ENDOGENOUS PAIN MODULATION IN LOW BACK PAIN

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Lay Abstract

Low back pain (LBP) may occur because of changes in our nervous system, rather than a physical injury. However, there is no previous research on if exercise can improve these changes. The purpose of this thesis was to develop and test a protocol to assess how the body processes pain, and if this can change after exercise. We summarized past research on how four tests to assess pain processing have been performed. The results showed many differences in how these tests were performed and reported. More consistency and guidelines are needed to improve how these tests are conducted. Next, we conducted a study aimed to assess the feasibility of a protocol to see if changes occur in how the body processes pain after an exercise therapy program. The results of this study showed the protocol was feasible, and trends in improvement on some but not all measures.

Abstract

A significant driver of pain in low back pain (LBP) is alteration to endogenous pain modulation (EPM). EPM can be measured using quantitative sensory tests (QST), which provides important information on nociceptive pathways. Exercise therapy is recommended as the first line of care for LBP; however, there is limited information on the mechanisms of action that lead to symptom improvements.

The first manuscript was a scoping review that summarized protocols used to assess EPM using QST such as pain pressure threshold (PPT), temporal summation (TS), conditioned pain modulation (CPM) or exercise-induced hypoalgesia (EIH) in LBP. Scientific databases were searched for articles that used QST or EIH protocols in LBP. In total, 193 studies were included in this review: 172 used PPT, 54 used TS and 53 used CPM and 5 investigated EIH. There was high variability in the type of equipment, timing, trials, and testing location with many studies not reporting this information. The results demonstrate a need for standardized protocols and reporting guidelines as well as further research to aid in selecting the most appropriate QST parameters for different clinical presentations.

The second manuscript was a pilot study that assessed the feasibility of a protocol investigating if changes in EPM occur after exercise therapy. Participants were recruited through a larger trial (WELBack) and were randomized to receive one of two exercise therapies. Participants attended two testing sessions (before and after an 8-week treatment) consisting of PPT, TS, CPM and EIH. Thirty-six participants were recruited and completed baseline assessments. In total, 32 (88.9%) participants completed the

follow-up assessment. The results demonstrated that the protocol was feasible. Improvements to patient reported outcomes were seen, but not to all EPM measures. Future work should consider changes to the CPM protocol, and a fully powered study to investigate EPM changes after exercise therapy.

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Declaration of Academic Achievement

For all the manuscripts, Lee-Ran Goodman developed the research questions, designed the studies, collected, and analyzed the data and wrote the initial drafts.

Chapter 2 & 3

Dr. Luciana Macedo helped to refine and guide the research questions, data collection, extraction, and analysis.

Dr. Lisa Carlesso, Dr. Ada Tang, and Dr. Luciana Macedo helped with revision/editing and provided feedback for the manuscript.

Table of Contents

List of Tables

Chapter 2

Chapter 3

List of Figures

Chapter 2

Chapter 3

List of Appendices

List of Abbreviations

AMED – Allied and Complementary Medicine Database

CNS – Central Nervous System

CPM – Conditioned Pain Modulation

CS – Conditioning Stimulus

CS – Central Sensitization

CINHAL – Cumulative Index to Nursing and Allied Health Literature

EIH – Exercise Induced Hypoalgesia

EPM – Endogenous Pain Modulation

IASP – International Association for the Study of Pain

JBI – Joanna Briggs Institute

LBP – Low Back Pain

NSLBP – Non-Specific Low Back Pain

PNS – Peripheral Nervous System

PPT – Pain Pressure Threshold

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PS – Peripheral Sensitization

QST – Quantitative Sensory Testing

RCT – Randomized Controlled Trial

TS – Temporal Summation

TS – Test Stimulus

1 Chapter 1: Introduction

1.1 Back Pain

Low back pain (LBP) is one of the most common musculoskeletal problems, and a leading cause of years lived with disability worldwide. [1] LBP refers to pain, stiffness or muscle weakness in the areas below the costal margin and above the inferior gluteal fold. [2] It affects many individuals, having a profound impact on many aspects of their lives including work, social, and overall well-being. [3] LBP has been associated with low quality of life including significant functional limitations, anxiety and depressive symptoms. [4] Strategies are needed to help manage the pain, physical function, and overall well-being of those with LBP. This chapter will present an overview of LBP, how pain is processed, and methods of quantifying, assessing, and managing pain in this population.

1.1.1 Epidemiology

In 2019, it was estimated that the prevalence of LBP was 619 million people globally, and this number is expected to rise with the increasing aging population. [1 5] The lifetime prevalence of LBP has been reported to be 49-90%, [6] with the highest incidence being in individuals aged 80-84. [7] LBP can be classified based on symptom duration, diagnosis or clinical presentation (i.e., radiculopathy, stenosis), and on the type of pain mechanisms. Regardless of the type of classification, it is often recommended that targeted treatment approaches should be considered to address the heterogeneous presentation of LBP. [8]

1.1.2 Duration of Pain

The duration of back pain can be classified as acute (4 weeks or less), subacute (4 weeks to 3 months), and chronic (persists more than 3 months). [8] For most individuals

with acute cases, symptoms will resolve on their own, and these individuals do not require any treatment. [8] However, about 10-15% of individuals will continue to experience pain and symptoms for greater than 3 months and will develop chronic LBP. [6] [9] For those with chronic LBP, about 75% will experience an activity-limiting flare within a year. [10] Similarly, many (~70%) who recover from an acute episode will have a recurrence within a year. [11] This type of episodic LBP with remission, recurrences and flares is often referred to as recurrent LBP, although it may be hard to diagnose given the often-fluctuating nature of symptoms. [12]

1.1.3 Diagnosis

Diagnoses of back pain are most often classified into specific, serious, or non-specific conditions. Specific low back pain accounts for approximately 10% of LBP and is characterized by LBP with a specific related structural cause confirmed through clinical investigation and imaging. [13] [14] Some examples of specific LBP include lumbar disc herniations, lumbar spinal stenosis and rheumatoid arthritis. [15] Specific LBP is sometimes accompanied by radicular pain, which is presented as pain radiating into one or both legs, loss of sensation and/or muscle weakness. [16] In these cases, pain often presents with nociceptive or neuropathic characteristics. Serious LBP has a very low prevalence and incidence and includes red flag conditions such as fractures, infection, and cancer. [13] [17] Approximately 85% of people who have LBP have non-specific low back pain (NSLBP) which is defined as LBP that is not attributable to any known cause, such as a particular pathology or tissue damage. [18] [19] It is believed that for individuals with NSLBP a high proportion present with features of nociplastic pain. [20]

NSLBP or back pain in general can be classified according to diagnosis using the International Classification of Disease (ICD-11). [21] The ICD-11 includes specific codes for different back pain conditions, but also a newly established diagnosis for chronic pain. [21] Particularly for NSLBP and nociplastic dominant pain, a diagnosis of chronic pain secondary to musculoskeletal pain is likely the most appropriate diagnostic classification. [21] Although NSLBP is still the most used term in the literature, the recognition of chronic pain conditions in ICD-11 has been crucial in shedding light into the burden and importance of nociplastic pain as a disease by itself, reducing stigma and improving access to care for all patients with chronic pain. [21]

1.1.4 Pain Phenotypes

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". [22] Pain phenotypes include: nociceptive, neuropathic, and nociplastic pain. It is recognized that these often do not exist alone, as people may present with a combination of two or three of these mechanisms. [20 23] Nociceptive pain is the unpleasant sensory and emotional experience that is associated with actual or threatened damage to non-neural tissues and is highly driven by the process of nociception through the activation of nociceptors. [24 25] Nociception is the process where information from the periphery about the potential for, or actual tissue damage is transmitted to the brain. [26] On the other hand, neuropathic pain occurs because of a lesion or disease of the somatosensory nervous system and can be caused by damage to nerves through nerve impairment or nerve injury. [25 27] Neuropathic

pain is often associated with allodynia, which occurs when a pain response is triggered from stimuli that normally would be considered non-painful. [24 27] Previously, chronic pain was thought to only arise from either nociceptive or neuropathic pain. [20] The third definition, nociplastic pain was added more recently to encompass a broader definition of pain that did not fit into either the nociceptive or neuropathic categories. Nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". [24] It is the result of different mechanisms that lead to altered functioning of sensory pathways involved with pain processing. [20] These mechanisms can be driven by the peripheral nervous system (PNS) i.e. peripheral sensitization, or the central nervous system (CNS), i.e. central sensitization, psychological factors, or any combination of them. [20 28] The common theme with nociplastic pain is that pain is amplified through increased facilitative activity or a decrease in descending inhibition, [20] and patients often show signs of hypersensitivity such as mechanical, heat or cold allodynia. [28] Nociplastic pain can present in a variety of ways, such as localized to a specific area, in the case of chronic primary musculoskeletal pain like LBP, or be widespread, such as fibromyalgia, with different degrees of severity. [20]

1.2 Ascending and Descending Modulation of Pain

1.2.1 Nociception

The experience of pain depends on the complex central processing of ascending signals from the periphery and descending modulatory signals that can be inhibitory and

facilitatory. [29] There are 4 general stages in the process of the pain experience: (1) sensory perception of a noxious stimulus, (2) transmission of signals from the periphery to the dorsal horn (DH), (3) modulation and transmission of signals to higher brain centers within the CNS and (4) pain experience. [27 30] The process of pain perception is mediated by specialized sensory receptors known as nociceptors, and later processed and interpreted by the brain. These receptors are connected to primary afferent neurons including the myelinated Aδ-fibers and unmyelinated C- fibers, which are associated with the experience of pain. [26 27] Aδ-fibers conduct information relatively fast and are primarily responsible for detecting thermal and mechanical nociception. [27] On the other hand, unmyelinated C-fibers conduct information slowly and are primarily responsible for detecting thermal, mechanical and chemical nociceptive stimuli, and it is activated from poorly localized stimuli such as burning. [27] Other sensory receptors that are important in pain perception include A-β fibers which contribute to touch and mechanical suppression of pain, as well as kinesthetic position and the identification of pain location. [31] In the presence of noxious stimuli, these nociceptors are activated, and signals are transduced along the axons of peripheral neurons, where they terminate in the DH located in the spinal cord. [26 27] The DH plays an important role of integrating multiple inputs that enter the spine, including both ascending from the periphery and descending from supraspinal centers in the spinal cord. [27]

Signals that arrive in the DH are sent through the ascending pathway of the spinothalamic tract. There are 2 parts to the spinothalamic tract, the lateral spinothalamic tract, which carries information on noxious and temperature sensation, and the anterior

spinothalamic tract, which transmits information on crude touch and firm pressure. [27] Both tracts transmit information to the thalamus and the somatosensory cortex. [26 27] The thalamic nuclei known as the ventral posterior lateral nucleus and the ventromedial nucleus are where these nociceptive pathways terminate. These nuclei then relay information to various regions including the amygdala, hypothalamus, periaqueductal grey (PAG), rostral ventral medulla (RVM), basal ganglia, insula, and anterior cingulate cortex. [26 27] These areas process the somatosensory input and send out neural impulses which, in combination with cognitive and emotional factors, serve to modulate the ascending signals through descending mechanisms in the CNS and influence the perception of pain. [26]

1.2.2 Endogenous Pain Modulation

Endogenous pain modulation (EPM) or descending central modulation of pain, refers to the wide range of actions that the CNS can take to reduce or augment pain. [32] The system responsible for pain modulation involves a network of neurons within the CNS that connects multiple brain areas with the spinal cord. [33] These brain areas include the prefrontal cortex, anterior cingulate cortex, insula, PAG, amygdala, hypothalamus, dorsolateral pons/tegmentum and the RVM. [26 33] The thalamus contributes to both pain facilitation and inhibition through the mediodorsal nuclei and ventromedial nuclei respectively. [29] When incoming signals from the periphery are relayed to the CNS, the actions of these different brain regions converge at the brainstem and send signals back down to the DH via descending projections. [26 32] These can be inhibitory to reduce incoming nociceptive messages from the periphery, or facilitatory to augment the

incoming signals. [32] Interneurons in the DH can also inhibit or allow impulses to be transmitted to higher brain centers and provide a site where the CNS can control the transmission of signals. [26]

