sensitisation is defined as “Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields” (112). This process is associated with the sustained firing of the nociceptive primary afferent neurons in the peripheral nervous system (PNS) (119).The chemical mediators associated with peripheral sensitisation result in reduced thresholds to mechanical inputs, increased resting discharge of joint nociceptors, and the activation of silent nociceptors. Collectively, these effects can greatly increase the peripheral nociceptive input from the joint to the CNS.

2.4.3 Neuropathic mechanisms

Neuropathic pain is fundamentally different from nociceptive pain. The latter stems from actual or potential tissue damage, while neuropathic pain arises from damage to the nervous system itself (120). Neuropathic pain is defined as 'pain caused by a lesion or disease of the somatosensory system' (112), which includes peripheral nerve fibres (Aδ, and C fibres) and neurons in the CNS (120). As OA

develops, a proportion of individuals describe symptoms that could be interpreted as neuropathic. While the underlying mechanism of neuropathic pain in OA are still poorly understood, it has been suggested that nerve damage can occur in the injured joint, dorsal root ganglia, and spinal cord. However, these assertions are primarily based on animal studies (121). Nerve damage, in turn, manifests as distinct clinical features that set neuropathic pain apart from chronic nociceptive pain. These symptoms are often burning, shooting, electric shock-like, or tingling/paraesthetic in nature, and may be accompanied by numbness or paroxysmal attacks of severe pain (121). Unlike nociceptive pain, neuropathic pain can be widespread or radiating, extending beyond the knee to the thigh, shin, or foot, and is more likely to occur spontaneously without a mechanical trigger (114). It is often persistent, present both during activity and at rest (including at night), and can coexist with nociceptive pain (122).

A systematic review identified that between 20 and 40% of individuals with knee OA experience signs and symptoms of neuropathic pain (123). However, the presence and prevalence of neuropathic pain in OA remains controversial, as these estimates typically rely on self-report questionnaires that may at least partly reflect neuroplastic changes in nociceptive pathways of the CNS, independent of nerve damage (124-126).

2.4.4 Central mechanisms and nociplastic pain

The increase in joint nociceptive activity associated with peripheral sensitisation, (and potentially, peripheral neuropathic mechanisms) may contribute to changes in central nociceptive processing. These changes are consistent with the concept of nociplastic pain, as defined by the International Association for the Study of Pain, which refers to pain that arises from altered nociception despite no clear evidence of ongoing tissue damage or disease/injury of the somatosensory system (112). In knee OA, nociplastic pain is thought to be present in a subgroup of patients, particularly those in whom central mechanisms dominate over peripheral nociceptive inputs (127).

Central sensitisation, defined as the “Increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input” (112), is one of

the main mechanisms underlying nociplastic pain. It encompasses several physiological changes such as lowered activation thresholds for both noxious and non-noxious inputs, enhanced synaptic efficiency of both large and small diameter afferent fibres, spontaneous neuronal firing and enlargement of receptive fields. (128). While central sensitisation cannot be directly measured in humans, several studies involving neuroimaging and quantitative sensory testing (QST) provide evidence for central sensitisation in people with knee OA (129-131). QST measures assumed to reflect central sensitisation, such as widespread increases in sensitivity to mechanical and thermal inputs (i.e. remote from the painful joint), heightened temporal summation of pain and impaired endogenous pain modulation have been frequently demonstrated in people with knee OA, particularly those who experience more severe pain (132-135). Furthermore, when compared to controls, limbic areas of the brain, such as the cingulate cortex, thalamus and amygdala, which play essential roles in nociceptive processing, have been found to be significantly more active in people with OA (131, 136). Importantly, the central mechanisms of OA reflect not only sensitisation of nociceptive pathways in the spinal cord and brain, but changes in endogenous pain modulation. These include enhanced activity of descending pain facilitatory pathways (137), and the loss of descending pain inhibitory mechanisms (138), particularly in people with more severe OA pain (135).

A key system of pain inhibition that has attracted particular attention in the past decades, due to their relative accessibility for measurement compared to other aspects of endogenous pain modulation, is the diffuse noxious inhibitory control (DNIC) system (139, 140). Initially conducted on animal models in the late ‘70s, Le Bars demonstrated that a localised nociceptive stimulus could recruit these inhibitory pathways and produce a diffuse hypoalgesia, otherwise known as the “pain inhibits pain” paradigm (139, 140). Under normal conditions, the DNIC system functions to inhibit nociception at remote regions when a new nociceptive stimulus is detected (139). The DNIC system is a spinal-medullary-spinal pathway that ascends through the spinoreticular tract and synapses in the brainstem. It is mediated by neurons in the subnucleus reticularis of the caudal medulla, which receives nociceptive input and then projects to the spinal cord dorsal horn. Here,

it functions to inhibit pain by reducing the activity of nociceptive neurons. The term "DNIC" is advised for describing the neurophysiological phenomenon including the pathway and neurons, while conditioned pain modulation (CPM) is recommended to represent the paradigm used to assess this phenomenon in humans. CPM not only reflects the overall impact of a secondary noxious stimulus altering the effects of a primary noxious input but also includes additional factors such as expectation, which are presumed to play a greater role in human responses (141). CPM will be discussed in further details in section 1.9.1. During the CPM paradigm, a strong noxious stimulus to a remote body part can induce hypoalgesia to the test noxious stimulus, which can last several minutes and sometimes even abolish the activity of nociceptive neurons (142-144). Impaired CPM is a consistently reported finding in knee OA pain research(91, 145-147). This can contribute to dysfunctional descending inhibition and/or facilitation of nociception, increased pain intensity, and spread pain to distant areas of the body (91, 145-147). While there is considerable evidence to support the involvement of impaired endogenous pain modulation in knee OA-related pain, it is important to acknowledge that conflicting findings and evidence exists. Notably, while CPM is generally reduced in OA patients compared to pain-free individuals, there is significant individual variability(146, 148). Some people with OA have impaired CPM, while others have normal CPM. Notably, there is increasing evidence that psychological, social and lifestyle factors, such as chronic stress, anxiety, depression, sleep disturbances, social support, influence the onset and continuation, of central sensitisation, including impaired endogenous pain modulation - underscoring the complex interplay of biological and psychosocial factors in knee OA pain (131).

2.4.5 Psychosocial factors

Psychological factors such as depression, anxiety, beliefs and expectations can alter pain perception (149). Knee OA has been associated with depressive symptoms, decreased self-efficacy, increased pain catastrophising and kinesiophobia (fear of movement) (150-152). Axford et al. (153) reported that over 40% of people with lower limb OA suffered from clinically significant anxiety or depression compared to 5-17% in the general population. Depressive symptoms

have been found to act as a strong predictor of worsening knee pain (150), while having high anxiety has been found to predict new joint pain over a 12-month follow up period (154). Cruz-Almeida et al. (150) identified that people with knee OA plus the greatest psychological distress, experienced widespread pain and the highest levels of clinical pain and disability.

Moreover, positive psychological factors such as resilience, optimism and self-efficacy are associated with lower pain intensity, and greater life satisfaction in those with knee OA (155). Additionally, the role of beliefs and expectations about illness/pain is integral to the perception and perpetuation of pain experiences in knee OA. It has been suggested that these cognitive factors can influence expectations regarding pain duration, treatment efficacy and the perceived level of debilitation (67). Moreover, given that these beliefs are modifiable, they are considered an important target in the prevention and treatment of OA pain and disability (156-158).

In addition to psychological factors, social factors also contribute significantly to the pain experience in knee OA. Social isolation, lower socioeconomic status, and reduced social support have all been linked to worse pain outcomes in those with knee OA (159, 160). The social environment can influence pain behaviours and coping strategies, either facilitating or hindering engagement with rehabilitation and pain management strategies. For example, individuals with strong social support systems are more likely to adopt active coping mechanisms, such as regular physical activity, which can mitigate pain and improve function (63). Conversely, social stressors, such as a lack of social support and social comparison can exacerbate pain perception and decrease engagement with beneficial health behaviours (63).

There is a well-established neurophysiological basis for the influence of psychosocial factors on nociceptive processing. Regions of the neuromatrix, such as the anterior cingulate cortex, prefrontal cortex, and insula, are intimately involved in processing and interpreting nociceptive input and have strong connections with the periaqueductal gray (PAG), a key region involved in descending nociceptive modulation (161), facilitating the brain’s capacity to either

amplify or inhibit nociceptive signals from the periphery (162). This interaction highlights the role of affect and cognition in shaping pain experiences, suggesting that interventions that manipulate psychological and social factors could optimise pain modulation through central mechanisms.

2.4.6 Summary

In summary, the mechanisms contributing to pain in knee OA highlight both its complexity and heterogeneity, supporting the view of knee OA as a syndrome rather than a single disease. Individual differences in pain mechanisms, such as peripheral sensitisation, the presence of neuropathic pain, central sensitisation (including impaired endogenous pain modulation), psychological and social factors, help to explain the varying pain experiences and frequently poor relationships between imaging findings and pain intensity in people with knee OA (163). This underscores the importance of a biopsychosocial understanding of OA pain, where the interplay of biological, cognitive, emotional, social, and physiological factors must be considered. A comprehensive approach to knee OA management should address not only the biological underpinnings of pain, but also the modifiable psychological and social dimensions that can influence pain and disability.

2.5 Overview of management of knee OA

The management of knee OA can involve a range of different treatment approaches. These can be broadly divided into two categories: non-surgical and surgical management. First-line treatment begins with conservative, non-surgical modalities (164). It should only move to surgical intervention once conservative methods have been thoroughly trialled and are no longer deemed effective in managing joint pain and the decline in physical function (165). There are currently no established pharmacological interventions for OA that can effectively halt or delay disease progression. Pharmacological pain management may be necessary if first-line non-pharmacological management fails to control pain adequately. Pharmacological interventions, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), intraarticular therapies (such as corticosteroids), and, in some cases, opioids or

antidepressants (e.g. duloxetine) can relieve pain (33, 35). However, these interventions often have limited efficacy and carry risk of significant potential harms, such as gastrointestinal and cardiovascular side effects (26, 33, 36-38), liver function abnormalities (39, 40), accelerated joint degeneration (41), and addiction (34, 42, 43). Consequently, clinical guidelines emphasise that pharmacological interventions should be used at the lowest effective dose and for the shortest duration possible.

Recent evidence-based guidelines typically promote non-pharmacological interventions such as exercise, education, and weight control as first-line treatment for people with knee OA, all with strong recommendations and consistent evidence for improving pain, function mood, and self-efficacy (44-50). Exercise, ideally incorporating aerobic, strengthening, and neuromuscular training, is strongly recommended (44-46, 48, 49) and will be discussed in detail in the following section. Weight loss is recommended for those with overweight or obesity, particularly when combined with exercise (44-49). Arthritis education and self-management programs also carry strong recommendations, offering small-to-moderate but consistent benefits with minimal risk (44-50). Beyond these core strategies, several non-pharmacological interventions can specifically target psychological and lifestyle factors. Cognitive behavioural therapy (CBT), which has a conditional recommendation in OA guidelines, has demonstrated small improvements in pain and psychosocial outcomes in OA (166, 167), and CBT for insomnia (CBT-I) has RCT evidence showing improved sleep and reduced pain in patients with knee OA who report sleep disturbance (168, 169). Mind-body interventions such as tai chi (strong recommendation) (32, 45, 49, 50) and yoga (conditional recommendation) (32, 45, 49) can improve pain, function, balance, depression, and self-efficacy, while mindfulness-based stress reduction (170) and acceptance and commitment therapy (ACT) (171) show preliminary or mixed results in OA but more consistent benefits across broader chronic pain populations. Addressing lifestyle factors such as sleep, mood, and unhelpful beliefs through these psychological and mind-body approaches can help to modulate pain experiences, reduce the risk of central sensitisation, and support sustained engagement in physical activity (166, 168, 172, 173). Other adjunctive

non-pharmacological treatments, including thermal therapy (e.g., hot packs), electrotherapies, acupuncture, and supportive devices such as braces, shoe insoles, and footwear, are generally given conditional recommendations, as evidence quality is typically low and effects tend to be modest and short term (49, 50).

2.6 Exercise therapy for knee OA

Exercise therapy is regarded as first-line care in the management of knee OA, regardless of patient age, disease stage, radiographic severity, pain intensity, functional ability and co-morbidity status (35, 167, 174, 175). Exercise offers similar, or better, effects for pain relief when compared to commonly used pharmacological interventions, such as NSAIDS (35). Clinical practice guidelines consistently emphasise exercise as a core treatment for knee OA, highlighting its effectiveness in reducing pain, improving function and enhancing quality of life (45, 49, 176). Moreover, engaging in regular physical activity can also delay or prevent the need for joint replacement surgery (177). In addition to these effects, exercise also improves mood and offers systemic benefits by addressing secondary consequences of physical inactivity, helping to prevent cardiovascular, bone-related and neurological disorders (51). Furthermore, the risks associated with exercise therapy are minimal compared to pharmacological interventions.

2.6.1 Exercise parameters

Exercise programs for knee OA can be delivered through individual sessions, group classes, home-based regimens, or a combination of these methods (175). Systematic reviews suggest that these various delivery mechanisms provide equivalent advantages in terms of alleviating pain and enhancing functional capabilities (50, 178, 179). There are several different types of exercise commonly used in the treatment of knee OA, including but not limited to resistance training, walking, biking, stretching, swimming, tai chi, yoga, and water aerobics (175). These can typically be classified into several major categories according to their primary objectives. These include: aerobic, specifically (aimed at enhancing cardiorespiratory fitness), resistance (designed to increase muscle strength), neuromuscular (geared towards enhancing the capacity to execute specific

activities), and mind-body activity (175). All forms of exercise appear to provide benefit for people with knee OA (74) (178), but aerobic and, in particular, resistance training are commonly recommended in clinical guidelines (180), due to the strength and consistency of their supporting evidence.

Exercise 'dose' can be a collective term for programme variables such as duration, frequency, intensity, repetitions, and rest intervals. Dose remains an important consideration when designing and implementing an exercise therapy intervention. However, precise guidelines for people with knee OA are lacking (31). Some evidence suggests that dose–response effects may occur for certain outcomes in knee OA, although findings are inconsistent and effect sizes are generally small, with several trials reporting no overall between-group differences (181). While it appears that exercise can be beneficial when delivered through both lower and higher intensities (182), for exercise to be most beneficial, it must provide a sufficient stimulus in order to elicit an adaptation that results in improved symptoms, reduced impairments and increased function (31). Juhl et al. (74) reported that, on average, effect sizes for pain (SMD 0.68) and disability (SMD 0.67) were larger in programmes with a single exercise type performed at least three times per week compared with those with fewer than two sessions per week (pain SMD 0.41). However, the 95% confidence intervals for these estimates overlapped, indicating the possibility of no true difference. These findings were based on indirect comparisons across trials rather than head-to-head RCTs directly comparing session frequencies. The authors also suggested a minimum of 12 exercise sessions to achieve meaningful effects. Similarly, Ettinger and colleagues (183) observed an association between higher exercise adherence and greater improvements in walking ability, disability, and pain in a large 18-month trial involving 439 people with knee OA. While this suggests a potential dose–response relationship, the findings are observational within the trial and may not establish causality. Long-term adherence remains important, as benefits are typically lost within 6 months of exercise cessation (184, 185).

2.6.2 Key challenges in implementing exercise therapy in knee OA

Despite the well-established relationship between exercise interventions and positive therapeutic outcomes, there remains a global under-utilisation of

exercise in people with knee OA and long-term adherence to exercise for people with OA remains a problem (60). Exercise adherence in those with knee OA is influenced by the dynamic and complex interplay between physical, psychological, and social factors (63). Some important factors that influence the implementation and maintenance of exercise in people with knee OA include patient illness and treatment beliefs, flares in pain, and inter-individual variability in response to exercise (62). Due to their relevance to this thesis, these factors will be discussed in more detail below.

2.6.3 Patient illness and treatment beliefs and expectations

Understanding the barriers to exercise adherence in knee OA necessitates the exploration of attitudes, beliefs, and expectations patients might have about OA and exercise as a form of treatment. From a social-cognitive perspective, individuals' decisions regarding specific courses of action are influenced by their personal beliefs as they anticipate that their chosen activities will lead to expected outcomes (186). This concept was discussed in-depth in a mixed methods systematic review by Hurley et al. (52),who suggested that patients' attitudes towards their health and treatment modalities could significantly impact their motivation and willingness to adhere to recommended exercise regimens.

Perceptions of both physical and psychological improvements from exercise can markedly influence behaviour. Specifically, individuals who anticipate greater benefit, are typically more inclined to engage in exercise than those who perceive fewer benefits (187, 188). This impact of outcome expectancy on physical activity engagement is increasingly substantiated by empirical research across diverse populations (189, 190). Furthermore, this is consistently observed in chronic pain conditions, including knee OA (191-193). In a large-scale survey of older adults with knee pain, Holden, Nicholls (69) reported that patients identified uncertainty regarding the effectiveness of exercise in managing knee pain, with many participants believing that more severe OA is less likely to respond to exercise (69). The study also reported the common misconception that participation in physical activity and exercise, in the presence of OA, may cause damage to the affected joint. Similarly, a review by Dobson et al. (64) highlighted that people with knee OA often believe that exercise has limited effectiveness for OA and/or that exercise

would result in negative consequences such as increased pain or other symptoms. This highlights the importance of addressing initial beliefs and expectations to maximise patient engagement and adherence (69), but also how early changes in symptoms with exercise can either reinforce or challenge a patient's existing views about exercise, influencing their likelihood to continue the behaviour.

2.6.4 Variability in pain relief and adherence to exercise in knee OA

Although meta-analyses show, on average, moderate improvements in pain and function with exercise in knee OA (176, 179), the magnitude of these benefits is often modest, particularly for pain, and varies substantially between individuals (194). Moreover, as with many non-pharmacological interventions, the quality of evidence supporting these effects is variable, with trials frequently at risk of bias due to issues such as lack of blinding, heterogeneous interventions, and small sample sizes. Large, methodologically rigorous trials have sometimes failed to find clinically important differences in pain outcomes. For example, the START trial (195), found that high-intensity strength training did not significantly reduce knee pain or knee joint compressive forces compared with either low-intensity strength training or an attention control over 18 months, with between-group differences in pain well below the minimal clinically important difference. These findings reinforce that, while exercise remains a recommended first-line intervention, its effects on pain and function may be modest, and expectations should be managed accordingly.

Individual beliefs and expectations also appear to influence outcomes. People with positive pre-exercise beliefs about the benefits of exercise tend to adhere better, whereas those with negative expectations may drop out early, especially if they experience initial symptom exacerbation (52). Adherence to exercise is crucial for optimising clinical outcomes, as the benefits of exercise tend to decline over the long term (60). For instance, Bennell et al. (184) found that the beneficial effects on pain and disability were lost six months after a 12-week exercise program had ended. Factors influencing adherence in individuals with knee OA, include a complex interplay of physical, psychological, and social factors (63). Patients who adhere to regular exercise are more likely to experience sustained

improvements, while non-adherence may contribute to diminishing positive effects over time (62).

Additionally, while underexplored, there is increasing evidence of individual variability in outcome, with different levels of change observed in symptoms and impairments from the same exercise programme (72-74). For example, Lee et al. (65) identified several different pain trajectories in people with knee OA undertaking a 12-week exercise programme consisting of strengthening, stretching and range of motion exercises. Importantly, ~25% of participants either had no improvement in pain or experienced delayed improvements that only began several weeks after starting the exercise programme (65).

2.6.5 Flares in pain

Evidence suggests that for a proportion of those suffering from knee OA, exercise can be an antecedent for an intense, transient pain experience, otherwise known as a flare (72). Indeed, such flares may contribute to a person's hesitancy to engage in exercise treatment for knee OA (196). Flares in pain are more common at the beginning of an exercise programme and are known to disrupt daily life and negatively impact exercise adherence (66). For example, Sandal et al. (71) investigated the trajectory of acute flares of joint pain during an 8-week neuromuscular exercise programme in individuals with knee or hip OA. These authors reported that exercise-induced pain flares were common and should be expected in the infancy of the programme but that these diminish in both frequency and intensity over time and are largely absent after 6-8 weeks of training. The study looked at exercise-induced pain in the first two weeks for participants who dropped out of the programme compared to those who were compliant. The authors reported that the average intensity of pain flares within the first 2 weeks were significantly higher, for the non-compliant group, compared to the compliant group. Similarly, Beckwee et al. (66) found that exercise-induced pain was inversely correlated with adherence ($r = -0.42$) during the first 3 weeks of a home exercise programme in people with knee OA. Furthermore, Jack et al.(197) found that early exercise-induced pain exacerbation, was a significant predictor of long term adherence to exercise at an 18 month point, following individuals with OA. Overall, exercise-induced flares appear negatively associated with adherence,

affecting not only initial engagement but also long-term commitment to exercise programs in people with knee OA.

2.6.6 Variability in long term pain relief

Beyond initial symptom responses, long-term pain relief following exercise also varies widely across individuals with knee OA. At a group level, randomised controlled trials of exercise interventions in people with OA often observe modest effects, with average pain reductions of less than 10 on 100-point numerical rating scales (198). Meta-analyses suggest moderate improvements in pain and function on average (176), but the effects are not uniform across participants. Studies have reported that while some individuals experience clinically meaningful improvements, others do not. For instance, a large cohort study following 32,599 individuals undergoing exercise therapy found that only 44% of knee OA patients met the criteria for at least a 15 mm reduction in pain on a Visual Analog Scale (VAS) at three months (Roos et al., 2022). This finding is consistent with large registry based data from more than 26,000 participants with knee OA across three different countries, of whom less than 50% were classified as pain responders (≥2/10-point change on a numerical pain rating scale) following a structured 8-week programme involving 2–3 education sessions and 12 supervised exercise sessions (70).

In summary, there are several different factors that can hinder the uptake and adherence to effective exercise therapy in people with knee OA, of which, three important ones have been highlighted in this section Unhelpful illness and treatment beliefs, such as misconceptions about the potential for exercise to worsen symptoms or accelerate joint degeneration, can prevent patients from engaging fully in prescribed regimens. These beliefs may be reinforced when individuals experience early flares in pain upon starting an exercise programme. For some, these transient but intense increases in joint pain can confirm pre-existing fears about exercise, making them more likely to discontinue exercise, ultimately limiting the therapeutic benefits of the intervention. Additionally, there is significant inter-individual variability in both short-term pain responses and long-term pain relief with exercise, with many patients failing to achieve clinically meaningful improvements in pain. To optimise exercise-based interventions for

people with knee OA, it may be important to better understand the acute effects of exercise on pain, and the reasons underpinning the marked variability observed across individuals.

2.7 Exercise-induced hypoalgesia

Exercise -induced hypoalgesia (EIH), can be defined as a short-term reduction in pain or pain sensitivity that lasts for up to 30 minutes after an acute bout of exercise (76, 77). EIH is most commonly quantified by applying a painful stimulus to the body before and after a defined dose of exercise and measuring changes in pain sensitivity, such as changes in pain thresholds or decreased pain intensity to a standardised painful stimulus (76). In populations with pain, clinical measures of pain for example, overall pain intensity, pain at rest, pain during movement, evoked pain, are also utilised as measures of EIH (86, 199, 200).

In 1979, Black et al. (201) first described the occurrence of EIH in their paper entitled “The painlessness of the long-distance runner”. The authors observed higher pressure pain threshold (PPT) and pressure pain tolerance following a 40-minute run compared to before the run (201). Since then, numerous studies have demonstrated a reduction in pain sensitivity (i.e. hypoalgesia) during and following exercise (77). In healthy individuals who are pain-free, aerobic exercise generally results in widespread EIH. However, with resistance exercise, the outcome can be slightly different. A decrease in pain sensitivity in the area near where the muscle contraction occurred, a phenomenon referred to as local EIH, is frequently observed (76). In contrast, remote EIH (hypoalgesia observed in areas of the body spatially remote from or not directly involved in the exercised region), is less consistently observed and is often of smaller magnitude compared to local EIH (202).

2.7.1 Potential mechanisms of EIH in humans

Opioid system

The most studied mechanism of the EIH response in humans involves the endogenous opioid system. Muscle contractions during exercise of sufficient intensity and duration trigger primary nociceptive afferents (fibre group III (A-delta)

and IV (C)) in skeletal muscles, subsequently activating the endogenous opioid system through the release of peripheral and central beta-endorphins (203, 204). Human studies using positron emission tomography ligand activation with unselective (18F Diprenorphin; (205) and mu-opioid selective (11C-Carfentanil; (206) ligands were able to identify exercise-induced endogenous opioid release in brain areas such as the thalamus, anterior cingulate, orbitofrontal and insular cortices after a single session of aerobic exercise (2 hours endurance running and high intensity cycling, respectively). Notably, exercise intensity-dependent effects on endogenous opioid release, have been demonstrated with this method (206), indicating that this could also be a mechanism underlying the exercise dose dependency on EIH observed in numerous studies (77, 207). In line with this hypothesis, significant elevations in serum beta-endorphins usually occur with exercise intensities greater than 75% VO_{2max} (208), although hypoalgesia can occur at intensities below this level (209, 210).

While the opioid system can be an important driver of the EIH response, non-opioid mechanisms also appear to play an important role. Several studies have investigated the potential contributions of a non-opioid mechanism by administering naloxone, an opioid antagonist, prior to aerobic exercise (201, 211-213). In two studies (201, 213), naloxone did not affect hypoalgesia, but in a further study (211), a dose-dependent effect of naloxone was found with only high dose (10 mg) naloxone blocking the hypoalgesic response. A final study found that naloxone blocked hypoalgesia to ischemic pain but not thermal pain (212). These findings suggest an EIH response insensitive to opioid antagonists can also occur, providing evidence for nonopioid mechanisms in EIH.

Serotonergic system

Animal studies suggest that the serotonergic system may also be involved in EIH (214). While evidence to date in humans is limited, Tour et al. (215) investigated the impact of three functional genetic polymorphisms on EIH in healthy, pain-free individuals (n=134) and individuals with fibromyalgia (n=130). These included the single nucleotide polymorphism rs1799971 in the OPRM1 gene (influences mu-opioid receptor activation), rs6295 in the HTR1a gene (controls serotonin 1A receptor expression), and the polymorphisms 5-HTTLPR and rs25531 in the

serotonin transporter gene, which together modulate 5-HTT expression. These authors found important gene-to-gene interactions between various combinations of opioid and serotonin genes and EIH, with no significant different across pain-free individuals and people with fibromyalgia, suggesting that serotonergic pathways, and their interaction with the opioid system, likely play a role in EIH in humans

Endocannabinoid system

Another proposed mechanism contributing to EIH is the endocannabinoid system. Cannabinoid receptors have been identified throughout pain-modulatory areas of the PNS and CNS and produce hypoalgesia when stimulated (216). Aerobic exercise of moderate intensity activates the endocannabinoid system (217), and antinociception after aerobic exercise is partly mediated by the endocannabinoid system in rats (218). The hypothesis of the involvement of the endocannabinoid system in the EIH response is further supported by a study in humans, demonstrating a significant decrease in temporal summation of heat pain after isometric exercise in conjunction with a significant increase in circulating endocannabinoids (219). However, in the same study, there was no significant association between the increase in endocannabinoid-related lipid analogues and the increase in PPT following exercise, suggesting potential differences depending on the nociceptive pathway assessed (219). Ghafouri et al. (199) examined endocannabinoid-related lipids in the trapezius muscle of women with chronic pain and healthy controls before and after shoulder exercise. The authors found that an increase in muscle pain intensity after exercise, was associated with lower levels of interstitial endocannabinoid lipids, suggesting that reduced activation of the endocannabinoid system may be associated with impaired EIH (199). Further research is required to investigate if this relationship can be seen in other chronic pain conditions such as knee OA.

Immune system

Exercise appears to modulate the immune system both locally at the site of muscle contraction and, systemically, including within the CNS (220). In the long term, regular exercise results in a reduction of inflammation, promoting a shift toward more anti-inflammatory cytokines and fewer pro-inflammatory cytokines

(221, 222). However, the acute effects of exercise are more complex and often pro-inflammatory. Following exercise, there is an immediate increase in pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), which occurs within minutes of exercise cessation (223).This acute pro-inflammatory response may activate and sensitise nociceptive pathways, particularly in people with persistent pain conditions, where increased levels of TNF-α and IL-6, may partly explain impaired EIH and exercise-induced pain flares (224-226). However, our understanding of the role of the immune system in EIH is still in its infancy.

Autonomic nervous system

A “stressor” is any stimulus or event that evokes a physiologic stress response, including exercise (227, 228). The physiological processes involved include increased activation of sympathetic and withdrawal of parasympathetic nervous system activity. This is accompanied by an increased secretion of catecholamines (norepinephrine, epinephrine, and serotonin), and a subsequent rise in heart rate, blood pressure and respiration rate (227). The autonomic nervous system is also responsible for blood distribution (vasodilatation) to the exercising muscle, which has potential implications for muscle fatigue, ischemia, and muscle nociceptor activation in the context of EIH (76). Exercise induced changes in blood pressure have been suggested as a possible mechanism for EIH (229), as baroreceptor activation is known to stimulate endogenous descending pain inhibitory pathways (230, 231). In healthy participants Koltyn and Umeda (229), found that during and post exercise, increases in blood pressure were associated with increased in pain thresholds, suggesting a link between cardiovascular responses and hypoalgesia. However, the exact relationship remains unclear, as subsequent studies did not consistently demonstrate a dose-response relationship between changes in blood pressure and pain perception following exercise (232, 233).

Additional mechanisms

According to the gate control theory, EIH that occurs local to the exercising muscle, may be at least partly explained by the neural "gating" mechanism at the spinal cord level, where non-painful stimuli, such as exercise induced sensations of muscle stretch and pressure, can inhibit the transmission of nociceptive signals

from the dorsal horn of the spinal cord to the brain, thereby reducing pain (234, 235). Indeed, this may contribute to differences in EIH measured at different sites, where local EIH is typically more pronounced than remote EIH.

Finally, a behavioural-based hypothesis is that exercise functions as a distraction that modulates pain perception through attentional mechanisms (236). Following a period of physical exertion, the body enters a state of heightened responsiveness, characterised by an elevated heart rate, blood pressure, perspiration, and breathlessness (237). Given that pain perception is diminished when an individual's attention is directed towards another stimulus during the experience of pain, the physiological alterations induced by exercise may serve to divert attention from the painful stimulus, thereby lessening pain perception (234).

While most research has examined biological and psychological influences on EIH, it should be acknowledged that social factors such as social support, socioeconomic status, and broader contextual influences may also contribute to pain modulation. Brellenthin et al. (238), provide preliminary evidence in healthy participants that broader psychosocial variables, including family environment and mood states, can influence pain sensitivity and EIH. This suggests that a wider psychosocial context may shape pain modulation responses. However, these factors have not been systematically studied in chronic pain populations such as knee OA, where social influences may be equally or even more important. The absence of this work highlights a gap in the literature and these unmeasured variables may represent important contributors to the variability in EIH reported in Chapter 3.

2.8 EIH in people with knee OA

While EIH is well documented in healthy pain-free populations, its response is more variable in populations with chronic pain (76-78, 202), including those with knee OA (78-81, 88, 239-241). An overview of studies that have assessed EIH in people with knee OA specifically is provided in Table 1, with the variability in findings summarised further below.

Table 1. *Studies of EIH in knee OA*

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Burrows et al., 2014	33 total (11 KOA, 11 old healthy, 11 young healthy)	6M/5F for each group	KOA, old and young healthy, mean age 65.9, 61.3, and 25.0, respectively	Resistance exercise (upper and lower body): 3 exercises, 3 sets of 10 repetitions each at 60% 1RM (crossover)	Pressure Pain Threshold (PPT), Pressure Pain Tolerance (PPTol)	Absolute ΔPPT (kg/cm^2) pre→post; also reported as group means; PPTol Δ		KOA group showed increase in PPTs only after only after upper body resistance exercise, not lower body; healthy groups showed increase in PPTs for both exercises. PPTol not increased after exercise in KOA or control groups.	QST only
Farrokhi et al., 2017	27 KOA patients	7M/20F	KOA, mean age ~63.7, all with radiographic tibiofemoral OA grade ≥2	Continuous 45-min walking vs. interval (3 x 15-min bouts with 1-hour rest between)	NPRS	NPRS recorded each minute; analyses compare levels over time (e.g., 30 & 45 min) within condition; not expressed as Δ/%/ratio		Interval walking resulted in no pain increase, while continuous walking led to significant pain increase (~2-3/10 points on	Clinical only

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
								NRS) at 30 and 45 minutes.	
Fingleton et al., 2017	40 knee OA, 20 controls	18M/22F	Knee OA, mean age ~64, diagnosis per ACR criteria	Aerobic cycling (submaximal test at 75% of age-predicted maximum heart rate for 4-10 minutes) and Isometric knee extension (10% MVC held up to a maximum of 5 minutes or until they reached exhaustion).	PPT at knee, quadriceps, and forearm	Absolute ΔPPT (kPa) pre→post at knee/quad/forearm; compared across CPM strata; no normalisation	CPM	Knee OA with abnormal CPM showed ~15-20kPa decrease in PPTs after aerobic and isometric exercise, while KOA with normal CPM and controls showed ~20 to 25%/kPa increase in PPTs after both exercises. Scatterplots suggested moderate relationship between magnitude of EIH and CPM responses, but no formal	QST only

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
								statistical test reported.	

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Germanou et al., 2013	10 KOA patients, 10 controls	0M/20F	Obese women, KOA patients, mean age ~59.9	Isokinetic knee flexion/extension (6 sets of 10 reps at maximal effort, velocities of 90°/s, 120°/s, and 150°/s, with 30-second rest intervals between sets)	WOMAC pain	WOMAC pain pre→post isokinetic bout; repeated-measures analysis; not %/ratio		No change in WOMAC pain after exercise.	Clinical only
Hansen et al., 2020	24 KOA patients	8M/16F	KOA, mean age ~64	2-Minute Lateral Raise: Participants performed shoulder abduction using an elastic band adjusted to ensure 2 minutes to failure. 30 repetitions were completed at a controlled pace.	PPT at deltoid (local), quadriceps (remote), knee and tibialis anterior. cPPT,	Normalised EIH ratio = PPT_post / PPT_pre (site-wise), also composite normalized EIH; cPPT & cPTT reported. Baseline-corrected		Significant increase in PPTs at deltoid (~15-20 kPa) immediately after the 2-minute exercise but were not sustained over time or observed at remote sites. No change in cPPT or cPTT with either exercise.	QST only

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Kosek et al., 2013	113 KOA and HOA patients, 43 controls	39M/74F	KOA and HOA patients undergoing TKR/THR, mean age ~68	Isometric knee extension (at 50% MVC held up to a maximum of 5 minutes or until they reached exhaustion)	PPT	Normalised to baseline (PPT_post/PPT_pre), and change computed by subtracting the normalised baseline value; i.e., baseline-corrected ratio		Significant increase in PPTs at quadriceps and deltoid during exercise (~10-20%) in KOA and HOA patients and healthy controls; No sex differences in EIH response.	QST only
Neelapala et al., 2018	70 KOA patients	31M/39F	KOA patients, mean age ~62, moderate pain (NRS ≤ 7/10), radiologically confirmed	Isometric quadriceps exercises (10 reps, 6-sec hold, intensity not reported) vs. resting control (5 minutes of comfortable sitting)	PPT	% change in PPT from baseline at the knee (e.g., +23.7%); not ratio	None reported	Isometric quadriceps exercise increased PPT by 23%. No change with rest.	QST only

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Vaegter et al., 2017	14 KOA patients	7M/7F	Age ~66.3, awaiting TKR, KOA diagnosis	Aerobic cycling (submaximal test at 75% of age-predicted maximum heart rate for 15 minutes (including 2 minutes warm-up and 10 minutes at target intensity) and Isometric knee extension (30% MVC held for 90 seconds), quiet rest (5 minutes)	PPT at 4 sites (bilateral quadriceps, trapezius, biceps), cPPT, cPTT on lower leg	Absolute ΔPPT (kPa) and % change (100×after/before) at 4 manual sites and cuff measures, recorded pre→post (0 and 15 min).	CPM	PPTs increased significantly immediately after exercise for both aerobic and isometric exercise (~20-30kPa), but at 15 minutes only during isometric exercise (~10-15kPa). No change in cPPT or cPTT with either exercise.	QST only

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Wideman et al., 2014	107 KOA patients	75F/32M	KOA, mean age ~60.7, with comorbid insomnia in 63.6% of participants	6-minute walking task with repeated knee discomfort ratings on 0 (no discomfort to 100 (extreme discomfort scale)	Change in knee discomfort from baseline to peak (SPA index).	SPA index = peak discomfort during 6MWT − first (pre-task) rating; authors note an alternate pre-vs-post difference but report peak−first	WOMAC, PCS, Depression (POMS), Pittsburgh Sleep Quality Index (PSQI), PPT (knee, shoulder), TS (knee, finger)	Knee discomfort ratings increased ~10-15/100 points during 6MWT. Significant associations between SPA index and PCS, WOMAC, and TS at the knee. No significant association between SPA index and depression, sleep quality, PPTs or TS at finger. OA grade, PCS and TS at knee were significant predictors of SPA index.	Both

Study Reference	Sample Size	Sex Ratio (M/F)	Population Characteristics	Exercise Protocol	Measures of EIH	EIH computation	Other relevant Measures	Key Findings	Pain Outcome Type
Wideman et al., 2016	108 KOA patients	32M/76F	KOA patients, mean age ~60.7, primarily obese (62%)	6MWT, TUG tasks with discomfort ratings at on 0 (no discomfort to 100 (extreme discomfort) scale immediately before and after.	Change in knee discomfort from before to after 6MWT and TUG (SPA index).	Task-specific sensitivity analysed as post-task discomfort with pre-task discomfort entered as a covariate (i.e., change controlled for baseline)		Knee discomfort ratings increased ~20/100 points during 6MWT, but did not change with TUG.	Clinical only

Abbreviations: KOA = Knee osteoarthritis; HOA = Hip osteoarthritis; TKR = Total knee replacement; THR = Total hip replacement; TJR = Total joint replacement; EIH = Exercise-induced hypoalgesia; PPT = Pressure pain threshold; PPTol = Pressure pain tolerance; NPRS = Numeric pain rating scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index; 1RM = One-repetition maximum; RPE = Rate of perceived exertion; MVC = Maximum voluntary contraction; CPM = Conditioned pain modulation; DOMS = Delayed onset muscle soreness; HADS = Hospital Anxiety and Depression Scale; PCS = Pain catastrophizing scale; NRS = Numeric rating scale; TSP = Temporal summation of pain; POMS = Profile of mood states; PSQI = Pittsburgh Sleep Quality Index; SPA = Sensitivity to physical activity; 6MWT = Six-minute walk test; TUG = Timed up and go test.

2.8.1 Differences in EIH for experimentally induced versus pain clinical pain

A key conceptual issue in the EIH literature is whether outcomes are based on experimentally induced pain or on clinical pain reports. These approaches often yield different patterns of findings, highlighting that they capture related but distinct constructs. QST measures such PPT and CPM provide mechanistic insight into central pain modulatory function under controlled conditions, whereas clinical outcomes reflect the multidimensional lived experience of pain in knee OA, including biomechanical, psychological, and contextual influences.

As summarised in Table 1, studies in knee OA have varied in their choice of outcomes to quantify EIH. Some have used QST measures such as PPT or CPM, while others have assessed clinical pain outcomes including pain ratings during activity or self-reported measures such as the WOMAC or numerical rating scales. This distinction is important, as the pattern of findings is not always consistent across these domains.

Studies using QST often demonstrate measurable changes in pain sensitivity following exercise, even when clinical pain remains unchanged (78, 81, 91). In contrast, studies using clinical outcomes (73, 240-242), have sometimes reported increased or unchanged pain during exercise, despite concurrent evidence of EIH on QST measures. This suggests that QST and clinical pain capture related but not identical constructs.

QST measures provide insight into central pain modulatory mechanisms under controlled conditions, whereas clinical pain reflects the complex and multidimensional lived experience of knee OA, including biomechanical, psychological, and contextual influences. Including both types of outcomes in the present thesis was therefore an intentional decision, ensuring that both mechanistic and patient-centred effects of exercise were evaluated.

At a group level, several studies have shown a normal or intact EIH response (i.e. hypoalgesia) in individuals with OA. In a randomised study by Neelapala et al. (79),

knee OA participants were found to have a functioning EIH response following repeated isometric quadricep contractions of short duration (10 repetitions x 6 seconds, intensity not described) with PPTs measured at the knee increasing by a mean (SD) of 23.7% (34.9%). Similarly, in a study of individuals with end-stage hip and knee OA, Kosek et al. (80) found a significant EIH response at both local and remote sites, following isometric knee extension (50% MVC) held to failure (mean time was= 4.1 minutes, SD = 1.3 minutes), with normalised PPTs measured at the knee increasing by about 20% (the exact values were not stated in the text). Additionally, Vaegter et al. (81) found a significant EIH response in individuals with end-stage knee OA following both aerobic cycling and isometric knee extension. After aerobic cycling for 15 minutes (reaching 75% VO2max), PPTs measured locally at the quadriceps increased by on average by 30% and remotely at the trapezius, increasing by 16%. Similarly, after isometric knee extension (30% MVC, held for 90 seconds), PPTs measured locally at the quadriceps increased by 13% and remotely at the trapezius by 11%.

In contrast, other studies exploring EIH in knee OA have shown a more variable response (78, 88, 239-241). When using change in PPT to evaluate EIH, Fingleton et al. (91) demonstrated that knee OA participants with intact CPM measured before exercise, experienced normal EIH, after both aerobic bicycling at 75% of VO2max and isometric knee extension at 10% MVC for 5 minutes. However, on average participants with abnormal CPM experienced hyperalgesia after both aerobic exercise and isometric contraction (53). Burrows et al. (78) found impaired EIH at both local and remote sites when dynamic resistance exercise (3 exercises of 10 repetitions at 60% of 1 repetition maximum) was undertaken utilising the painful knee. However, when a similar bout of upper limb exercises (3 exercises of 10 repetitions at 60% of 1 repetition maximum) were performed, a normal EIH response was observed both locally, in the upper limb, and distally, at the painful knee (78). Similarly, Hansen et al. (88), reported that EIH was impaired at the symptomatic knee, as no hypoalgesic effect was observed remotely following resisted lateral arm raises for 2 minutes. The EIH response was only observed locally, at the shoulder, following shoulder exercise and not remotely, at the symptomatic knee (88).

Using clinical measures of pain, which are not feasible in healthy populations, has yielded findings consistent with impaired EIH. For instance, Germanou et al. (241), reported no change in The Western Ontario and McMaster The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain immediately after a bout of dynamic resistance exercise; 6 sets of 10 repetitions of maximum contraction knee extensions/flexions. Farrokhi et al. (240), reported a hyperalgesic response following 30 minutes of continuous walking, where pain intensity significantly increased from baseline ($Z = 3.32$, $P = 0.006$), in a study of 27 participants with knee OA. Similar findings have been demonstrated by Wideman et al.(73), who reported increased sensitivity to physical activity during a 6-minute walk test. In their study, participants experienced a 130% increase in knee discomfort.Knee discomfort was measured on a scale from 0, being no discomfort, to 100 being extreme discomfort, indicating heightened sensitivity to activity. Another study by Wideman et al. (242), found that during the same 6-minute walk test, discomfort levels increased by ~10-15 points on the same 0-100 scale immediately after the task.

Together, these studies highlight the variability of EIH responses observed across studies of people with knee OA. Importantly, variability in EIH has been linked to pain responses at the initiation of exercise, as well as the long term pain-relieving effects of exercise. Specifically, impaired EIH or hyperalgesia in response to an initial bout of exercise has been associated with exercise-induced pain flares in other chronic pain conditions, such as chronic neck and shoulder pain (243), low back pain (83, 87), fibromyalgia (244, 245) and chronic fatigue syndrome (86). Impaired EIH is therefore likely to contribute to pain flares in people with knee OA.

Furthermore, an important study by Hansen et al. (88) provides preliminary evidence of the prognostic significance of EIH in a knee OA population specifically. In this study, participants with knee OA underwent a 6-week neuromuscular exercise programme. EIH was assessed at baseline (pretreatment) by measuring changes in PPT before and after a short bout of exercise. The authors found that individuals with a higher pretreatment EIH response experienced greater improvements in pain and disability over the course of the 6-week exercise programme. This study suggests that pretreatment EIH could serve as a valuable

prognostic tool for predicting long-term pain relief after exercise therapy in knee OA patients, as those with lower EIH responses at baseline were less likely to benefit from the exercise intervention.

For these reasons, factors that explain variability in EIH between people may be important to understand, in order to optimise the therapeutic benefits of exercise-based interventions in knee OA. The following sections will discuss potential reasons for this variability, including the various methods used to elicit and measure EIH, as well as individual factors known to influence variability in EIH. Where possible, reference will be made to findings from studies in people with knee OA specifically.

2.8.2 Measurement of EIH

Type of exercise

The exercise types most commonly used in studies of EIH are aerobic, and isometric, with, dynamic resistance exercises less widely used (77, 246). Aerobic exercises have typically included stationary cycling, running, or step exercise. Isometric resistance exercise involves a static contraction against resistance, in which the joint angle does not change, whereas dynamic resistance exercise involves muscle contractions against resistance that produce joint movement, such as isotonic or isokinetic exercise (77). A 2012 meta-analysis examining pain perception (pain thresholds and pain intensity) following a single exercise session in healthy adults, concluded that exercise reduced experimental pain perception with mean effect sizes ranging from moderate (aerobic) to large (isometric and dynamic resistance) (77). In contrast, a more recent review by Wewege and Jones (246) reported minimal EIH effects following isometric exercise. Differences in methodology likely explain these discrepancies: Naugle et al. (77) included small uncontrolled pre–post studies with a broad range of paradigms, whereas Wewege and Jones applied stricter inclusion criteria and focused on higher-quality controlled designs. Taken together, these findings suggest that aerobic, dynamic resistance, and isometric resistance exercises can all induce EIH, but the strength and consistency of the effect depends on the specific exercise parameters used, as discussed in more detail below.

Dose

Most research exploring the relationship between exercise dose, including intensity and duration, and EIH has been conducted in healthy, pain-free populations. For aerobic exercise such as cycling and running, hypoalgesia is most consistently observed following exercise at higher intensities at or above 75% maximal aerobic capacity (VO_{2max}) (247-249), compared with low-intensity exercises (248-250). However, this is not always consistent. For example, some studies have found no change in pain sensitivity following exercise at 75% VO_{2max} or heart rate reserve (HRR) (251, 252), whereas others have reported hypoalgesia at lower intensities, such as 30% HRR (253). Hoffman et al. (248) found that EIH occurs after 30 minutes of treadmill running at 75% VO_2 max but not after 10 minutes at the same intensity. Thus, there may be an interaction between intensity and duration of exercise.

For dynamic resistance exercise, intensity is generally based on a percentage of the load that can be lifted once (1 repetition maximum or 1-RM). Research in this area is still limited, although conventional bouts of resistance exercise (e.g. 4 exercises, each performed for 3 sets of 10 repetitions) at 75% 1-RM have been shown to produce hypoalgesia (254, 255). No studies have directly compared different dynamic resistance exercise doses on the EIH response.

For isometric exercise, intensity is typically determined as a percentage of maximum voluntary contraction (MVC) (256). This involves a static muscle contraction without changing the joint angle. The combination of intensity and duration appear to be important for eliciting EIH during isometric contractions. In studies examining the relationship between task failure during isometric contractions and EIH, findings suggest that prolonged contractions held to failure may enhance hypoalgesic responses, particularly at moderate intensities. Polaski et al. (257) emphasise the importance of both intensity and duration in achieving EIH, highlighting that sustained efforts may activate endogenous pain inhibitory mechanisms. Similarly, Naugle et al. (77) review findings that maximal effort tasks sustained to failure, such as isometric knee extensions, significantly increase pressure pain thresholds locally and remotely. While these studies do not specifically isolate task failure as a research focus, they underscore the critical

role of prolonged muscle activation in pain modulation. For example, both brief maximal-intensity contractions (2-3 s at 80-100% MVC) (79), and low-to-moderate-intensity contractions (>2 min at 25-40% MVC) have been found to elicit EIH (215). Of note, PPT was increased only after low-intensity isometric contractions (25% MVC) held to exhaustion, but not when the contraction was held for only 2 minutes, suggesting that duration may be important for very low-intensity isometric contractions (258). However, the precise combination of intensity and duration that is needed to elicit EIH during isometric contractions remains equivocal. For example, Vaegter et al. (250), found a significant increase in PPT in 80 healthy participants after submaximal isometric knee extensions. However, the magnitude of the hypoalgesic response was not different between low-intensity (30% MVC) and high-intensity (60%MVC) contractions or between contractions of 90- or 180-seconds duration (250). Similar findings were demonstrated after isometric hand-grip exercises (25% MVC) for 1, 3, and 5 minutes (233). Subjective intensity, as measured by rating of perceived exertion (RPE), has also been investigated in healthy individuals, with some studies finding a direct link between higher RPE and greater hypoalgesic effects(238, 259), while others have not (260), further highlighting the inconsistency in dose response relationship.

In knee OA specifically, several studies have explored how different exercise types impact EIH, with varied results depending on exercise modality, intensity, and duration. The majority of studies have utilised resistance exercise to elicit EIH (78-80, 88, 91, 241), with a focus on isometric exercise (79, 80, 91).

Resistance exercise has shown mixed results. Hansen et al.(88) found that resisted upper body exercises (lateral arm raises) elicited EIH locally at the shoulder but not at the painful knee. Germanou et al. (241), using dynamic knee extensions (6 sets of 10 repetitions), found no change in WOMAC pain scores, suggesting limited EIH effects when the painful knee is targeted. Burrows et al. (78) also reported impaired EIH at both local and remote sites when resistance exercises targeted the painful knee, but upper limb exercises resulted in a normal EIH response, indicating that avoiding the symptomatic joint may be beneficial.

Isometric exercise has shown more consistent benefits. Neelapala et al. (79) reported a 23.7% increase in pressure pain thresholds (PPTs) following repeated isometric quadriceps contractions. Kosek et al. (80) found that isometric knee extensions held to failure increased PPTs by around 20% both locally and remotely, indicating widespread analgesic effects. Similarly, Vaegter et al. (81) demonstrated intact EIH after isometric knee extensions, even in end-stage knee OA, with moderate intensity (30% MVC) proving effective.

Aerobic exercise findings have been more variable. Farrokhi et al. (240) observed a hyperalgesic response during continuous walking for 30 minutes, while interval-based exercise appeared better tolerated. In contrast, Vaegter et al. (81) showed that aerobic cycling at 75% VO2max for 15 minutes increased PPTs both locally and remotely. Wideman et al. (73, 242) found that knee OA patients experienced increased discomfort during a 6-minute walk test, indicating sensitivity to prolonged aerobic activity.

Dose considerations are critical in optimising EIH responses in knee OA. Evidence suggests that isometric exercises performed at moderate intensities (25-50% MVC) held for longer durations (e.g., >120 seconds) produce consistent hypoalgesia (79, 80). In contrast, dynamic resistance exercises may yield better results when upper limb muscles are targeted, as lower limb exercises involving the painful knee often produce inconsistent EIH (78). Aerobic exercise might require interval-based formats to prevent pain exacerbation, especially during continuous high-intensity walking (240).

Based on the available evidence, a combination of intensity and duration is crucial for achieving EIH. In healthy individuals, both brief, high-intensity contractions (>80% MVC) and aerobic exercise at higher intensities (≥75% VO2max) can elicit EIH, while lower intensity efforts (25-40% MVC) and aerobic activities may require longer durations (e.g. >120 seconds or extended continuous exercise) to achieve similar effects. In knee OA, isometric exercises performed at moderate intensities (30-50% MVC) and held for extended periods are the most reliable for producing EIH. Resistance exercises may need modifications, such as targeting non-painful muscle groups, to enhance their hypoalgesic effects. Aerobic exercise in knee OA

presents more variability, continuous aerobic activities can increase discomfort, whereas shorter, interval-based formats are better tolerated and more effective in reducing pain. Tailoring exercise prescriptions to the individual's pain modulation capacity, as well as adjusting exercise type, intensity, and duration, can optimise hypoalgesic benefits and improve functional outcomes for knee OA patients.

Measures of pain/pain sensitivity

EIH has been quantified using a number of different measures of pain sensitivity, including the change in pressure, thermal, and electrocutaneous pain thresholds (77), pressure pain tolerance (261), and temporal summation of thermal (238) and mechanical pain (262). Changes in thermal pain thresholds may also be at least partly caused by exercise-induced changes in skin or body temperature rather than inhibitory pain mechanisms (263), suggesting they are not the best method to use. A majority of studies have used PPT as an outcome measurement for EIH, which is more responsive as an outcome measurement (77, 246). The same preference for PPT assessments is evident in studies of EIH in knee OA specifically, where 6 out of 9 studies have used pre to post exercise change in PPT to quantify EIH (78-81, 88).

Sensitivity to pressure stimuli is typically assessed using a manual pressure algometer, with the instrument applied perpendicular to the skin, and the force gradually increased at a standardised rate (e.g. 30 kPa/s) until the point where sensation of pressure first becomes painful (264). Manual pressure algometry has been extensively used and validated in clinical and experimental research as a quantitative method of assessing deep tissue pain sensitivity (265, 266). PPTs are often assessed at multiple sites, in a random order, given that location of the stimulus appears to modulate EIH; when stimuli are applied locally, to a limb involved in the exercise, hypoalgesia seems more robust than when they are applied remotely (i.e., to a limb not, or less, involved in the exercise). In quantifying EIH, it is common practice to record an average of at least two PPTs at each site (88, 260, 267-270). To express EIH, relative and absolute values have been used, without a universal preference. Relative terms, such as percentage change from baseline, or ratio measures, provide a sense of proportional change and can help to reduce variance introduced by large individual differences in baseline pressure

pain sensitivity. For relative measures of EIH, post-exercise PPTs are often normalised to pre-exercise PPTs, signifying increased PPTs (hypoalgesia) for values above 1 and decreased PPTs (hyperalgesia) for values below 1 (80, 82, 88, 271). On the other hand, absolute values offer a direct, and arguably more interpretable measure of change in pain sensitivity in the actual units of measurement. Both methods presented together, may provide a more comprehensive picture of EIH and are frequently reported in the literature (88, 260, 267-270). Regardless of whether reported in absolute or relative terms, the EIH response from multiple test sites can be computed to provide an overall EIH measure (80, 82, 88, 271). Although convenient, this method simplifies multi-point data from each participant into a single measure. Such a simplification may hinder the identification of different sources of variability in EIH measurements, including differences between local and remote EIH.

The use of PPT has been shown to be a valuable measure of pain sensitivity in relation to pain and exercise (77, 272), and allows measurement of EIH in pain-free participants, recent reviews have emphasised the need to include clinical measures of pain intensity. It's considered that these may more accurately reflect the “real life” pain experience that motivate patients to seek care (76, 246). Despite an intuitive link between pain thresholds and self-reported pain intensity, they are functionally distinct constructs (272), and the relationship between change in pain threshold and clinical pain intensity e.g. resting pain, clinically evoked pain, after exercise remains underexplored (76).For instance, Christensen et al.(200) reported changes in pressure pain sensitivity after a shoulder abduction exercise program in individuals with chronic neck pain. However, rather than observing acute exercise effects, they found a reduction in pressure pain sensitivity over time, while pain intensity on the VAS actually increased, illustrating a potential disconnect between pain sensitivity thresholds and clinical pain experiences. Thus evaluating EIH through changes in PPT alone may not always align with changes in clinical pain intensity. Consequently, a more holistic approach to understanding EIH could involve the evaluation of both experimental and clinical pain in chronic pain populations.

In examining clinical measures of EIH, various evoked pain models (EPMs) have been used to standardise the induction of pain, enabling precise pre- and post-exercise comparisons. For example, Wideman and colleagues (73, 242) have examined sensitivity to physical activity in individuals with knee OA using functional tasks, asking participants to rate their level of knee discomfort before and after completing a 6-minute walk test (6MWT) (73, 242) and Timed up and go (TUG) (242). The authors demonstrated an ~10-15 point increase in knee discomfort after the 6MWT. These findings underscore the utility of activity-related evoked pain models, particularly in knee OA, where pain during movement is often more disabling than resting pain (73). While functional tasks, such as the 6MWT used by Wideman et al.(73, 242), offer valuable insights into pain modulation, a stepping task may be easier to implement in both research and clinical settings, as it requires less space and is quicker to complete. Going up and down stairs are frequently nominated as painful activities for people with knee OA (273) and stepping tasks mirror many therapeutic exercises prescribed in rehabilitation programs, enhancing the model's clinical relevance and applicability. Furthermore, stepping tasks allow for individualised pain stimulus intensity based on fitness or pain tolerance, facilitating a personalised approach to pain management (274). Moreover, it is important to note that traditional measures of pain intensity, such as the VAS or Numeric Rating Scales (NRS), reflect changes in resting pain. However, many individuals with knee OA do not experience significant pain at rest, making these scales less effective in capturing the true impact of exercise on pain. This highlights the need for evoked pain models, such as stepping tasks, which may provide a more accurate reflection of activity-related pain in knee OA (Wideman et al., 2014). The Staircase-Evoked Pain Procedure (StEPP), which utilises a stepping task, offers a standardised method for assessing evoked pain (274). Not only does it capture activity-induced discomfort more effectively, but it may also be more sensitive to changes compared to traditional measures of resting pain. Importantly, this approach allows for individualised pain stimulus intensity based on fitness or pain tolerance, supporting a personalised approach to pain management (274). While traditional pain measures, such as the VAS or Numeric Rating Scales (NRS), primarily capture resting pain, many individuals with knee OA do not experience significant pain at rest. This highlights

the need for evoked pain models, like the StEPP task, to provide a more accurate reflection of activity-related pain.

Despite these advantages, no studies to date have specifically examined EIH using an evoked pain model of a stepping task. Its clinical relevance and ease of implementation position it as a promising method for future research into EIH in a knee OA population.

Reliability

Evidence on EIH reliability is limited, with most studies conducted in healthy, pain-free individuals. Five studies have assessed test-retest reliability of EIH, reporting ICCs from 0.03 to 0.61, indicating low to moderate between-session reliability (260, 267-270). Four studies focused on aerobic exercise, and one used isometric resistance exercise with a wall squat (260), which showed moderate reliability (ICC = 0.48). The wall squat's lack of standardisation may have contributed to this variability, and greater reliability might be achieved with standardised protocols, such as resistance exercises on an isokinetic dynamometer (275). From a variability perspective, low reliability limits confidence that observed differences in EIH reflect genuine biological variability rather than measurement error. This is especially important in chronic pain populations, where variability in EIH may be larger due to heterogeneous pain modulation capacity, but has not been quantified due to a lack of reliability data. To date, there are no published studies evaluating test–retest reliability of EIH in people with chronic musculoskeletal pain, including knee OA, and no studies examining within-session reliability. The latter is relevant because several EIH protocols, involve repeated post-exercise measurements in the same session. If within-session reliability is poor, apparent changes over repeated measurements may be artefacts rather than true physiological changes.

Although EIH-specific within-session data are lacking, other pain modulation paradigms such as CPM have demonstrated higher within-session reliability (276), suggesting EIH may follow a similar pattern. PPT, a common EIH outcome, demonstrates good within-session reliability (ICCs 0.80–0.95) in healthy populations (266, 277) and 0.70–0.90 in knee OA patients (278).

In sum, in capturing EIH, a wide variety of measurement properties such as exercise types, dosages, and measurements have been used. Given the methodological inconsistencies, an accepted consensus is inconclusive. Furthermore, many of these measurement properties have not been investigated in clinical populations such as knee OA. To improve methodological quality, future studies could consider using intensity-controlled exercises, including more clinically relevant pain induction methods, such as an EPM and appropriate computation of intraclass correlation coefficients and averages of multiple measurements, both relative and absolute. It remains vital to explore the potential mechanisms of EIH to provide a theoretical basis for these measurements, especially in clinical populations such as those with knee OA.

2.8.3 Individual factors that may influence EIH.

It is evident that there are high levels of EIH response variability within chronic pain populations, and our understanding of what drives this variability is still limited (76, 202). A deeper understanding of these factors could have clinical significance, helping to optimise the beneficial effects of exercise in the management of knee OA. The following section provides an overview of the existing evidence regarding the association between different demographic, psychological and neurophysiological factors and the magnitude of EIH in both healthy pain-free populations and, where possible, in populations with chronic pain, including knee OA.

Demographic factors

Age

Research into age-related variations in EIH has produced mixed outcomes. Lemley et al. (279) observed that EIH was present in both older men and women after isometric exercise, suggesting that the capacity for EIH is maintained in older age. Similarly, Vaegter et al. (250) found no age-related differences in EIH responses in a cohort under 65 years of age. However, Naugle et al. (280) documented a reduced EIH response in older adults (range 55-74 years) as compared to younger adults (range 19-30 years),and Ohlman et al. (281), demonstrated an absence of significant heat pain reduction after isometric exercise in older adults. These

discrepancies may be explained by differences in the age ranges studied, with cohorts under 65 showing largely intact EIH, while those including participants over 70 show attenuation, suggesting a possible age-threshold effect. In addition, pain testing modality may play a role: studies using pressure-based outcomes often find preserved EIH, whereas those using thermal pain measures report weaker or absent responses, potentially reflecting age-related changes in thermal nociception. Finally, task differences (short isometric contractions vs longer aerobic bouts) and sample sizes likely contribute to variability. Together, these findings suggest that EIH is at least partly preserved into mid-life, but may diminish in later decades and be dependent on the modality used to assess pain sensitivity.

Sex

Several studies have examined sex differences in EIH, primarily in healthy, pain-free populations. Equivocal results have been reported in a number of studies of healthy populations; studies report no some sex differences (207, 219, 238), whereas several other studies report more robust EIH in women after both isometric (282-285) and aerobic exercise (250, 286). Although the potential mechanisms remain unclear, it is possible that increased EIH may be at least partially ascribed to lower baseline pain thresholds in women (283), potentially leading to a larger relative change in pain sensitivity with exercise. However, some studies have observed stronger EIH in females despite no baseline sex differences in pain sensitivity (282, 284, 285). When it comes to sex differences in EIH among chronic pain populations, much less is known. One study explored possible sex differences in EIH in people with chronic WAD but failed to find any differences (287). These inconsistencies may reflect differences in study design (absolute vs relative change scores, task type, outcome measures) and whether samples were sufficiently powered to detect sex differences. Hormonal factors (e.g., menstrual cycle phase) and psychosocial influences may also contribute but are often not controlled for. In chronic pain populations, sex differences appear less pronounced, as shown in knee OA (80), suggesting that disease-related pain modulation deficits may overshadow sex-related effects.

Psychological factors

Psychological factors have been suggested to be involved in endogenous pain modulation (288). The presence of negative psychological factors like depression, anxiety, and pain catastrophising, might influence pain perception in higher centres and endogenous pain modulation through descending pain inhibitory pathways (289, 290). Several studies have examined the relationship between EIH and psychological factors, both in pain-free controls and, to a lesser extent, chronic pain populations (238, 291). Pain catastrophising, defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" (292), has been demonstrated to attenuate the EIH response (238) and has been associated with increased ratings of perceived exertion (RPE) and muscle pain during exercise in pain free populations (238, 293, 294). Brellenthin et al. (238) also found that higher pain catastrophising was associated with reduced EIH in healthy individuals. The authors additionally found significant associations between less EIH and lower mood state, fear of pain, and having a family member with chronic pain (238).