The PAG plays an important role of integrating ascending nociception signals with descending signals from the midbrain and forebrain. [29] It produces descending pain modulatory effects through its connections with the RVM. [34] Signals from the PAG, which is located in the midbrain, reach the spinal cord directly or indirectly through the RVM. [33 35] The RVM can facilitate or inhibit nociceptive inputs and acts as a relay station for the control of descending modulation through its different cell types. [29 34] Descending projections from the RVM travel through the dorsolateral funiculus to reach DH neurons in the spinal cord where there is a first opportunity for modulation to occur .[35] These DH neurons then form synaptic connections with primary afferent neurons, second and third order neurons and interneurons that transmit nociceptive signals to supraspinal sites. [29 35] The dorsal reticular nucleus also communicates with the PAG, RVM, thalamus and amygdala to produce modulatory signals that get sent to the spinal cord. [35]

1.3 Neuromatrix Theory of Pain

The neuromatrix theory of pain, proposed by Ronald Melzack, suggests that pain is a multidimensional experience produced by multiple influences. With this theory, Melzack expanded on the gate-control theory of pain to describe how the CNS plays an important role in the processing of noxious stimuli. [36 37] This theory moves away from the idea that pain is simply caused by an injury or damage to tissues and suggests that we have a genetically built-in matrix of neurons for the whole body, which produces nerve

impulse patterns and the somatosensory qualities we feel. [36 38] This new conceptual nervous system is made up of 4 components: the body-self neuromatrix, the neurosignature, the sentient neural hub, and the activation of the neuromatrix. [37 38]

The body-self neuromatrix is a large widespread network of neurons that consists of loops between different structures of the brain, including between the thalamus and cortex as well as the cortex and limbic system. [38] The synaptic make-up of the neuromatrix is influenced initially by genetics, and then later modified by sensory influences, and generates specific patterns of nerve impulses known as 'neurosignatures'. [36 38 39] The neurosignature is a continuous outflow from the body-self neuromatrix and is produced through repeated cyclical processing and synthesis of nerve impulses through the neuromatrix. [38] The continuous stream of nerve impulses can go on to activate different neural networks in the spinal cord to produce muscle patterns and movement. [38] The activity of areas along the transmission routes of the major sensory projection systems (ex. dorsal horns, and somatosensory projection areas of the thalamus and cortex) produce certain patterns of nerve impulses, which then projects to other areas involved with the pain experience, such as the anterior cingulate cortex (ACC), [39] and the localization of pain at specific sites. [36] Although these neurosignatures are developed to increase efficiency of signaling, it can also lead to maladaptation with the pain experience.

Another important factor is the role that both physical and psychological stress plays on pain processing and the development of chronic pain states. [38] Stress is a biological system that is activated when there are threats to the body's state of

homeostasis. These threats can be physical injury, infection, pathology, or psychological threats, and initiate different mechanisms that aim to return the body back to a state of homeostasis. [36 38] One mechanism is the release of the hormone cortisol. The release of cortisol produces and maintains a high level of glucose, which is necessary after injury. [38] To do this, cortisol breaks down the protein in muscle and prevents the replacement of calcium in bone and suppresses the immune system. [38] Therefore, sustained cortisol release can be highly destructive as it can cause weakness, fatigue, decalcification of bone, and can accelerate the degeneration of the hippocampus. [38] The cumulative negative effects of cortisol, alongside other factors, may contribute to the development of chronic pain states. [38]

The neurosignature for pain experience is determined by many different factors that connect back to the synaptic architecture of the neuromatrix which we know is first influenced by genetics and later altered by experience. [38 39] These inputs to the neuromatrix can be from sensory, affective and cognitive factors that influence the output patterns seen contributing to the experience of pain. [38] These influences include physical, psychological or environmental stressors and can be from within the body, other areas of the brain, and the result of influences on the stress-regulatory systems. [38] The cognitive influences may be either tonic or phasic inputs from the brain. Tonic inputs include cultural learning, past experiences, and personality, while phasic inputs are factors like attention, expectation, anxiety and depression. [38] The sensory influences may be visceral inputs like inputs from the visual and vestibular system or may be tonic or phasic in nature. [38] The motivational-affective influences may be from endocrine and immune

systems such as the hypothalamic-pituitary-adrenal system, the noradrenalin-sympathetic system, or endogenous opiates and the limbic system. [38]

The outputs often produce different dimensions of the pain experience, including pain perception, action programs and stress regulation programs, and the resulting homeostatic and behavioural responses. [38] Pain perception outputs include the 3 input categories (cognitive-evaluative, sensory-discriminative, and motivational-affective). [38] Action programs encompass involuntary and voluntary action patterns, social communication and coping strategies. [38] Stress regulation programs include endocrine and immune molecules such as cortisol, noradrenaline, cytokines, endorphins and in general the activity of the immune system. [38] When regulation of homeostasis fails, the neuromatrix can produce destructive conditions that may give rise to chronic pain that is different from pain that is caused by sensory inputs. [38] The influence that genetics have on the makeup of the neuromatrix may determine or predispose individuals to the development of chronic pain states. [38]

1.4 Alterations to Pain Processing

For many individuals with chronic pain conditions, there is poor correlation with tissue abnormalities or pathology seen on imaging and the extent of pain, hyperalgesia and allodynia that is associated. [33] It is thought that individuals with NSLBP may have pain that is primarily nociplastic, or a combination of nociplastic with nociceptive and neuropathic pain. This suggests that there may be abnormalities of pain processing within the CNS. [33] Normally, the nervous system receives incoming signals from the periphery, and the CNS processes and interprets these signals to arrange appropriate responses

through descending central modulation. It is widely recognized that individuals with chronic pain can develop hyperexcitability of the CNS and alterations to EPM. [40] Increased sensitivities to stimuli resulting in pain might develop through peripheral or central mechanisms such as peripheral sensitization (PS) or central sensitization (CS) respectively. [33]

1.4.1 Peripheral Sensitization

Peripheral sensitization (PS) refers to the increased firing of nociceptors commonly due to the reduction of membrane thresholds and/or an amplification in their responsiveness causing them to be more labile. [41 42] It is restricted to the site of tissue injury and contributes to the sensitization of the nociceptive pathways leading to pain hyperalgesia at the site of damage. [42] PS occurs when peripheral terminals of primary sensory neurons are exposed to chemical mediators at the site of inflammation and damaged tissue. [41 42] The involvement of many different molecules leads to acute and long-term increase in the excitability of nociceptors. [41] However, injury or inflammation in the periphery is generally needed for PS to occur. [42]

1.4.2 Central Sensitization

Central sensitization (CS) is an abnormal state of responsiveness of the nociceptive system and is defined by the IASP as an "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent inputs. [24 42] In many people with chronic non-specific pain, CS may explain why they experience pain in the absence of any nociceptive or neuropathic origin, or in the absence of enough tissue damage or pathology to explain the associated pain. [28] CS encompasses various

dysfunctions of the CNS including altered sensory processing in the brain, reduced activity of descending modulation such as dysfunction in conditioned pain modulation and, increased activity of pain facilitatory pathways such as enhanced temporal summation. [43] In individuals with CS conditions, the pain neuromatrix is overactive, with increased activity in areas such as the insula, ACC, dorsolateral frontal cortex, and the parietal associated cortex. [43]

CS results from changes in the functioning of neurons within the CNS, which may include enhanced functioning of somatosensory neurons in the DH of the spinal cord as well as neurons in nociceptive pathways. [29] [42] This can be seen through increases in membrane excitability, synaptic efficacy or reduced inhibition. [42] Normally, when repeated or particularly intense noxious stimuli are present, such as in the presence of tissue damage, the threshold for neural activation is lowered, which leads to subsequent stimuli being amplified. [42] In the absence of active tissue damage, this threshold returns to normal. [42] Depending on the intensity, frequency and duration of synaptic activity, increases in synaptic function can be observed, which leads to sensitization. [29] With CS, subthreshold synaptic inputs, which normally would not generate an action potential are recruited and contribute to the neuron's output. [42] This changes the neuron's response to subsequent inputs by increasing how excitable the neuron is, or by blocking neurotransmitters that inhibit neuron activity. [42]

1.5 Assessing Pain Perception Pathways

1.5.1 Quantitative Sensory Testing

Quantitative Sensory Testing (QST) is a term that describes a form of psychophysical testing that can be used to assess sensory and nociception pathways. [44] QST encompasses various tests with standardized instructions that measure patients' responses to quantifiable sensory stimuli. [28 44] It requires active participation from the patient and allows the examiner to measure and quantify somatosensory functioning in both small and large sensory nerve fibers. [44] Although these tests allow for the quantification of sensory stimuli, they are not objective measures and are instead an expression of the participants perception. [44] QST provides a proxy measure for the assessment of CS, as it cannot be directly measured in humans. [45] QST provides valid and valuable information and can be used for various purposes in research and sometimes in clinical settings. This includes examining pain mechanisms, investigating differences in pain sensitivity and pain modulation and examining different pain disorders and their somatosensory profiles. [44 46] They can also be used to detect sensory loss or gain and can be used for assessing hypersensitivity to stimuli such as pressure, heat and cold. [28 47] QST have the potential to provide important information on the nociceptive pathways of patients with different chronic pain states, [40] including neuropathic, [44] and nociplastic pain.

QST can be broadly categorized into 2 groups: static and dynamic measures. Static QST measure noxious stimuli experienced at a single time point and encompasses measures such as magnitude ratings and threshold determinations through pain detection,

pain thresholds or pain tolerances to various stimuli. [48] Some examples include thermal detection and pain thresholds, mechanical pain threshold and pressure pain threshold. In comparison, dynamic QST measures provide information on central integration and descending control. Tests for central integration include temporal summation (TS) and spatial summation, while tests for descending control include conditioned pain modulation (CPM). [48] Taken together TS and CPM provide information on the efficiency of the endogenous pain modulatory system. QST can also provide information on both peripheral and central sensitization. The presence of central sensitization, for example, can be indirectly evaluated by using tests such as temporal summation where applying repeated stimuli will result in increased pain perception. [47] Similarly, changes with central inhibitory pain modulation can be identified through the conditioned pain modulation test. [47] Both static and dynamic QST can provide useful information on the participant's somatosensory profile and whether peripheral or central sensitization may be at play.

1.5.1.1 Pain Pressure Threshold

One common static QST used to assess pain sensitivity in individuals with LBP is pressure pain thresholds (PPT). PPT is defined as the minimum amount of pressure over a given area where steadily increasing non-painful pressure stimulation turns into painful pressure stimulation. [49] PPTs are measured using a pressure algometer and provide information on deep muscular tissue sensitivity. [49] It has been demonstrated that individuals with chronic NSLBP and individuals with chronic pain conditions in general have lower PPT values when compared with healthy individuals, suggesting that generalized mechanical hyperalgesia is present. [50] [51]

1.5.1.2 Temporal Summation

Temporal summation (TS) refers to an increase in pain perception from repetitive noxious stimuli as compared to a single stimulus. [52] It can be induced by various stimuli including mechanical, electrical and heat, [52] and invokes neural mechanisms related to pain facilitation. [53] TS is thought to assess an ascending pain facilitatory mechanism called wind-up, where dorsal horn neurons are increasingly excited in response to repeated noxious stimuli in a short period of time. [54 55] In individuals without chronic pain, pain intensity typically increases with repeated stimuli, [55] however; in individuals with chronic pain, this response may be enhanced and may represent a feature of central sensitization. [32 54]

1.5.1.3 Conditioned Pain Modulation

Conditioned pain modulation (CPM) refers to the phenomenon of "pain inhibiting pain" where the presence of a second stronger noxious stimulus (conditioning stimulus) at a remote area of the body, decreases the pain perception from an initial noxious stimulus (test stimulus). [52 56] CPM is thought to measure human like diffuse noxious inhibitory control (DNIC) phenomena, [32] through activation of neural mechanisms related to the descending inhibitory pathways that involve the brainstem and dorsal horn. [53 54 57] The application of a conditioning stimulus reduces neuronal activity of the dorsal horns in the spinal cord, decreasing pain and hyperalgesia. [58] Under normal conditions, pain after application of a test nociceptive stimulus is attenuated by the application of an additional tonic conditioning stimulus to a remote body region. [40] However, in populations with chronic pain, CPM is varied and has been shown to be impaired or working efficiently. [59]

[60] CPM can measure diminished descending modulation which may manifest as allodynia or hyperalgesia. [20] Increased TS and decreased CPM may indicate dysfunction with central pain modulation. [54]

Although QST can provide valuable information on sensory and nociception pathways as well as central pain modulation, they are not without their limitations. QST can give us information about possible abnormalities of the nociceptive system, however they cannot tell us what specific structures or mechanisms might be behind it. With QST it is not possible to identify whether increased pain perception is the result of changes in neural excitability or might stem from exaggerated pain perception at higher brain centers. [40] There is limited information on the psychometric properties of QST in LBP populations, especially since differences in protocols may influence the results obtained. However, some studies have shown QST to have acceptable reliability in individuals with LBP. [61] Despite these challenges, QST is still considered the gold standard for investigating changes in pain states within the pain literature.