In chronic pain populations, the relationships between EIH and psychosocial factors remains uncertain. In their 2021 systematic review, Munneke et al. (291) found that only one out of four studies involving people with chronic pain conditions, demonstrated a significant association between EIH and psychological factors. This study, which included 61 participants with musculoskeletal pain of mixed origin (37 with LBP; 16, 7, and 1 with neck, shoulder, and elbow pain, respectively), found a significant correlation between higher state-trait anxiety and increased EIH. This followed a bicycling exercise with PPT measured at the trapezius and the biceps brachii (85). However, there was no significant correlation between anxiety and EIH when all PPT sites were combined (4 sites) to evaluate EIH. Moreover, Vaegter et al. (85) found that in people with chronic WAD, neither pain catastrophising nor kinesiophobia, were associated with EIH response after isometric or aerobic exercise. Another study by Vaegter et al. (295) that separated patients with chronic pain of various aetiologies into low and high kinesiophobia, found no significant difference in EIH responses between the groups. Smith et al (287) investigated relationships between EIH and

psychological factors in people with chronic WAD. They concluded that EIH was not associated with either catastrophising or kinesiophobia (287).

Additionally, Bement et al (296) found no correlation between state or trait anxiety and EIH in women with fibromyalgia. Wideman et al. (73) investigated the role of pain catastrophising in individuals with knee OA, focusing on evoked pain rather PPT. They found that higher levels of pain catastrophising were significantly associated with increased sensitivity to physical activity, where participants reported greater discomfort during walking tasks.

The inconsistency may reflect differences in which psychological constructs were assessed (catastrophising, anxiety, kinesiophobia), whether QST or activity-related pain outcomes were used, and sample sizes (many <50). Together, the evidence suggests that catastrophising may be more relevant for activity-related or evoked pain in knee OA than for resting pain or QST outcomes, but this remains underexplored.

Neurophysiological factors

Conditioned pain modulation

CPM is often referred to as the “pain inhibits pain” phenomenon. High-intensity or prolonged-duration exercise is often painful, and exercise-induced pain may act as a conditioning stimulus to inhibit experimentally induced pain (297). Similar to EIH, the CPM paradigm typically induces a multisegmental decrease in pain sensitivity that may involve both serotonergic (298, 299) and opioidergic (140, 300) mechanisms. As a result, it has been proposed that EIH and CPM may share mutual mechanisms and that EIH operates, at least partly, due to the activation of the same descending inhibitory pathways involved in CPM, which are triggered by exercise-induced activation of muscle nociceptors (76).

Several studies have investigated the relationship between CPM and EIH in pain free (285, 301, 302), and clinical populations (84, 85, 91, 303, 304). Studies in healthy adults indicate a modest correlation between the two phenomena. For instance, Lemley et al. (285) found that CPM predicted EIH, with a moderate strength of association (adjusted $r^2 = 0.23$). Stolzman and Hoeger Bement (302) observed that the correlation varied depending on the location, with a significant

association at the deltoid but not at the quadriceps or nail bed. Additionally, Ellingson et al.(305), examined thermal pain sensitivity in 21 healthy women following 10 minutes each of non-painful exercise, painful exercise, and rest. They observed that exercise led to reduced pain sensitivity both during and after exercise, with this reduction being inversely related to exercise-induced muscle pain.

Few studies have examined the relationship between CPM and EIH in chronic pain populations. In a study involving patients with whiplash-associated disorders, Smith et al. (84) found that participants with a more efficient CPM mechanism experienced improved EIH at the hand, while less efficient CPM was associated with an impaired EIH response at the neck post-isometric exercise.

In participants with knee OA specifically, Fingleton et al.(239), demonstrated an intact EIH response to both aerobic and isometric exercise in participants who also had a normal CPM response but not in participants with an impaired CPM response. Despite shared mechanisms, the association between CPM and EIH tends to be moderate at best, and some studies have not observed exercise-related improvements in CPM(250, 304, 306). Furthermore, because CPM only occurs with a painful conditioning stimulus, it cannot explain EIH observed after non-painful exercise (79, 261, 270). Additionally, several studies in pain-free adults have demonstrated differences in both the time course and spatial distribution of EIH and CPM (250, 307). Vaegter et al. (250) found that CPM only occurred during the period of application of the painful conditioning stimulus, whereas in the same group of participants, EIH continued 15 minutes after isometric contraction, at which time the CPM effect was absent. Furthermore, the magnitude of EIH was greatest at sites local to the exercising muscles and weakest at remote body sites (250). Conversely, the magnitude of CPM was greatest at remote sites and weaker at sites closer to the painful conditioning stimulus. Overall, the evidence indicates that these two endogenous pain inhibitory processes may share common mechanisms, but that at least part of the EIH response is independent of CPM.

Offset analgesia

Another experimental paradigm that has recently been developed to evaluate endogenous pain modulation is offset analgesia (OffA). OffA is characterised by a considerable (disproportionate) decrease in pain perception following a slight decrease in noxious stimulation intensity. It is typically elicited using a three-stimulus heat pain paradigm consisting of a 5 s noxious heat stimulus (T1) followed by a 1 °C increase in temperature for 5 s (T2), and then a final 20 s period (T3) equal in temperature to T1 (308). In healthy individuals, pain ratings during T3 are typically much lower than in T1, despite the equivalence of noxious stimulus temperature at these two time periods (309). This difference in pain rating is the OffA, as it occurs after the reduction in noxious temperature from T2. OffA is thought to be a temporal filtering mechanism which enhances the detection of noxious stimulation and induces post-stimulus pain inhibition (310, 311). A systematic review by Szikszay et al. (309) found that pain-free participants show a larger OffA response compared to patients with chronic pain. The relationships between OffA and other endogenous pain modulation paradigms are poorly understood (312-316). To date, only one study has looked at the relationship between EIH and OffA in a healthy population (312). The authors found no correlation between local or remote EIH measures and OffA, and that OffA was not modulated by exercise (312). However, no studies have explored the relationship between EIH and OffA in chronic pain conditions such as OA, where both EIH and OffA may be impaired.

Temporal summation

Another measurement of central nociceptive processing that may influence the EIH response is temporal summation (TS). TS is characterised by an increase in pain perception during a series of repeated nociceptive stimuli at a frequency of ≥ 0.33 Hz (317), reflecting the degree of central integration of nociceptive input. When facilitated (318), TS is considered a biomarker of increased central sensitisation (141) and can be reduced by NMDA receptor antagonists (230). Less temporal summation before exercise is associated with greater EIH in healthy individuals (319), although the relationship between baseline TS and EIH is less clear in chronic pain populations (84, 85).In a related study of people with chronic

whiplash-associated disorders (WAD), Smith et al. (84) observed that those with increased TS demonstrated impaired EIH responses, suggesting that facilitated TS may interfere with the pain-relieving effects of exercise in chronic pain populations. In a study of participants with chronic musculoskeletal pain of various aetiologies, Vaegter et al. (85) found that patients with high pain sensitivity had reduced EIH after aerobic and isometric exercises and increased TS of pain after aerobic exercise but not isometric exercise, in comparison with patients with low pain sensitivity. The authors concluded that it was unclear whether the findings indicated that the high pain sensitivity group had facilitated TS because of less robust EIH, whether they had a less robust EIH because of facilitated TS, or whether facilitated TS and less robust EIH can exist independently. In knee OA specifically, Wideman et al. (73) found that increased TS at the knee was associated with heightened sensitivity to physical activity during a standardised walking task and was linked to reduced EIH. These findings suggest that facilitated TS may interfere with the pain-relieving effects of exercise in chronic pain populations.

In summary, the mechanisms underlying EIH remain incompletely understood but likely involve complex interactions between central and peripheral pain modulation systems. In knee OA, considerable variability in the EIH response has been observed and found to be associated with factors such as the type of exercise (e.g., local vs. remote resistance) and pre-existing CPM efficiency. When using an evoked pain model, associations have been identified between EIH and TS at the knee, pain catastrophising and physical function as measured by the WOMAC. However, these associations remain underexplored in this population. The measurement of EIH, typically via PPTs, has been inconsistent in methodology, contributing to variability in reported outcomes. Importantly, no targeted interventions have been developed to enhance EIH as a therapeutic strategy in people with knee OA, despite its potential clinical benefits in reducing pain flares, improving exercise adherence, and enhancing long-term pain relief. The following section will explore therapeutic strategies aimed at optimising the analgesic effects of exercise in knee OA.

2.9 Therapeutic strategies to enhance EIH

Several therapeutic approaches have been investigated to enhance exercise EIH, including both pharmacological and non-pharmacological strategies. Pharmacologically, interventions such as opioid antagonists such as naltrexone, have been explored to understand their interaction with endogenous pain modulation systems (219, 320). Research by Meeus et al. (304) has shown that acetaminophen (paracetamol) can reinforce descending inhibitory pathways, particularly serotonergic pathways, which may support EIH by improving CPM and reducing TS in patients with rheumatoid arthritis and chronic fatigue syndrome with comorbid fibromyalgia. Their study found that paracetamol helped stabilise or reduce TS after exercise, suggesting that it could be beneficial in initiating exercise therapy in these patients by suppressing exercise-induced pain and supporting endogenous pain inhibition mechanisms.

Non-pharmacological strategies have also shown promise in enhancing EIH. For example, research on blood flow restriction (BFR) exercise has found that applying high-pressure BFR during resistance training can significantly increase pain thresholds and prolong the hypoalgesic effect for up to 24 hours compared to light and heavy resistance exercise in healthy participants (321). Additionally, non-invasive brain stimulation techniques and pre-exercise educational interventions are emerging as innovative non-pharmacological strategies to modulate pain perception and optimise EIH responses. The following sections will focus on these approaches, specifically examining the potential of pre-exercise education and transcranial direct current stimulation (tDCS) to enhance EIH in individuals with chronic pain conditions like knee osteoarthritis.

2.9.1 Pre-exercise Education

It has been well-documented that specific pre-treatment education can modulate the experience of pain as part of pain management (68, 89, 322-324), likely mediated by altering expectations of pain relief (323, 325). The role of expectations in relation to EIH has only been studied in healthy, pain-free populations to date. A parallel group, randomised controlled trial by Jones et al (89), involving aerobic exercise, reported that a 15-minute positive information intervention about the

effects of an acute bout of aerobic exercise on pain sensitivity, elicited significantly larger EIH responses compared to a group that received neutral biomedical information. Specifically, the positive education group was informed about EIH, including the mechanisms, duration, and types of exercise likely to produce EIH, whereas the neutral group received general information about pain scales and the distinction between pain intensity and unpleasantness. The positive group not only experienced greater pain relief (increased PPT) but also reported that the information changed their perceptions about the pain-relieving effects of exercise, indicating a cognitive shift that augmented EIH. In contrast, another parallel group randomised controlled trial by Vaegter et al. (322), involving isometric wall squats, found that a very brief (2-3 minute) intervention of positive information about the effects of exercise did not significantly enhance the magnitude of EIH (absolute change in PPT of 85 kPa, 22% increase) compared to neutral information (absolute change in PPT of 59 kPa, 14% increase). The positive information group in this study was told that exercise could reduce pain, while the neutral group received instructions on how to perform the exercise without any mention of pain.

Interestingly, Vaegter and colleagues (322) found that the EIH response was effectively abolished in a third group of participants receiving negative pre-exercise information, with a 4% decrease in PPT (-16 kPa) following exercise (322). This outcome demonstrates the potent influence of negative expectations on EIH response, signifying the necessity to carefully construct pre-exercise information. Furthermore, the authors found a moderate positive correlation between exercise expectations and EIH magnitude across all participants, and therefore concluded that pain expectations are likely an important contributor to variance in the EIH response (322).

No studies have explored the role of expectations in relation to the EIH response in a population with chronic pain, including knee OA. However, it has been proposed that the lower EIH response from exercise observed in people with chronic pain may be influenced by specific beliefs and negative expectations built on inaccurate narratives, previous experiences with ineffective treatments, or a history of flares following exercise (76). There is also an extensive body of evidence

that education-based interventions such as pain neuroscience education can modify pain-related beliefs and functional outcomes in people with chronic pain (326-328), including knee OA (158), particularly when combined with exercise (329, 330). Together, these findings suggest that education-based interventions that positively alter/build expectations regarding the effects of exercise on pain, may improve EIH among people with knee OA, and should be investigated further.

Broader context from chronic exercise and guideline-based recommendations

Although direct evidence for pre-exercise education in relation to acute EIH is sparse, education is already recognised as a core treatment in knee OA management within international clinical guidelines. For example, the Osteoarthritis Research Society International (OARSI) and American College of Rheumatology (ACR) guidelines both recommend education in combination with exercise as a first-line approach (45, 50). Education is typically aimed at improving self-management, addressing misconceptions about pain and exercise, and building confidence in physical activity as safe and beneficial. Some programmes adopt a pain neuroscience education focus, targeting unhelpful beliefs about the relationship between pain and tissue damage (331), whereas others emphasise condition-specific self-management, including weight management, joint protection, and activity pacing (332).

Importantly, guideline recommendations are not limited to explaining “what OA is” but explicitly highlight the role of education in reducing fear of movement, promoting adherence to exercise, and preventing disengagement when pain flares occur. These aims align closely with the rationale for pre-exercise educational strategies: if expectations about exercise and pain can be shaped in a positive way, patients may not only adhere more consistently but also experience enhanced hypoalgesic responses.

Framing the limited acute EIH literature within this broader evidence base strengthens the rationale for the present thesis. Chapter 4 specifically addresses this gap by examining how pre-exercise information can modulate the acute pain-

relieving effects of exercise in people with knee OA, thereby extending guideline-based principles of education into the acute experimental context.

2.9.2 Transcranial direct current stimulation (tDCS)

tDCS is a non-invasive brain stimulation technique increasingly being investigated in the management of knee OA, as it is safe, painless and much cheaper to administer than other forms of brain stimulation (333-338). Furthermore, a growing body of evidence suggests its synergistic effects with exercise, open avenues for combined therapeutic modalities (339). tDCS operates by applying a small direct current over the scalp using two moistened sponge electrodes, an anode and a cathode (340, 341). Most commonly, two electrodes of approximately 25 to 35 cm^2 are used with a current intensity of 2 mA. This technique is known to increase or decrease the resting membrane threshold of neurons directly under the electrodes, depending on the polarity of the stimulation (340). These alterations subsequently affect the excitability of interconnected cortical regions (341). In pain management studies, the anode electrode is typically placed over the primary motor cortex (M1), and the cathode electrode is positioned over the opposite supraorbital area (SO), a configuration referred to as M1-SO (342). Randomised controlled trials provide preliminary evidence that tDCS using the M1-SO configuration may reduce OA pain, either when delivered alone or in combination with other interventions (334-337, 343).

The M1-SO tDCS configuration is thought to bring about pain relief via several potential mechanisms. Computational models suggest that the combination of both electrodes could influence activity in the thalamus and somatosensory regions via corticothalamic pathways from M1. Other brain areas potentially affected include the frontostriatal circuit, the limbic system, the anterior cerebral cortex and the PAG area (341, 344, 345) all of which are involved in the processing and/or modulation of nociception. (344, 346). Furthermore, a single session of M1-SO tDCS has been shown to enhance endogenous opioid release in the brain (347) and enhance the CPM response (348) in healthy, pain-free participants. As both of these mechanisms may contribute to EIH, it seems possible that the combination of M1-SO tDCS and exercise may augment EIH, compared to exercise alone.

To date, only one study has directly investigated the effect of tDCS on EIH (90). This study was conducted in healthy participants experiencing experimentally induced musculoskeletal pain and compared 20 minutes of 1 mA active tDCS of the primary motor cortex (M1), to sham tCDS in combination with an isometric gripping protocol (90). The authors reported an accelerated onset of EIH in the active tDCS group with greater pain reduction on movement, immediately following exercise compared to the sham tDCS group (90). However, the results were complicated by large baseline differences in the primary outcome measures between groups. Additionally, the use of the 1 mA tDCS intensity and an experimental model of pain might be considered limitations, as they may not fully represent clinical pain conditions, such as knee OA. The 1 mA intensity may be suboptimal, as it is on the lower end of the stimulation range, potentially leading to less pronounced neuromodulatory effects and insufficient activation of pain modulation pathways (349). Furthermore, experimental pain models typically involve short-term, controlled stimuli that do not capture the complex, chronic, and multifactorial nature of pain experienced in conditions like knee OA (314, 350, 351).Despite these promising signs, a clear gap in the research remains: the effects of tDCS on EIH have not been investigated in people specifically suffering from knee OA. The potential benefits of tDCS in combination with exercise in patients with knee OA, particularly regarding enhancing EIH, are intriguing and warrant further examination.

Chapter 3 Factors associated with inter-individual variability in EIH magnitude in people with knee OA: A cross-sectional cohort study

3.1 Background

As discussed in Chapter Two, exercise is recommended as first line care in the management of knee OA by international evidence-based guidelines (2, 3) and is a well-documented intervention for alleviating pain and enhancing physical function in people with knee OA (4, 5). However, in practice, the therapeutic application of exercise is hindered by underutilisation and adherence issues (64, 352), exacerbated, in part, by the variability of the pain-relieving effects of exercise (65, 71). Notably, exercise-induced pain flares occur more frequently at the beginning of an exercise programme (62) and can substantially affect adherence in people with knee OA (66, 353). This variability may be partially explained by individual differences in EIH, defined as an immediate reduction in pain and/or pain sensitivity that persist for up to 30 minutes following an acute bout of exercise (76, 77). However, in people with knee OA, the EIH response may be more variable, with some studies demonstrating a normal EIH response (79, 80, 85, 91) at the group level, while other studies have shown unchanged pain sensitivity (241) or an increase in pain sensitivity (hyperalgesic response) (78, 91, 240) following exercise. Notably, in other chronic pain populations, a hyperalgesic response to exercise been linked to exercise induced pain flares (73, 93, 94).

The longer term response to exercise can also be variable in people with OA, with large population based studies suggesting that ~50% of people will achieve a moderate, clinically important improvement in joint pain after completing an 8 week exercise programme, while ~50% will not (70). The different pain responses to exercise programmes seen in knee OA may be related to impaired EIH (91), with recent evidence demonstrating that reduced baseline EIH predicts less improvement in pain and function over the course of 12 exercise sessions in people with knee OA (88).

At present, our understanding of the factors influencing inter-individual variability in EIH is incomplete, particularly in chronic pain conditions, such as OA. Most studies have been conducted in healthy, pain-free populations, and have examined various clinical, psychological, and neurophysiological factors that may influence the magnitude of EIH. However, findings are mixed, with no single factor, including clinical (e.g. age, sex) (281), psychological (e.g. expectations, pain catastrophising) (291), or neurophysiological measures (e.g. CPM, TS) (291), consistently shown to predict EIH magnitude. Similarly, while some studies have linked exercise intensity—both objective (e.g. % of VO2Max) and subjective (e.g. perceived exertion)—with EIH, dose-response relationships are inconsistent (238, 248, 259, 260). Furthermore, EIH occurs both locally and remotely, with larger and more consistent responses often seen at the local site (76), close to the exercising muscle, suggesting at least partly different underlying mechanisms for local and systemic changes in pain sensitivity.

Few studies have specifically investigated factors influencing EIH in people with knee OA. Kosek et al. (80) found that although women with OA had lower overall PPTs, EIH responses did not differ between sexes. Fingleton et al. (91) showed that people with an intact CPM response, that is an increase in PPTs with the cold pressor test, had a normal EIH response to aerobic and isometric exercise. In contrast, those with an impaired CPM response, experienced increased pain sensitivity after both aerobic and isometric exercise, suggesting a parallel dysfunction in EIH. Wideman et al. (73) investigated this relationship using and evoked pain model of EIH. They found that increased sensitivity of physical activity among people with knee OA was significantly associated with higher scores on the WOMAC pain and function subscales, as well as greater pain catastrophising and TS responses at the knee. The variability in EIH responses and the limited research in knee OA highlight the need for further studies.

Understanding the factors that influence EIH could help to optimise the design and delivery of exercise-based interventions in people with knee OA, improving adherence and potentially maximising the pain-relieving effects of exercise in this population.

Thus, the objectives of this study were twofold: Firstly, to identify key factors that may be associated with EIH magnitude in response to a standardised bout of exercise in individuals with knee OA, and secondly, to quantify the contribution of these factors to the observed variance in EIH among individuals with knee OA.

3.2 Materials and Methods

3.2.1 Design and Participants

This was a cross-sectional study and secondary analysis of baseline (pre-intervention) data from a larger double-blind, randomised non-inferiority trial, comparing two different types of serotonin-noradrenaline reuptake inhibitors for the treatment of knee OA pain (Australia New Zealand Clinical Trials Registry: ACTRN12619001082190). The original protocol and secondary analysis were approved by the New Zealand Central Health and Disability Ethics Committee (19/CEN/27).

Participants were recruited from primary care practices, through newspaper advertisements, online advertisements (e.g. Arthritis NZ website, social media channels) and from orthopaedic first surgical appointments at local hospitals in the Auckland region of Aotearoa New Zealand. Inclusion criteria for the original study were males and females ≥ 40 years of age who had radiographic knee OA and met the American College of Rheumatology (ACR) clinical criteria for the diagnosis of knee OA. That is, they had knee pain for > 14 days of each month for ≥ 3 months, and had an average pain rating in the last 24 hours of ≥ 4/10 at the time of initial screening. Individuals were excluded if they were currently using antidepressant medication or any other medication with a serotonergic effect; had used a monoamine oxidase inhibitor (MAOI) in the last 14 days; have narrow-angle glaucoma; had a body mass index (BMI) ≥ 40; had a diagnosis of any other type of arthritis; had a joint injection or surgery on the index knee (the knee that the participant identified as being their symptomatic or more symptomatic knee) within the last 3 months at the time of screening; had impending surgery in the next 3 months.

Additional exclusions are: had medical contraindication to the use of rescue medications (acetaminophen and NSAIDs); were taking any excluded medications that could not be discontinued; were using warfarin; were women who were pregnant, breast feeding or planning to get pregnant; had a previous diagnosis of a major psychiatric disorder; had a history of alcoholism; had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 100 IU/L or total bilirubin > 27.4 umol/L; had a glomerular filtration rate of < 30ml/min; had a history of myocardial infarction in the last 12 months at the time of screening, QTc interval >500ms: had unstable coronary artery disease or recent unexplained cardiac symptoms; had uncontrolled hypertension (>140 mmHg systolic or ≥90 mmHg diastolic BP); had a history of seizures, had a history of multiple falls in the last 12 months at the time of screening; or had an inability to perform psychophysical sensory testing e.g. documented sensory loss. Additionally, participants were instructed to refrain from consuming caffeine or any pain medications for 12 hours before the data collection session.

3.2.2 Sample Size

A sample size of n=119 was used for this exploratory analysis aimed to identify factors associated with EIH magnitude. While not formally powered, the sample size is sufficient to detect a medium size effect for each of the 15 individual factors planned in this study, as suggested by Green (354).

3.2.3 Procedures

During the baseline session of the primary trial, prior to the delivery of any interventions, participants completed several questionnaires and underwent quantitative sensory testing, including the EIH paradigm (see Figure 1). These assessments are described below. The Lower Limb Task Questionnaire (LLTQ) (355), and the Brief Pain Inventory (BPI) (356), were collected for descriptive purposes. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) was used as a guideline for reporting (357).

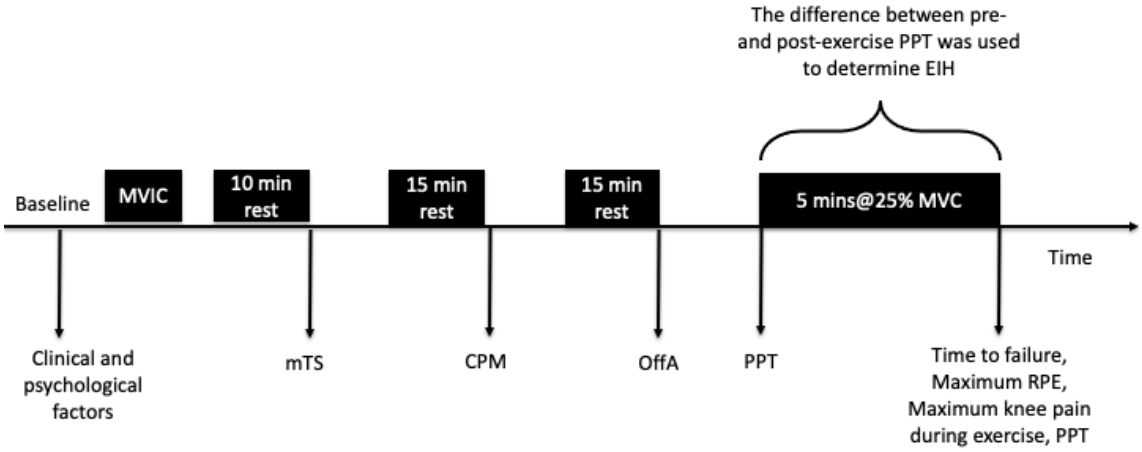


Figure 1. *Experimental protocol. Abbreviations: CPM, conditioned pain modulation; CSI; Central Sensitisation Inventory; EIH, exercise induced hypoalgesia ExBelief, Beliefs About Exercise and Pain; HADS, Hospital Anxiety and Depression Scale; OffA; Offset Analgesia; PCS, Pain Catastrophizing Scale; TSK, Tampa Scale for Kinesiophobia; mTS, mechanical temporal summation; MVIC, maximum voluntary isometric contraction; PPT, pain pressure threshold; RPE, rating of perceived exertion.*

Dependent Variables

The dependent variables for this study were the absolute and relative EIH values (EIH_{abs}, EIH_{rel}) determined by the change in pressure pain threshold (PPT) from immediately before (PPT_{pre}) to immediately after (PPT_{post}) a single bout of submaximal isometric quadriceps exercise (77, 358). PPT_{pre} was assessed at two sites, in a random order: locally at the medial joint line (3 cm medial to the midpoint on the medial edge of patella) of the index knee and remotely at the volar surface of the contralateral forearm (5 cm distal to the lateral epicondyle) (239). The same test-site order was used for PPT_{post}. PPTs were assessed using a handheld pressure algometer (SbMedic, Sweden) with a 1 cm rounded tip and a ramping rate of 30 kpa/s. Participants were instructed to press a button at the moment they first experienced any pain from the probe and the pressure achieved

in kPa (PPT) was recorded. Three PPT measurements were recorded for each site and the average used for the primary analysis. There is little consensus whether to report EIH as the absolute (in kPa) or relative (ratio or percentage) change in PPT from pre-to post-exercise. Both are frequently used in the literature (260, 268, 269), and we chose to report and analyse both EIH_{abs} and EIH_{rel} at both local (knee) and remote (forearm) sites. EIH_{abs} was the numerical difference between PPT_{post} and PPT_{pre}, such that positive values reflect an increase in PPT (hypoalgesia) following exercise, while negative values reflect decreased PPT (hyperalgesia). EIH_{rel} was a ratio of PPT_{post} to PPT_{pre}, such that values greater than 1.0 reflect an increase in PPT (hypoalgesia) following exercise, while values less than 1.0 reflect decreased PPT (hyperalgesia) (80).

Isometric Exercise Protocol

To allow individualisation of quadriceps isometric exercise intensity, participants first completed an assessment of their maximum voluntary isometric contraction (MVIC) on the most symptomatic (index) knee, defined as the knee with the highest self-reported pain during daily activities. MVIC testing was performed using a Biodex Multi-Joint System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA), with the hip and knee positioned at 85° and 90° of flexion, respectively. A standardised warm up of 4, 5-s isometric quadriceps contractions at 25%, 50%, 50% and 75% of perceived maximum effort was performed, followed by 3, 5-s maximum effort voluntary contractions with a 30 s rest period between contractions. Consistent verbal encouragement was given for all contractions and MVIC was taken as the peak torque (Nm) produced during any of the three maximum effort contractions (258, 359).

To induce EIH, a single submaximal isometric contraction of the quadriceps at a target force of 25% of MVIC was performed on the same dynamometer. Participants were positioned as was described previously and were instructed to maintain the target force until failure (inability to sustain 25% of their MVIC for ≥ 5-s) or to a maximum of 5 min. Participants were provided continuous visual feedback of their quadriceps force and were given consistent verbal encouragement to ensure that true contraction failure or the 5-min maximum time was reached (77, 359). Time to failure (in seconds) was recorded.

Independent Variables

Participant's age and sex were captured as part of the baseline demographic documentation. In addition, the following variables from the test session were included as independent variables:

Clinical Factors

Time to Failure (seconds)

During the isometric exercise protocol, time taken to reach true contraction failure was recorded in seconds in order to capture participants' muscular endurance and fatigue resistance.

Maximum Rating of Perceived Exertion (RPE)

During the isometric exercise protocol, a rating of perceived exertion (RPE) on Borg's 6–20 scale (360), with 6 defined as "no exertion at all" and 20 as "maximal exertion" was obtained every 30 seconds. The psychometric properties of the RPE scale are well established, with high validity and reliability in assessing perceived exertion during physical activities (360). The maximum RPE obtained during the isometric contraction task was recorded.

Maximum Knee Pain During Exercise

Immediately after completing the isometric exercise protocol, participants were asked to rate the maximum knee pain they experienced at any time during the contraction, on a scale from 0 to 100 where 0 = no pain at all and 100 = the worst pain imaginable (361).

Neurophysiological Factors

Conditioned Pain Modulation

CPM was assessed following the protocol described by Yarnitsky et al. (362), using a Pathway ATS thermal stimulator (30 mm × 30 mm thermode; Medoc, Israel) and a temperature-controlled water bath (Contherm Scientific, New Zealand). The test stimulus (Pain60) was determined by applying heat to the volar surface of the non-dominant forearm, beginning at 32 °C and increasing at a rate of 1 °C/s until the participant reported a pain intensity of 60/100 on a numerical rating scale. A safety cut-off of 50 °C was applied. The Pain60 temperature was then applied for 30 s,

during which continuous pain ratings were recorded using an electronic visual analogue scale (eVAS). Following a 15-minute rest, the conditioning stimulus was delivered by immersing the contralateral hand in a 46.5 °C circulating hot water bath for 60 s. The test stimulus was reapplied after 30 s of immersion, and CPM was calculated as the difference in mean pain ratings during the test stimulus alone and during concurrent application with the conditioning stimulus. Peak pain intensity of the conditioning stimulus was also recorded.

Offset Analgesia

Offset analgesia (OffA) is characterised by a disproportionate decrease in pain perception following a slight decrease in noxious stimulation intensity. OffA was elicited using a three-stimulus heat pain paradigm consisting of a 5 s noxious heat stimulus (T1) followed by a 1°C increase in temperature for 5 s (T2), and then a final 20 s period (T3) equal in temperature to T1 (308). The same thermode as described previously, was attached to the forearm with a Velcro strap and maintained at a baseline temperature of 35°C. Three different types of stimulus trials were used: experimental condition, control condition, and constant temperature condition. The experimental condition train consisted of T1 = Pain50 (temperature that induces pain ratings of 50 on a 0-100 scale, determined as per Pain60; 5 s), , T2 = Pain50+1°C (5 s), and T3 = Pain50 (20 s). The eVAS was used to provide a continuous measure of pain during these 30 s. The peak to peak decrease in pain rating from T2 to T3 was taken as a measure of offset analgesia (308). The control trial used the same T1 and T2 stimuli as the experimental trial but had a T3 of 35°C. The constant temperature trial assessed pain intensity during constant temperature stimulation of 35°C for 30 s (308).