1.5.2 Exercise Induced Hypoalgesia

Exercise-induced hypoalgesia (EIH) is not defined as a QST but is another measure that can be used to assess function of nociception pathways in response to exercise. EIH is defined as a decrease in pain sensitivity that is observed after a single bout of exercise. [62] [63] EIH is measured using QST (such as heat thresholds, TS and CPM), by taking a measurement before exercise, and then again after exercise and comparing the difference between the two. [62] In pain-free populations, exercises such as aerobic, dynamic resistance, and isometric have been shown to produce EIH responses at both

exercising and non-exercising muscles, and the effect has been shown to last ≤ 30 minutes after exercise. [64] This EIH response has been shown through an increase in pain pressure thresholds after exercise, with a larger response seen closer to exercising muscles, compared to non-exercising muscles. [64] There is a scarcity of studies on the effects of EIH in chronic pain populations such as LBP. Current evidence suggests a variability in response, as a single exercise session has been shown to produce reductions in pain (hypoalgesia), a reduced hypoalgesic effect, or even increases in pain (hyperalgesia). [64 65] There is some evidence to suggest that EIH involves the activation of central inhibitory pathways, through mechanisms such as increasing the circulation of endogenous opioids, serotonin and endocannabinoids. [65] In many chronic pain conditions, there is increased pain facilitation (seen with increased temporal summation) as well as decreased pain inhibition (seen with decreased conditioned pain modulation), which may explain the lack of hypoalgesia, or hyperalgesia seen with exercise. [65]

1.6 Management of Low Back Pain

LBP management will depend on the type of pain, duration, and diagnosis. The recommended management for NSLBP includes conservative strategies that take into consideration biopsychosocial factors that are known to largely influence the pain experience of these individuals. [23] This could include pain neuroscience education, exercise therapy and psychological therapies such as cognitive behavioural therapy (CBT). [23 66] Exercise is recommended as the first line of care for the management of chronic LBP, where 8-12 weeks of exercise therapy has been shown to produce clinically important reductions in pain and disability. [8 64] Exercise therapies with or without

psychological intervention components (i.e., CBT principles) have been found to provide psychosocial benefits, such as reductions in stress, depression, and catastrophizing, which are known mediators in the relationship between exercise, pain and function. [65 67-69]

There are many different types of exercise therapies used for the management of LBP. Moderate certainty evidence suggests that exercise treatments in general are more effective compared to no treatment, usual care or placebo for pain and functional outcomes. [67] When compared to other conservative treatments, the evidence suggests that exercise has only small to moderate effects for pain and disability. [67] A recent network meta-analysis found evidence that exercises like Pilates, McKenzie therapy and functional restoration exercise were more effective than other types of treatments in reducing pain intensity and functional limitations in chronic LBP. [70] Two of the most implemented exercise therapies for LBP include motor control exercises and graded activity. Motor control exercises address the nociceptive mechanisms of back pain and may be better suited for individuals with more dominant nociceptive pain, [71 72] while graded activity aim to reduce pain and disability through addressing aspects of patients mood and cognition such as fear of movement, catastrophizing, and unhelpful beliefs about back pain as well as improving muscle strength, balance and endurance, which may be better suited for individuals with dominant nociplastic pain. [71 72] There is evidence to suggest that both motor control and graded activity are effective in reducing pain and disability in individuals with NSLBP, [73 74] however it has been shown that there is no difference in outcomes between the 2 interventions. [71]

Regardless of the type of exercise therapy, there is a scarcity of information on the mechanisms of action that lead to an improvement in pain and disability such as if and how EPM can be altered and act as a mediator of outcomes or if the change in EIH response after a course of exercise therapy can be improved. In general, greater levels of physical activity are associated with less pain facilitation and more pain inhibition, however most studies on the role of exercise in EPM have been conducted in healthy individuals. [65] [75] Some studies that have investigated EIH in individuals with chronic pain suggest that by exercising non-painful muscles, hypoalgesia might be induced, which may have important implications for how exercise is prescribed clinically. [64] It has been suggested that repeated regular exercise may be able to restore impairments to conditioned pain modulation or pain inhibition. [65] However, there have not been any studies that have looked at whether exercise therapy may be able to improve EPM in individuals with LBP specifically.

1.7 Aims & Objectives

The overall objective of this thesis is to develop and test a protocol that will investigate EPM before and after exercise therapy in patients with LBP based on what is most used in the LBP literature.

1.7.1 Study One

Study one is a scoping review that aims to summarize the protocols used to assess EPM using EIH or QST, including PPT, TS, CPM, and EIH, in individuals with LBP. The specific research questions that will be addressed are:

1. What equipment is used to test PPT, TS, CPM?

2. What are the testing sites used to assess PPT?
3. What are the test stimuli, conditioning stimuli, and parameters used for CPM?
4. What is the length of administering the conditioning stimuli for CPM?
5. What is the testing modality, frequency, and site used for TS?
6. What is the exercise frequency, intensity, type, and time for EIH?
7. How long between sessions of measurements are participants allowed to rest?

1.7.2 Study Two

Study two is a pilot feasibility study that aims to evaluate 1) the feasibility of a study protocol to investigate if changes in EPM occurs after exercise therapy (8-week intervention), 2) what is the trend in EPM change after exercise therapy and, 3) whether this response is different between graded activity (a functionally based exercise program that uses cognitive behavioural principles to address psychosocial factors), and motor control exercises (a more localized exercise programs that targets contraction and coordinator of spine muscles).

1.8 References

1. Ferreira ML, De Luca K, Haile LM, et al. Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *The Lancet Rheumatology* 2023;5(6):e316-e29. doi: 10.1016/s2665-9913(23)00098-x
2. Li W, Gong Y, Liu J, et al. Peripheral and Central Pathological Mechanisms of Chronic Low Back Pain: A Narrative Review. *Journal of Pain Research* 2021;Volume 14:1483-94. doi: 10.2147/jpr.s306280
3. Manchikanti L, Singh V, Falco FJE, et al. Epidemiology of Low Back Pain in Adults. *Neuromodulation: Technology at the Neural Interface* 2014;17:3-10. doi: https://doi.org/10.1111/ner.12018
4. Ge L, Pereira MJ, Yap CW, et al. Chronic low back pain and its impact on physical function, mental health, and health-related quality of life: a cross-sectional study in Singapore. *Scientific Reports* 2022;12(1):20040. doi: 10.1038/s41598-022-24703-7
5. Wu A, March L, Zheng X, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. *Annals of Translational Medicine* 2020;8(6):299-99. doi: 10.21037/atm.2020.02.175
6. Scott NA, Moga C, Harstall C. Managing Low Back Pain in the Primary Care Setting: The Know-Do Gap. *Pain Research and Management* 2010;15(6):392-400. doi: 10.1155/2010/252695
7. Wang L, Ye H, Li Z, et al. Epidemiological trends of low back pain at the global, regional, and national levels. *European Spine Journal* 2022;31(4):953-62. doi: 10.1007/s00586-022-07133-x
8. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine* 2017;166(7):514-30. doi: 10.7326/M16-2367
9. Balagué F, Mannion AF, Pellisé F, et al. Non-specific low back pain. *The Lancet* 2012;379(9814):482-91. doi: https://doi.org/10.1016/S0140-6736(11)60610-7
10. Macedo LG, Maher CG, Hancock MJ, et al. Predicting Response to Motor Control Exercises and Graded Activity for Patients With Low Back Pain: Preplanned Secondary Analysis of a Randomized Controlled Trial. *Physical Therapy* 2014;94(11):1543-54. doi: 10.2522/ptj.20140014

11. Menezes Costa LDC, Maher CG, Hancock MJ, et al. The prognosis of acute and persistent low-back pain: a meta-analysis. *Canadian Medical Association Journal* 2012;184(11):E613-E24. doi: 10.1503/cmaj.111271
12. Stanton TR, Latimer J, Maher CG, et al. How do we define the condition 'recurrent low back pain'? A systematic review. *European Spine Journal* 2010;19(4):533-39. doi: 10.1007/s00586-009-1214-3
13. Mohamed SHP, Seyed MA. Low Back Pain: A Comprehensive Review on the Diagnosis, Treatment Options, and the Role of Other Contributing Factors. *Open Access Macedonian Journal of Medical Sciences* 2021;9(F):347-59. doi: 10.3889/oamjms.2021.6877
14. Farasyn AD, Meeusen R, Nijs J. Validity of cross-friction algometry procedure in referred muscle pain syndromes: preliminary results of a new referred pain provocation technique with the aid of a Fischer pressure algometer in patients with nonspecific low back pain. *Clinical Journal of Pain* 2008;24(5):456-62. doi: 10.1097/ajp.0b013e3181643403
15. Casiano VE, Sarwan G, Dydyk AM, et al. Back Pain. StatsPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC. 2024.
16. Dydyk AM, Khan MZ, Singh P. Radicular Back Pain. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC. 2024.
17. Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis & Rheumatism* 2009;60(10):3072-80. doi: https://doi.org/10.1002/art.24853
18. O'Sullivan P, Waller R, Wright A, et al. Sensory characteristics of chronic non-specific low back pain: A subgroup investigation. *Manual Therapy* 2014;19(4):311-18. doi: 10.1016/j.math.2014.03.006
19. Otero-Ketterer E, Peñacoba-Puente C, Ferreira Pinheiro-Araujo C, et al. Biopsychosocial Factors for Chronicity in Individuals with Non-Specific Low Back Pain: An Umbrella Review. *International Journal of Environmental Research and Public Health* 2022;19(16):10145. doi: 10.3390/ijerph191610145
20. Fitzcharles M-A, Cohen SP, Clauw DJ, et al. Nociplastic pain: towards an understanding of prevalent pain conditions. *The Lancet* 2021;397

21. Treede R-D, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 2019;160(1):19-27. doi: 10.1097/j.pain.0000000000001384
22. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 2020;161(9):1976-82. doi: 10.1097/j.pain.0000000000001939
23. Nijs J, Kosek E, Chiarotto A, et al. Nociceptive, neuropathic, or nociplastic low back pain? The low back pain phenotyping (BACPAP) consortium's international and multidisciplinary consensus recommendations. *The Lancet Rheumatology* 2024
24. International Association for the Study of Pain. IASP Terminology [Available from: https://www.iasp-pain.org/resources/terminology/?navItemNumber=576#Centralsensitization accessed June 19 2023.
25. Smith ESJ. Advances in understanding nociception and neuropathic pain. *Journal of Neurology* 2018;265(2):231-38. doi: 10.1007/s00415-017-8641-6
26. Garland EL. Pain Processing in the Human Nervous System. *Primary Care: Clinics in Office Practice* 2012;39(3):561-71. doi: 10.1016/j.pop.2012.06.013
27. Yam M, Loh Y, Tan C, et al. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *International Journal of Molecular Sciences* 2018;19(8):2164. doi: 10.3390/ijms19082164
28. Nijs J, Lahousse A, Kapreli E, et al. Nociplastic Pain Criteria or Recognition of Central Sensitization? Pain Phenotyping in the Past, Present and Future. *Journal of Clinical Medicine* 2021;10(15):3203. doi: 10.3390/jcm10153203
29. Staud R. The important role of CNS facilitation and inhibition for chronic pain. *International Journal of Clinical Rheumatology* 2013;8(6):639-46. doi: 10.2217/ijr.13.57
30. Institute of Medicine (US) Committee on Pain D, and Chronic Illness Behavior. The Anatomy and Physiology of Pain. In: Osterweis M, Kleinman A, Mechanic D, eds. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. Washington (DC): National Academies Press (US) 1987.

31. Crawford LK, Caterina MJ. Functional Anatomy of the Sensory Nervous System: Updates From the Neuroscience Bench. *Toxicologic Pathology* 2020;48(1):174-89. doi: 10.1177/0192623319869011
32. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *The Journal of the International Association for the Study of Pain* 2015;156 Suppl 1(4):S24-s31. doi: 10.1097/01.j.pain.0000460343.46847.58
33. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Review of Neurotherapeutics* 2012;12(5):577-85. doi: 10.1586/ern.12.41
34. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Current Opinion in Supportive & Palliative Care* 2014;8(2):143-51. doi: 10.1097/spc.0000000000000055
35. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *Journal of Clinical Investigation* 2010;120(11):3779-87. doi: 10.1172/jci43766
36. Melzack R. From the gate to the neuromatrix. *Pain* 1999;82:S121-S26. doi: https://doi.org/10.1016/S0304-3959(99)00145-1
37. Trachsel LA, Munakomi S, Cascella M. Pain Theory. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC. 2024.
38. Melzack R. Pain and the Neuromatrix in the Brain. *Journal of Dental Education* 2001;65(12):1378-82. doi: 10.1002/j.0022-0337.2001.65.12.tb03497.x
39. Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Manual Therapy* 2003;8(3):130-40. doi: https://doi.org/10.1016/S1356-689X(03)00051-1
40. Curatolo M. Diagnosis of Altered Central Pain Processing. *Spine* 2011;36:S200-S04. doi: 10.1097/BRS.0b013e3182387f3d
41. Gangadharan V, Kuner R. Pain hypersensitivity mechanisms at a glance. *Disease Models & Mechanisms* 2013;6(4):889-95. doi: 10.1242/dmm.011502
42. Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *The Journal of Pain* 2009;10(9):895-926. doi: 10.1016/j.jpain.2009.06.012
43. Nijs J, Malfliet A, Ickmans K, et al. Treatment of central sensitization in patients with ‘unexplained’ chronic pain: an update. *Expert Opinion on Pharmacotherapy* 2014;15(12):1671-83. doi: 10.1517/14656566.2014.925446

44. Backonja M-M, Walk D, Edwards RR, et al. Quantitative Sensory Testing in Measurement of Neuropathic Pain Phenomena and Other Sensory Abnormalities. *The Clinical Journal of Pain* 2009;25(7):641-47. doi: 10.1097/AJP.0b013e3181a68c7e
45. Chang W-J, Jenkins LC, Humburg P, et al. Human assumed central sensitization in people with acute non-specific low back pain: A cross-sectional study of the association with brain-derived neurotrophic factor, clinical, psychological and demographic factors. *European journal of pain (London, England)* 2023;27(4):530-45. doi: https://dx.doi.org/10.1002/ejp.2078
46. Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016;157(9):1851-71. doi: 10.1097/j.pain.0000000000000602
47. Weaver KR, Griffioen MA, Klinedinst NJ, et al. Quantitative Sensory Testing Across Chronic Pain Conditions and Use in Special Populations. *Front Pain Res (Lausanne)* 2021;2:779068. doi: 10.3389/fpain.2021.779068 [published Online First: 20220128]
48. Uddin Z, MacDermid JC. Quantitative Sensory Testing in Chronic Musculoskeletal Pain. *Pain Medicine* 2016;17(9):1694-703. doi: 10.1093/pm/pnv105
49. Imamura M, Alfieri FM, Filippo TRM, et al. Pressure pain thresholds in patients with chronic nonspecific low back pain. *Journal of Back and Muskuloskeletal Rehabilitation* 2016;29:327-36.
50. Imamura M, Chen J, Matsubayashi SR, et al. Changes in pressure pain threshold in patients with chronic nonspecific low back pain. *Spine (03622436)* 2013;38(24):2098-107. doi: 10.1097/01.brs.0000435027.50317.d7
51. Amiri M, Alavinia M, Singh M, et al. Pressure Pain Threshold in Patients with Chronic Pain. *American Journal of Physical Medicine & Rehabilitation* 2021;100(7):656-74. doi: 10.1097/PHM.0000000000001603
52. Mackey IG, Dixon EA, Johnson K, et al. Dynamic Quantitative Sensory Testing to Characterize Central Pain Processing. *Journal of Visualized Experiments* 2017(120) doi: 10.3791/54452
53. Overstreet DS, Michl AN, Penn TM, et al. Temporal summation of mechanical pain prospectively predicts movement-evoked pain

severity in adults with chronic low back pain. *BMC Musculoskeletal Disorders* 2021;22(1) doi: 10.1186/s12891-021-04306-5
54. Kong J-T, You DS, Law C, Sze Wan, et al. Association between temporal summation and conditioned pain modulation in chronic low back pain: baseline results from 2 clinical trials. *Pain Reports* 2021;6(4) doi: 10.1097/PR9.0000000000000975
55. Aspinall SL, Jacques A, Leboeuf-Yde C, et al. Pressure pain threshold and temporal summation in adults with episodic and persistent low back pain trajectories: a secondary analysis at baseline and after lumbar manipulation or sham. *Chiropractic & Manual Therapies* 2020;28(1) doi: 10.1186/s12998-020-00326-5
56. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Current Opinion in Anesthesiology* 2010;23(5):611-15. doi: 10.1097/ACO.0b013e32833c348b
57. McPhee M, Graven-Nielsen T. Alterations in Temporal Summation of Pain and Conditioned Pain Modulation Across an Episode of Experimental Exercise-Induced Low Back Pain. *The Journal of Pain* 2019;20(3):264-76. doi: 10.1016/j.jpain.2018.08.010
58. Correa JB, Costa LOP, de Oliveira NTB, et al. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. *Experimental brain research* 2015;233(8):2391-9. doi: https://dx.doi.org/10.1007/s00221-015-4309-6
59. Lewis GN, Rice DA, McNair PJ. Conditioned Pain Modulation in Populations With Chronic Pain: A Systematic Review and Meta-Analysis. *The Journal of Pain* 2012;13(10)
60. Carlesso LC, Law LF, Wang N, et al. Association of Pain Sensitization and Conditioned Pain Modulation to Pain Patterns in Knee Osteoarthritis. *Arthritis Care Res (Hoboken)* 2022;74(1):107-12. doi: 10.1002/acr.24437 [published Online First: 20211217]
61. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia & Pain Medicine* 2015;40(6):665-73. doi: 10.1097/AAP.0000000000000289
62. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future

Directions. *The Journal of Pain* 2019;20(11):1249-66. doi: 10.1016/j.jpain.2019.03.005
63. Niwa Y, Shimo K, Ohga S, et al. Effects of Exercise-Induced Hypoalgesia at Different Aerobic Exercise Intensities in Healthy Young Adults. *Journal of Pain Research* 2022;Volume 15:3615-24. doi: 10.2147/jpr.s384306
64. Vaegter HB, Jones MD. Exercise-induced hypoalgesia after acute and regular exercise: experimental and clinical manifestations and possible mechanisms in individuals with and without pain. *New Directions for Physical Rehabilitation of Muskuloskeletal Pain Conditions* 2020;5(5)
65. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *The Journal of Physiology* 2017;595(13):4141-50. doi: 10.1113/jp273355
66. Yang J, Lo WLA, Zheng F, et al. Evaluation of Cognitive Behavioral Therapy on Improving Pain, Fear Avoidance, and Self-Efficacy in Patients with Chronic Low Back Pain: A Systematic Review and Meta-Analysis. *Pain Research and Management* 2022;2022:1-15. doi: 10.1155/2022/4276175
67. Hayden JA, Ellis J, Ogilvie R, et al. Exercise therapy for chronic low back pain. *Cochrane Database of Systematic Reviews* 2021(9)
68. Costa LDCM, Maher CG, McAuley JH, et al. Self-efficacy is more important than fear of movement in mediating the relationship between pain and disability in chronic low back pain. *European Journal of Pain* 2011;15(2):213-19. doi: 10.1016/j.ejpain.2010.06.014
69. George SZ, Wittmer VT, Fillingim RB, et al. Comparison of graded exercise and graded exposure clinical outcomes for patients with chronic low back pain. *J Orthop Sports Phys Ther* 2010;40(11):694-704. doi: 10.2519/jospt.2010.3396
70. Hayden JA, Ellis J, Ogilvie R, et al. Some types of exercise are more effective than others in people with chronic low back pain: a network meta-analysis. *Journal of Physiotherapy* 2021;67(4):252-62. doi: https://doi.org/10.1016/j.jphys.2021.09.004
71. Macedo LG, Latimer J, Maher CG, et al. Effect of Motor Control Exercises Versus Graded Activity in Patients With Chronic Nonspecific Low Back Pain: A Randomized Controlled Trial. *Physical Therapy* 2012;92(3):363-77. doi: 10.2522/ptj.20110290
72. Macedo LG, Hodges PW, Bostick G, et al. Which Exercise for Low Back Pain? (WELBack) trial predicting response to exercise treatments for

patients with low back pain: a validation randomised controlled trial protocol. *BMJ Open* 2021;11(1):e042792. doi: 10.1136/bmjopen-2020-042792
73. Zheng Z, Wang J, Gao Q, et al. Therapeutic evaluation of lumbar tender point deep massage for chronic non-specific low back pain. *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan* 2012;32(4):534-7.
74. Macedo LG, Smeets RJEM, Maher CG, et al. Graded Activity and Graded Exposure for Persistent Nonspecific Low Back Pain: A Systematic Review. *Physical Therapy* 2010;90(6):860-79. doi: 10.2522/ptj.20090303
75. Law LF, Sluka KA. How does physical activity modulate pain? *Pain* 2017;158(3):369-70. doi: 10.1097/j.pain.0000000000000792

2 Chapter 2: Quantitative Sensory Testing (QST) and Exercise Induced Hypoalgesia (EIH) in Low Back Pain (LBP): A Scoping Review

Quantitative Sensory Testing (QST) and Exercise Induced Hypoalgesia (EIH) in Low Back Pain (LBP): A Scoping Review

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2.1 Abstract

Introduction: A significant driver of pain in individuals with low back pain (LBP) is alterations to endogenous pain modulation (EPM). EPM can be measured using quantitative sensory testing (QST), however; there are inconsistencies in the way QST has been implemented across the low back pain literature. The objective of this scoping review was to summarize protocols used to assess EPM using QST (pain pressure threshold (PPT), temporal summation (TS), conditioned pain modulation (CPM)) or exercise-induced hypoalgesia (EIH) in LBP.

Methods: Databases Medline, Embase, CINAHL and AMED were searched on June 15, 2023, for articles that used QST or EIH protocols in LBP populations. Title and abstract screening, full text evaluation, and data extraction (participants, study design, setting, details on QST and EIH protocols) were performed in pairs.

Results: Of the 193 studies included in the review, 172 used PPT, 54 used TS and 53 used CPM; only 5 studies investigated EIH. For all QST, there was high variability in the type of equipment, timing, trials, and testing location with many studies not reporting this information. There was a variety of testing modalities for TS, test stimuli, and conditioning stimuli for CPM. For CPM and EIH, PPT was the most common testing modality.

Discussion/Conclusions: This scoping review provides a summary of QST and EIH protocols in LBP that may be used as a guide for assessment in future studies. These

results demonstrate a need for the development of standardized protocols and reporting guidelines.