Mechanical Temporal Summation

Mechanical temporal summation (mTS) is a dynamic psychophysical test of pain sensitivity, characterised by an increase in pain perception during a series of repeated nociceptive stimuli at a frequency of ≥ 0.33 Hz (317). mTS was examined using a 180 g (# 6.45) Von Frey Monofilament (North Coast Medical, USA) over the volar forearm (362). A single stimulus was applied followed by 10 repetitive stimuli, with an inter-stimulus interval (ISI) of 1 s applied within an area 1 cm in diameter. Participants were asked to rate the level of pinprick pain intensity on a

scale from 0 to 100 for the single stimulus and the final (10th) stimulus of the train. The difference in pain intensity between the last (10th) stimulus of the train and the single stimulus was taken as the measure of mTS (362).

Psychological Factors

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item questionnaire used to assess anxiety and depression symptoms, with the anxiety and depression subscales scored from 0-21, with higher scores indicating more symptoms (153). This widely used instrument shows adequate validity and reliability in various populations, including people with OA (363-366).

The Pain Catastrophising Scale (PCS)

The 13-item PCS outcome measure was used to assess catastrophic thinking related to pain, with total scores ranging from 0-52 (367). Scores above 30 are typically considered clinically relevant and associated with poorer outcomes in pain populations. The PCS has adequate internal consistency, validity and test-retest reliability in both pain-free individuals and people with chronic pain (368, 369).

The Tampa Scale of Kinesiophobia (TSK)

The TSK is a 17-item questionnaire used to assess fear of movement. The degree of agreement with each item is rated on a five-point scale, with total scores ranging from 17 to 68. Higher scores reflect greater fear of movement or re-injury. A score above 37 is generally considered indicative of high kinesiophobia. This tool has been previously utilised in people with knee OA and shown to be valid and reliable (370).

Central Sensitisation Inventory (CSI)

The CSI is a reliable self-report questionnaire that has been validated demonstrates good psychometric properties (371, 372). It consists of 2 parts, of which part A is a self-report questionnaire that includes 25 items about the frequency of central sensitisation-related symptoms, scored on a 5-point Likert scale ranging from 0 to 4 (373). Higher total scores are taken to indicate

a higher burden of of central sensitisation-related symptoms. Previous research provided CSI severity levels as a guideline for interpreting CSI scores: subclinical = 0 to 29; mild = 30 to 39; moderate 40 to 49; severe 50 to 59; and extreme = 60 to 100 (374).

Beliefs About Exercise and Pain (ExBelief)

Participants' belief about the acute pain-relieving effects of exercise was assessed using a single questionnaire item: "Pain can be reduced from just a single session of exercise". This item was previously used in a study investigating the role of expectations on the EIH response in healthy, pain-free participants, where a significant correlation was found between the score on the item and the magnitude of the subsequent EIH response, measured as the pre-to post-exercise change in PPT. The item was scored on a 7-point Likert scale (0=strongly disagree, 6= strongly agree) (89).

Expected Pain Change

Following MVIC testing, participants were familiarised with the upcoming EIH testing procedure to be completed in order to obtain pain expectancy scores. To do this, participants were told that they would be instructed to maintain a target torque of 25% of their MVIC for a maximum of 5 mins or until failure of target torque. They were then asked to maintain a target torque of 25% of MVIC for 10-s and asked to rate (0-100 on the NPRS) what they expected their familiar knee pain to be if they were to hold the contraction to failure as just described to them. The difference between the two pain scores (expected knee pain intensity - resting knee pain intensity) was taken as the measure of expected change in pain.

Statistical Analysis

Wilcoxon signed-rank tests were used to determine whether absolute post-exercise PPTs were significantly different from pre-exercise PPTs, at the local (knee) and remote (forearm) sites. A primary statistical analysis was conducted to evaluate what key clinical, psychological and neurophysiological factors were associated with the magnitude of EIH in individuals with knee OA. This question was answered in terms of both EIH_{abs} and EIH_{rel} at both the knee and forearm. Thus, four linear regression models were constructed, two for each location. The

models regress EIH_{abs} and EIH_{rel} on age, sex, CPM, OffA, TS, max RPE, depression, anxiety, PCS, TSK, ExBelief, Expected Pain Change and order of PPT tests. All these variables were entered as continuous except sex and order of PPT tests, which were entered as dichotomous. Model coefficient, standard error, t-value, degrees of freedom and p-value were used to evaluate the relationship between EIH and the independent variables. Statistical significance level was set at 0.05.

A secondary statistical analysis was conducted to examine the extent to which the EIH variance in individuals with knee OA was explained by the observed (clinical, psychological and neurophysiological) and unobserved variables. To answer the second question for each location separately, EIH_i (3 repetitions per location) was fitted with linear mixed regression models. EIH_i for *ith* repetition was obtained by normalising the *ith* post-exercise PPT value by the average of the three pre-exercise PPT values, or PPT_{pre}. Although it is not the established method for analysing EIH data, this method resulted in three EIH data points per individual for each location instead of a single data point per individual. Multiple data points allowed for the use of linear mixed regression, which would decompose the dependent variable variance, into between-participant and within-participant variance. In these models, similar to the linear regression model, EIH_i was regressed on the observed variables. To account for differences across repetitions, the models included repetition as a continuous variable. Moreover, the models estimated between-participant variance. The independent clinical, psychological and neurophysiological factors which have a statistically significant relationship with EIH_i were reported. Using a hierarchical two-step approach along with decomposition of variance components from the linear mixed models, the proportion of variance explained by the observed variables, between-participant variance and residual (remaining/error) variance was reported. The between-participant variance was attributed to unobserved participant-level variables. The residual variance may be attributed to instrument imprecision and inadequate data modelling such as non-linear relationships between the investigated variables and EIH magnitude. The models were fitted in R (375-378). The assumptions of normality and homogeneity of variance for model residuals were evaluated with QQ-plots and fitted-values versus residuals plots. The presence of

multicollinearity was assumed at a variance inflation factor (VIF) of 10 and to mitigate multicollinearity, some of the variables were excluded based on clinical judgement (379).

3.3 Results

Participant Characteristics

A total of 129 individuals provided written informed consent and underwent baseline (pre-intervention) testing. Following this, 10 participants were excluded: 8 due to equipment failure that precluded the collection of all neurophysiological measures, and 2 upon the discovery of undisclosed neurological conditions during the data collection procedures that may have affected the validity of some measures. Consequently, the data of 119 participants (92% of the initial cohort) were included in the final analysis (Table 2).

***Table 2**. Participant characteristics for the study (n=119). Data are presented as mean (SD) or median (IQR) unless otherwise stated.*

Age (y)	67.8	(9.5)
Sex (females (%))	53	(45%)
Height (cm)	170	(10)
Weight (kg)	82.2	(15.5)
BMI (kg/m2)	27.9	(25-31)
Ethnicity: frequency/percentage		
New Zealand European	101	(85%)
New Zealand Māori	7	(6%)
Tongan	1	(1%)
Chinese	2	(2%)
Indian	2	(2%)
Other	6	(5%)
Duration of knee pain (months)	48	(24-120)
LLTQ (0-100)	25.8	(5.7)
HADS- Depression (0-21)	4	(2-6)
HADS- Anxiety (0-21)	5	(3-7)
TSK (11-44)	25	(5.1)
PCS (0-52)	10	(5-17)
BPI-Ave (0-10)	4	(3-5)
BPI-Worst (0-10)	8	(4-10)
BPI-Least (0-10)	3	(1.5-4)
BPI-Interference (0-10)	4.1	(2)
CSI (0-100)	45	(20-60)
mTS (0-100)	29.7	(9.6)
CPM (0-100)	-4	(-14.8-3.3)
OffA (0-100)	-19	(17.4)
Peak Torque (Nm)	117	(91-116)
EIH testing order (knee first (%))	57	(48%)
Expected change in knee pain (0-100)	45	(20-60)
Actual change in knee pain (0-100)	0	(0-2)
Maximum knee pain during contraction (0-100)	10	(0-50)
Time to failure (s)	300	(246-300)
Max RPE (6-20)	19	(17-20)

Abbreviations: BMI, Body Mass Index; BPI, Brief Pain Inventory; CSI, Central Sensitisation Index; CPM, Conditioned Pain Modulation; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; LLTQ, Lower Limb Task Questionnaire; m, meters; min, minutes; MVIC, Maximum Voluntary Isometric Contraction; OffA, Offset Analgesia; PCS, Pain Catastrophising Scale; s, seconds; SD, Standard Deviation; TSK, Tampa Scale for Kinesiophobia; TS, Temporal Summation.

Table 3. *Absolute and relative Pressure Pain Threshold (PPT) at the knee and forearm pre- and post-isometric knee extension exercise. Values are displayed as median (interquartile range).*

Measurement	Pre exercise	Post exercise	Change type	Change value
PPT Knee	252 (176-353)	293 (190-413)*	Absolute (kPa) Relative (ratio)	28 (1-93) 1.12 (1.01-1.35)
PPT Forearm	249 (188-356)	250.7 (199-388)*	Absolute (kPa) Relative (ratio)	12 (-19.3-57.7) 1.06 (0.91-1.22)

*represents significant within group change from pre- to post-exercise $p<0.01$

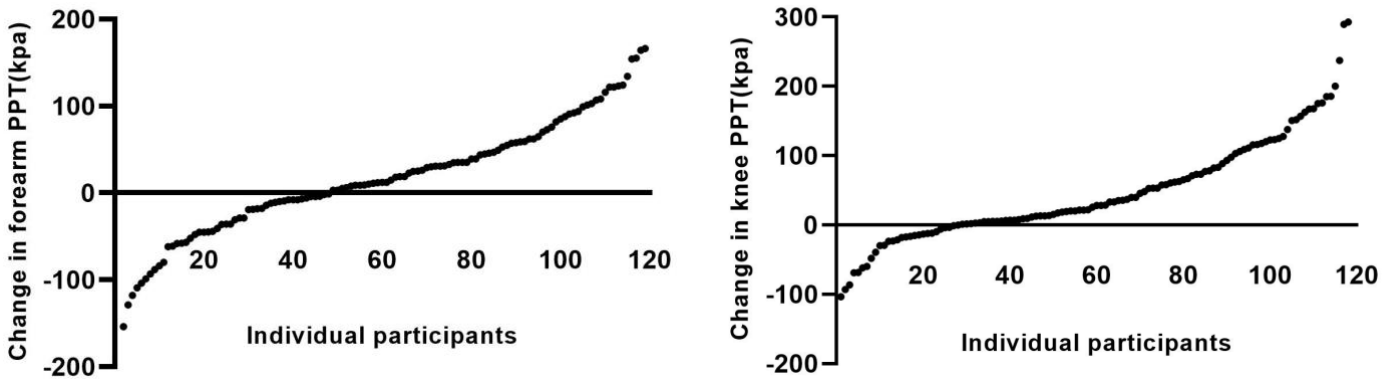


Figure 2. *Distribution of the absolute change in knee pressure pain thresholds from pre- to post-isometric exercise of the quadriceps (i.e. the EIH response) for individual participants at the forearm (remote site, n=119, left plot) and at the knee (local site, n=119, right plot), ordered from the most hyperalgesic (left) to the most hypoalgesic (right) response. The pre- to post-isometric exercise change in pressure pain thresholds ranged from -246 kPa to 166 kPa at the forearm (remote site), with no change or a hyperalgesic response in 48/119 (40.34%) individuals. Similarly, the pre- to post-isometric exercise change in pressure pain thresholds ranged from -104 kPa to 388 kPa at the knee (local site), with no change or a hyperalgesic response in 27/119 (22.69%) individuals.*

On average, a significant local (knee) and remote (forearm) EIH response was demonstrated when expressed both as an absolute and relative change (Table 3. Despite this, the variability in the individual EIH response was large (Figure 3), with 48/119 (40%) and 27/119 (23%) of individuals showing no change or an increase in PPT sensitivity (hyperalgesia) at the remote and local test sites, respectively.

Factors associated with EIH magnitude at the knee and forearm

Relationships between baseline variables and absolute EIH

No significant association was observed between any of baseline variables and the absolute change in knee PPT (all p > 0.06). Change in forearm PPT demonstrated a significant association with HADS-anxiety, such that a one-unit increase in anxiety corresponded with a decrease of 7.1 ± 2.8 kPa in the absolute change in forearm PPT from pre- to post-exercise (p= 0.01).

Relationships between baseline variables and relative EIH

For EIH_{rel} at the knee, an increase in age was positively associated with EIH ratio, where each additional year of age was linked to a 0.007± 0.003 increase in the EIH ratio from pre- to post-exercise (p = 0.02). Similarly, age showed a positive association with EIH_{rel} at the forearm, resulting in an increase of 0.006 ± 0.003 in the EIH ratio for each additional year of age (p = 0.04). Moreover, each one-unit increase in HADS-anxiety was linked to a decrease of 0.022 ± 0.009 in the EIH ratio at the forearm (p = 0.02).

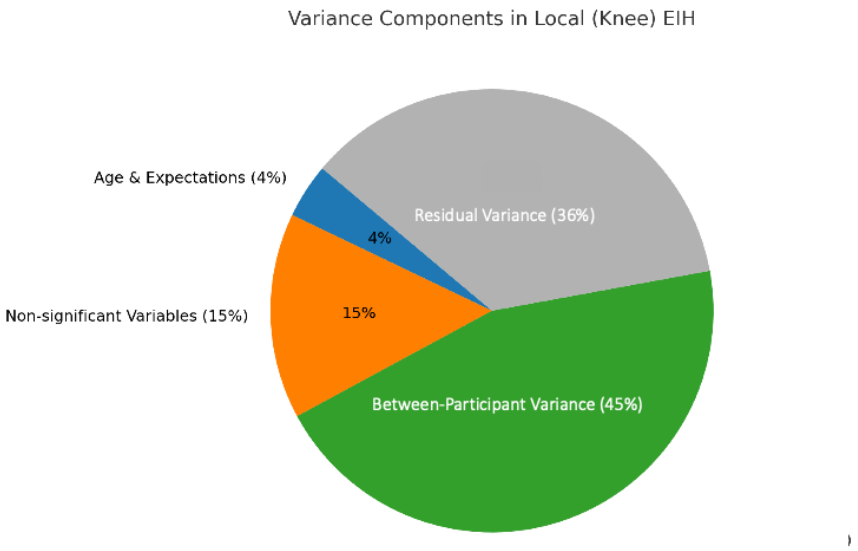
Sources of variance in EIH magnitude at the knee and forearm

A linear mixed-effects model revealed a significant relationship between knee EIH and two associated variables: age and expected change in pain. Specifically, for the knee, age was positively associated with EIH (b = 0.007, SE = 0.003, t(119) = 2.581, p = .01), indicating that older participants had larger EIH scores. Conversely, expected change in pain was negatively associated with EIH (b = -0.002, SE = 0.0009, t(119) = 2.010, p = .047), indicating that participants expecting greater increases in knee pain with exercise had lower EIH.

Variance decomposition indicated that 4.5% of the variance was accounted for by age and Expected Pain Change. Notably, 15.1% of the EIH variance was explained by non-significant observed variables and differences across repetitions, with a

substantial 44.9% attributable to unobserved between-participant characteristics. Residual variance constituted 35.5%, unexplained by the model (Figure 4).

In terms of forearm EIH, the model coefficients for age (b = 0.005, SE = 0.003, $t(119) = 2.234$, p = .027) and anxiety (b = -0.022, SE = 0.009, $t(190) = -2.537$, p = .012) were significant, indicating that the magnitude of forearm EIH was greater in participants who were older and had lower HADS-anxiety scores. Variance decomposition showed that age and anxiety uniquely explained 6.5% of the variance. Similarly, 7.3% of the variance was explained by the same non-significant investigated variables as in the knee EIH model. The largest proportion of variance, 46.5%, was due to unobserved between-participants characteristics, and the remaining 39.7% was residual variance, unexplained by the model (Figure 3).



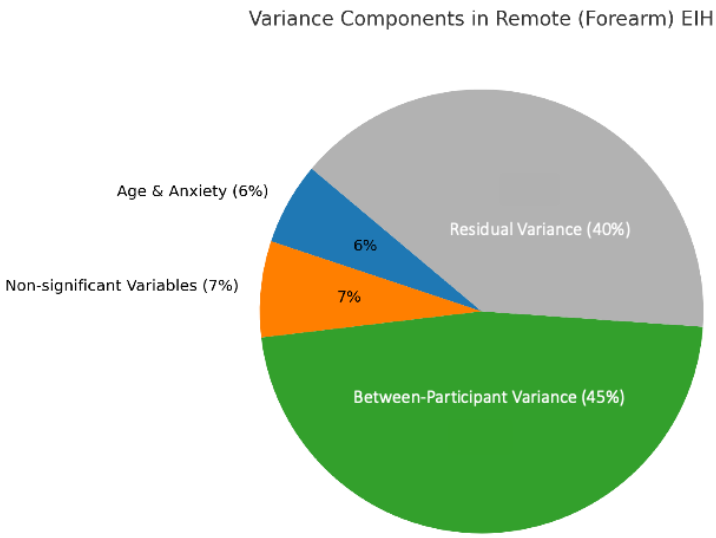


Figure 3. *Proportions of variance in EIH magnitude at the knee and forearm.*

3.4 Discussion

In this cross-sectional, secondary analysis of people with knee OA, we observed a statistically significant increase in PPTs at the knee (local EIH) and the contralateral forearm (remote EIH) following a sustained, submaximal isometric knee extension exercise. These findings support previous studies examining EIH in a knee OA population that have also shown a significant EIH effect at the group level (79-81). However, other studies have shown variability in EIH among people with knee OA (78, 88, 239-241), with some participants demonstrating an impaired EIH response. Similar inter-individual variability was observed in this study, where 23-40% of participants demonstrated no change or an increase in pressure pain sensitivity (hyperalgesia), rather than a hypoalgesic response to exercise (Figure 2).

The primary aims of this study were to identify potential clinical, psychological, and neurophysiological variables that were associated with inter-individual differences in EIH magnitude in people with knee OA, and to quantify the extent to which the observed variables contributed to the variance in EIH magnitude. The key findings were as follows. Across all models, only age was positively associated with EIH magnitude, while anxiety and expected change in pain were negatively associated with the magnitude of EIH. Despite including a broad range of potential

associated factors, all included variables accounted for less than 20% of the overall variance in EIH magnitude, across models. A large proportion of variance, ~44-47% across models, was due to unmeasured differences between participants.

The current study identified a positive association between age and EIH, with an increase in age reflecting greater EIH_{rel} , but not EIH_{abs} , at both the knee and forearm. The age of the participants ranged from 40 to 91. The size of this effect was such that for each decade increase in age, post-exercise PPT increased by ~7% at the forearm and ~6% at the knee, when expressed relative to pre-exercise PPT values. This contrasts with existing evidence regarding age-related differences in EIH, with some studies observing no significant variation in EIH across age (250), while others have reported a diminished EIH response in older adults (280). A key factor in these discrepancies may lie in methodological differences. Vaegter et al. (250) examined only individuals under 65, limiting the ability to capture changes in older age groups. In contrast, Naugle et al. (280) compared two distinct age groups, young adults (19–30 years) and older adults (55–74 years), using a wide age range and including a much younger cohort than the current study.

The association with EIH_{rel}, but not EIH_{abs}, in this study suggests that lower baseline PPTs in older adults may contribute to a proportionally larger relative change in pain sensitivity post-exercise. While our models adjusted for baseline PPTs as covariates, this adjustment partially reduced, though did not completely eliminate, the impact of initial values. Differences in covariate inclusion between studies could also explain variations in findings. For example, studies like Ohlman et al. (281) have shown that higher physical activity levels predict greater EIH in older adults (60–77 years), implying that physically active older adults may retain better pain modulatory capacity. In studies without such adjustments, age may act as a proxy for other factors, such as physical activity or psychological variables. These findings emphasise the importance of considering covariates that may interact with age when investigating EIH.

We could not replicate previous findings of a correlation between pain catastrophising and EIH magnitude in people with knee OA (73). In contrast to

Wideman et al. (73), we found no association between pain catastrophising and EIH. A possible explanation is a floor effect**:** median PCS in our sample was 10 / 52 (IQR 5–17), well below the ≥30 threshold often considered clinically meaningful. Previous work shows that catastrophising moderates EIH only when baseline scores are higher and that situational (state) catastrophising rather than dispositional PCS may be the stronger predictor of post-exercise hypoalgesia (238). However, lower anxiety was associated with a greater EIH_{abs} and EIH_{rel} at the forearm (remote site), but not the knee (local site). These findings contrast with several previous studies (238, 285, 293, 296, 380-382) that failed to find a significant association between EIH and anxiety. Notably, one study has shown a correlation between EIH and anxiety in a chronic pain population but with opposite findings. In his study, Vaegter et al. (85) included participants with musculoskeletal pain of mixed origin (37 with LBP; 16, 7, and 1 with neck, shoulder, and elbow pain, respectively) and found a significant positive correlation between combined state-trait anxiety and EIH after aerobic exercise when PPT was measured at the trapezius and the biceps brachii (85). However, there was no significant correlation between anxiety and EIH with isometric exercise or with aerobic exercise when all PPT sites were combined (4 sites). The finding in the current study, that people with knee OA who had lower anxiety tended to have increased EIH at the forearm, could have several explanations and suggests that anxiety more strongly influences EIH due to systemic factors, as opposed to local factors, close to the exercising muscle. One possible mechanism is the reduction of endogenous opioid tone associated with higher anxiety levels. In a study that replicated a genetic model of high anxiety and OA-like pain, the authors found that anxiety can alter endogenous opioid function, leading to decreased effectiveness of opioid analgesics (383). Specifically, anxiety may increase the release of cholecystokinin (CCK), a peptide that antagonises endogenous opioids, thereby diminishing their pain-relieving effects. Furthermore, the study demonstrated that the presence of high anxiety and chronic pain resulted in elevated levels of endogenous opioids, such as beta-endorphin, which were associated with altered opioid receptor function and reduced opioid analgesia. Such changes may contribute to reduced EIH as the endogenous opioid system is thought to play a key role in mediating the EIH response (77, 207). Another potential mechanism

may include the role of inflammation. Anxiety has been linked to increased levels of inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), which may increase pain sensitivity and reduce the body's ability to modulate pain through exercise (289, 384). It should be noted that the median (IQR) anxiety score on the HADS was 5 (3-7) in our sample, indicating that most of our participants were experiencing mild symptoms of anxiety, below the suggested cut off of 8 points that may be considered clinically important (385). Therefore, it remains unknown how higher levels of anxiety may influence EIH in people with knee OA.

A higher expected increase in knee pain was associated with a reduced EIH response. Pain-related expectations are widely acknowledged to influence treatment outcomes and have previously been demonstrated to affect EIH through the use of pre-exercise information in studies of healthy, pain free control participants (89, 322). In a randomised controlled trial of healthy, pain free participants (322), a 22% increase in PPT was observed in a group given positive information about pain reduction with exercise, whereas the group given the opposite information had a 4% decrease in PPT at the exercising muscle following a 3-minute isometric exercise. In a similar randomised controlled trial (89), positive pre-exercise education enhanced EIH when compared to neutral pre-exercise education. Both studies observed a significant correlation between expectations and the magnitude of the EIH response.

The present study extends these findings to a chronic pain population, showing for the first time that pre-exercise pain expectations are linked to EIH magnitude in knee OA. Notably, our participants' expected change in pain [45 (20–60)] contrasted sharply with their actual change [0 (0–2)], highlighting a substantial expectation–outcome mismatch. This is consistent with broader evidence in chronic pain, where negative beliefs and expectations about exercise (e.g., anticipating pain flare-ups or further joint damage) are strongly associated with reduced adherence, higher disability, and increased pain (69, 386, 387). In knee OA specifically, qualitative studies show that many patients expect exercise to worsen their symptoms, particularly when pain has previously been aggravated by activity (387). Such expectations are powerful enough to shape pain experiences,

potentially via top-down modulation of endogenous pain inhibitory systems (68, 325).

These findings underscore the importance of addressing beliefs and expectations in the clinical management of knee OA. Education that reframes pain and exercise as safe and beneficial, combined with gradual exposure and positive reinforcement, may help align expectations with actual experiences of exercise, thereby enhancing both adherence and the hypoalgesic effects of exercise. This suggests a potential therapeutic role for interventions such as pain neuroscience education, which have been shown to modify unhelpful pain beliefs and improve functional outcomes when combined with exercise (158, 328, 329). To our knowledge, this is the first study linking pre-exercise pain expectations to the magnitude of EIH in a population with chronic pain. These results suggest that expectations of the value of exercise, whether as potentially beneficial or harmful, may directly influence the EIH response in people with knee OA, and therefore represent an important treatment target for future intervention studies.

Similar to one previous study in a knee OA population (80), we observed no association between sex and EIH magnitude. Furthermore, no association was found between EIH and CPM, regardless of the test site for EIH. These findings align with some studies (285, 302, 305), but not others (250, 304, 306), which have generally found weak to moderate associations between CPM and EIH responses. Notably, these findings contrast to those of the only previous study to assess this relationship in a knee OA population (239), which found that participants who demonstrated an intact CPM response also had a normal (hypoalgesic) EIH response after both aerobic and isometric exercise, whereas in participants with an impaired CPM response, exercise failed to induce EIH. This discrepancy may relate to differences in the study population, or differences in the paradigms used to assess EIH and CPM. The EIH paradigm used in the current study was very similar to that used by Fingleton et al. (91), with a submaximal isometric knee extension exercise protocol and similar locations and methods of quantifying EIH. However, a notable difference between the studies was the CPM protocols used. The current study used a thermal test stimulus (heat) and painfully hot thermal conditioning stimulus, presented in parallel. This paradigm was chosen for the

purposes of the primary study. In contrast, Fingleton et al. (91) assessed the change in a mechanical test stimulus (PPT) serially, after a painfully cold conditioning stimulus. There is growing evidence that using different CPM paradigms, such as different conditioning stimuli or presenting the test and conditioning stimuli in parallel compared to series, may produce different results that, in least in part, reflect different underlying mechanisms (388, 389). Wideman et al. (73) add further complexity by demonstrating an association between EIH and TS when measured at the knee, but not at a remote site (dorsal side of middle finger). Our findings partially align with this, as we similarly found no association between TS and EIH when TS was assessed remotely at the forearm. However, since our study did not evaluate TS at the knee, we cannot directly compare our results to Wideman's findings at that site. Additionally, Wideman's study focused on the sensitivity to physical activity (SPA) index, emphasising evoked pain responses during physical tasks rather than changes in PPT. These differences in the study focus and testing locations might explain the contrasting outcomes, suggesting that the interaction between TS and EIH may depend on both the anatomical site and the specific pain model employed.

To our knowledge, this study is the first to use variance decomposition to estimate the proportion of variance in EIH explained by different sources. Despite the inclusion of a large range of independent variables, the observed factors, including age, anxiety, and expected change in pain, as well as the other non-significant associated variables, accounted for <20% of the total variance in EIH magnitude, across models. The substantial unobserved between-participant variance across models, underscores the need for further investigation into other factors that might better elucidate the individual differences in EIH in people with knee OA. This finding is similar to another recent study, where unobserved between-participant differences (24% to 34%), largely exceeded the contributions of commonly considered factors such as age, sex and conditioning stimulus intensity, to the magnitude of CPM responses (<12%) (390). Some potential unobserved factors that may contribute to EIH variability in people with knee OA, include genetic factors, immune responses, and/or autonomic nervous system function. With respect to genetic factors, Tour et al. (215) explored how single

nucleotide polymorphisms related to opioid and serotonin receptors, affect EIH in individuals with and without fibromyalgia (FM). Three specific genetic polymorphisms were examined: rs1799971 in the OPRM1 gene, rs6295 in the HTR1a gene, and combined polymorphisms 5-HTTLPR and rs25531 in the 5-HTT gene, affecting the opioid and serotonergic systems, respectively. While no individual genetic polymorphism significantly affected EIH in either group, interactions between opioid and serotonin polymorphisms influenced EIH in both pain-free controls and people with FM, suggesting that at least part of the individual variability in EIH is heritable. Thus, it seems plausible that genetic factors may also influence inter-individual variability in EIH in people with knee OA.

In addition to genetic influences, habitual physical activity status may also play a role. Several studies in pain-free adults have shown that more physically active individuals tend to demonstrate robust EIH responses, whereas sedentary or less active individuals often show impaired or absent EIH (207, 279, 281, 391). These findings suggest that physical activity may help preserve endogenous pain inhibitory capacity, particularly with advancing age. While not examined in the present study, recent work in knee OA has reported that physical activity levels moderate EIH and interact with autonomic function (392, 393), underscoring the importance of directly assessing habitual physical activity in future work.

Additional variables that may warrant further investigation include individual differences in immune and autonomic nervous system function. While regular exercise tends to reduce inflammation (221, 222), the acute effects of exercise are more complex and tend to be pro-inflammatory, including increased release of IL-6 and tumor necrosis factor-α within minutes of exercise ceasing (226, 394, 395). As pro-inflammatory cytokines both activate and sensitise the nociceptive system, differences in the acute inflammatory response to exercise, might explain some of the inter-individual variability in the EIH response in people with knee OA, as has been suggested in other chronic pain conditions (77, 396, 397). In knee OA specifically, a single bout of exercise has been found to increase the level of anti-inflammatory cytokines such as IL-10, but the extent to which this varies across

individuals is unclear (398). Additional work exploring the relationship between the acute immune response to exercise and EIH in knee OA is warranted.

Additionally, recent evidence suggests the autonomic nervous system (ANS) may play a role in EIH variability among people with knee OA. For example, Bossenger et al. (359), found that, at a group level, isometric exercise did not elicit EIH in individuals with knee OA or FM, in contrast to pain-free controls. Those with knee OA also exhibited lower resting cardiac vagal tone and a diminished autonomic reactivity to exercise, when compared to pain-free controls. More recently, a cross-sectional analysis of 45 people with knee OA (392) reported that people with impaired EIH, had lower levels of moderate-to-vigorous physical activity, while, in a healthy pain-free population, cardiac vagal tone was found to moderate EIH in those with low-moderate levels of physical activity (393). Taken together, these findings suggest that individual differences in ANS function and potentially, its interaction with habitual levels of physical activity, may contribute to EIH variability and should be explored further in people with knee OA.

Finally, the large residual variance observed in this study may be attributed to instrument imprecision (e.g., in the reliability of PPT measurement) and inadequate data modelling, such as non-linear relationships between some of the variables and EIH magnitude.

Strengths of this study include the large range of investigated variables measured and the use of variance decomposition to estimate the relative contribution of different factors to EIH variability. However, there are also some potential limitations to consider. Notably, the study's cross-sectional observational nature, limits the ability to determine causality when assessing the relationship between EIH and the various independent variables included in this study. Longitudinal and/or interventional research is needed to better understand whether modifying these or other factors may enhance the EIH response in people with knee OA. Additionally, despite our relatively large sample size compared to previous literature, our analysis was only powered to detect a medium effect size between the investigated variables and EIH. Thus, it is possible we were unable to detect smaller, yet still important relationships between the included variables and EIH

magnitude. Furthermore, as a secondary analysis of data from volunteers participating in a randomised controlled trial with quite specific inclusion and exclusion criteria, the findings may not be broadly generalisable to all people living with knee OA. Furthermore, it is important to emphasise that the results of this study only relate to EIH induced by a sustained submaximal isometric contraction of the quadriceps. Previous studies have shown that aerobic and isometric exercise elicit EIH of a similar magnitude, both in healthy controls (11) and knee OA specifically (16). However, it remains possible that both the EIH response, and the factors that contribute to its variance between people, may be different with other types of exercise. Further research is needed to elucidate whether different factors influence EIH during other exercise paradigms.

3.5 Conclusions

Older age, lower anxiety, and a lower expected increase in knee pain were associated with increased EIH magnitude after sustained isometric exercise in people with knee OA. These findings underscore the possibility that interventions addressing anxiety and pain expectations could improve EIH responses to resistance exercise in this population. However, a large amount of variance in the EIH response was unexplained or related to unmeasured between-participant factors, suggesting that further research is needed to better understand the sources of individual differences in the magnitude of the EIH response in people with knee OA, including across different exercise paradigms.

Chapter 4 Effects of pre-exercise education on EIH in people with knee OA: A double blind, randomised controlled trial

4.1 Background

In Chapter Three, we identified that lower anxiety and a lower expected increase in knee pain with exercise, were associated with enhanced EIH in people with knee OA. These findings illuminate the possibility that interventions addressing anxiety and pain expectations could improve EIH responses to resistance exercise in this population. However, despite the potential importance of EIH in the management of pain, studies aiming to enhance EIH are sparse. In healthy, pain-free controls, using targeted education (15 mins) to positively modify expectations about the beneficial, hypoalgesic and safe effects of exercise was shown to increase EIH compared to a control education condition (89). Furthermore, in another study of healthy pain-free controls, negatively manipulating expectations (2-3mins), by suggesting a likely painful response with exercise decreased EIH responses compared to neutral or positive education interventions (322).

The effects of pre-exercise education, designed to modify expectations of pain relief, have not yet been examined in an OA population. Such an intervention may be particularly relevant to knee OA, where negative beliefs, attitudes and expectations about exercise are pervasive, such as the belief that if exercise increases pain it will accelerate joint deterioration (399, 400). Additionally, given the chronic pain population in this study, it was possible to assess EIH using both traditional measures such as PPT as the primary outcome, and more clinical assessments of pain, including resting knee pain intensity and evoked pain intensity as secondary outcomes. This approach broadens the scope of potential clinical applications for EIH findings. Highlighting these different measures reinforces the relevance of EIH as a clinically meaningful concept, particularly in populations experiencing chronic pain such as knee OA.

Thus, the aim of this study was to investigate the impact of pre-exercise education on EIH in people with knee OA. It was hypothesised that a larger EIH response

would be evident in individuals receiving targeted, positive education emphasising the safety and pain-relieving benefits of exercise in knee OA compared to a control education condition.

4.2 Materials and Methods

This double-blind randomised controlled trial (RCT) with a two-group parallel design and 1:1 allocation ratio was conducted between September and December 2022. The 2010 Consolidated Standards of Reporting Trials (CONSORT) statement (401) and 2017 CONSORT of Non-pharmacological Treatments Extension, were used as guidelines for reporting (402). All procedures were approved by the Health and Disability Ethics Committee (21STH129) and Auckland University of Technology Ethics Committee (21/241), and written informed consent was obtained from participants before testing. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000731897).

4.2.1 Participants

Participants were recruited through online and paper advertisements and from existing research databases. Additionally, paper advertisements were left with local knee surgeons, rheumatologists and physiotherapy clinics in the Auckland region of Aotearoa New Zealand.

Participants were included if they were adults ≥ 45 years of age, met The National Institute for Health and Care Excellence clinical criteria for the diagnosis of knee OA (aged ≥ 45 years and had activity-related joint pain and had either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes), had ongoing knee pain for ≥ 3 months, and had an average knee pain intensity of ≥3/10 on a numerical pain rating scale (NPRS) in the last week at the time of screening, where 0 = “no pain” and 10 = “worst pain imaginable” (403). Participants were excluded if they had an inability to speak or write English, medical conditions preventing safe participation in physical activity, an inability to climb 2 flights of stairs, a total knee replacement, knee surgery in the past 6 months, a recent history of lower limb resistance training (≥2 times per week for a minimum of 6 weeks within the past 6 months), any other form of arthritis (e.g. rheumatoid arthritis), a history of musculoskeletal pain or injury in the lower limb

(other than osteoarthritis) in the past 6 months, any neurological condition, any unstable/uncontrolled cardiovascular condition, a current diagnosis of a major psychiatric disorder, or any cognitive impairment.

4.2.2 Sample Size

A total of 42 participants were required (21 in each group) to achieve a probability of 80% that the study will detect a difference in EIH between interventions at a one-sided 0.05 significance level, with an effect size of Cohen's d = 0.8. We utilised a one-sided test due to the directional nature of our hypothesis, which posited that EIH would be larger with positive education compared to control education. A one-sided test was deemed appropriate as our primary interest was to determine whether the new intervention (positive pre-exercised education) was superior to current education interventions for OA, which tend to have a more biomedical focus (control pre-exercise education). This approach is consistent with the recommendations of Ludbrook (404), who supports the use of one-sided tests when the alternative hypothesis is specific and directional. A previous study investigating a similar pre-exercise education intervention on the EIH response in a pain free population, demonstrated a large effect size of r = 0.49 (89). When converted, this r value corresponds to a Cohen's d of 1.12 (405), indicating a very large effect. The disparity between r and d metrics of effect size is well-documented, with McGrath and Meyer (406) proposing that traditional benchmarks for r of small, moderate and large effect may be too conservative. To account for increased variability in the EIH response in people with OA (91), a more conservative effect size of Cohen's d = 0.8 was chosen for the sample size calculation.

4.2.3 Randomisation, Allocation Concealment and Blinding

Participants were randomised to the intervention or control group in a 1:1 ratio using a computer-generated randomisation schedule (sealedenvelope.com) with permuted blocks of 2 and 6. An independent researcher, who was not involved in participant recruitment, selection or data collection, distributed and stored the randomisation sequence in sealed, opaque envelopes to maintain allocation concealment. All participants and outcome assessors were blinded to treatment

allocation to reduce potential bias. Participants were told that the trial would "compare two different types of education and exercise interventions on knee osteoarthritis pain". In addition, the statistician responsible for data analysis was blind to group allocations. By necessity, the researcher delivering the interventions was not blinded.

4.2.4 Procedures

The experimental procedures are outlined in Figure 4. Each participant attended the laboratory during 2 clinical visits scheduled 24-72 hours apart ('Visit 1' and 'Visit 2'). Each visit took approximately 2 hours. During the first visit, participants provided demographic and clinical data for descriptive purposes, including age, sex, ethnicity, weight (kg), height (m), knee pain duration (years) and current medication use. Participants additionally completed questionnaires regarding their pain, mental health, and physical function, as well as knowledge and beliefs related to pain and exercise. These included the Brief Pain Inventory (BPI) (356), Hospital Anxiety and Depression Scale (HADS) (407), Lower Limb Tasks Questionnaire (355), Pain Catastrophising Scale (PCS) (367), Tampa Scale of Kinesiophobia (TSK) (408), Knee Osteoarthritis Knowledge Scale (KOAKS) (409) and a single item from Jones et al. (89) specifically related to EIH beliefs "Pain can be reduced from just a single session of exercise" which is scored on a 7 point Likert scale from 0 = "strongly disagree" to 6 = "strongly agree".

To allow standardisation of exercise intensity during the evaluation of EIH in visit 2, participants then completed an assessment of their maximum voluntary isometric contraction (MVIC) of the quadriceps muscle group at the index knee on a Biodex Multi-Joint System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA). In the instance where participants had bilateral knee OA, the most painful knee was chosen as the index knee for all further testing. Hip flexion was fixed to 85° and knee flexion fixed to 90°. A standardised warm up of four, 5-s isometric quadriceps contractions at 25%, 50%, 50% and 75% of perceived maximum effort was performed, followed by three, 5-s maximum effort voluntary contractions with a 30 s rest period between contractions. Consistent verbal encouragement was given for all contractions and MVIC was taken as the peak torque (Nm) produced during any of the three maximum effort contractions. Following MVIC testing,

participants were familiarised with the upcoming EIH testing procedure to be completed in visit 2, to obtain pain expectancy scores. To do this, participants were told that during visit 2 they would be instructed to maintain a target torque of 25% of their MVIC for a maximum of 5 mins or until failure of target torque. They were then asked to maintain a target torque of 25% of MVIC for 10-s and asked to rate (0-100 on the NPRS) what they expected their familiar knee pain to be, if they were to hold the contraction to failure as just described to them. Following the collection of all baseline data, the sealed envelope with the participant's study number was opened and used to randomly allocate them into one of two groups: positive pre-exercise education (intervention) or a control pre-exercise education (control). At the end of visit 1, they subsequently took part in the first of two education sessions (described in 4.2.5).

During the second visit, participants took part in their second education session and then undertook the EIH assessment. To quantify the EIH response, PPTs, resting knee pain and evoked knee pain were collected before and after a single bout of exercise involving a sustained, submaximal isometric contraction of the quadriceps. After the completion of the two education sessions but before the isometric exercise and collection of EIH measures, both groups were asked to complete the KOAKS and EIH beliefs single questionnaire item again, as a manipulation check for the education intervention(s). In this study, we used the single-item questionnaire to replicate the methodology of Jones et al. (89), who conducted research on healthy, pain-free individuals. Despite the questionnaire's lack of established validity and reliability, its use is justified to ensure methodological consistency, facilitate direct comparisons between studies, and contribute to the broader understanding of pain assessment and education in knee OA. This approach allowed us to isolate condition-specific differences in beliefs and provides preliminary data that may guide future research.

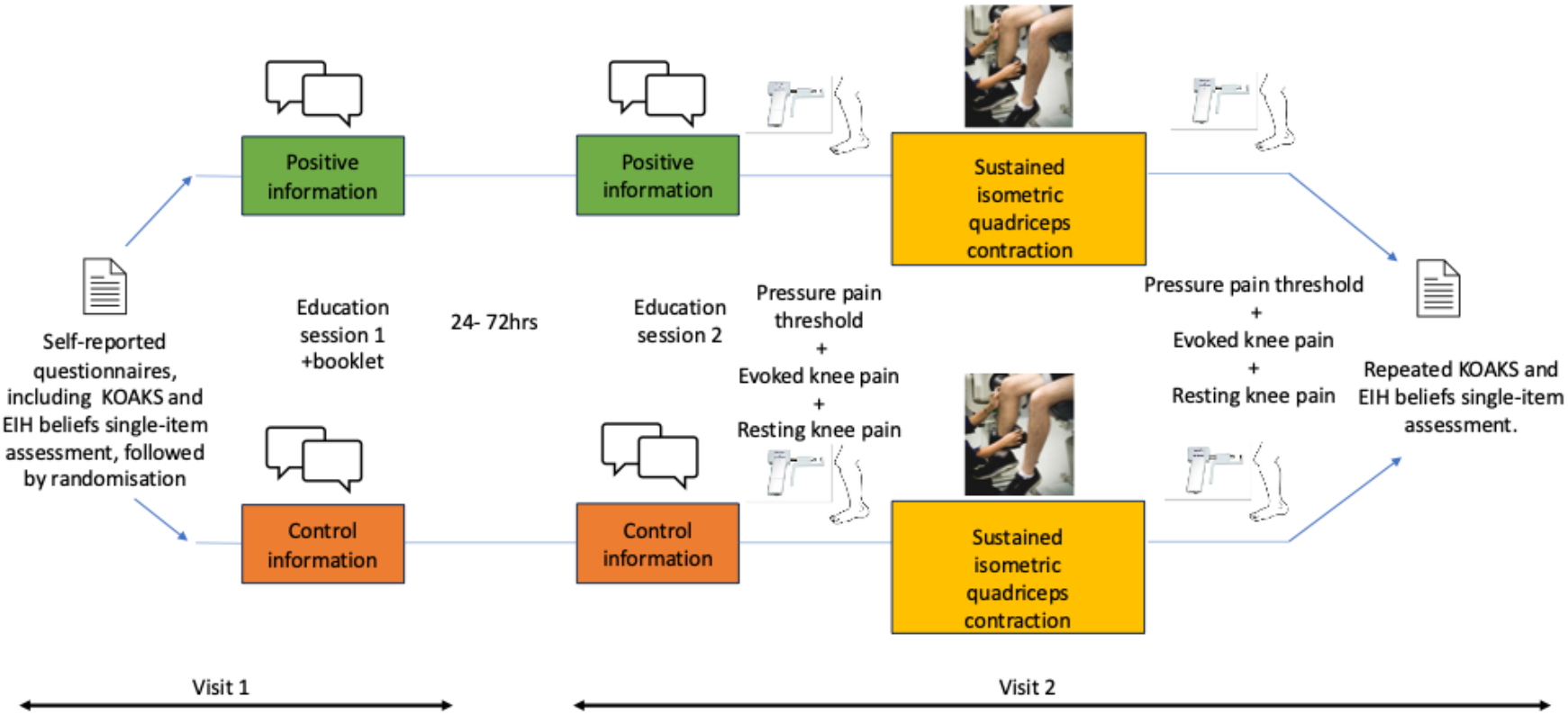

Positive information
Positive information
Sustained isometric quadriceps contraction
Self-reported questionnaires, including KOAKS and EIH beliefs single-item assessment, followed by randomisation
Education session 1 +booklet
24- 72hrs
Education session 2
Pressure pain threshold + Evoked knee pain + Resting knee pain
Pressure pain threshold + Evoked knee pain + Resting knee pain
Repeated KOAKS and EIH beliefs single-item assessment.
Control information
Control information
Sustained isometric quadriceps contraction
Visit 1
Visit 2

Figure 4. *Experimental procedures. Participants were randomised to receive positive education about knee OA and EIH (intervention) or education about knee OA, exercise and pain (control). Each education session for both groups lasted approximately 30 minutes and participants were given a booklet to take home and read after the 1st visit. At the second visit, following the second education session, EIH was quantified by measuring the participant's PPTs, evoked knee pain and resting knee pain before and after performing a sustained isometric quadriceps contraction at 25% of their MVIC for five minutes, or until failure.*

4.2.5 Interventions

The intervention consisted of two education sessions (one-on-one interactive style discussions), 24-72 hours apart ('Session 1' and 'Session 2') delivered by the same postgraduate qualified physiotherapist. The script, resources and supporting illustrations for the education sessions are included as supplementary material (see Appendix A) and are summarised here after. Each of the two education sessions lasted approximately 30 minutes and was closely matched in duration for the intervention and control groups. All sessions began with 10 minutes rapport building (see Appendix B). Standardisation of the interventions was achieved by following a rehearsed script that had been refined through pilot testing for session 1 and utilising the existing script described by Jones et al. (89) for session 2.Participants were also provided with printed booklets with the same content to take home and were asked to read between sessions 1 and 2, to reinforce the key messages. Participant engagement in the educational sessions was facilitated through regular questioning to check understanding, clarify uncertainty and, wherever possible, relating the content back to the personal experiences of the participant.

Positive education

In the intervention group the first education session included information specifically tailored to counter common misconceptions and beliefs regarding OA pain and its management, with a largely biopsychosocial focus (400, 410) (see Appendix B). During the second 30 min session, the intervention group's content included specific education related to EIH. This included describing the reduction in pain that normally occurs following a short bout of exercise, the type(s) of exercise likely to cause it, its duration and the potential underlying mechanisms. It followed the intervention group script provided by Jones et al. (89), with minor modifications (see Appendix B).

Control education

In the control group, the first education session included traditional OA education content sourced from a reputable and contemporary international website (411), with a largely biomedical focus (see Appendix B). Two sentences were modified

slightly to ensure that information specific to exercise and pain was neutral and sufficiently different from the information provided in the positive education intervention. Additionally, the “Where can I find out more?” page was modified to remove phone numbers and addresses based in the United Kingdom. The second education session included information about pain ratings (e.g., the difference between pain intensity and pain unpleasantness) and how pain sometimes differs between athletes and nonathletes. It followed the control group script provided by Jones et al. (89) (see Appendix B).

4.2.6 Isometric Exercise

To induce EIH, a single submaximal isometric contraction of the quadriceps at a target torque of 25% of MVIC was performed on a Biodex Multi-Joint System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA). Participants were positioned in sitting, with hip flexion fixed at 85° and 90° knee flexion. The participant was instructed to maintain the target torque until failure, defined as the inability to sustain 25% of their MVIC for ≥ 5s, or to a maximum of 5 min. Continuous visual feedback of their quadriceps torque was displayed on a computer screen placed directly in front of the participant. During the isometric contraction, a rating of perceived exertion (RPE) on Borg’s 6–20 scale (360), with 6 defined as “no exertion at all” and 20 as “maximal exertion”, was obtained every 30s. Participants were given consistent verbal encouragement to ensure that true contraction failure or the 5 min maximum time was reached and their time to failure (in seconds) was recorded. Following this, participants were asked to rate their maximum knee pain during the isometric contraction on a scale from 0 “no pain” to 100 “worst pain imaginable”. The decision to use submaximal isometric exercise to failure is underpinned by its established effectiveness in producing EIH. A systematic review by Naugle et al. (77), found that isometric contractions at low to moderate intensities (10-50% MVC) maintained for longer durations (such as task failure, ≥ 5 minutes) are particularly effective in eliciting an EIH response.

Primary Outcome Measures

The primary outcome measures for this study were the absolute and relative change in PPTs from immediately before, to immediately after the sustained isometric quadriceps exercise. PPT is a well-established outcome measure in pain

research including studies of EIH, providing a reliable measure of mechanical pain threshold (77). Before exercise, PPTs were assessed at two sites, in a random order: at the medial joint line (3 cm medial to the midpoint on the medial edge of patella) of the index knee and remotely at the volar surface of the contralateral forearm (5 cm distal to the lateral epicondyle) (239). The same test-site order was used for post-exercise measurement of PPTs. PPTs were assessed using a hand held pressure algometer (SbMedic, Sweden) with a 1 cm rounded tip and a ramping rate of 30 kpa/s. Participants were instructed to press a button at the moment they first experienced any pain from the probe (PPT) and the pressure achieved in kPa was recorded. The average of three PPT measurements was recorded for each site. There is little consensus whether to report EIH as the absolute (in kPa) or relative (ratio or percentage) change in PPT from pre-to-post-exercise, and both are frequently used in the literature (260, 268, 269). We chose to report and analyse both absolute and relative changes in PPTs at both local (knee) and remote (forearm) sites. For relative measures, post exercise PPT was expressed as a ratio of pre-exercise PPT for each individual at each site, such that values greater than 1.0 reflect an increase in PPT (hypoalgesia) following exercise while values less than 1.0 reflect decreased PPTs (hyperalgesia) (80).

Secondary Outcome Measures

Secondary outcomes included changes in resting knee pain intensity and evoked knee pain intensity via the Staircase-Evoked Pain Procedure (StEPP) (412), performed before and after isometric exercise. Resting knee pain was assessed using a 0- 100 point NPRS with anchors of 0 = “no pain” and 100 = “worst pain imaginable”. Evoked pain intensity was measured on the same 0-100 scale before and after completing the StEPP, which consisted of stepping up and down onto a 20 cm high platform 24 times. To ensure consistency in StEPP performance across time and participants, the test was always started on the index knee and the left and right limbs were alternated between each up/down cycle. Participants were instructed to use their normal gait for completing this task and were encouraged to complete the task despite increasing pain, without stopping if possible. For safety reasons, participants were allowed to use their hands to steady themselves on the back of the Biodex chair if needed but were otherwise asked to complete the

StePP without support. The time taken to complete the StEPP was recorded in seconds. Evoked pain was defined as the change in pain (0-100 NPRS) from before to immediately after completing the StEPP.

A fixed order of outcome measure testing was used for all participants, to ensure that, as much as possible, the change in outcome measures reflected the effects of isometric exercise alone (i.e. EIH) rather than a combination of isometric exercise and altered pain sensitivity induced by measurement of the other outcomes. Thus, before isometric exercise, the order of assessment was evoked knee pain (StEPP test), 10 min rest, PPTs, then resting joint pain. A 15-minute rest period was given between the pre-exercise StEPP test and PPT measurement to allow any lingering effects of the StEPP test on pain sensitivity to dissipate. Immediately after isometric exercise, the order was resting joint pain, PPT and then evoked knee pain (StEPP test). Post-exercise, resting joint pain was assessed immediately after exercise to capture immediate changes in resting pain levels induced by the isometric exercise alone, and because resting joint pain measures only took a few seconds to complete and would not influence the primary outcome, PPTs. PPTs were then immediately evaluated to determine the EIH response to exercise. Evoked knee pain (StEPP test) was performed last to ensure that any lasting effects on pain sensitivity did not influence the other outcome measures.

Adverse events

Adverse events were defined as any untoward or undesirable medical occurrence during or within 24 hours of the intervention, regardless of whether it was considered causally related. These included, but were not limited to, dizziness, headache, unexpected musculoskeletal pain, or other new or worsening symptoms. Severity was classified as mild (no limitation of activity), moderate (some limitation of activity), or severe (preventing normal activities or requiring medical attention). Relationship to the intervention was rated as related, possibly related, or unrelated. Increases in resting knee pain were monitored for all participants. An increase of ≥2 points on the 0–10 Numeric Pain Rating Scale (NPRS) from pre- to post-intervention was considered clinically important (413)

and was classified as an adverse event only if accompanied by additional symptoms or unexpected severity.

Statistical Analysis

Normality of the data was assessed through visual inspection and descriptive statistics were calculated using the Shapiro-Wilk statistic. As the isometric contraction duration (seconds), maximum knee pain during isometric contraction and peak RPE rating (6-20) were non-normally distributed, these outcomes were compared across groups using Mann-Whitney U tests, to determine if the isometric exercise dose was similar. For each group, Wilcoxon signed-rank tests were undertaken to determine if the time taken to complete the evoked pain test (StEPP) was similar before, compared to after, the isometric contraction.

For all primary and secondary outcome measures, an analysis of covariance (ANCOVA) was performed. The model regressed the post-exercise score or the change score (post- minus pre-intervention scores) on the pre-exercise or pre-intervention scores, along with baseline covariates (age, anxiety subscale of the HADS, expected change in pain, and single item belief score) (414).These covariates were chosen based on the findings of Chapter Three and to minimise the potential of any pre-intervention differences in these variables influencing the findings. Model diagnostics included the assessment of normality and homogeneity of variance of the model residuals. Multicollinearity was evaluated for all the covariates with the variance inflation factor (VIF) (379). Any variable with a VIF score greater than 10 was excluded from the analysis. Mean differences across groups (the treatment effect) and mean score or mean change scores within each group (pre- to post-intervention effects), along with 95% confidence intervals (CIs) are reported. Between group effect sizes were calculated by dividing the mean difference between groups by the pooled standard deviation (SD) and interpreted according to Cohen's criteria: of 0.2 = small, 0.5 = medium, and 0.8 = large (415). To examine the potential relationship between beliefs about EIH and the extent of EIH that occurred post hoc exploratory correlation analyses were undertaken. These analyses examined the relationship between the primary outcome measure (pre-to-post exercise change in PPTs) and: 1) the pre-to-post

intervention change in EIH beliefs and: 2) the absolute post intervention EIH beliefs score using Spearman's rank correlation co-efficient.

The data were analysed using the R environment for statistical computing (378, 416) and SPSS version 25 (IBM Corp, Armonk, NY). Any p-value less than 0.05 was considered significant.

4.2.7 Results

Participant Characteristics

A total of 67 participants were screened for eligibility, of which 25 (39%) were excluded for being ineligible, while 42 participants (65%) (20 females, 22 males) with an average age of 66 ± 7.5 years were recruited (Table 4, Figure 5). Baseline characteristics of the two groups were similar (Table 4). All participants completed the PPT testing, evoked pain testing (StEPP test) and sustained isometric contraction, with no adverse events reported.

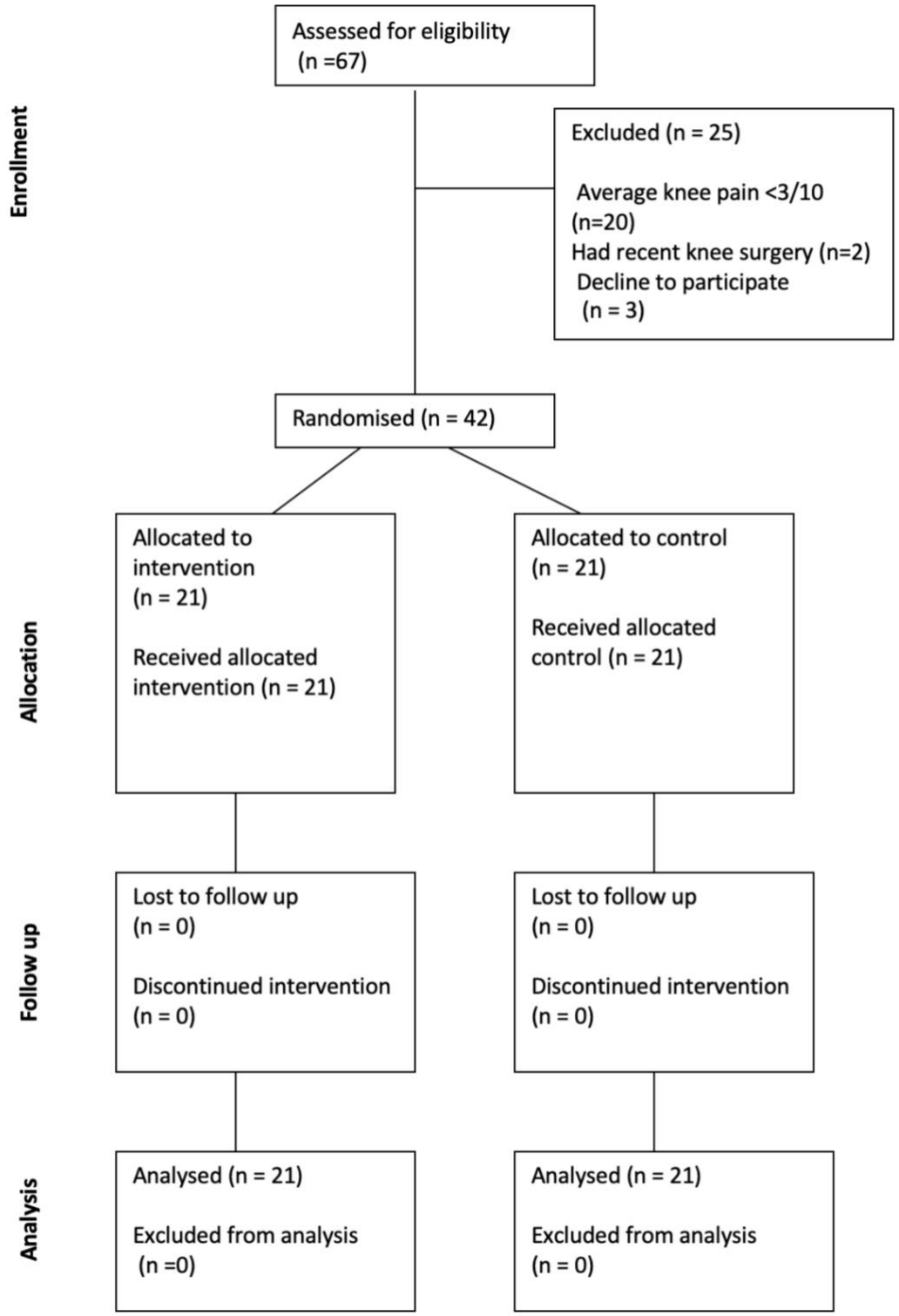


***Figure** 5. CONSORT flow diagram of the progress through the phases of the randomised trial for each group.*

Table 4. *Baseline participant characteristics. Data are presented as mean (SD) or median (IQR) unless otherwise stated.*

	Intervention Group	Control Group
Sample size (n)	21	21
Female sex (%)	13 (62%)	9 (43%)
Ethnicity: frequency (%)		
New Zealand European	16 (76%)	16 (76%)
New Zealand Māori	1 (5%)	0 (0%)
Samoan	0 (0%)	1 (5%)
Other European	3 (14%)	3 (14%)
Other ethnicity	1 (5%)	1 (5%)
Height (cm)	170 (7)	174 (10)
BMI (kg/m2)	28.4 (6.0)	30.1 (5.8)
Duration of knee pain (months)	60 (18-138)	72 (36-120)
LLTQ (0-100)	18 (14-27)	21 (14.5-25)
HADS- Depression (0-21)	3 (2-5.5)	4 (1-5.5)
HADS- Anxiety (0-21)	5 (2-8.5)	4 (2.5-7)
TSK (11-44)	30 (21-31.5)	29 (25- 32.5)
PCS (0-52)	8 (4-10)	5 (4-14)
BPI-Ave (0-10)	3 (1.5-4)	3 (2-4.5)
BPI-Worst (0-10)	5 (3-7)	5 (3-7.5)
BPI-Least (0-10)	0 (0-1.5)	0 (0-1)
BPI-Interference (0-10)	2.6 (1.6-5.1)	2.7 (1.9-5.4)
Peak Torque (Nm)	142 (108-175)	160 (120.5-173.5)
Pain expectancy (0-100)	30 (11.5- 60)	25 (0.5-50)
Single item EIH beliefs (0-7)	2 (1-4)	3 (1-5)
KOAKS (11-55)	33 (33-34)	36 (34-39)
EIH testing order (knee first (%))	12 (57%)	9 (43%)
Taking any pain medication (%)	3 (14%)	2 (10%)
Types of regular pain medication: frequency (%)		
Paracetamol	1 (5%)	0 (0%)
Anti-inflammatories	1 (5%)	2 (10%)
Opioids	0 (0%)	0 (0%)
Anti-convulsants	1 (5%)	0 (0%)
Anti-depressants	0 (0%)	0 (0%)

Abbreviations: BMI, body mass index; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; KOAKS, Knee Osteoarthritis Knowledge Scale; LLTQ, Lower Limb Task Questionnaire; m, meters; min, minutes; PCS, Pain Catastrophizing Scale; s, seconds; SD, Standard Deviation; TSK, Tampa Scale for Kinesiophobia.

Similarity of the Exercise Interventions and StEPP test performance

There was no significant between-group differences in the time to failure ($p = 0.51$), maximum knee pain during exercise ($p = 0.50$) nor peak RPE ($p = 0.81$) during the sustained isometric contraction (Table 5). There was no difference in the time to complete the StEPP test before compared to after isometric exercise for either the intervention group ($p = 0.05$) or the control group ($p = 0.20$) .

Table 5. *Expected change in pain, target torque, peak Rating of Perceived Exertion (RPE), time to failure, maximum knee pain during contraction on the Numerical Pain Rating Scale (NPRS) and StEPP time to completion across the intervention and control groups. Values are displayed as mean (SD) or median (IQR) unless otherwise stated.*

Measure	Intervention Group	Control Group	p-value
Expected change in pain NPRS (0-100)	34.1 (27.2)	28.5 (26.5)	0.50
Target Torque (Nm)	36.0 (12.5)	38.4 (10.9)	0.48
Peak RPE (6-20)	20 (19-20)	20 (19-20)	0.81
Time to failure (s)	300 (241.75-300)	300 (251.25-300)	0.51
Maximum knee pain during contraction NPRS (0-100)	27.5 (0.5-47.50)	27.5 (0.0-57.50)	0.50
StEPP time to completion (Pre-intervention)(s)	65 (59-75.5)	75.5 (66.75-86.75)	
StEPP time to completion (Post-intervention)(s)	63.5 (55.5-74)	70.5 (65.25-88)	

Abbreviations: IQR, interquartile range; NPRS, Numerical Pain Rating Scale; RPE, Rating of Perceived Exertion; SD, standard deviation.

Manipulation checks

The pre- to post-intervention change in EIH-related beliefs was greater in the positive education group compared to the control education group, with a medium effect (mean difference = 1.3 95% CI [0.5,2.1], p = 0.001, d= 0.50 (Table 6). In contrast, while the change in OA-related knowledge and beliefs assessed by the KOAKS questionnaire favoured the positive education group with a very small effect, this did not reach statistical significance (mean difference = 1 95% CI [-1,3]p = 0.34, d=0.15 and neither group significantly increased their KOAKS score from pre to post-intervention (both p > 0.22).