2.1.1 Keywords

Conditioned Pain Modulation; Endogenous Pain Modulation; Exercise Induced Hypoalgesia; Pain Pressure Threshold; Temporal Summation

2.2 Introduction

Low back pain (LBP) is a multifactorial condition influenced by biological, psychological, and social factors. [1] There is evidence to suggest that a significant driver of LBP is maladaptive changes in the central nervous system (CNS) with contribution from peripheral mechanisms. [2] Normally, the CNS takes a wide range of actions to reduce or augment pain through inhibitory or facilitatory mechanisms, respectively, known as endogenous pain modulation (EPM). [3] Impairments to EPM can lead to amplifications of neural signaling in the CNS, resulting in hypersensitivity to nociceptive signals, known as central sensitization. [4] This increase in pain sensitivity can also be a result of peripheral mechanisms such as increased excitability of nociceptors, [5] leading to peripheral sensitization. [6]

Alterations to nervous system signaling in humans can be assessed using the surrogate measures of quantitative sensory testing (QST). [6] QST is a form of psychophysical testing used to assess sensory pathways involved in pain perception. [7] There is no gold standard for detecting altered pain processing in humans, [8] although QST are the most widely used assessments to test nervous system hypersensitivity. [9] Commonly used QST include pain pressure threshold (PPT), temporal summation (TS) and conditioned pain modulation (CPM), which have been shown to have acceptable within- and between-session test-retest reliability in chronic LBP. [10] PPT can be used to document changes in peripheral nervous system (PNS) and CNS function, while TS and CPM can be used to assess changes in CNS function. These tests can also aid with understanding the pathways and mechanisms that may be affected, [11] including ascending

pathways, and the descending pain modulatory system. [12] There are inconsistencies in the way that QST have been implemented across the LBP literature with differences in testing site, number of trials, rest time, testing parameters and modalities for PPT, [13] TS, [14,15] and CPM. [16] Given that there are many different QST protocols used in the literature, this makes it challenging to compare results across different studies and warrants a synthesis of the literature. There have been some efforts to standardize protocols for QST[17-19] but these efforts are challenged by the need for large consensus, significant efforts for implementation, and paucity of evidence in understanding the mechanisms and pathways behind different protocols to inform why one protocol may be selected over others. It is important to consider protocols for LBP and other pain conditions separately as the measures may be specific to the location or type of pain. [20]

Exercise induced hypoalgesia (EIH) is not considered a QST but is another measure that can be used to assess EPM. EIH is a short-term endogenous pain inhibitory response, defined as an acute reduction of pain sensitivity following a bout of exercise. [21,22] Unlike the findings of EIH in pain-free populations, in individuals with chronic pain, the EIH response to a single session of exercise can vary including hypoalgesia, reduced hypoalgesia or hyperalgesia. [23] There are also inconsistencies with the way that EIH is measured across the LBP literature including the type, duration, and intensity of exercise. [21,24,25] This makes comparing between studies difficult, suggesting the need for better standardization of protocols. Identifying how EPM is measured in the literature is the first step in this direction.

Thus, the objective of this scoping review was to summarize the protocols used to assess EPM using EIH or QST, including PPT, TS, CPM, and EIH in individuals with LBP. Identifying the most used protocols is the first step in developing a consensus on the most appropriate protocols and eventually a standardized protocol for use in LBP.

2.3 Review Questions

What are the specific protocols used to assess PPT, TS, CPM, and EIH in the scientific literature in individuals with LBP? More specifically:

8. What equipment is used to test PPT, TS, CPM?
9. What are the testing sites used to assess PPT?
10. What are the test stimuli, conditioning stimuli, and parameters used for CPM?
11. What is the length of administering the conditioning stimuli for CPM?
12. What is the testing modality, frequency, and site used for TS?
13. What is the exercise frequency, intensity, type, and time for EIH?
14. How long between sessions of measurements are participants allowed to rest?

2.4 Eligibility criteria

2.4.1 Participants

Studies conducted with adults, over the age of 18 with a diagnosis of LBP were included. Criteria for the type of LBP was not specified, including no restrictions for the type of diagnosis or duration of LBP. Studies describing back pain in general were included, however those specifying upper back pain were excluded. Studies that include

mixed populations (ex. LBP and other types of chronic pain) were excluded, however studies comparing LBP to pain-free populations were included.

2.4.2 Concept

Any studies that used QST protocols, for PPT, TS, CPM, including any type of stimuli (temperature, pressure, chemical, vibration) at any testing site were included. Studies that used an EIH protocol with any form of exercise, frequency, intensity, duration, QST test paradigm, stimulus, and measurement sites were also included.

2.4.3 Context

There were no restrictions placed for recruitment setting, type of LBP, sex, gender, or race of participants.

2.4.4 Types of Sources

This scoping review included both experimental and quasi-experimental study designs including randomized controlled trials (RCT), non-randomized controlled trials, before and after studies and interrupted time-series studies that examined LBP using a QST or EIH protocol. In addition, analytical observational studies including prospective and retrospective cohort studies and case-control studies were included. This review also included cross-sectional studies but excluded case series and individual case reports. We deviated from the protocol and excluded any study protocols, to capture only methods that were used in the final published study.

2.5 Methods

A scoping review was used to summarize and examine the protocols used for QST and EIH in individuals with LBP. This scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews, [26] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for scoping reviews. [27] This protocol was registered a priori in Open Science Framework (OSF) (DOI 10.17605/OSF.IO/ZMC64).

2.5.1 Search Strategy

The search strategy aimed to locate published journal articles. A McMaster University Health Sciences librarian was consulted during the process of building the search strategy. A search on Medline, Embase, CINAHL and AMED was undertaken (from inception to June 15, 2023) to identify articles that used QST or EIH protocols in LBP. Search strategy per database was developed using key terms for back pain and combined with terms for QST and EIH (Appendix I). The reference list of all included sources of evidence was screened for additional studies. Studies published in any language were included. There was no date limit placed on studies.

2.5.2 Study/Source of Evidence selection

Following the search, all identified citations were collated and uploaded into Covidence and duplicates removed. Following a pilot test (n=10), titles and abstracts were screened by a pair of independent reviewers against the inclusion criteria (LG and RD, ED or SM), followed by paired full text screening (LG and RD). Disagreements were

resolved with discussion, and if necessary, a third reviewer. The results of the search, study inclusion, and reasons for exclusion are reported using the PRISMA guidelines for scoping reviews. [27]

2.5.3 Data Extraction

Data was extracted from papers by one reviewer (LG, ED) and a second reviewer double checked (RD). The data extracted included specific details about the participants such as type of back pain, average duration of back pain, average age, sex, and inclusion/exclusion criteria indicated in the study. Additional details about the study design and setting (ex. community or clinic) were also extracted. Finally, details on QST and EIH protocols were extracted. For PPT, this included the specific equipment used, number of trials, stimulation rate and testing location. For TS we extracted test modality, equipment, and parameters, testing site, stimulation frequency, and number of trials. For CPM, information regarding the conditioning stimulus type, timing and site, test stimulus type, timing and site, and time between trials was extracted. Lastly, for EIH this included the frequency, intensity, time, and type of exercise.

2.5.4 Data Analysis and Presentation

Data is presented qualitatively using tables and frequency of specific protocols.

2.6 Results

A total of 10,973 studies were screened using title and abstracts for inclusion. Following, we screened 320 full texts of which 193 were included in the review. The

main reasons for exclusion were abstracts or protocols using non-eligible QST protocol, or the wrong patient population (Figure 1).

Characteristics of included studies are presented in Table 1, including the study design, study setting, type and duration of back pain, age range or mean age, and whether the study compared to pain free controls. Of the 193 included studies, the most used QST method was PPT, with 172 studies. There were 54 studies that included a protocol for TS, 53 for CPM and only 5 studies investigated EIH. Most studies were RCTs (n=74, 38%) and cross-sectional in design (n=47, 24%), and investigated chronic duration of pain (n=128, 66%). There were only 13 studies that had referenced the German Research Network on Neuropathic Pain QST protocol (7%).[28-40] Only 7 studies provided information on rest time between different tests (4%).[41-47]

2.6.1 Pain Pressure Threshold

There were 176 PPT protocols used within the 172 studies measuring PPT (Table 2). Digital/electronic algometers were used most, comprising over half of all protocols (n=95, 54%), with other devices including analog algometers (n=23, 13%), cuff algometry (n=5, 3%), as well as custom built devices (n=2, 1%), while some studies did not report the equipment used (n=3, 2%).The number of trials taken ranged from 1-4, with the most common being 3 trials (n=85, 48%). Similarly, timing between trials ranged from 5 seconds to 10 minutes with 30 seconds being the most widely used (n=35, 20%). For stimulation rate, there were differences in both the rates and units used with 30 kPa/s being the most common (n=20, 11%). The most common local site that was tested was the most painful site of the back (n=46, 26%). For distal sites, there were 20 general

locations tested, with the lower leg (n=35, 20%) being the most used. Almost all the studies defined PPT as some variation of "the point when the feeling of pressure turned into the feeling of pain", however, 6 protocols used an NRS or VAS to measure PPT instead. Many studies did not report the unit of measure (n=90, 51%), number of trials (n=51, 29%), timing between trials (n=104, 59%), stimulation rate (n=62, 35%) or definition of PPT used (n=24, 14%).

2.6.2 Temporal Summation

There were 55 TS protocols used within the 54 studies measuring TS (Table 3). Among these, there were four general modalities that were reported; punctuate (n=25, 45%), pressure (n=12, 22%), thermal (n=11, 20%), and electrical (n=7, 13%).

The most common device used for punctuate was the weighted pinprick stimulator (n=17, 68%). For the pinprick stimulator, the most common weight used was 256 mN (n=8, 47%), and for the monofilament this was 26g (n=3, 38%) and 300g (n=3, 38%). All studies that reported a stimulation frequency used 1 Hz (1 per second) (n=23, 92%). The most common number of trials was 2 (n=3, 12%) and 5 (n=3, 12%). For rating frequency, most studies had participants rate a single stimulus for baseline rating (n=14, 56%) and rate at the end of a series of 10 stimuli for the second rating (n=11, 44%). To calculate the TS effect, all studies that reported a calculation used some variation of subtracting the first rating (single stimulus, first of train) by the second rating (series of stimuli, last in train) (n=15, 60%). The hand was the most common testing site (n=9, 36%). Several studies failed to report the stimulation frequency (n=2, 8%), calibration (n=3, 12%), number of trials (n=16, 64%), or test site (n=3, 12%).

The second most common modality was pressure, with the algometer being the most common device used with half the studies (n=6, 50%), followed by cuff pressure algometry (n=5, 42%), with one study using a custom-built device (8%). A previously determined pressure threshold or tolerance value was used most often as the calibration (n=9, 75%). The most common frequency of stimulation was 0.5 Hz (1 second on, 1 second rest) (n=9, 75%). For rating frequency, most studies reported measuring at the 1st stimulation out of 10 (n=5, 42%), as well as rating all subsequent stimulations (n=6, 60%). Almost all studies that reported a calculation for TS subtracted the rating of the 10th stimulus from the 1st (n=3, 25%). Several studies did not report the stimulation frequency (n=2, 16%), number of trials (n=11, 92%), or the test site (n=4, 33%). Results for all modalities including thermal and electric are available in Table 3.

2.6.3 Conditioned Pain Modulation Test Stimulus

There were 53 studies that included an assessment for CPM (Table 4). A total of seven different test stimuli were used across all studies including PPT (n=27, 51%), pain pressure suprathreshold (n=4, 8%), pain pressure tolerance (PPTol) (n=4, 8%), cuff algometry (n=6, 12%), sustained pressure (n=2, 4%) thermal (n=8, 15%) and electrical (n=2, 4%). Most studies used a stimulation rate of 30 kPa/s (n=7, 23%), with three preconditioning trials (n=5, 16%) and three trials either during or after application of the conditioning stimulus (CS) (n=5, 16%). The most painful site of the lower back was the most common testing site (n=9, 29%). Some studies doing parallel CPM specified the time into CS before taking the test stimulus again (n=11, 35%), while others just mentioned it was taken during CS (n=6, 19%). For studies conducting sequential CPM,

the majority assessed the TS immediately after applying CS (n=10, 32%). Some studies did not report the stimulation rate used (n=7, 23%), or how many trials were done.

For cuff algometry, all studies used a computerized cuff-algometry system (Nocitech), with the test site on the leg. The parameters varied with some having rapid 1 second cuff inflations and rating the pain felt (n=2, 33%), and others finding the PPT or PPTol values of the participant. Half the studies reported doing two preconditioning trials (n=3, 50%). For studies doing parallel CPM, some specified that they assessed the test stimulus 80 seconds into each CS (n=2, 33%) or simultaneously with the 3rd stimulus (n=2, 33%). For studies conducting sequential CPM, TS was assessed after CS or after all tasks, with one study reporting also measuring TS five minutes after the application of CS.

For thermal, all studies used a thermal stimulator, either the TSA-2 Neurosensory Analyzer (Medoc) (n=4, 50%) or the Pathway Model ATS (Medoc) (n=4, 50%). All studies that reported a baseline temperature used 32°C (n=3, 38%), with all studies using an individually tailored temperature for the target temperature, with a variety of durations. The most common test site was the forearm (n=5, 63%). Most studies reported assessing the test stimulus before CS (n=5, 63%), during CS (n=3, 38%), and immediately after CS (n=2, 25%).