Table 6. *Pre- to post-education intervention change scores in single item exercise induced hypoalgesia (EIH) beliefs and Knee Osteoarthritis Knowledge Scale (KOAKS). Values are displayed as estimated marginal means (standard error) unless otherwise stated.*

Measure	Intervention Group	Control Group	Between Group Difference (95% CI)	p-value
EIH beliefs (0-7)	2.1 (0.3)*	0.8 (0.3)*	1.3 (0.5, 2.1)	0.001
KOAKS (11-55)	0.9 (0.7)	-0.1 (0.7)	1 (-1, 3)	0.34

Abbreviations: CI, Confidence Interval; EIH, Exercise Induced Hypoalgesia; KOAKS, Knee Osteoarthritis Knowledge Scale; SE, Standard Error. *represents significant within group change from pre-to post-intervention $p<0.05$.

Primary Outcomes

Analysis of the absolute change in PPT revealed no significant differences between the intervention and control education groups at the knee (mean difference 10 kPa [95% CI -40 to 60 kPa]; $p = 0.57$, d = 0.08) or the forearm (mean difference -10 kPa [95% CI -50 to 30 kPa]; $p = 0.56$, d = -0.08). Similarly, there was no between-group difference in the relative change in PPT at either the knee (mean difference 0 [95% CI -0.2 to 0.19]; $p = 0.97$, d = 0) or the forearm (mean difference 0 [95% CI -0.3 to 0.2]; $p = 0.90$, d = 0).

On average, both groups demonstrated a significant increase in PPT reflecting a local EIH response (knee) with an increase in PPTs from pre-to post-exercise, while remote EIH (forearm) was smaller, and only statistically significant when expressed as a relative change. (

Table **7**). Despite an intact local EIH response at the knee, there was notable variability in the EIH response in both the positive and control education groups (Figure 6).

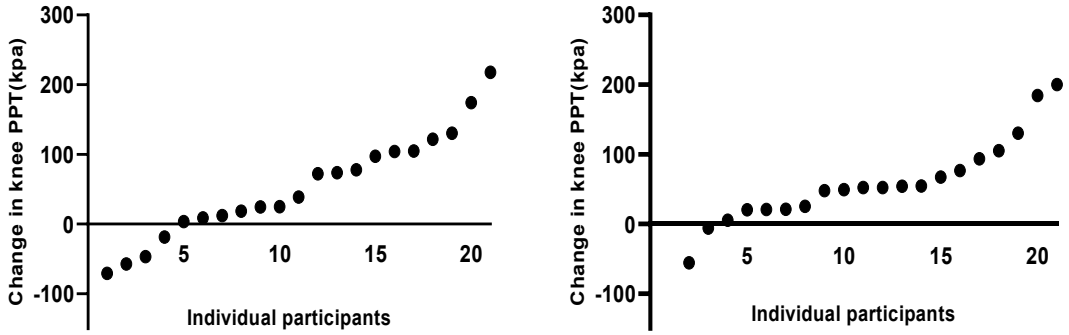


Figure 6. *Absolute change in knee pressure pain thresholds from pre- to post-isometric exercise for individual participants in the positive education group (n=21, left plot) and control education group (n=21, right plot), ordered from the most hyperalgesic (left) to the most hypoalgesic (right) response.*

Secondary Outcomes

There was no significant between-group difference in the pre to post- exercise change in resting pain (mean difference -8 [95% CI -18 to 2]; p = 0.11, d = -0.25) or evoked pain (mean difference 1 [95% CI -7 to 8]; p = 0.90, d = 0.04) (

Table **7**).

Table 7. *Primary and secondary outcome measures across the intervention and control groups. Pre- and post-exercise values are displayed as mean (standard deviation) or median (interquartile range), while change scores are estimated marginal means (standard error) or median (interquartile range).*

Measure	Intervention group	Control group	Between group Difference [95% CI]	*p*-value
Knee PPT				
Pre-exercise (kPa)	317 (231)	241 (177)		
Post-exercise (kPa)	370 (266)*	291 (167)*		
Absolute EIH (kPa)	60 (20)	40 (20)	10 [-40, 60]	0.57
Relative EIH (ratio)	1.24 (0.07)*	1.24 (0.07)*	0 [-0.2, 0.19]	0.97
Forearm PPT				
Pre-exercise (kPa)	281 (103)	315 (140)		
Post-exercise (kPa)	309 (205)	319 (152)		
Absolute EIH (kPa)	10 (10)	20 (10)	-10 [-50, 30]	0.56
Relative EIH (ratio)	1.07 (0.08)	1.09 (0.08)	0 [-0.3, 0.2]	0.90
Resting Pain (0-100 NPRS)				
Pre-exercise	11.48 (13.32)	8.05 (11.07)		
Post-exercise	9.95 (14.71)	12.95 (18.62)		
EIH (Resting Pain Change)	-2 (3)	6 (3)	-8 [-18, 2]	0.11
Evoked Pain (0-100 NRPS)				
Pre-exercise	15.14 (17.69)	12.19 (11.87)		
Post-exercise	11.67 (21.05)	9.00 (11.32)		
EIH (Evoked Pain Change)	-3 (3)	-4 (3)	1 [-7, 8]	0.90

Abbreviations: CI, Confidence Interval; kPa, Kilopascals; NPRS, Numeric Pain Rating Scale; PPT, Pressure Pain Threshold. *represents significant within session change from pre-to post-intervention $p<0.05$

Relationship between EIH beliefs and primary outcomes

For the entire sample, there were no significant relationships between absolute or relative EIH (Δ in PPT) and either the pre-to-post-intervention change, nor the absolute post-intervention score of the single item EIH beliefs question (rho -0.18 – 0.23, all $p > 0.26$).

4.3 Discussion

To our knowledge this is the first study to investigate the effect of pre-exercise education on EIH in individuals with knee OA, and the third study overall to examine this question. It is also the first to do so in a population with chronic pain, where negative exercise beliefs are likely more common and entrenched. The study findings show that, compared to a pre-exercise control education condition that was matched for time and therapist contact, positive pre-exercise education is associated with a greater increase in the belief that a single exercise session can reduce pain, with a large between group effect size. However, there was no significant effect on overall knee OA knowledge, nor the magnitude of the subsequent EIH response, assessed as the change in PPT (primary outcome), or change in resting knee pain and evoked knee pain (secondary outcomes). Furthermore, there was no significant association between the pre- to post-exercise change in PPTs and EIH-related beliefs.

Despite utilising a near-identical script for the education interventions, the results from this study differ from the findings of Jones et al. (89), who observed that in healthy, pain free control participants, positive pre-exercise education enhanced EIH when compared to a control pre-exercise education, with a large effect size. In addition, a significant positive correlation was observed between the magnitude of the post-intervention EIH response and the degree to which participants agreed with the single item question “pain can be reduced from just a single session of exercise” (89). In that study, a single 15-minute education session, without written materials, produced a large change in this belief and a measurable EIH enhancement. In contrast, the present study delivered two 30-minute sessions supplemented with a booklet, resulting in a smaller belief change and no EIH enhancement. This difference may indicate that in people with knee OA, modifying

expectations is more difficult and that belief change alone may not be sufficient to alter acute pain modulation.

Our findings are more in line with Vaegter et al. (322), who demonstrated that brief (2-3min) positive pre-exercise education did not increase EIH in healthy pain-free controls. Conversely, negative pre-exercise education diminished EIH. This observation is consistent with the concept that negative experiences tend to exert a more profound influence on psychological states than positive ones (417), which may in turn influence endogenous pain modulation pathways. It could be that the educational interventions of our study were not sufficiently dissimilar to elicit differential outcomes on EIH. The decision to avoid a negative intervention, despite its potential to enhance the difference between groups, was based on the ethical consideration to avoid nocebic effects in a clinical population suffering from chronic pain. Furthermore, our focus was on whether providing positive education offers benefits compared to a control condition designed to closely align with current biomedical education. This arguably has more clinical relevance than simply establishing its superiority over deliberately nocebic approaches, as it aims to direct treatment strategies towards interventions that do more than avoid harm but rather actively contribute to patient care.

It is well established that people with knee OA commonly have misperceptions about their condition and frequently hold negative attitudes and beliefs about exercise (52). These may be resistant to change, particularly in the short term. This is supported by the lack of appreciable change in the KOAKS score from pre- to post-intervention in either group in our study. A more intensive education intervention or a longer follow up time may be required to see an observable shift in OA related knowledge and beliefs (418). Related to this, despite the larger increase in confidence in the positive education group that “pain can be reduced from just a single session of exercise”, this may not necessarily have aligned with the personal experiences or expectations of participants in relation to their own pain, especially if they have previously found exercise to be painful or challenging. This mismatch, a form of cognitive dissonance, reflects the complex decision-making process knee OA patients face, as described by Darlow et al. (400),

balancing knowledge of the therapeutic role of exercise with the fear of increasing pain or causing further joint damage.

Alternatively, it may be that EIH is only weakly related to expectations in people with knee OA. The mechanisms of EIH remain incompletely understood and are thought to be mediated by a range of different physiological mechanisms (76, 202). It has been suggested that the variability of EIH observed in people with chronic pain may reflect maladaptive changes in neuroimmune function (e.g. endogenous pain inhibitory pathway, immune and/or autonomic nervous system dysfunction) (76). Perhaps, in the presence of such maladaptive changes, cognitive factors such as expectations are less important in determining the overall magnitude of the EIH response. This is supported by our findings in Chapter 3, where EIH-related beliefs were not found to be associated with EIH magnitude and the combination of age and expected change in knee pain with exercise only explained ~4.5% of the total variance in EIH. Furthermore, a recent systematic review concluded that cognitive and emotional factors appear to have a stronger influence on EIH in pain-free individuals than in those with chronic pain conditions (291).

Strengths of this study include its robust double-blind RCT design and the inclusion of secondary outcome measures that may have more direct clinical relevance than PPT alone. However, there are also some potential limitations to consider. Notably, an isometric exercise protocol was employed to induce EIH, while Jones et al. (89), used an aerobic exercise protocol. The selection of an isometric protocol aligns with the prevailing methodology in EIH research in OA (80, 81, 91, 359) and, arguably, is more clinically relevant, as local resistance training is routinely prescribed in the management of OA. Previous studies have shown that aerobic and isometric exercise elicit EIH of a similar magnitude, both in healthy controls (77) and knee OA specifically (91). For these reasons, it seems unlikely that the type of exercise used to elicit EIH would have affected our results, although this remains a possibility. Importantly, our population of people with OA appeared to have mild to moderate symptoms and we only examined the immediate effects of an education intervention on EIH after a single bout of exercise. As such, our findings may not translate to people with more severe knee

OA symptoms or to the longer-term effects of positive pre-exercise education with repeated bouts of exercise, which should be examined in future studies. For example, the combination of pain neuroscience education and exercise has been shown to lead to greater short term improvements in pain than exercise alone (330).

4.4 Conclusions

Despite modifying EIH-related beliefs, two 30-minute sessions of positive pre-exercise education did not enhance the EIH response compared to control pre-exercise education in our cohort of people with knee OA. This contrasts with findings in healthy adults, where shorter, single-session positive education has been shown to enhance EIH, and supports the view that in chronic pain populations, more entrenched negative beliefs and possible neurophysiological impairments may limit the acute modulatory role of expectations. Future studies should investigate different types of interventions, including more intensive or multi-session pre-exercise education, delivered alongside repeated and tolerable exercise exposures, and combined with flare-management strategies, to determine whether belief change can be translated into stronger EIH in people with knee OA. This may minimise exercise induced flares in pain and increase both efficacy and engagement with exercise-based rehabilitation in the longer term.

Chapter 5 Effects of a single session of 2 mA anodal tDCS on EIH in people with Knee OA: A double blind, randomised crossover trial

5.1 Background

In Chapter Four, we explored the effects of positive pre-exercise education on EIH in people with knee OA, compared to a control education intervention. While positive education led to a significantly greater increase in the belief that "pain can be reduced from just a single session of exercise" compared to the control condition, it did not enhance the hypoalgesic response to a subsequent bout of isometric exercise. These findings emphasise the need for alternative approaches to optimise EIH in knee OA, which may in turn minimise exercise-induced pain flares, and improve both the efficacy of and adherence to, exercise-based rehabilitation.

Despite the potential importance of EIH in the management of chronic pain, studies aiming to enhance EIH are sparse. Transcranial direct current stimulation (tDCS) has emerged as a promising, non-invasive intervention, with evidence suggesting it may reduce knee OA pain when applied over the primary motor cortex (M1), particularly in combination with exercise (333-338). tDCS and exercise have both been proposed to independently reduce pain via opioidergic mechanisms and increased descending nociception inhibition (76, 419-421).

To date, only one study has directly investigated the effect of tDCS on EIH specifically (90). This randomised, crossover, sham-controlled trial was conducted in healthy participants with experimentally induced musculoskeletal pain and compared 20 minutes of 1 mA anodal tDCS over M1 to sham tDCS, combined with an isometric handgrip protocol. Its strengths included a robust experimental pain model, within-subject design, and careful timing of PPT assessments that allowed detection of the onset of EIH. The authors reported an accelerated onset of EIH after anodal tDCS, with greater reductions in pain on movement immediately after exercise, when compared to sham tDCS. However, several methodological limitations reduce the certainty of these findings,

including small sample size, baseline differences in pre-exercise PPTs between sessions, the use of 1 mA stimulation (which may be less effective than 2 mA) (349) and the absence of a chronic pain population, limiting clinical generalisability. The present study builds on Borovskis et al. by addressing these gaps: we used 2 mA stimulation, targeted a clinical population with knee OA to explore EIH in a relevant chronic pain context, and incorporated clinically meaningful outcomes (resting and evoked knee pain) in addition to PPTs. This design enables us to evaluate whether the potential facilitatory effects of tDCS on EIH observed in healthy volunteers extend to people with persistent musculoskeletal pain, where EIH is often impaired.

Thus, in sum the aim of this study was to examine whether a single session of 2 mA anodal tDCS over M1 could enhance the EIH response to isometric exercise, compared to sham tDCS in individuals with knee OA. It was hypothesised that, compared to sham tDCS, 2 mA anodal tDCS would lead to larger pre to post isometric exercise reductions in pressure pain sensitivity, resting pain and evoked pain.

5.2 Materials and Methods

5.2.1 Design and Participants

This double-blind randomised crossover trial (RCT) was conducted between September and December 2022. The 2010 Consolidated Standards of Reporting Trials (CONSORT) statement (401) and 2019 CONSORT of Extension to Randomised Crossover Trials (422) were used as guidelines for reporting. All procedures were approved by the Health and Disability Ethics Committee (21STH128) and Auckland University of Technology Ethics Committee (21/242), and written informed consent was obtained from participants before testing. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000787886).

Participants were recruited through online and paper advertisements and from existing research databases. Additionally, paper advertisements were left with local knee surgeons, rheumatologists and physiotherapy clinics in the Auckland

region of Aotearoa New Zealand. Participants were included if they were adults ≥ 45 years of age, met The National Institute for Health and Care Excellence (NICE) clinical criteria for the diagnosis of knee OA (aged ≥ 45 years and had activity-related joint pain and had either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes), had ongoing knee pain for ≥ 3 months, and had an average knee pain intensity of ≥3/10 on a numerical pain rating scale (NPRS) in the last week at the time of screening, where 0 = “no pain” and 10 = “worst pain imaginable” (403). The use of NICE clinical criteria to diagnose knee OA aligns with current guidelines that emphasise clinical diagnosis of OA over routine imaging (423). This approach is supported by evidence suggesting that imaging is often unnecessary unless atypical features or alternative diagnoses are suspected (424). Therefore, participants were included, based on clinical presentation rather than radiographic confirmation, in accordance with best practice recommendations.

A minimum 7-day washout period between visits was chosen to avoid any potential carry-over effects from the intervention. This duration was considered sufficient because (1) the physiological effects of a single tDCS session on cortical excitability are typically short-lived, resolving within 90 minutes to 24 hours (425, 426), (2) EIH responses to a single bout of isometric exercise have been shown to return to baseline within hours (250), and (3) no residual analgesic effects from either tDCS or exercise have been reported beyond 48 hours. The 7-day interval therefore provided a substantial margin of safety beyond the expected duration of any intervention effects, consistent with recommendations for conservative washout periods in crossover designs.

Participants were excluded if they had an inability to speak or write English, medical conditions preventing safe participation in physical activity, an inability to climb 2 flights of stairs, ever had a total knee replacement or knee surgery in the past 6 months, a recent history of lower limb resistance training (≥2 times per week for a minimum of 6 weeks within the past 6 months), any other form of arthritis (e.g. rheumatoid arthritis), a history of musculoskeletal pain or injury in the lower limb (other than osteoarthritis) in the past 6 months, any neurological condition, any unstable/uncontrolled cardiovascular condition, a current

diagnosis of a major psychiatric disorder, any cognitive impairment, or any contraindications to tDCS (e.g., history of epilepsy, taking regular medications that may lower seizure threshold).

5.2.2 Sample Size

A total of 27 participants were required to achieve a probability of 80% that the study will detect a difference in EIH between active and sham tDCS at a one-sided 0.05 significance level, with at least a moderate effect size of d = 0.5. There has only been one previous study of tDCS on EIH and, due to the way the data were presented, it was not possible to calculate an effect size (90). Furthermore, our primary outcome measure was the pre to post-intervention change in PPT, and is not yet known what magnitude of change in this variable should be considered clinically important. Thus, we choose to calculate our sample size based on the ability to detect a moderate effect. Previous research (348), comparing a single session of active tDCS to sham tDCS has shown a large effect (d = 0.89) on conditioned pain modulation (CPM), which may have at least partly overlapping mechanisms to EIH (76). As such, an effect size of d = 0.5 can be considered conservative. As in Chapter 4, a one-sided test was deemed appropriate as our primary interest was to determine whether the active intervention was superior to sham. This approach is consistent with the recommendations of Ludbrook (404), who supports the use of one-sided tests when the alternative hypothesis is specific and directional.

5.2.3 Randomisation, Allocation Concealment and Blinding

The order of interventions (active vs sham tDCS) was randomised for each participant in a 1:1 ratio using a computer-generated randomisation schedule (sealedenvelope.com) with permuted blocks of 2 and 4. An independent researcher, who was not involved in participant recruitment, selection or data collection, distributed and stored the randomisation sequence in sealed, opaque envelopes to maintain allocation concealment. All participants and outcome assessors were blinded to intervention order, to reduce potential bias. Participants were told that the trial would “compare real and fake brain stimulation with exercise on knee osteoarthritis pain”. The therapist delivering the

interventions was blinded to whether active or sham stimulation was applied. Two different tDCS units (labelled A and B) were pre-programmed by another investigator uninvolved in participant recruitment, screening or testing to deliver either active or sham stimulation. After completing the baseline assessments for each participant, the therapist delivering the intervention, opened an opaque sealed envelope to see which unit (A or B) to use in the first Visit. In addition, the statistician responsible for data analysis was blind to intervention order.

5.2.4 Procedures

The experimental procedures are outlined in Figure 7. Each participant attended the laboratory during two sessions scheduled a minimum of 7 days apart ('Visit 1' and 'Visit 2'). Each visit took approximately 2 hours. During Visit 1, participants provided demographic and clinical data for descriptive purposes, including age, sex, ethnicity, weight (kg), height (m), knee pain duration (years) and current medication use. Participants additionally completed questionnaires regarding their pain, mental health, and physical function. These included the Brief Pain Inventory (BPI) (356), Hospital Anxiety and Depression Scale (HADS) (407), Lower Limb Tasks Questionnaire (355), Pain Catastrophising Scale (PCS) (367), and the Tampa Scale of Kinesiophobia (TSK) (408).

To allow standardisation of exercise intensity during the evaluation of EIH, at the beginning of each visit, participants completed an assessment of their maximum voluntary isometric contraction (MVIC), of the quadriceps muscle group. The index knee was secured to a Biodex Multi-Joint System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA). In the instance where participants had bilateral knee OA, the most painful knee was chosen as the index knee for all further testing. Hip flexion was fixed to 85° and knee flexion fixed to 90°. A standardised warm up of four, 5-s isometric quadriceps contractions at 25%, 50%, 50% and 75% of perceived maximum effort was performed, followed by three 5-s maximum effort voluntary contractions with a 30 s rest period between contractions. Consistent verbal encouragement was given for all contractions and MVIC was taken as the peak torque (Nm) produced during any of the three maximum effort contractions. Following MVIC testing and a 15-minute rest period, participants were familiarised with the upcoming EIH testing procedure to be

completed, to obtain pain expectancy scores. To do this, participants were told that they would be instructed to maintain a target torque of 25% of their MVIC for a maximum of 5 mins or until failure of target torque. They were then asked to maintain a target torque of 25% of MVIC for 10-s and asked to rate (0-100 on the NPRS) what they expected their familiar knee pain to be if they were to hold the contraction to failure as just described to them.

Baseline measures of evoked knee pain, PPTs, and resting joint pain were then measured, prior to the intervention. Following the collection of all aforementioned baseline data, the sealed envelope with the participant's study number was opened and used to randomly allocate them into one of two groups: active tDCS (intervention) or sham tDCS (control).

Before the isometric exercise, participants received 20 mins of tDCS (active/sham) and performed an assessment of blinding success. Evoked pain, resting pain and PPTs were re-assessed after isometric exercise to enable measures of EIH. Visit 2 was the same Visit 1, excluding questionnaire-based data, but participants received the crossover active/sham tDCS intervention and the outcome measures were repeated (Figure 7).

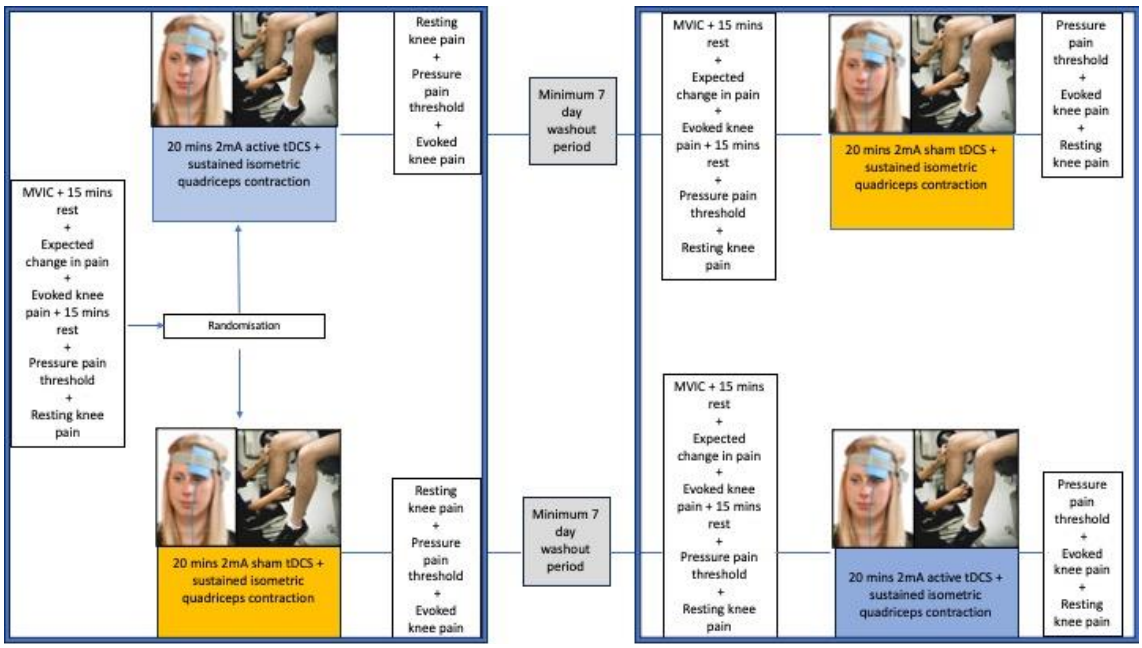


Figure 7. *Experimental procedures. Following baseline measurements, participants were randomised to receive active tDCS (intervention) or sham tDCS (control). Each tDCS session for both visits lasted 20 minutes. Following the tDCS session, EIH was quantified by measuring the participant's PPTs, evoked knee pain and resting knee pain before and after performing a sustained isometric quadriceps contraction at 25% of their MVIC for five minutes, or until failure. After a minimum 7-day washout period, participants returned and performed an identical testing session but with the alternative tDCS protocol (active/sham) depending on their initial allocation.*

Abbreviations: PPT, pressure pain threshold; RPE, rating of perceived exertion; tDCS, transcranial direct current stimulation; MVIC, maximum voluntary contraction.

Interventions (2 mA Active and Sham tDCS)

Participants were comfortably seated in the dynamometer chair while receiving tDCS and were asked to remain quiet for the duration of the intervention. During the active tDCS session, participants received 20 min of 2 mA anodal stimulation, which was applied using an HDCell (MagStim Co, UK) and 7 x 5 cm electrodes (0.057 mA/cm^2). In the design of this trial, a significant consideration was the selection of an optimal current intensity for active tDCS that balances efficacy with the potential for blinding participants. While effective blinding has been shown at 1 mA intensity (427), blinding effectiveness can be compromised at intensities higher than this due to increased sensation and potential skin erythema observed in participants and assessors (428). To address these concerns, our protocol included pre-application of alcohol prep pads to induce uniform

erythema across all participants as suggested by Guleyupoglu et al. (429). Despite potential blinding challenges, the choice of 2 mA is supported by the deeper location of leg representations in the motor cortex (430), its more consistent effects on cortical excitability (431, 432), and the effective use of 2 mA stimulation in a variety of clinical populations, including people with knee OA (334, 336, 337, 433). The electrode sponges were soaked in saline solution prior to application. The anode was placed over the C3 or C4 scalp location according to the International 10–20 EEG system (434), contralateral to the affected knee. The cathode was placed over the contralateral supraorbital region. Stimulation intensity was ramped up to 2 mA over 30 s, applied for 20 min and then ramped down to 0 mA over 30s.

In the sham tDCS session, participants received an identical intervention as the active tDCS session except that stimulation intensity was ramped up to 2 mA over 30 s and then immediately ramped down to 0 mA over 30 s to provide the initial itching sensation (435). Prior to the first session, participants were informed that they may or may not perceive any sensation during the application of tDCS.

In both the active and sham sessions, participants watched the same nature documentary (without narration) to maintain alertness and control arousal during the 20 minute stimulation period, thereby minimising state differences in brain excitability due to visual input (436). This practice is consistent with the technical guidelines for tDCS, which recommend employing strategies to prevent sleepiness and promote wakefulness (437, 438). Immediately after the 20 minutes of tDCS (active/sham), to assess blinding success, participants were asked “Do you think you received real brain stimulation, fake brain stimulation or are you not sure?” (439, 440).

Isometric Exercise

Immediately after tDCS, to induce EIH, a single submaximal isometric contraction of the quadriceps at a target torque of 25% of MVIC was performed using the Biodex dynamometer. Participants were positioned in sitting, with hip flexion fixed at 85° and 90° knee flexion. The participant was instructed to maintain the target torque until failure, defined as the inability to sustain 25% of their MVIC for ≥ 5s, or

to a maximum of 5 min. Continuous visual feedback of their quadriceps torque was displayed on a computer screen placed directly in front of the participant. During the isometric contraction, a rating of perceived exertion (RPE) on Borg's 6–20 scale (360), with 6 defined as "no exertion at all" and 20 as "maximal exertion", was obtained every 30 s. Participants were given consistent verbal encouragement to ensure that true contraction failure or the 5 min maximum time was reached. If contraction failure occurred, the time to failure (in seconds) was recorded. Following this, participants were asked to rate their maximum knee pain during the isometric contraction on a scale from 0 "no pain" to 100 "worst pain imaginable".

5.2.5 Primary Outcome Measures

The primary outcome measures for this study were the change in PPTs from immediately before to immediately after the intervention (active tDCS plus exercise or sham tDCS plus exercise). Before the intervention, PPTs were assessed at two sites, in a random order: at the medial joint line (3 cm medial to the midpoint on the medial edge of patella) of the index knee and remotely at the volar surface of the contralateral forearm (5 cm distal to the lateral epicondyle) (239). The same test-site order was used for post-exercise measurement of PPTs. PPTs were assessed using a hand held pressure algometer (SbMedic, Sweden) with a 1 cm rounded tip and a ramping rate of 30 kpa/s. Participants were instructed to press a button at the moment they first experienced any pain from the probe (PPT) and the pressure achieved in kPa was recorded. The average of three PPT measurements was recorded for each site. As there is little consensus whether to report EIH as the absolute (in kPa) or relative (ratio or percentage) change in PPT from pre- to-post-exercise, and both are frequently used in the literature (260, 268, 269), we chose to report and analyse both absolute and relative changes in PPTs at both local (knee) and remote (forearm) sites. For relative measures, post exercise PPT was expressed as a ratio of pre-exercise PPT for each individual at each site, such that values greater than 1.0 reflect an increase in PPT (hypoalgesia) following exercise while values less than 1.0 reflect decreased PPTs (hyperalgesia) (80).

5.2.6 Secondary Outcome Measures

Secondary outcomes were changes in resting knee pain intensity and evoked knee pain intensity via the Staircase-Evoked Pain Procedure (StEPP) (412). These assessments were also performed before and after the exercise intervention. Resting knee pain was assessed in sitting, with the knee fixed at 90 degrees of flexion in the dynamometer arm, using a 0-100 point NPRS with anchors of 0 = “no pain” and 100 = “worst pain imaginable”. Evoked pain intensity was measured on the same 0-100 scale immediately before and after completing the StEPP, which consisted of stepping up and down onto a 20 cm high platform 24 times. To ensure consistency in StEPP performance across time and participants, the test was always started on the index knee and the left and right limb was alternated between each up/down cycle. Participants were instructed to use their normal gait for completing this task and were encouraged to complete the task despite increasing pain, without stopping if possible. For safety reasons, participants were allowed to use their hands to steady themselves on the back of the Biodex chair if needed, but were otherwise asked to complete the StePP without support. The time taken to complete the StEPP was recorded in seconds. Evoked pain was defined as the change in pain (0-100 NPRS) from before to immediately after completing the StEPP.

As explained in Chapter 4, a fixed order of outcome measure testing was used for all participants, to ensure that, as much as possible, the change in outcome measures reflected the effects of the intervention alone, rather than a combination of the intervention and altered pain sensitivity induced by measurement of the other outcomes. Thus, before intervention, the order of assessment was evoked knee pain (StEPP test), 15 min rest, PPTs, then resting knee pain. Immediately after the intervention, the order was resting knee pain, PPT and then evoked knee pain (StEPP test).

5.2.7 Adverse events

Adverse events were defined as any untoward or undesirable medical occurrence during or within 24 hours of the intervention, regardless of whether it was considered causally related. These included, but were not limited to, dizziness,

headache, skin irritation or tingling under the tDCS electrodes, unexpected musculoskeletal pain, or other new or worsening symptoms. Severity was classified as mild (no limitation of activity), moderate (some limitation of activity), or severe (preventing normal activities or requiring medical attention). Relationship to the intervention was rated as related, possibly related, or unrelated. Increases in resting knee pain were monitored for all participants. An increase of ≥2 points on the 0–10 NPRS from pre- to post-intervention was considered clinically important (413) and was classified as an adverse event only if accompanied by additional symptoms or unexpected severity.

5.2.8 Statistical Analysis

Normality of the data was assessed through visual inspection and descriptive statistics were calculated using the Shapiro-Wilk statistic. As the isometric contraction duration (seconds), maximum knee pain during isometric contraction, and peak RPE rating (6-20) were non-normally distributed, these outcomes were compared across the active tDCS and sham tDCS sessions using Mann-Whitney U tests to determine if the isometric exercise dose was similar between visits 1 and 2. Within each session, Wilcoxon signed-rank tests were undertaken to determine if the time taken to complete the evoked pain test (StEPP) was similar before, compared to after, the isometric contraction.

For the primary outcome measure of change in PPT from pre- to post-intervention, analyses were conducted in both absolute and relative units separately for each location (knee, forearm). Changes in the secondary outcome measures of resting pain and evoked pain were only analysed in absolute units. Linear mixed regression models were used to evaluate differences in the primary and secondary outcomes across sessions (active tDCS + exercise vs sham tDCS + exercise) and within session. The models for the absolute units regressed the difference in PPT from post- to pre-intervention assessments on the pre-intervention assessment and stimulation type (active tDCS, sham tDCS). The pre-intervention assessment was included as an independent variable to account for potential regression-to-mean effects. The models for the relative units regressed the ratio of PPTav from

post- to pre-intervention assessments on the pre-intervention assessment and stimulation type (active tDCS, sham tDCS). All mixed models included participant-wise random intercepts to account for within-participant correlations arising from repeated measures. Mean differences across sessions and mean scores for each session are reported along with their 95% confidence intervals and t-, p-values. Between session effect sizes are presented as the mean difference divided by the pooled standard deviation and interpreted according to Cohen's criteria of 0.2 = small, 0.5 = moderate and 0.8 = large (415). Model diagnostics included the assessment of normality and homogeneity of variance of the model residuals.

Blinding was assessed with the blinding index proposed by Bang, Ni, & Davis (439). This index was calculated for each treatment arm. Zero denoted random guessing at the chance level (50%). A positive value denoted the ratio of participants who correctly guessed their treatment arm, and a negative value denoted the ratio of participants who incorrectly guessed the opposite arm. Values between -0.2 and 0.2 can be considered successful blinding (440).

Data were analysed in the R environment for statistical computing (375, 414, 416) and SPSS version 25 (IBM Corp, Armonk, NY). Any p-value less than 0.05 was considered significant.

5.3 Results

5.3.1 Participant Characteristics

A total of 34 participants were screened for eligibility, of whom 7 (21%) were excluded for being ineligible or because they declined to participate, while 27 participants (79%) (15 females, 12 males) with a mean (± SD) age of 66 (± 10) years were recruited (Table 8, Figure 8). Baseline characteristics were similar in the participants randomised to receive active tDCS first compared to those randomised to receive sham tDCS first (Table 9), although those receiving sham stimulation first tended to be older, with a longer disease duration and were more likely to be taking pain medications. All participants completed all the experimental procedures, with no adverse events reported.

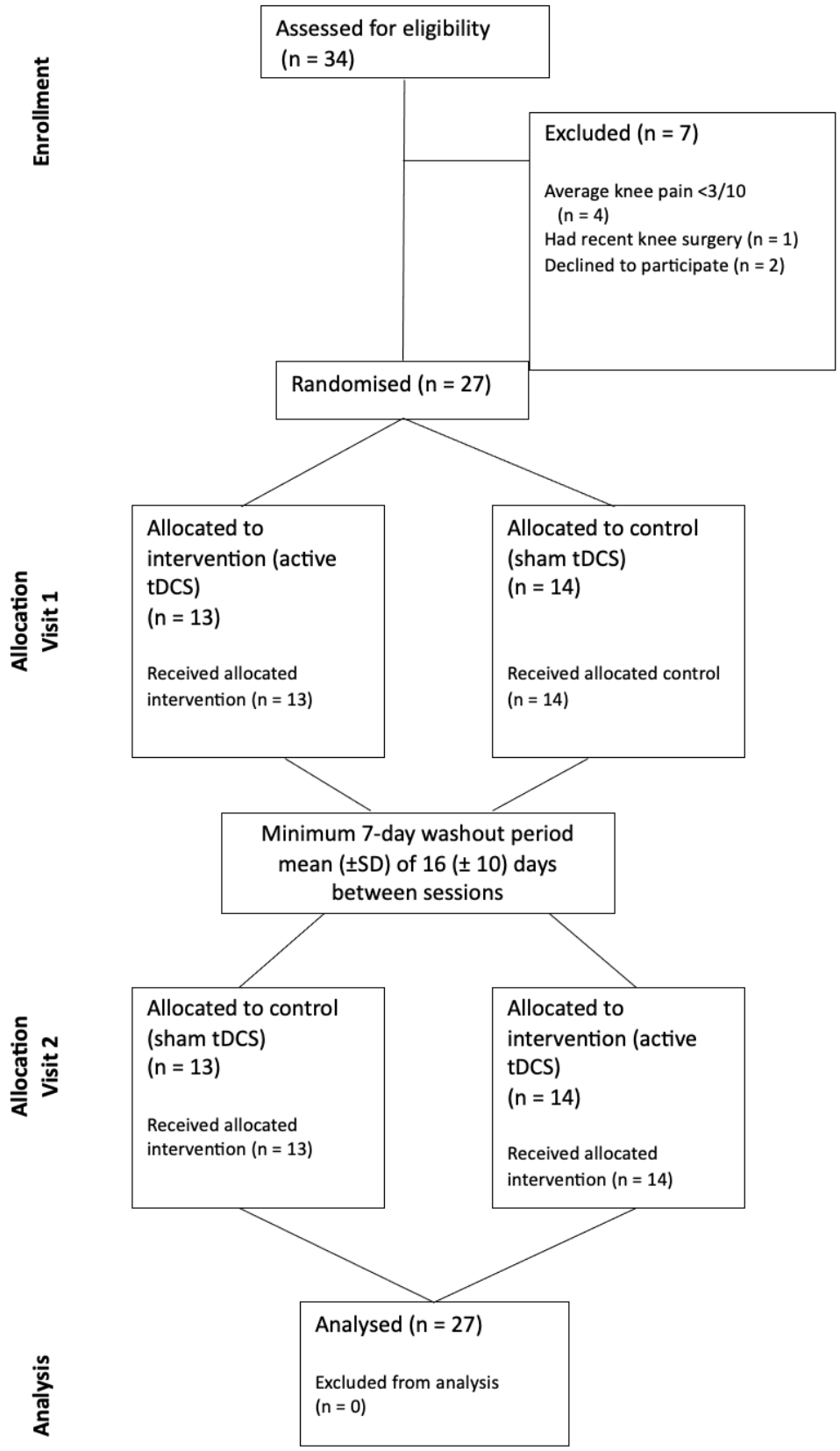


Figure 8. *CONSORT flow diagram of the progress through the phases of the randomised crossover trial for each group*

Table 8. *Baseline characteristics for participants randomised to receive the active tDCS or sham tDCS session first. Data are presented as mean (SD) or median (IQR).*

	Active tDCS first (n=13)	Sham tDCS first (n=14)
Age (y)	61.6 (8.2)	70.6 (9.7)
Sex (females %)	7 (54%)	8 (57%)
Ethnicity: frequency (%)		
New Zealand European	13 (100%)	10 (71%)
Other European	0 (0%)	3 (21%)
New Zealand Māori	0 (0%)	1 (7%)
Height (cm)	174 (11.3)	169 (8.1)
Weight (kg)	92.4 (24.4)	73.6 (13.9)
BMI (kg/m2)	30.3 (5.6)	25.6 (3.8)
Duration of knee pain (months)	60 (45-122)	152 (66-255)
LLTQ (0-100)	20.5 (2.9)	21.9(5.9)
HADS- Depression (0-21)	4.1 (2.7)	4.5 (2.3)
HADS- Anxiety (0-21)	3.9 (2.2)	5.8 (3)
TSK (11-44)	38.8 (7.5)	37.3 (5.5)
PCS (0-52)	5 (4-7.5)	6 (1.75-12.25)
BPI-Ave (0-10)	2.6 (1.5)	2.9 (1.4)
BPI-Worst (0-10)	3 (2.5-6.5)	3 (2-5.75)
BPI-Least (0-10)	0 (0-2.0)	0 (0-1)
BPI-Interference (0-10)	1.6 (1.1-2.6)	2.9 (1.6-3.8)
Peak Torque (Nm)	170.9 (77.3)	139.4 (53.4)
EIH testing order (knee first (%))	52	48
Taking any pain medication (%)	2 (15%)	4 (29%)
Types of regular pain medication:		
Paracetamol	1 (8%)	2 (14%)
Anti-inflammatories	0 (0%)	2 (14%)
Opioids	1 (8%)	0 (0%)
Anti-convulsants	0 (0%)	0 (0%)
Anti-depressants	0 (0%)	0 (0%)

Abbreviations: BMI, body mass index; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; KOAKS, Knee Osteoarthritis Knowledge Scale; LLTQ, Lower Limb Task Questionnaire; m, meters; min, minutes; PCS, Pain Catastrophising Scale; s, seconds; SD, Standard Deviation; TSK, Tampa Scale for Kinesiophobia.

Bang's blinding index was 0.12 in the active tDCS session and - 0.04 in the sham tDCS session, indicating successful participant blinding (441). Furthermore, there were no significant differences in the target torque, time to failure, peak RPE during exercise, maximum knee pain during exercise or StEPP time to completion between the active and sham tDCS sessions, suggesting that the dose of isometric exercise and StEPP test performance was comparable in the two intervention sessions

Table 9. *Target torque, peak Rating of Perceived Exertion (RPE), time to failure, maximum knee pain during contraction on the Numerical Pain Rating Scale (NPRS) and StEPP time to completion across the active and sham tDCS sessions, for all participants (n=27). Values are displayed as mean (SD) or median (IQR) unless otherwise stated.*

Measure	Active tDCs	Sham tDCS	p-value
Target Torque (Nm)	38.0 (16.2)	38.3 (16.6)	0.76
Peak RPE (6-20)	20 (19-20)	20 (19-20)	1.00
Time to failure (s)	300 (240-300)	300 (230-300)	0.33
Maximum knee pain during contraction NPRS (0-100)	34.8 (30.3)	38.0 (30.4)	0.44
StEPP time to completion (Pre-intervention)(s)	64 (57-74)	65 (58-80)	
StEPP time to completion (Post-intervention)(s)	64 (58-72)	65 (57-76)	

Abbreviations: IQR, Interquartile Range; NPRS, Numerical Pain Rating Scale; RPE, Rating of Perceived Exertion; SD, Standard Deviation.

5.3.2 Primary Outcomes

Analysis of the absolute change in PPT revealed no significant differences between the active tDCS and sham tDCS sessions at the knee (mean difference 0 kPa [95% CI -50 to 40 kPa]; p = 0.82, d= 0) or the forearm (mean difference -20 kPa [95% CI -60 to 30 kPa]; p = 0.45, d=-0.19) (Table 10). Similarly, there was no significant between-session difference in the relative change in PPT at either the knee (mean difference 0.01 [95% CI -0.18 to 0.2]; p = 0.88, d= 0.02) or the forearm (mean difference -0.06 [95% CI -0.2 to 0.08]; p = 0.40, d= -0.16) (Table 10).

During both sessions, a significant local EIH response was observed at the knee, with an increase in PPTs from pre to post-intervention using both absolute and relative measures (all p ≤ 0.001). Despite this, there was notable inter-individual variability in the magnitude of the EIH response after both the active and sham tDCS interventions (Figure 9). A remote EIH response at the forearm was also observed during both sessions using relative measures (both p≤ 0.001), but only during the sham session, when expressed as an absolute change (p = 0.008) (Table 10).

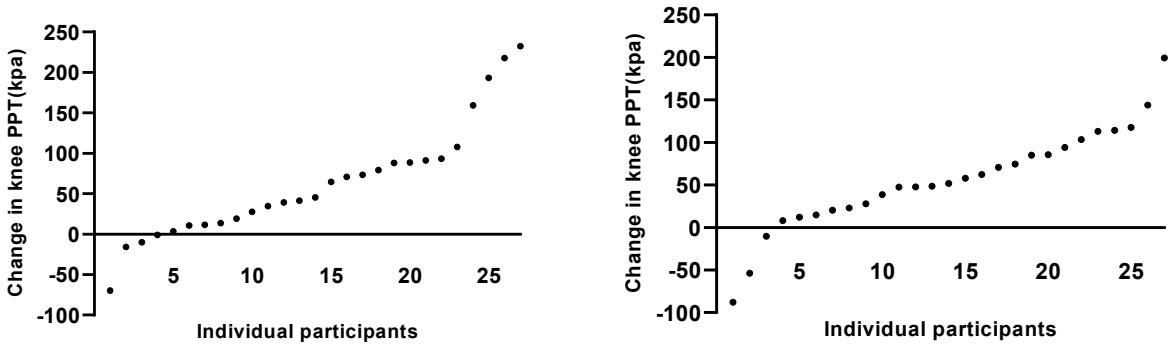


Figure 9. *Distribution of the absolute change in knee pressure pain thresholds from pre- to post-intervention for individual participants after M1 anodal tDCS plus isometric exercise (n=27, left plot) and sham tDCS plus isometric exercise (n=27, right plot), ordered from the most hyperalgesic (left) to the most hypoalgesic (right) response.*

5.3.3 Secondary Outcomes

There was no significant between-session difference in the pre- to post-intervention change in resting pain (mean difference 1 [95% CI -13 to 15]; p = 0.89,d= 0.03). Notably, resting pain increased in both sessions (Active tDCS mean

increase: 12/100 [95% CI 2 to 22]; p = 0.02) and (Sham tDCS mean increase: 11/100 [95% CI 1 to 21]; p = 0.03) from pre- to post-intervention.

Additionally, there was no significant between-session difference in the pre- to post-intervention change in evoked pain (mean difference 1 [95% CI -7 to 8]; p = 0.89, d= 0.05). However, evoked pain decreased from pre to post-intervention in both sessions (Active tDCS mean change: -6/100 [95% CI -12 to -1]; p = 0.03) and (Sham tDCS mean change: -7/100 [95% CI -12 to -1]; p = 0.02).

Table 10. *Primary and secondary outcome measures across the active tDCS and sham tDCS sessions. Pre and post-intervention values are displayed as displayed as mean (standard deviation) or median (interquartile range), while change scores are estimated marginal means (standard error) or median (interquartile range).*

Measure	Active tDCS	Sham tDCS	Between session Difference [95% CI]	*p*-value
Knee PPT				
Pre-exercise (kPa)	211 (96)	242 (112)		
Post-exercise (kPa)	274 (121)*	298 (144)*		
Absolute EIH (kPa)	60 (20)	60 (20)	0 [-50, 40]	0.82
Relative EIH (ratio)	1.30 (0.07)*	1.29 (0.06)*	0.01 [-0.18, 0.20]	0.88
Forearm PPT				
Pre-exercise (kPa)	267 (86)	299 (106)		
Post-exercise (kPa)	312 (98)	318 (105)		
Absolute EIH (kPa)	20 (10)	40 (10)*	-20 [-60, 30]	0.45
Relative EIH (ratio)	1.12 (0.05)*	1.18 (0.05)*	-0.06 [-0.2, 0.08]	0.40
Resting Pain (0-100 NPRS)				
Pre-intervention	0.00 (0.00-0.00)	0.00 (0.00-0.00)		
Post-intervention	10.00 (0.00-20.00)	5.00 (0.00-20.00)		
EIH (Resting Pain Change)	12 (5)*	11 (5)*	1 [-13, 15]	0.89
Evoked Pain (0-100 NRPS)				
Pre-intervention	15.00 (8.50-27.50)	15.00 (5.00-30.00)		
Post-intervention	2.00 (0.00-10.00)	10.00 (5.00-27.50)		
EIH (Evoked Pain Change)	-6 (3)*	-7 (3)*	1 [-7, 8]	0.14

Abbreviations: CI, Confidence Interval; kPa, Kilopascals; NPRS, Numeric Pain Rating Scale; PPT, Pressure Pain Threshold.*represents significant within session change from pre-to post-intervention $p<0.05$

5.4 Discussion

To our knowledge this is the first study to investigate whether a single session of 2 mA anodal tDCS over the primary motor cortex could enhance EIH compared to sham tDCS in individuals with knee OA. Contrary to our hypothesis, we observed no significant differences in the EIH response, as assessed by the change in PPT (primary outcome) or change in evoked pain or resting joint pain (secondary outcomes) between sessions. Participants were effectively blinded to the type of tDCS they received, and the dose of exercise was comparable across sessions.

Our results differ from previous findings in healthy controls that a single session of 2 mA anodal tDCS, enhances endogenous analgesia, as measured by CPM (442). Our results also more directly differ from the findings of Borovskis et al. (90), who observed that in healthy participants experiencing experimentally-induced musculoskeletal pain, 20 minutes of 1 mA anodal tDCS of M1 enhanced EIH compared to sham tDCS during an isometric gripping task (90).

One potential reason for this discrepancy may be differences in the nature of pain conditions studied. Experimentally induced pain in healthy participants is typically transient and does not appear to strongly affect pain modulation pathways (314, 350, 351). In contrast, knee OA pain is chronic, involving complex, multifactorial mechanisms such as local and systemic inflammation and persistent neuroplastic changes in nociceptive pathways. Moreover, it is possible that more than one session of tDCS is required to modify EIH in people with knee OA. This is supported by previous intervention studies involving tDCS in people with knee OA, where improvements in clinical pain intensity and measures of endogenous pain inhibition such as CPM have been observed after 5-16 sessions of tDCS (333-337, 433). One study in particular showed superior effects with 15 sessions, compared to 5 or 10 sessions (343). This suggests that while single-session effects of tDCS on EIH may be observed in acute pain models, multiple sessions may be necessary to achieve similar effects in chronic pain conditions like knee OA.

The known individual variability in the response to tDCS, particularly during single session interventions, may also have contributed to our findings (443, 444). Tremblay et al. (444) found significant individual differences in corticospinal

excitability to a single session of M1 anodal tDCS using different durations (10 and 20 minutes) and intensities (1 mA and 2 mA). The results showed no significant group-level effects and low responder rates, with only 20-35% of participants classified as expected responders, highlighting the large inter-individual variability in neurophysiological responses to a single session of tDCS. The complexity of dose-response relationships in tDCS is further supported by Esmaeilpour et al. (443), who concluded that increasing stimulation intensity does not lead to a straightforward enhancement of neurophysiological or behavioural outcomes. Instead, the response to tDCS appears to be influenced by multiple factors, including individual anatomical differences and the brain state during stimulation. As such, the individual variability in response to tDCS is likely more pronounced during a single session, where the effects might be more susceptible to transient changes in brain state, such as resting membrane threshold excitability. Multiple session interventions might mitigate some of this variability by providing repeated exposure, which could help to homogenise responses across individuals.

Importantly, our population of people with knee OA appeared to have mostly mild to moderate symptoms and many had a hypoalgesic response to exercise, even with sham tDCS stimulation, which might have made it difficult to observe additional benefits from the active tDCS intervention. For example, it is possible that the participants' endogenous pain modulation systems, including those involved in EIH, were already functioning well, leaving little room for further enhancement by anodal tDCS. This is consistent with previous findings that descending pain inhibitory pathway function is more impaired in individuals with more severe OA pain (Arendt-Nielsen et al., 2015; Fingleton et al., 2017b).

Another important, and related, consideration is the dose of exercise utilised in our study. There was a median time to failure of 300 seconds and a median peak RPE of 20 in both the active tDCS and sham tDCS sessions, indicating participants sustained high levels of perceived exertion for an extended period of time across both conditions. This may have resulted in a particularly effective protocol for inducing a robust EIH response (258), making it difficult to enhance EIH any further with anodal tDCS.

A notable strength of this study is the inclusion of secondary measures of EIH that may have more direct clinical relevance to people with knee OA than quantifying EIH using PPT alone. Of interest, despite observing a significant increase in PPT at the knee, indicating reduced pressure pain sensitivity, and decreased evoked knee pain, we observed a modest, but statistically significant increase in resting knee pain from pre- to post-intervention. This may reflect the low levels of resting pain in our population, making it difficult to observe any decrease in pain. However, this finding aligns with previous research by Christensen et al.(200) who reported a decrease in pressure pain sensitivity alongside increased pain intensity on the VAS after a shoulder abduction exercise program in individuals with chronic neck pain. This illustrates a potential disconnect between pain sensitivity thresholds and clinical pain experiences.The reasons for this are unclear but may relate to known differences in the neural mechanisms of pain at rest compared to evoked pain in people with OA (445), or local effects at the joint (e.g. increased nociception) that are subsequently counteracted by systemic effects (e.g. increased descending inhibition) after exercise. It is also possible that the measurement of resting pain immediately after exercise does not capture the full extent of inhibition, which may take time to build up and overwhelm any transient increase in nociception. Future research could explore which measures of EIH (pressure pain sensitivity, resting pain, evoked pain) are better predictors of clinically important outcomes in response to exercise in people with knee OA, such as flares in pain, or the magnitude of pain relief with long term exercise programmes.

Despite the strengths of this study, including its robust, randomised, double-blind cross over design, there are also some potential limitations to consider. Notably, an isometric exercise protocol was employed to induce EIH, while others (81, 91) have used aerobic exercise protocols. The selection of an isometric protocol aligns with the prevailing methods used to elicit EIH in previous studies involving people with OA (80, 81, 91, 359) and, arguably, is more clinically relevant as local resistance training is routinely prescribed in the management of knee OA. Furthermore, previous studies have shown that aerobic and isometric exercise elicit EIH of a similar magnitude, both in healthy controls (77) and people with knee OA specifically (91). For these reasons, it seems unlikely that the type of

exercise used to elicit EIH would have substantially affected our results. Finally, the absence of prior research investigating tDCS to enhance EIH in knee OA to inform the calculation of the sample size, may elevate the risk of Type II error in the current study. Despite this limitation, the calculated between session effect sizes for the primary and secondary outcomes, which ranged from (Cohen's *d* = -0.19 to 0.05) indicates that a single session of anodal tDCS is unlikely to yield a clinically important effect when compared to sham tDCS, at least in our population.

5.5 Conclusions

A single session of 2mA anodal tDCS over M1 did not enhance the EIH response to isometric exercise compared to sham tDCS in people with knee OA. The lack of effect may be attributed to an insufficient dose of tDCS, the inherent variability in the physiological responses to a single session of tDCS, and/or the already robust EIH response observed in our population of people with knee OA. Perhaps in part this was due to our exercise paradigm. Future studies should consider employing multiple tDCS sessions prior to exercise and/or targeting populations with more severe OA symptoms to better understand the potential of tDCS in enhancing EIH. Developing effective methods to enhance EIH may have important clinical implications in people with knee OA, helping to minimise exercise induced flares in pain and increase both the efficacy of and engagement with exercise-based rehabilitation in the longer term.

Chapter 6 Summary and Conclusions

6.1 Introduction

EIH has been shown to be more variable in people with chronic pain conditions, including knee OA. Impaired EIH may lead to flares in pain following exercise, negatively affecting exercise adherence, and reducing the magnitude of pain relief with regular exercise training. The factors that impair and/or facilitate EIH in individuals with knee OA are not well understood and remain underexplored, posing a challenge to optimising exercise-based interventions for pain relief.

This thesis aimed to improve our understanding of EIH in individuals with knee OA through a series of three interrelated studies. These studies focused on 1) identifying factors contributing to variability in EIH magnitude; 2) examining whether positive pre-exercise education may be able to enhance EIH, compared to a control education; and 3) evaluating whether a single session of 2 mA anodal tDCS over the primary motor cortex may increase EIH, compared to sham stimulation.

6.2 Key findings

6.2.1 Chapter 3: Factors associated with inter-individual variability in EIH magnitude in people with knee OA.

In Chapter Three, a cross-sectional observational cohort study was undertaken in 119 participants to identify clinical, psychological, and neurophysiological factors that may be associated with EIH magnitude, in people with knee OA. This is the largest study of its kind in a chronic pain population to date. Additionally, variance decomposition was used to explore the contribution of these factors to the observed and unobserved variance in EIH among this population. This is an important advancement as it allows for the estimation of the variance contribution of the dependent variables, unmeasured between-participant variables and any residual variance within the model. In contrast to other studies (78, 80, 91), both absolute and relative measures of EIH were used, to allow ease of comparison with other studies.

At a group level, the results of the study showed a significant increase in PPTs at the knee (local EIH) and the contralateral forearm (remote EIH) following a sustained, submaximal isometric knee extension exercise. However, the magnitude of both the local and remote EIH responses varied substantially between individuals, with 23% of participants demonstrating a decrease (hyperalgesia) or no change in PPTs in response to exercise locally at the knee and 40% remotely at the forearm. In contrast to previous research in OA that identified an association between EIH and CPM (91), EIH and TS (73) and EIH and pain catastrophising (73), no significant associations were found between EIH and any of these variables. Across all models, age, anxiety, and expected change in pain were associated with EIH magnitude. Age was positively associated with EIH, with older individuals tending to experience greater EIH. In contrast, anxiety and expected change in pain were negatively associated with EIH, meaning that individuals with higher anxiety or who anticipated more pain from exercise, tended to experience less EIH. This finding contrasts with some prior studies that observed either no age-related differences in EIH (250) or a diminished response in older adults (280). Methodological differences, such as variations in age group categorisation and the inclusion of covariates like baseline PPTs or physical activity levels, likely contribute to these discrepancies. While our models adjusted for baseline PPTs, this adjustment only partially mitigated their influence, suggesting that lower baseline pain thresholds in older adults may contribute to a proportionally larger relative change in pain sensitivity following exercise.

Moreover, despite including a broad range of variables, less than 20% of the variance in EIH magnitude could be explained by these variables. The substantial variance both between individuals, as well as across local and remote locations, underscores the need for further investigation into other variables that might elucidate the differences in EIH magnitude in those with knee OA, and into the potential differences in the mechanisms of EIH at local and remote sites in response to isometric exercise. Since conducting our study, subsequent research has highlighted the potential influence of habitual physical activity status (392, 393) and autonomic nervous system function (359, 393) on EIH, and their potential interaction (393), that warrants further investigation. Earlier studies in pain-free

populations have also demonstrated that higher physical activity levels are associated with more robust EIH responses (281, 285, 391, 446). Collectively, this evidence suggests that habitual physical activity may be an important determinant of endogenous pain modulation across populations, though it has rarely been explored in knee OA specifically. Future studies should therefore evaluate physical activity status in people with knee OA, as this may contribute to inter-individual variability in the EIH response.

In addition, studies in other chronic pain populations have identified genetic variables (215) and differences in the acute inflammatory response to exercise (77, 396, 397) that may contribute to EIH, and require further investigation in knee OA specifically. Additionally, much of the unaccounted variance could be attributed to individual differences that were not observed in the current study, as well as discrepancies related to the test locations, (e.g., knee, forearm) and measurement imprecision (e.g., in the reliability of PPT measurement).

6.2.2 Chapter 4: Effects of pre-exercise education on EIH

The findings from Chapter Three indicated that pre-exercise pain expectations and anxiety were associated with the magnitude of EIH in people with knee OA. Furthermore, previous research demonstrated that pre-exercise education, designed to manipulate participant beliefs and/or expectations, could influence the EIH response in healthy, pain-free populations (89). Building on these findings, Chapter Four was a parallel group, double-blind randomised controlled trial, designed to investigate the impact of positive pre-exercise education on EIH in individuals with knee OA, compared to a control education condition.

Positive pre-exercise education led to a greater increase in the belief that pain could be reduced from a single session of exercise than the control condition, with a large effect size. But it did not significantly affect overall knee OA knowledge or the magnitude of the EIH response, as measured by change in PPT, resting pain or evoked pain. These study findings contrasted with Jones et al. (89), who demonstrated increased EIH with positive pre-exercise education in healthy, pain-free individuals, but aligned with Vaegter et al. (322), who reported brief positive pre-exercise education did not enhance EIH, again in a pain-free population.

Although speculative, it is possible that cognitive dissonance, the discomfort experienced when individuals hold conflicting beliefs, played a role in the lack of significant changes in EIH response. Specifically, participants may have held conflicting beliefs between the expectation that pain can be reduced by a single session of exercise and their own lived experiences of pain during exercise. This may be particularly relevant in people with knee OA, who commonly have misperceptions about their condition and frequently hold negative attitudes and beliefs about exercise (52). These beliefs may be resistant to change, particularly in the short term, and may take more intensive educational interventions, or a longer follow up period to observe changes in.

Alternatively, it may be that the relationship between impaired EIH and cognitive factors such as expectations, is weak in people with knee OA, or that beliefs may be related to a third variable, that has a more direct causal association with EIH. Additionally, mechanisms that are at least partly independent of cognitive factors, such as maladaptive neuroplastic changes in the nociceptive system or an altered acute inflammatory response to exercise, could also play a larger role in determining the EIH response in people with knee OA, compared to healthy, pain-free controls.

6.2.3 Chapter 5: Effects of anodal tDCs on EIH

In Chapter Four, the findings showed that while beliefs about exercise and pain could be influenced by positive pre-exercise education, this did not translate into a significant improvement in EIH. A possible reason for this, is underlying neuroplastic changes in the nociceptive system in people with knee OA. This set the stage for Chapter Five, where it was investigated whether anodal tDCS, which has previously been shown to enhance endogenous descending pain inhibition (442) and accelerate the onset of EIH in healthy controls (90), could enhance EIH in individuals with knee OA.

A double-blind randomised crossover trial was conducted, comparing EIH after a single session of 2 mA anodal tDCS applied over the primary motor cortex to sham tDCS. Participants were successfully blinded to the type of tDCS they received. However, there was no significant difference in EIH between the active and sham

tDCS sessions, including pre- to post-exercise measures of PPT, resting pain and evoked pain. These findings could relate to the composition of our study population or the exercise protocol utilised. Our participants had a robust hypoalgesic response to exercise, even after the sham tDCS session, that may have made it difficult to improve further with active tDCS. Alternatively, it may be that the single session dose of tDCS was insufficient to improve EIH in our population, particularly given the chronicity of their condition, or that individual variability in the neurophysiological effects of tDCS affected our findings, amplified by the single session design.

6.3 Implications for Clinical Practice

The findings of this thesis underscore the variability of EIH responses among people with knee OA. This aligns with previous research in a knee OA population that has demonstrated no change (88) and an increase in pain following exercise (91), though it is important to note that variability is also observed in pain-free populations (76, 77, 246). Given the variability of EIH in people with knee OA, it is evident that a one-size-fits-all approach to exercise implementation may be inadequate. Clinicians should be aware of the potential for hyperalgesia, which likely contributes to exercise induced flares in pain, negatively affecting adherence and treatment outcomes. Similar variability has been observed in response to longer-term exercise interventions in knee OA, with some individuals achieving substantial improvements in pain and function while others show minimal or no benefit (176, 195, 447). Large cohort studies suggest that factors such as baseline pain severity, physical activity levels, and psychological status may influence these chronic exercise responses, but the predictors of long-term non-response are not yet well established (448). Whether the same variables that influence acute EIH also predict long-term exercise-induced pain relief remains an important unanswered question. This variability highlights the necessity for more individualised exercise interventions that aim to maximise the analgesic benefits of exercise while minimising the risk of exacerbations or flares. Alternatively, clinicians may need to accept that flares are inevitable for some individuals and provide education and reassurance to encourage adherence despite flares.

The findings from Chapter 3 are the first to link pre-exercise expectation to EIH in a population with chronic pain. These findings point to the potential relevance of psychological factors, such as expectations and anxiety in understanding EIH. However, it is important to acknowledge that these factors may account for only a small amount of the variability in EIH responses.

Notwithstanding, there is potential value in exploring approaches that personalise exercise design based on individual differences in psychological and physiological factors. For example, for those with knee OA that experience exercise induced hyperalgesia, it may be beneficial to start with, or modify exercise, to lower exercise intensities or types of exercise that minimise pain exacerbations (e.g. through reduced weightbearing, or impact loading). This aligns with recent novel evidence which has found that exercise at lower intensities can elicit significant EIH responses in healthy pain-free participants (253). Another potentially useful approach may be to begin with or focus on upper limb exercise. This supports previous knee OA research which has reported a reduction in pain in response to upper limb exercise yet no change or an increase in pain in response to lower limb exercise (78). Additionally, pre-exercise education could play a role in addressing maladaptive beliefs and reducing anxiety by emphasising the safety of exercise, the tendency for pain flares to subside over time, and the numerous health benefits of physical activity (e.g. improvements in psychological status, cardiovascular health, bone density, and metabolic health), even if complete pain relief is not always achievable.