For calculating the CPM effect, many studies looked at the difference from before CS to after or during CS, (test stimulus after/during – test stimulus before) (n=21, 40%), while others had the reverse (test stimulus before – test stimulus after) (n=7, 13%). There

were 9 studies that had calculated the CPM effect as a percent change from baseline (17%). There were two studies that calculated a percentage of the baseline (TS during CS / TS before CS x 100) (3%). One study mentioned that the TS during CS application was compared with baseline, and another rated each of the TS and averaged for analysis. There were a handful of studies that did not report how they calculated the CPM effect (n=11, 21%). Results for all modalities including electrical and sustained pressure are available in Table 4.

2.6.4 Conditioned Pain Modulation Conditioning Stimulus

For CS, there were 3 stimuli that were used across all studies: cold water immersion (n=31, 58%), cuff occlusion (n=14, 26%), and thermal (n=8,15%), with cold water immersion being the most used (Table 5). Majority of the studies only reported using a cold/ice water bath as their device (n=19, 61%), while the rest had different brands of refrigeration units. The most common temperature for the cold water was 4°C (n=5, 16%), with temperatures ranging from 0-12°C. Some studies reported that they had the water circulating (n=15, 48%), but most did not report this information. The most common time for CS application was 2 minutes (or until the pain became unbearable) (n=9, 29%) with times ranging from 30 seconds to 3 minutes. Many studies however did not report how long participants kept their hand in the water (n=5. 16%). Of the studies that reported, two trials were the most common (n=4,13%). Many studies did not report the rest time between trials (n=24, 77%). Only 4 studies reported rest time between trials, and all were 2 minutes between trials (13%). For testing site, most studies had the participant immerse their hand in the cold water (n=27, 87%) with the hand contralateral

to the side of back pain being the most common (n=8, 26%). Other sites included the leg (n=1, 3%) and the foot (n=3, 9%).

For cuff occlusion, most studies used a computerized cuff-algometry system (n=6, 43%), and others used cuff algometry + exercise (n=5, 36%) as the CS. Most studies had the cuff inflated to 70% of the patient's pain pressure tolerance that was obtained previously (n=5, 36%). The most common timing for CS application was until all test stimuli measurements were taken (n=3, 21%), but some studies did not report this information (n=2, 14%). Almost all the studies did not report how many trials were performed (n=13, 93%), however, one study reported 4 trials (7%). For test site, most studies had the cuff on the participants arm (n=8, 57%), with the rest using the leg (n=6, 43%).

For thermal, all eight studies reported using a thermal stimulator, with half using the TSA-2001 (Medoc) and the other half using Thermotest (Somedic). There was a variety of temperatures being used, with 40°C (n=4, 50%) as the most common baseline temperature, and 1°C above (n=4, 50%) or 1°C below (n=4, 50%) the participants heat pain threshold as the target temperature, and 1°C/s as the most common ramp up temperature (n=4, 50%). The most common timing for CS application was 90 seconds (n=4, 50%) or until all the test stimuli measurements were completed (n=2, 25%), but some studies did not report this information (n=2, 25%). Of the studies that reported trials, each had multiple trials but at different test locations in a specific order that corresponded with different test stimulus locations.

2.6.5 Exercise Induced Hypoalgesia

There were five studies that reported a protocol for EIH (Table 6). Of these studies, two had participants performing a lifting task, one involved strength exercises focused on the whole body, another had participants perform back and wrist isometric exercises, and the last one was a 6-minute walk test. The study assessing core strengthening and functional exercises, required participants to perform 35-40 minutes of exercise, while the isometric exercises were a maximum of four minutes or until exhaustion. The 6-minute walk test consists of walking continuously for six minutes on a 20-meter course and calculating how far the participant can walk. In all five studies, PPT was taken before and after the exercises. Two studies reported their calculation for EIH, which were different for both. The study with isometric back and wrist exercises defined EIH as the percent change in PPT from pre to post exercise, while the 6-minute walk test study calculated EIH as the difference between PPT before and after exercise.

2.7 Discussion

The results of this study demonstrated a wide variety of protocols used to assess EPM in individuals with LBP. We found a wide range of parameters for the different QST measures, including differences in test site, timing, stimulation rates, and test modalities. Although we were able to identify the most used parameters, it is worth noting that often less than 50% of studies used the same parameters demonstrating a lack of standardization. Additionally, regardless of the protocol used, there was often poor reporting, with significant information missing that would not allow for replication. For PPT protocols, most studies used a digital algometer, performed three trials at a

stimulation rate of 30 kPa/s, with the most common being the most painful site of the lower back. For TS protocols, most studies used a punctuate modality, with a 256 mN weight pinprick stimulus at a frequency of 1 Hz. The most common CPM parameters included PPT as the test stimulus and cold-water immersion of the hand in 4°C circulating water as the CS. There were no standard EIH protocol with significant variations in methods across all included studies. Within all studies assessing multiple QSTs, or with multiple trials, there was a general lack of information on the rest time between different tests and trials. Subsequent measures may influence those previously performed if not enough rest time is given between assessments. For example, having tests too close together could potentially result in a summative effect, enhancing temporal summation. In the few studies that provided rest times, we were unable to find any justification for the rest times used that indicated they were sufficient to extinguish any carry over effects.

As aforementioned, there have been some efforts in the literature to standardize the assessment of QST such as the publication of the German Research Network on Neuropathic Pain's protocol published in 2006.[17] Surprisingly, despite 187 of the 193 studies in this review being published after publication of the German protocol, only 13 studies in our review cited it. A study summarizing QST protocols in knee OA found a similar result with very few studies referencing this standardized protocol.[20] The limited use of this protocol is likely because it is lengthy, taking several hours to complete, and requires training, which does not make it feasible to use for most study procedures. The German protocol also does not include information on CPM which is the only measure

that provides information on descending inhibition. Recommendations on how to include CPM have been made by Yarnitsky et al., [19] however it does not include a standardized protocol to follow, only suggestions for how to perform the test. Thus, there is a clear need for consensus and publication of simple and easy to use standardized QST protocols, including important potential variations for different testing sites and modalities. Doing so may help clinical translation of QST protocols which is currently limited. There have been some efforts in developing 'bedside' QST protocols that are shorter and easier to use, [48-51] but there has been heterogeneity in the few that have been done and they have not been widely recommended or implemented.

Different modalities can be used to measure TS, as demonstrated by the four modalities found in this review. It is noteworthy that these modalities are processed by different nerve fiber types, and this may have an influence on the response obtained. For example, blunt pressure is detected by non-myelinated C fibers, whereas punctuate is detected by small, myelinated Aδ fibers. [52] Interestingly, most studies assessing TS do not take into consideration the pathways of different modalities such as fiber type or spinal pathway. In this review, only one study, Owens et al., [53] included more than one modality in the assessment of TS. However, the methods used to assess TS with the different modalities were different in terms of body site, number of repeated stimuli, and pain rating frequency. This can be problematic because even within the same modality, it is suggested that different parameters may have different outcomes. For example, with heat, ramping up temperature as compared to repetitive contacts from an already heated probe may produce different effects and activate different nociceptors. [54] Regardless of the

modality used, there is a scarcity of information on selecting the different types of modalities for different clinical populations and how they may be more appropriate for certain conditions based on either clinical presentation or known pathways.

Another common issue related to the assessment of TS is the frequency that participants are asked to report their pain to the stimuli. While some studies asked participants to rate their pain after a series of stimuli, many studies also asked for a pain rating after each stimulus. Interestingly, despite collecting multiple ratings, many studies only used first and last ratings in the calculations of TS. While it may be warranted to record ratings for each stimulus when peak pain is the outcome of interest, the rationale for only using the last rating is not always provided. Further, the potential consequences of using multiple ratings on the validity and reliability of TS are unknown when not used for calculation. For instance, although focusing on every single stimulus will not change the response happening in the spinal cord, it may lead to changes in the subjective reports of TS pain ratings, due to the focus on how pain is changing over time rather than how pain changes after multiple stimuli. Thus, more research and guidelines on the best parameters for assessment of TS is needed.

Similarly to TS, there are also multiple modalities that can be used for both the test and conditioning stimuli for CPM with different associated pathways. A similar finding of high variability in methods was revealed in a review summarizing QST measures in knee OA. [20] Recommendations by Yarnitsky et al. [19] suggest that administering the second test stimulus immediately following the CS (sequential paradigm) is preferred as it removes potential biases with distractions. However, other

recommendations have been made suggesting that administering the test stimulus at the same time as the CS (parallel paradigm) will produce a stronger effect. [3] There is no standardized protocol for testing CPM, and like TS, no guidance on when to select one protocol over another. Different methods of administration, i.e., sequential or parallel, as well as different sites of administration may be more appropriate to different conditions or research questions. When measuring the test stimulus for CPM at the site of pain, this provides information on how the brain behaves relative to the painful affected site, in comparison to testing an unaffected site which would provide information on how the brain functions normally. Currently, the lack of guidance and high variability in the way that the tests are being conducted, not only with test sites, but stimulation rate, timing and trials makes it challenging to compare results obtained between different studies. Regardless of the protocols used, it is important to describe the methods in detail so that the results can be interpreted with the methodology in mind. [55]

There were very few studies included in this review that investigated EIH in LBP populations, and almost all of them used a different type of exercise. In healthy adults, it has been shown that aerobic and resistance exercises can lead to an EIH response. [56] However, four of the five studies included in this review tested EIH using a short functional oriented task with only one study including a 40-minute strength training exercise at moderate intensity. It is unclear if a one task exercise protocol is of sufficient intensity to induce an EIH response. The studies included in this review show variability in their results, with some studies finding potential EIH responses, albeit lower than healthy individuals, [24] some showing no response, [57] while others show impairments or a

lack of EIH in individuals with LBP. [21,58] It seems that, although there is some rationale about the type of exercise being performed, none have taken into consideration the types of exercises that have been shown to have an EIH effect in healthy individuals. Previous literature has shown that widespread EIH can occur because of aerobic exercise, compared to resistance exercise which may only lead to local EIH responses. [56] This leads to uncertainty that the studies included in this review were measuring EIH, and if they were, whether it is in a relevant area of the body. Overall, there is a need for further investigation into EIH in LBP, as well as some guidelines on what types of exercise may be able to produce this response in LBP.

This study has summarized a large number of QST protocols used in back pain populations. One limitation is that we only summarized three of the many possible QST in this review. Additionally, we only included studies that focused on LBP populations and excluded studies with mixed chronic pain populations to try and gain an understanding of the protocols used with only back pain populations in mind. Because of the variability in reporting, we have attempted to condense and summarize as best as possible, and thus some of the information is not as detailed as provided in the original studies. This study was also limited to articles that were found through initial title and abstract search and their reference list, which may have resulted in some articles being excluded. A significant strength of this review is the use of a strict review protocol published a priori and the use of important methodological steps to reduce risk of bias and a robust search strategy.

In conclusion, this review summarized QST and EIH methodologies used in LBP populations. There was a wide variability in the parameters for each of these tests including testing modality, stimulus intensity, test duration, and timing. The findings of this review emphasize the need for standardized protocols and reporting guidelines to ensure that results can be accurately compared, as well as the need for further research to aid in selecting the most appropriate QST parameters for different clinical presentations.

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2.9 Conflicts of interest

There are no conflicts of interest to report for this study.