It is also important to consider the ecological validity of the pain outcome measures used. Measures such as evoked pain during movement may better reflect the real-world challenges faced by people with knee OA than resting PPTs alone, as they capture pain responses during functionally relevant activities (76). Incorporating such measures alongside PPTs could enhance the clinical interpretability of EIH-related findings and their direct relevance to patient goals.

From a clinical perspective, the results from Chapter 4 indicate that while short, positive educational interventions were able to change participants' belief that a single session of exercise can lead to pain relief, this did not translate into

improvements in EIH in individuals with knee OA. This highlights the challenge of modifying pain related outcomes through educational efforts alone, even when shifts in beliefs toward exercise are achieved. The minimal change observed in OA knowledge and attitudes after the intervention suggests that more intensive educational efforts or extended follow-up, might be required to achieve meaningful changes in illness and treatment beliefs, and, perhaps, EIH. Additionally, the potential disconnect between the positive messages delivered and the participants' personal experiences, particularly if they have previously encountered pain during exercise, may lead to cognitive dissonance.

This highlights the importance of tailoring educational content to better reflect the lived experiences and concerns of patients, as well as modifying exercise or performing it in a way that reduces threat and pain exacerbations for patients, particularly at the start of an exercise programme. This combination may have additive effects, as modifying exercise in this way may serve as a behavioural experiment, reinforcing the messages provided by tailored education and aiding cognitive restructuring through the provision of disconfirmatory evidence (449) . Doing so may increase the effectiveness of, and adherence to, these interventions.

The results from Chapter 5 indicate that, as it stands, single session tDCS cannot be recommended as a strategy for clinicians to enhance EIH in those with knee OA. However, as with Chapter 4, these implications apply to short dose interventions, illuminating the way for future research.

From a pragmatic perspective, it is important to acknowledge that tDCS is not currently a clinically accessible intervention in most physiotherapy settings. Unlike exercise and education, which can be readily implemented, tDCS requires specialised equipment, training, and further evidence before it could be considered feasible for routine practice. However, research is beginning to suggest that tDCS technology is becoming more portable, user-friendly, and affordable, which may improve its accessibility in the future (450). For now, the present findings should be considered primarily mechanistic, reinforcing the

central role of exercise and education as pragmatic strategies for physiotherapists seeking to harness EIH in people with knee OA

6.4 Implications for Future Research

The findings from this thesis highlight a number of areas that could be examined in the future.

1. Future research should prioritise examining the reliability of different exercise protocols in eliciting EIH, including within session reliability, in both pain free populations and populations with chronic pain, including knee OA. Establishing reliable protocols is essential, as it would ensure the utility of EIH as an outcome measure and provide a foundation for predicting its occurrence. Despite measuring a broad range of potential associative factors in Chapter 3, a large degree of variance in the EIH response remained unexplained. This highlights the potential value in exploring additional plausible influencing factors on EIH in knee OA, such as genetic differences, habitual physical activity status, the acute inflammatory response to exercise, and autonomic nervous system function, as well as interventions designed to influence some of these factors, such as vagal nerve stimulation. Additionally, future research should explore the clinical significance of different measures of EIH (e.g., PPT, resting pain, evoked pain). Determining which measure is most relevant to clinical outcomes, such as pain flares or long-term relief, would help researchers select the most relevant measure(s) of EIH and clinicians better understand how to interpret the literature and use exercise as a tool for managing pain in knee OA. Future studies could also extend follow-up beyond immediate pre- and post-exercise assessments to include delayed time points (e.g., 24 hours post-exercise), as this may better capture clinically relevant flares or sustained analgesic effects.
2. The findings from Chapter 5 provide evidence that a single session of 2mA anodal tDCS over M1 did not enhance the EIH response to isometric exercise compared to sham tDCS in people with knee OA. The lack of effect may be attributed to the insufficient dosing of tDCS, the inherent variability in the

physiological responses to a single session of tDCS, or the already robust EIH response observed in our population of people with knee OA. It would be of interest to determine whether employing multiple tDCS sessions prior to exercise would enhance EIH in this population, and/or whether targeting populations with more severe OA symptoms or those with an already established impairment in EIH would be more effective.

3. Another key area for future research is the exploration of different doses and types of exercise on EIH in knee OA. Studies that directly compare modalities such as resistance versus aerobic exercise, as well as varying exercise intensities, could provide crucial insights into optimising exercise interventions for pain management. Investigating how these variables impact EIH responses in knee OA could ultimately lead to more personalised exercise design aimed at achieving more consistent pain relief across all individuals with knee OA.

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Appendices

Appendix A. Literature Search Strategy

This appendix outlines the search methods used to inform the narrative review presented in Chapter 2. While not conducted as a systematic review, a structured and transparent process was followed to identify relevant literature.

Databases Searched

- AMED (Allied and Complementary Medicine Database)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- MEDLINE (via PubMed and OVID)
- OVID (cross-database search)
- SPORTDiscus
- Scopus

Time Frame

- Searches included all records published up to **December 2022**.

Language and Publication Type

- Only studies published in **English** were included.
- Only **peer-reviewed publications** were considered.
- Conference abstracts and grey literature were excluded.

Search Strings

Keywords and Boolean operators were adapted to each database's syntax. An example search string used in MEDLINE was:

("exercise-induced hypoalgesia" OR "exercise-induced analgesia" OR "exercise-induced hyperalgesia")
AND (exercise OR contraction OR isometric OR aerobic OR resistance OR isotonic OR strength training)
AND (osteoarthritis OR "knee osteoarthritis" OR OA OR arthrosis)
AND (pain OR painful OR flares OR analgesia OR hyperalgesia)

Supplementary Search Methods

- **Citation chaining**: Reference lists of prior reviews and key studies were hand-searched for additional relevant publications.
- **Iterative refinement**: Keywords were expanded during the process as new terms were identified.

Inclusion Criteria

- Human studies involving exercise and pain outcomes (EIH)
- Studies including participants with **knee osteoarthritis**
- Studies exploring interventions aimed at influencing EIH (e.g., education, tDCS)

Exclusion Criteria

- Non-English publications
- Animal studies
- Grey literature, theses, or conference abstracts

Active Control: Script for the education of participants with knee osteoarthritis, utilising the "Versus Arthritis: Osteoarthritis of the knee" handbook, excluding explicit information of exercise induced hypoalgesia.

Participant has been deemed eligible to participate in the study and arrives at the clinic and informed consent and introduction formalities are completed.

Session 1 (30 min)

At the beginning of session 1, the experimenter will introduce himself to the participant. Following this approximately 5 minutes will be spent on rapport building in order to help the particiapnt feel comfortable, build trust, increase confidence and form a therapeutic relationship.

Experimenter: "*When did you start having trouble with your knee?"*

Participant responds:

Experimenter: Acknowledges any key points and then.

"Would you be able to tell me in your own words, what is your understanding of knee OA?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"OA can affect people in a range of ways. What do you notice specifically about how it affects you?

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What helps your knee? …. How does this help ?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What do you do when your knee feels sore?" Why is that?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What do you think you should be doing that you don't? …. Why don't you?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

“How does that sound to you?”

Participant responds:

Experimenter: Acknowledges any key points and then.

“I would now like to chat about some support resources that are available.”

Experimenter: Talks through support options section as per Versus handbook then:

Experimenter: *"If you were to summarise what we chatted about today with your family/partner, what would you tell them?"*

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

“Alright, well I hope that information was useful for you and that you have learned something new about knee osteoarthritis. Now I would just like to quickly explain what is going to happen during your next session with me in a few days where we will be discussing exercise and performing some tests.”

Following description of session 2 procedures:

Experimenter: *“Thank you again for your time and for agreeing to participate in this study. I look forward to seeing you again for session 2.”*

Session 2 (30 min) script

At the beginning of session 2, the experimenter will again spend approximately 5 minutes on rapport building in order to help the particiapnt feel comfortable, build trust, increase confidence and form a therapeutic relationship.

Experimenter: *“Thanks again for coming along for your second session. To start things off, is there anything from the booklet or any questions you have having had a look through your booklet over the last few days?”*

Participant responds:

Experimenter: Summarise key points about modality and frequency and then ask:

Experimenter: *"Today we are going to focus more on exercise. Can you tell me what type of exercise or activity?, if any, you regularly participate in and how often?"*

Participant responds:

Experimenter: Summarise key points about modality and frequency and then ask:

"Have you ever engaged in exercise or activity that is intense enough to cause pain during or

immediately following the exercise?"

Participant responds:

Experimenter: Summarise relevant information and add

"Muscle pain during and immediately following strenuous exercise or activity is called acute muscle soreness and generally disappears shortly after finishing exercise. The pain is the result of energy metabolism, often referred to as 'metabolites' and one of these you might have heard of is lactic acid. The increase in these metabolites in our muscles sends stress signals to the brain, which eventually contribute to feeling exhausted from exercise. The feeling of exhaustion prompts us to rest and to let our muscles recover. So the pain during exercise has a role to protect us from exercising for too long or too hard. Are you familiar with this type of muscle pain during exercise?"

Participant responds:

Experimenter: Summarise relevant information and, with the aid of Figure 1, adds:

"Another type of muscle pain that occurs after strenuous or unaccustomed exercise or physical activity is termed delayed onset muscle soreness, or DOMS. The pain associated with DOMS often gets worse in the 24-72 hours following exercise before slowly reducing. The pain is thought to be caused by micro trauma

to the muscle fibres. You're particularly likely to get DOMS if you've been walking or running up and down hills. Have you ever experienced DOMS?"

Participant responds:

Experimenter: Responds to the participant's answer and adds:

"While DOMS can be quite painful, the muscles adapt quickly. If you get DOMS once from some exercise you probably won't get DOMS the second time you do that exercise – or at least not nearly so bad. It just indicates that our muscles are repairing after some unaccustomed exercise and are getting stronger. While most people know about how good regular exercise is for things like managing weight, improving lung and heart function, and even our mood, what we are starting to learn is that even a single bout of exercise can provide physical and psychological benefits. Have you come across much information about the benefits of just a single bout of exercise?

Participant responds:

Experimenter: Summarises key points raised by the participant and affirms these with the participant:

Participant responds:

Experimenter: Reflects on any relevant points the participant has raised and then:

"Yes, some research has shown that even short bouts of exercise, as little as 5 minutes, can improve fitness, health and wellbeing. However, some people who decide to commence more strenuous exercise experience acute muscle soreness or DOMS and this often discourages them from further participation in exercise. This study that you have volunteered to take part in is about pain during a bout of normal

intensity exercise for 5 mins and requires me to explain a bit more to you about pain during this type of exercise. I'll start by asking you a question. When you exercise, how do you determine if it is safe to continue if your pain increases or do you see the increase in pain as an indication to stop?"

Participant responds:

Experimenter: Summarise any relevant information provided and then:

"It's normal to feel an increase in discomfort during exercise and this is not an indication that you are causing further damage to the muscle or that you are hurting yourself. It is safe to continue to exercise when the increases in pain you experience are tolerable and feel manageable. This discomfort should level out during exercise and reduce shortly after you finish. If you feel the muscles are getting tired or hurting too much during the exercise, then you should just drop the intensity slightly back to an easier level. You can apply this to the exercise bout you are about to undertake for this study. Before we continue, do you have any questions about pain and discomfort during exercise?"

Participant responds:

Experimenter: Answers any of the questions raised by the participant and then:

"I would now like to talk about how levels of pain and exertion are typically

measured during exercise. Do you know anything about this?"

Participant responds:

Experimenter: Reflects on any relevant points the participant has raised and then:

"Because pain and exertion are both things that only you can feel, we ask you to tell us about these using rating scales .For example, I might ask you to rate your pain during exercise on a 0 to 100 scale whereby 0 is no pain and 100 is the worst possible pain. I could use a similar scale to ask you about your level of exertion during exercise, and this information would be useful for me to know how hard you are finding the exercise. Have you used these types of scales before?"

Participant responds:

"*Another useful aspect of these types of scales is that they can be used to assess different aspects of pain such as pain intensity and pain unpleasantness. Pain intensity describes how strong the pain is whereas pain unpleasantness describes*

how bothersome it is and just because something is intense, that doesn't necessarily mean that it is bothersome and vice versa. For example, you might find the pain from a hard massage to be quite intense but not necessarily unpleasant. There is some interesting research in athletes using these different types of pain ratings showing that sportsmen and women typically have lower ratings of pain unpleasantness and higher pain tolerances compared to non-athletes. Basically, athletes find things to be just as painful but are willing to tolerate them for longer. This is probably a big part of why endurance athletes like marathon runners and cyclists are able to exercise at high intensities for so long. Now I don't wish to create an impression that with exercise we can all become stoical like elite athletes and learn to ignore pain. The point is simply that we recognise the different aspects of the pain experience and how these interact with exercise. Do you have any questions about this?"

Participant responds:

Experimenter: summarises key points raised by the participant and then:

"Okay, well it's good that you are now a little more familiar with some of the causes of pain during exercise as well as how pain and exertion are measured during exercise as you are going to be asked to rate these sensations later on when you are exercising. Is it okay if I summarise the key points we talked about before we commence exercise?"

Key points on a card:

- It is normal to experience some muscle pain and discomfort during and for a short time following exercise and pain during exercise doesn't mean that you are causing lasting damage or injury.

- It is also normal to experience longer lasting muscle pain, or DOMS, after intense or unaccustomed exercise, but the muscles gradually adapt to this and the pain subsides

- During exercise at an intensity that causes some discomfort, tolerable increases in pain are normal and safe. We can monitor these increases in pain and discomfort during exercising using self-report scales.

"I just have a few final questions before we go on with the rest of the experiment."

[Experimenter presents the 5 questions below and asks the participant to indicate their level of agreement with each question. The experimenter then circles their response]

Experimenter: *"Thank you. Do you have any questions before we commence?"*
Participant responds:

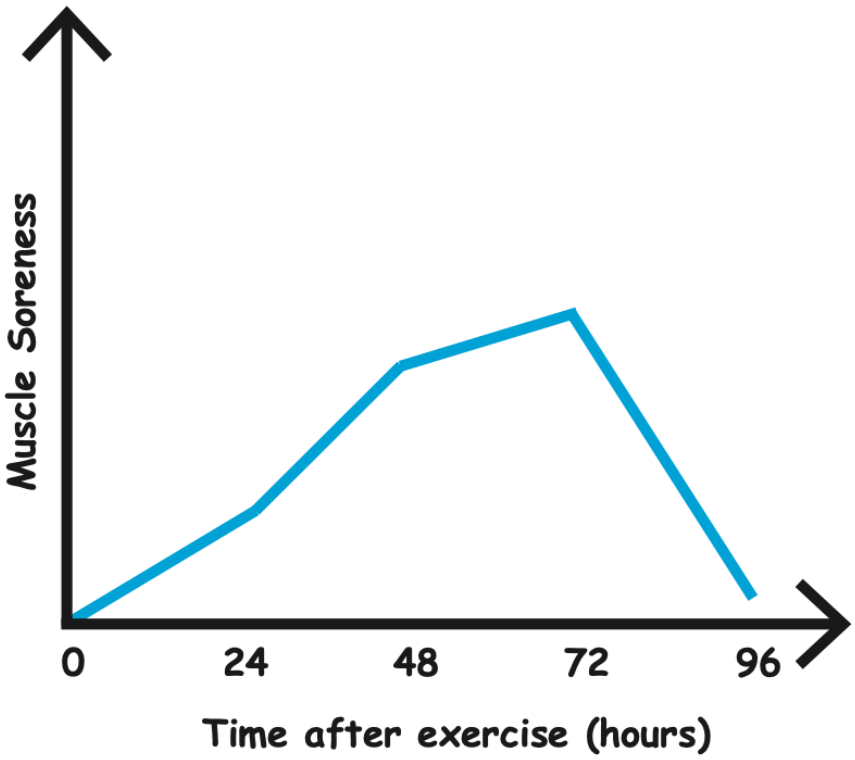
Experimenter: *"Alright, well I hope that information was useful for you and that you have learned something about pain during exercise. Now I would just like to quickly explain what is going to happen for the rest of the experiment, after which I will hand over to one of my colleagues who take you through the exercise bout and pain assessments."*

Following description of experimental procedures:

Experimenter: *"Thank you again for your time and for agreeing to participate in this study. I will leave you with my colleague and see you again when you're done."*

Delayed Onset Muscle Soreness (DOMS)

What is it?



Why does it occur?

Figure 1

Intervention: Script for the education of participants with knee osteoarthritis, utilising the "Information for people with Knee Arthritis" handbook, including explicit information of exercise induced hypoalgesia.

Participant has been deemed eligible to participate in the study and arrives at the clinic and informed consent and introduction formalities are completed.

Session 1 (30 min)

At the beginning of session 1, the experimenter will introduce himself to the participant. Following this approximately 5 minutes will be spent on rapport building in order to help the particiapnt feel comfortable, build trust, increase confidence and form a therapeutic relationship.

Experimenter: "*When did you start having trouble with your knee?"*

Participant responds:

Experimenter: Acknowledges any key points and then.

"Would you be able to tell me in your own words, what is your understanding of knee OA?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"OA can affect people in a range of ways. What do you notice specifically about how it affects you?

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What helps your knee? …. How does this help ?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What do you do when your knee feels sore?" Why is that?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

"How does that sound to you?"

Participant responds:

Experimenter: Acknowledges any key points and then.

"What do you think you should be doing that you don't? …. Why don't you?"

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

“How does that sound to you?”

Participant responds:

Experimenter: Acknowledges any key points and then.

“I would now to chat about some support resources that are available.”

Experimenter: Talks through support options section as per handbook then:

Experimenter: *"If you were to summarise what we chatted about today with your family/partner, what would you tell them?"*

Participant responds:

Experimenter: Answers any questions raised by the participant and reflects on any relevant points using the handbook and then:

“Alright, well I hope that information was useful for you and that you have learned something new about knee osteoarthritis. Now I would just like to quickly explain what is going to happen during your next session with me in a few days where we will be discussing exercise and performing some tests.”

Following description of session 2 procedures:

Experimenter: *“Thank you again for your time and for agreeing to participate in this study. I look forward to seeing you again for session 2.”*

Session 2 (30 min) script

Experimenter: *“Thank you for coming along for your second session. To start things off, is there anything from the booklet or any questions you have having had a look through your booklet over the last few days?”*

Participant responds:

Experimenter: Summarise key points about modality and frequency and then ask:

Experimenter: *“Today we are going to focus more on exercise. Can you tell me what type of exercise, if any, you regularly participate in and how often?”*

Participant responds:

Experimenter: Summarise key points about modality and frequency and then ask:

"Have you ever engaged in exercise that is intense enough to cause pain during or immediately following the exercise?"

Participant responds:

Experimenter: Summarise relevant information and add

"Muscle pain during and immediately following strenuous exercise is called acute muscle soreness and generally disappears shortly after finishing exercise. The pain is the result of end products of energy metabolism, often referred to as 'metabolites' and one of these you might have heard of is lactic acid. The increase in these metabolites in our muscles sends stress signals to the brain, which eventually contribute to feeling exhausted from exercise. The feeling of exhaustion prompts us to rest and to let our muscles recover. So the pain during exercise has a role to protect us from exercising for too long or too hard. Are you familiar with this type of muscle pain during exercise?"

Participant responds:

Experimenter: Summarise relevant information and add

"Another type of muscle pain that occurs after strenuous or unaccustomed exercise or physical activity is termed delayed onset muscle soreness, or DOMS. The pain associated with DOMS often gets worse in the 48-72 hours following exercise before slowly reducing. The pain is thought to be caused by micro trauma to the muscle fibres. You're particularly likely to get DOMS if you've been walking or running up and down hills. Have you ever experienced DOMS?"

Participant responds:

Experimenter: Responds to the participant's answer and adds:

"While DOMS can be quite painful, the muscles adapt quickly. If you get DOMS once from some exercise you probably won't get DOMS the second time you do that exercise – or at least not nearly so bad. It just indicates that our muscles are repairing after some unaccustomed exercise and are getting stronger. While most people know about how good regular exercise is for things like managing weight, improving lung and heart function, and even our mood, what we are starting to learn is that even a single bout of exercise can provide physical and psychological benefits. Have you come across much information about the benefits of just a single bout of exercise?"

Participant responds:

Experimenter: summarises key points raised by the participant and affirms these with the participant:

Participant responds:

Experimenter: reflects on any relevant points the participant has raised and then:

"Yes, some research has shown that even short bouts of exercise, as little as 5 minutes, can improve fitness, health and wellbeing. However, some people who decide to commence more strenuous exercise experience acute muscle soreness or DOMS and this often discourages them from further participation in exercise. This study that you have volunteered to take part in is about pain during a bout of normal

intensity exercise for 5 min and requires me to explain a bit more to you about pain during this type of exercise. I'll start by asking you a question. When you exercise, how do you determine if it is safe to continue if your pain increases or do you see the increase in pain as an indication to stop?"

Participant responds:

Experimenter: summarise any relevant information provided and then:

"It's normal to feel an increase in discomfort during exercise and this is not an indication that you are causing further damage to the muscle or that you are

hurting yourself. It is safe to continue to exercise when the increases in pain you experience are tolerable and feel manageable. This discomfort should level out during exercise and reduce shortly after you finish. If you feel the muscles are getting too tired or hurting too much during the exercise, then you should just drop the intensity slightly back to an easier level. You can apply this to the exercise bout you are about to undertake for this study. Before we continue, do you have any questions about pain and discomfort during exercise?"

Participant responds:

Experimenter: Answers any of the questions raised by the participant and then:

"I would now like to quickly talk about how levels of pain and exertion are typically measured during exercise. Do you know anything about this?"

Participant responds:

Experimenter: reflects on any relevant points the participant has raised and then:

"Because pain and exertion are both subjective sensations, they are normally assessed using self-report scales. For example, I might ask you to rate your pain during exercise on a 0 to 10 scale whereby 0 is no pain and 10 is the worst possible pain. I could use a similar scale to ask you about your level of exertion during exercise, and this information would be useful for me to know how hard you are finding the exercise. Have you used these types of scales before?"

Participant responds:

Experimenter: Answers any of the questions raised by the participant and then:

"The next thing I would like to discuss is something called exercise-induced hypoalgesia. Do you know anything about this?"

Participant responds:

Experimenter: Acknowledges any key points and then, with the aid of a 2, provides the following explanation:

"Exercise-induced hypoalgesia refers to a decrease in pain following exercise. A lot of studies show that this happens in both men and women and can last for about 30 minutes following exercise. So, when we ask a person to rate their level of knee pain before exercise it is typical that their rating of pain after exercise has dropped. This can happen following resistance exercise, walking, cycling, or running exercise and it tends to happen more if we exercise longer or harder. We don't know exactly what causes exercise-induced hypoalgesia, but it seems to involve the release of substances within the body that reduce pain. Endorphins or natural opioids are the most obvious example that you might have heard of. Have you heard of endorphins?"

Participant responds:

Experimenter: Acknowledges any key points and then, with the aid of Figure 2:

"These endorphins, along with other changes that occur with exercise, act to reduce the stress signals sent from the exercising muscles to the brain. The end result of this is that you experience less pain. This exercise analgesia might be why exercise is such an effective treatment for people with knee osteoarthritis. It's kind of a neat thing that the body becomes a little less sensitive to pain during exercise as it helps us to keep moving longer and to work harder. It's really cool that this effect lasts for a bit after we stop exercising, kind of like taking a painkiller. Do you have any questions about exercise-induced hypoalgesia?"

Patient responds:

[Experimenter presents and explains diagram of how exercise might act at various points in the pain pathway to reduce pain]

Experimenter: Responds to any questions then:

"Okay, well it's good that you are now a little more familiar with some of the causes of pain during exercise as well as how exercise can reduce pain and how this might be measured as you are going to be asked to rate these sensations when you are exercising later on. Is it ok if I summarise the key points we talked about before we commence exercise?"

Key points on a card:

- It is normal to experience some muscle pain and discomfort during and for a short time following exercise and pain during exercise doesn't mean that you are causing lasting damage or injury.

- It is also normal to experience longer lasting muscle pain, or DOMS, after intense or unaccustomed exercise, but the muscles gradually adapt to this and the pain subsides.

- During exercise at an intensity that causes some discomfort, tolerable increases in pain are normal and safe.

- Exercise-induced hypoalgesia is a reduction in pain that occurs after exercise and this can last for up to 30 min following exercise. It is common to experience exercise-induced hypoalgesia following resistance exercise like an isometric contraction, particularly when exercise is performed at higher intensities

"I just have a few final questions before we go on with the rest of the experiment."

[Experimenter presents the 5 questions below and asks the participant to indicate their level of agreement with each question. The experimenter then circles their response]

Experimenter: *"Thank you. Do you have any questions before we commence?"*

Participant responds:

Experimenter: *"Alright, well I hope that information was useful for you and that you have learned something about pain during exercise as well as how exercise can help to acutely reduce pain. Now I would just like to quickly explain what is going to*

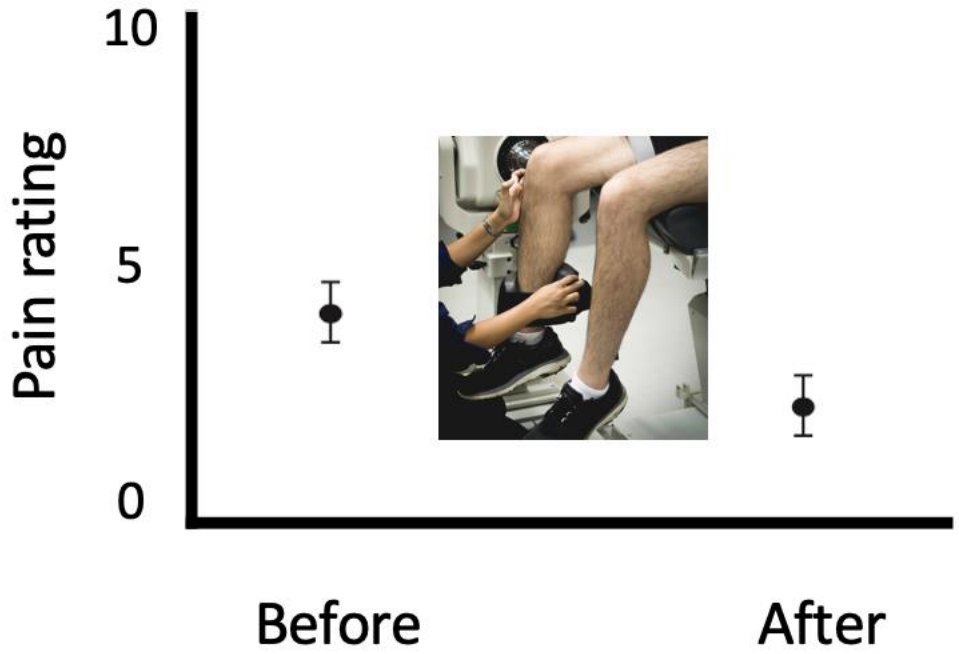
happen for the rest of the experiment, after which I will hand over to one of my colleagues who will take you through the exercise bout and some pain assessments."

Following description of experimental procedures:

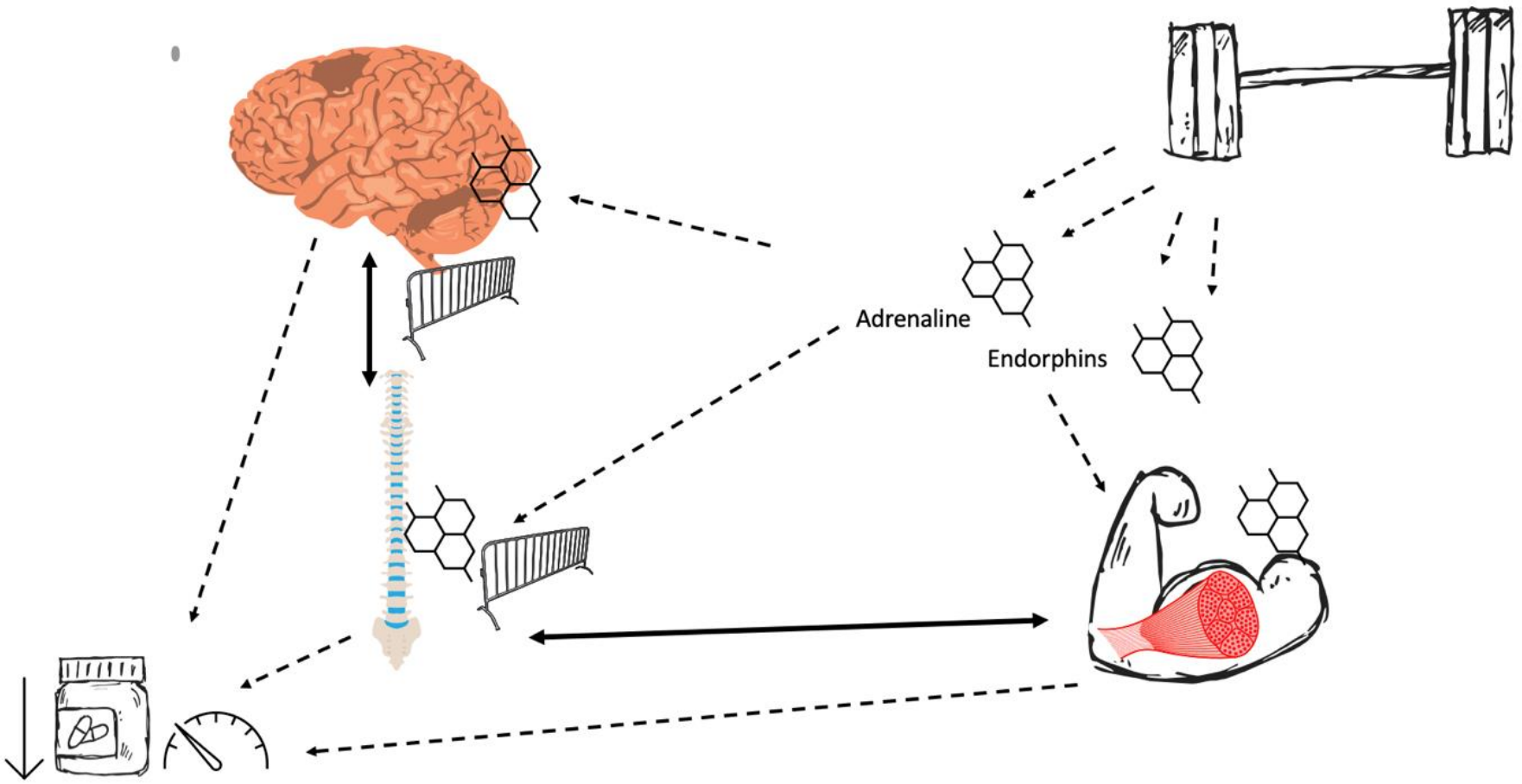
Experimenter: *"Thank you again for your time and for agreeing to participate in this study. I will leave you with my colleague and see you again when you're done."*

Exercise Induced Hypoalgesia

What is it?



Why does it occur?



Appendix C

Study 2 Ethical Approval

Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

17 August 2021

David Rice
Faculty of Health and Environmental Sciences

Dear David

Re Ethics Application: **21/241 Can a targeted pre-exercise education intervention enhance the exercise induced hypoalgesia (EIH) response in individuals with knee osteoarthritis (OA)**

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

Your ethics application has been approved for three years until 16 August 2024.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.
8. AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: davidtoomey2@gmail.com; gwyn.lewis@aut.ac.nz

Appendix D

Study 3 Ethical Approval

Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

17 August 2021

David Rice
Faculty of Health and Environmental Sciences

Dear David

Re Ethics Application: **21/242 Can a single session of 1mA active transcranial Direct Current Stimulation (tDCS) over the primary motor cortex enhance exercise induces hypoalgesia (EIH) compared to sham tDCS in individuals with knee Osteoarthritis (OA)?**

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

Your ethics application has been approved for three years until 17 August 2024.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
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