2.10 References

1. Otero-Ketterer E, Peñacoba-Puente C, Ferreira Pinheiro-Araujo C, et al. Biopsychosocial Factors for Chronicity in Individuals with Non-Specific Low Back Pain: An Umbrella Review. *International Journal of Environmental Research and Public Health* 2022;19(16):10145. doi: 10.3390/ijerph191610145
2. Roussel NA, Nijs J, Meeus M, et al. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain* 2013;29(7):625-38. doi: 10.1097/AJP.0b013e31826f9a71
3. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *The Journal of the International Association for the Study of Pain* 2015;156 Suppl 1(4):S24-s31. doi: 10.1097/01.j.pain.0000460343.46847.58
4. Nijs J, Lahousse A, Kapreli E, et al. Nociplastic Pain Criteria or Recognition of Central Sensitization? Pain Phenotyping in the Past, Present and Future. *Journal of Clinical Medicine* 2021;10(15):3203. doi: 10.3390/jcm10153203
5. Weaver KR, Griffioen MA, Klinedinst NJ, et al. Quantitative Sensory Testing Across Chronic Pain Conditions and Use in Special Populations. *Front Pain Res (Lausanne)* 2021;2:779068. doi: 10.3389/fpain.2021.779068 [published Online First: 20220128]
6. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Review of Neurotherapeutics* 2012;12(5):577-85. doi: 10.1586/ern.12.41
7. Pavlaković G, Petzke F. The role of quantitative sensory testing in the evaluation of musculoskeletal pain conditions. *Curr Rheumatol Rep* 2010;12(6):455-61. doi: 10.1007/s11926-010-0131-0
8. Curatolo M. Diagnosis of Altered Central Pain Processing. *Spine* 2011;36:S200-S04. doi: 10.1097/BRS.0b013e3182387f3d
9. Curatolo M, Arendt-Nielsen L. Central Hypersensitivity in Chronic Musculoskeletal Pain. *Physical Medicine and Rehabilitation Clinics of North America* 2015;26(2):175-84. doi: 10.1016/j.pmr.2014.12.002 [published Online First: 20150204]
10. Vuilleumier PH, Manresa JAB, Ghamri Y, et al. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia and Pain Medicine* 2015;40(6):665-73. doi: 10.1097/AAP.0000000000000289

11. Arendt-Nielsen L, Yarnitsky D. Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. *The Journal of Pain* 2009;10(6):556-72. doi: https://doi.org/10.1016/j.jpain.2009.02.002
12. Yam MF, Loh YC, Tan CS, et al. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *Int J Mol Sci* 2018;19(8) doi: 10.3390/ijms19082164 [published Online First: 20180724]
13. Amiri M, Alavinia M, Singh M, et al. Pressure Pain Threshold in Patients with Chronic Pain. *American Journal of Physical Medicine & Rehabilitation* 2021;100(7):656-74. doi: 10.1097/PHM.0000000000001603
14. Overstreet DS, Michl AN, Penn TM, et al. Temporal summation of mechanical pain prospectively predicts movement-evoked pain severity in adults with chronic low back pain. *BMC Musculoskeletal Disorders* 2021;22(1) doi: 10.1186/s12891-021-04306-5
15. Kong J-T, You DS, Law C, Sze Wan, et al. Association between temporal summation and conditioned pain modulation in chronic low back pain: baseline results from 2 clinical trials. *Pain Reports* 2021;6(4) doi: 10.1097/PR9.0000000000000975
16. Neelapala YVR, Bhagat M, Frey-Law L. Conditioned Pain Modulation in Chronic Low Back Pain A Systematic Review of Literature. *Clinical Journal of Pain* 2020;36(2)
17. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *PAIN* 2006;123(3):231-43. doi: 10.1016/j.pain.2006.01.041
18. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *European Journal of Pain* 2006;10(1):77-77. doi: 10.1016/j.ejpain.2005.02.003
19. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain* 2015;19(6):805-06. doi: 10.1002/ejp.605
20. Rankin J, Rudy-Froese B, Hoyt C, et al. Quantitative Sensory Testing Protocols to Evaluate Central and Peripheral Sensitization in Knee OA: A Scoping Review. *Pain Medicine* 2021;23(3):526-57. doi: 10.1093/pm/pnab285

21. Kuithan P, Heneghan NR, Rushton A, et al. Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain. *Pain Practice* 2019;19(7):740-50. doi: 10.1111/papr.12804
22. Hughes L, Patterson SD. The effect of blood flow restriction exercise on exercise-induced hypoalgesia and endogenous opioid and endocannabinoid mechanisms of pain modulation. *Journal of Applied Physiology* 2020;128(4) doi: 10.1152/japplphysiol.00768.2019
23. Vaegter HB, Jones MD. Exercise-induced hypoalgesia after acute and regular exercise: experimental and clinical manifestations and possible mechanisms in individuals with and without pain. *New Directions for Physical Rehabilitation of Muskuloskeletal Pain Conditions* 2020;5(5)
24. Patricio P, Mailloux C, Timothy, et al. Assessment of exercise-induced hypoalgesia in chronic low back pain and potential associations with psychological factors and central sensitization symptoms: A case–control study. *Pain Practice* 2022 doi: 10.1111/papr.13189
25. Meeus M, Herman L, Ickmans K, et al. Endogenous Pain Modulation in Response to Exercise in Patients with Rheumatoid Arthritis, Patients with Chronic Fatigue Syndrome and Comorbid Fibromyalgia, and Healthy Controls: A Double-Blind Randomized Controlled Trial. *Pain Practice* 2014;15(2) doi: 10.1111/papr.12181
26. Peters MDJ, Godfrey CM, McInerney P, et al. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Lockwood C, Porritt K, et al., eds. JBI Manual for Evidence Synthesis: JBI 2020.
27. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine* 2018;169
28. Bodes Pardo G, Lluch Girbés E, Roussel NA, et al. Pain Neurophysiology Education and Therapeutic Exercise for Patients With Chronic Low Back Pain: A Single-Blind Randomized Controlled Trial. *Archives of Physical Medicine & Rehabilitation* 2018;99(2):338-47. doi: 10.1016/j.apmr.2017.10.016
29. Reimer M, Witthöft J, Greinacher J, et al. Sensory Profiles in Patients with Low Back Pain with and Without Radiculopathy. *Pain Medicine* 2023;24(3):306-15. doi: 10.1093/pm/pnac129
30. Saha FJ, Brummer G, Lauche R, et al. Gua Sha therapy for chronic low back pain: A randomized controlled trial. *Complementary Therapies in Clinical Practice* 2019;34:64-69. doi: 10.1016/j.ctcp.2018.11.002

31. Tesarz J, Eich W, Treede R-D, et al. Altered pressure pain thresholds and increased wind-up in adult patients with chronic back pain with a history of childhood maltreatment: a quantitative sensory testing study. *PAIN* 2016;157(8):1799-809. doi: 10.1097/j.pain.0000000000000586
32. de Oliveira FCL, Cossette C, Mailloux C, et al. Within-Session Test-Retest Reliability of Pressure Pain Threshold and Mechanical Temporal Summation in Chronic Low Back Pain. *Clinical Journal of Pain* 2023;39(5):217-25. doi: 10.1097/AJP.0000000000001106
33. Gasser L, Lener S, Hartmann S, et al. Does preoperative opioid therapy in patients with a single lumbar disc herniation positively influence the postoperative outcome detected by quantitative sensory testing? *Neurosurgical review* 2022;45(4):2941-49. doi: https://dx.doi.org/10.1007/s10143-022-01818-z
34. Nees F, Loffler M, Usai K, et al. Hypothalamic-pituitary-adrenal axis feedback sensitivity in different states of back pain. *Psychoneuroendocrinology* 2019;101(7612148, qgc):60-66. doi: https://dx.doi.org/10.1016/j.psyneuen.2018.10.026
35. Starkweather AR, Heineman A, Storey S, et al. Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. *Applied Nursing Research* 2016;29:237-41. doi: 10.1016/j.apnr.2015.03.013
36. Tesarz J, Gerhardt A, Leisner S, et al. Distinct quantitative sensory testing profiles in nonspecific chronic back pain subjects with and without psychological trauma. *PAIN* 2015;156(4):577-86. doi: 10.1097/01.j.pain.0000460350.30707.8d
37. Wettstein M, Eich W, Bieber C, et al. Profiles of Subjective Well-being in Patients with Chronic Back Pain: Contrasting Subjective and Objective Correlates. *Pain Medicine* 2019;20(4):668-80. doi: 10.1093/pm/pny162
38. Ansuategui Echeita J, Dekker R, Schiphorst Preuper HR, et al. Maximal cardiopulmonary exercise test in patients with chronic low back pain: feasibility, tolerance and relation with central sensitization. An observational study. *Disability & Rehabilitation* 2022;44(21):6287-94. doi: 10.1080/09638288.2021.1962991
39. Marcuzzi A, Wrigley PJ, Dean CM, et al. From acute to persistent low back pain: a longitudinal investigation of somatosensory changes

using quantitative sensory testing—an exploratory study. *PAIN Reports* 2018;3(2) doi: 10.1097/PR9.0000000000000641
40. Rabey M, Slater H, O'Sullivan P, et al. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *PAIN* 2015;156(10):1874-84. doi: 10.1097/j.pain.0000000000000244
41. Foubert A, Cleenders E, Sligchers M, et al. Associations between psychological factors, pressure pain thresholds and conditioned pain modulation and disability in (sub)-acute low back pain: a three-month follow-up study. *Journal of Manual and Manipulative Therapy* 2023((Foubert, Cleenders, Meeus, Roussel) Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium(Foubert) Faculte des Sciences de la Motricite, Universite catholique de Louvain, Louvain-) doi: https://dx.doi.org/10.1080/10669817.2023.2174484
42. Klyne DM, Moseley GL, Sterling M, et al. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *Journal of Pain* 2018;19(8):942.e1-42.e18. doi: 10.1016/j.jpain.2018.02.017
43. Corrêa JB, Costa LOP, Oliveira NTB, et al. Effects of the carrier frequency of interferential current on pain modulation and central hypersensitivity in people with chronic nonspecific low back pain: A randomized placebo-controlled trial. *European Journal of Pain* 2016;20(10):1653-66. doi: 10.1002/ejp.889
44. Den Bandt HL, Ickmans K, Leemans L, et al. Differences in Quantitative Sensory Testing Outcomes between Patients With Low Back Pain in Primary Care and Healthy Controls. *Clinical Journal of Pain* 2022((Den Bandt, Voogt) Research Centre for Health Care Innovations, University of Applied Sciences Rotterdam, Rochussenstraat 198, Rotterdam 3015 EK, Netherlands(Den Bandt, Ickmans, Leemans, Nijs, Voogt) Pain in Motion Research Group, Dept. of Physiotherapy) doi: https://dx.doi.org/10.1097/AJP.0000000000001038
45. Leemans L, Elma Ö, Nijs J, et al. Transcutaneous electrical nerve stimulation and heat to reduce pain in a chronic low back pain population: a randomized controlled clinical trial. *Brazilian Journal of Physical Therapy* 2021;25(1):86-96. doi: 10.1016/j.bjpt.2020.04.001

46. Rabey M, Kendell M, Koren S, et al. Do chronic low back pain subgroups derived from dynamic quantitative sensory testing exhibit differing multidimensional profiles? *Scandinavian journal of pain* 2021;21(3):474-84. doi: https://dx.doi.org/10.1515/sjpain-2020-0126
47. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia & Pain Medicine* 2015;40(6):665-73. doi: 10.1097/AAP.0000000000000289
48. Sachau J, Appel C, Reimer M, et al. Test–retest reliability of a simple bedside-quantitative sensory testing battery for chronic neuropathic pain. *PAIN Reports* 2023;8(1):e1049. doi: 10.1097/pr9.0000000000001049
49. Koulouris AE, Edwards RR, Dorado K, et al. Reliability and Validity of the Boston Bedside Quantitative Sensory Testing Battery for Neuropathic Pain. *Pain Medicine* 2020;21(10):2336-47. doi: 10.1093/pm/pnaa192
50. Zhu GC, Böttger K, Slater H, et al. Concurrent validity of a low-cost and time-efficient clinical sensory test battery to evaluate somatosensory dysfunction. *European Journal of Pain* 2019;23(10):1826-38. doi: https://doi.org/10.1002/ejp.1456
51. Wasan AD, Alter BJ, Edwards RR, et al. Test-Retest and Inter-Examiner Reliability of a Novel Bedside Quantitative Sensory Testing Battery in Postherpetic Neuralgia Patients. *The Journal of Pain* 2020;21(7):858-68. doi: https://doi.org/10.1016/j.jpain.2019.11.013
52. Beissner F, Brandau A, Henke C, et al. Quick Discrimination of Adelta and C Fiber Mediated Pain Based on Three Verbal Descriptors. *PLoS ONE* 2010;5(9):e12944. doi: 10.1371/journal.pone.0012944
53. Owens MA, Bulls HW, Trost Z, et al. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Medicine* 2016;17(8):1452-64. doi: 10.1093/pm/pnv074
54. Eckert NR, Vierck CJ, Simon CB, et al. Methodological Considerations for the Temporal Summation of Second Pain. *The Journal of Pain* 2017;18(12):1488-95. doi: https://doi.org/10.1016/j.jpain.2017.07.009
55. Ramaswamy S, Wodehouse T. Conditioned pain modulation—A comprehensive review. *Neurophysiologie Clinique* 2021;51(3):197-208. doi: https://doi.org/10.1016/j.neucli.2020.11.002

56. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *The Journal of Pain* 2019;20(11):1249-66. doi: 10.1016/j.jpain.2019.03.005
57. Santos MS, Santos PdJ, Vasconcelos ABS, et al. Neuroendocrine effects of a single bout of functional and core stabilization training in women with chronic nonspecific low back pain: A crossover study. *Physiological reports* 2022;10(17):e15365. doi: https://dx.doi.org/10.14814/phy2.15365
58. Vaegter HB, Petersen KK, Sjodsholm LV, et al. Impaired exercise-induced hypoalgesia in individuals reporting an increase in low back pain during acute exercise. *European Journal of Pain* 2021;25(5):1053-63. doi: 10.1002/ejp.1726
59. Bruehl S, France CR, Stone AL, et al. Greater Conditioned Pain Modulation Is Associated With Enhanced Morphine Analgesia in Healthy Individuals and Patients With Chronic Low Back Pain. *Clinical Journal of Pain* 2021;37(1):20-27. doi: 10.1097/AJP.0000000000000887
60. Christensen KS, O'Sullivan K, Palsson TS, et al. Conditioned Pain Modulation Efficiency Is Associated With Pain Catastrophizing in Patients With Chronic Low Back Pain. *Clinical Journal of Pain* 2020;36(11):825-32. doi: 10.1097/AJP.0000000000000878
61. France C, Burns J, Gupta R, et al. Expectancy Effects on Conditioned Pain Modulation Are Not Influenced by Naloxone or Morphine. *Annals of Behavioral Medicine* 2016;50(4):497-505. doi: 10.1007/s12160-016-9775-y
62. Krafft S, Göhmann HD, Sommer J, et al. Learned control over spinal nociception in patients with chronic back pain. *European Journal of Pain* 2017;21(9):1538-49. doi: 10.1002/ejp.1055
63. Lardon A, Dubois J-D, Cantin V, et al. Predictors of disability and absenteeism in workers with non-specific low back pain: A longitudinal 15-month study. *Applied Ergonomics* 2018;68:176-85. doi: 10.1016/j.apergo.2017.11.011
64. McPhee ME, Graven-Nielsen T. Positive affect and distraction enhance whereas negative affect impairs pain modulation in patients with recurrent low back pain and matched controls. *PAIN* 2022;163(5):887-96. doi: 10.1097/j.pain.0000000000002442

65. Mensing G, Martel M, Wasan A, et al. Sex differences in the temporal stability of conditioned pain modulation (CPM) among patients with chronic back pain. *Journal of Pain* 2013;14(4 SUPPL. 1):S47. doi: https://dx.doi.org/10.1016/j.jpain.2013.01.526
66. Mlekusch S, Neziri AY, Limacher A, et al. Conditioned Pain Modulation in Patients With Acute and Chronic Low Back Pain. *The Clinical Journal of Pain* 2016;32(2):116-21. doi: 10.1097/ajp.0000000000000238
67. Moreira LPC, Mendoza C, Barone M, et al. Reduction in Pain Inhibitory Modulation and Cognitive-Behavioral Changes in Patients With Chronic Low Back Pain: A Case-Control Study. *Pain Management Nursing* 2021;22(5):599-604. doi: 10.1016/j.pmn.2021.05.004
68. Rabey M, Poon C, Wray J, et al. Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual therapy* 2015;20(6):763-68. doi: 10.1016/j.math.2015.02.011
69. Vuilleumier PH, Arguissain FG, Biurrun Manresa JA, et al. Psychophysical and Electrophysiological Evidence for Enhanced Pain Facilitation and Unaltered Pain Inhibition in Acute Low Back Pain Patients. *Journal of Pain* 2017;18(11):1313-23. doi: 10.1016/j.jpain.2017.05.008
70. Abd Elsadek RM, Amin D, Elsayed WH, et al. Effect of Active Release Versus Myofascial Release Technique in Low Back Myofascial Pain Syndrome. *Journal of Pharmaceutical Negative Results* 2023;14((Abd Elsadek) Matariyya Teaching Hospital, Cairo, Egypt(Amin, Elsayed) Physical Therapy Basic Science Department, Faculty Physical Therapy, Cairo University, Egypt(Elshafi) Orthopeadic Surgery Matariyya teaching Hospital, Cairo, Egypt):686-95. doi: https://dx.doi.org/10.47750/pnr.2023.14.S02.83
71. Alshami AM, Alqassab FH. The short-term effects of instrument-based mobilization compared with manual mobilization for low back pain: A randomized clinical trial. *Journal of Back & Musculoskeletal Rehabilitation* 2023;36(2):407-18. doi: 10.3233/BMR-220042
72. Alvarez SD, Velazquez Saornil J, Sanchez Mila Z, et al. Effectiveness of Dry Needling and Ischemic Trigger Point Compression in the Gluteus Medius in Patients with Non-Specific Low Back Pain: A Randomized Short-Term Clinical Trial. *International journal of environmental*

research and public health 2022;19(19) doi: https://dx.doi.org/10.3390/ijerph191912468
73. Aoyagi K, Sharma NK. Correlation Between Central Sensitization and Remote Muscle Performance in Individuals With Chronic Low Back Pain. *Journal of Manipulative & Physiological Therapeutics* 2021;44(1):14-24. doi: 10.1016/j.jmpt.2020.07.008
74. Balaguier R, Madeleine P, Vuillerme N. Intra-session absolute and relative reliability of pressure pain thresholds in the low back region of vine-workers: ffect of the number of trials. *BMC Musculoskeletal Disorders* 2016;17:1-11. doi: 10.1186/s12891-016-1212-7
75. Bandeira PM, Reis FJJ, Muniz FDN, et al. Heart Rate Variability and Pain Sensitivity in Chronic Low Back Pain Patients Exposed to Passive Viewing of Photographs of Daily Activities. *Clinical Journal of Pain* 2021;37(8):591-97. doi: 10.1097/AJP.0000000000000953
76. Barassi G, Mariani C, Supplizi M, et al. Capacitive and Resistive Electric Transfer Therapy: A Comparison of Operating Methods in Non-specific Chronic Low Back Pain. *Advances in experimental medicine and biology* 2022;1375(0121103, 2lu):39-46. doi: https://dx.doi.org/10.1007/5584_2021_692
77. Bid DD, Soni NC, Yadav AS, et al. A Study on Central Sensitization in Chronic Non-specific Low Back Pain. *Indian Journal of Physiotherapy & Occupational Therapy* 2017;11(4):165-75. doi: 10.5958/0973-5674.2017.00140.X
78. Bond BM, Kinslow CD, Yoder AW, et al. Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic nonspecific low back pain: a pilot randomized, controlled trial. *Journal of Manual & Manipulative Therapy (Taylor & Francis Ltd)* 2020;28(1):15-27. doi: 10.1080/10669817.2019.1572986
79. Buttagat V, Eungpinichpong W, Chatchawan U, et al. The immediate effects of traditional Thai massage on heart rate variability and stress-related parameters in patients with back pain associated with myofascial trigger points. *Journal of Bodywork & Movement Therapies* 2011;15(1):15-23. doi: 10.1016/j.jbmt.2009.06.005
80. Calvo-Lobo C, Diez-Vega I, Martínez-Pascual B, et al. Tensiomyography, sonoelastography, and mechanosensitivity differences between active, latent, and control low back myofascial trigger points: A cross-sectional study. *Medicine* 2017;96(10):1-7. doi: 10.1097/MD.0000000000006287

81. Carrasco-Martínez F, Ibáñez-Vera AJ, Martínez-Amat A, et al. Short-term effectiveness of the flexion-distraction technique in comparison with high-velocity vertebral manipulation in patients suffering from low-back pain. *Complementary Therapies in Medicine* 2019;44:61-67. doi: 10.1016/j.ctim.2019.02.012
82. Chen P-C, Wei L, Huang C-Y, et al. The Effect of Massage Force on Relieving Nonspecific Low Back Pain: A Randomized Controlled Trial. *International journal of environmental research and public health* 2022;19(20) doi: https://dx.doi.org/10.3390/ijerph192013191
83. Cho HY, Kim EH, Kim J. Effects of the CORE exercise program on pain and active range of motion in patients with chronic low back pain. *Journal of Physical Therapy Science* 2014;26(8):1237-40.
84. Clark NG, Hill CJ, Koppenhaver SL, et al. The effects of dry needling to the thoracolumbar junction multifidi on measures of regional and remote flexibility and pain sensitivity: A randomized controlled trial. *Musculoskeletal science & practice* 2021;53(101692753):102366. doi: https://dx.doi.org/10.1016/j.msksp.2021.102366
85. Dayanır IO, Birinci T, Kaya Mutlu E, et al. Comparison of Three Manual Therapy Techniques as Trigger Point Therapy for Chronic Nonspecific Low Back Pain: A Randomized Controlled Pilot Trial. *Journal of Alternative & Complementary Medicine* 2020;26(4):291-99. doi: 10.1089/acm.2019.0435
86. de Carvalho RC, Parisi JR, Prado WA, et al. Single or Multiple Electroacupuncture Sessions in Nonspecific Low Back Pain: Are We Low-Responders to Electroacupuncture? *Journal of Acupuncture & Meridian Studies* 2018;11(2):54-61. doi: 10.1016/j.jams.2018.02.002
87. de Castro Moura C, Alves Nogueira DA, de Cássia Lopes Chaves É, et al. PHYSICAL AND EMOTIONAL FACTORS ASSOCIATED WITH THE SEVERITY OF CHRONIC BACK PAIN IN ADULTS: A CROSS-SECTIONAL STUDY. *Texto & Contexto Enfermagem* 2022;31:1-13. doi: 10.1590/1980-265X-TCE-2020-0525
88. de Oliveira RF, Liebano RE, da Cunha Menezes Costa L, et al. Immediate Effects of Region-Specific and Non-Region-Specific Spinal Manipulative Therapy in Patients With Chronic Low Back Pain: A Randomized Controlled Trial. *Physical Therapy* 2013;93(6):748-56. doi: 10.2522/ptj.20120256
89. de Oliveira RF, Costa LOP, Nascimento LP, et al. Directed vertebral manipulation is not better than generic vertebral manipulation in

patients with chronic low back pain: a randomised trial. *Journal of Physiotherapy (Elsevier)* 2020;66(3):174-79. doi: 10.1016/j.jphys.2020.06.007
90. Degenhardt BF, Johnson JC, Fossum C, et al. Changes in Cytokines, Sensory Tests, and Self-reported Pain Levels After Manual Treatment of Low Back Pain. *Clinical spine surgery* 2017;30(6):E690-E701. doi: https://dx.doi.org/10.1097/BSD.0000000000000231
91. Demirel A, Oz M, Ulger O. The effect of minimal invasive techniques and physiotherapy on pain and disability in elderly: A retrospective study. *Journal of Back & Musculoskeletal Rehabilitation* 2019;32(1):63-70. doi: 10.3233/BMR-171113
92. Dissanguan D, Sitilertpisan P, Joseph LH, et al. Immediate Effects of a Novel Lumbar Support Device on Pain Modulation and Core Muscle Function in Patients with Chronic Non-Specific Low Back Pain: a Randomized Controlled Trial. *Muscles, Ligaments & Tendons Journal (MLTJ)* 2021;11(3):439-48. doi: 10.32098/mltj.03.2021.08
93. Ebadi S, Ansari NN, Ahadi T, et al. No immediate analgesic effect of diadynamic current in patients with nonspecific low back pain in comparison to TENS. *Journal of Bodywork & Movement Therapies* 2018;22(3):693-99. doi: 10.1016/j.jbmt.2017.11.003
94. Eftekharsadat B, Fasaie N, Golalizadeh D, et al. Comparison of efficacy of corticosteroid injection versus extracorporeal shock wave therapy on inferior trigger points in the quadratus lumborum muscle: a randomized clinical trial. *BMC Musculoskeletal Disorders* 2020;21(1):1-11. doi: 10.1186/s12891-020-03714-3
95. Fagundes Loss J, de Souza da Silva L, Ferreira Miranda I, et al. Immediate effects of a lumbar spine manipulation on pain sensitivity and postural control in individuals with nonspecific low back pain: a randomized controlled trial. *Chiropractic & Manual Therapies* 2020;28(1):1-10. doi: 10.1186/s12998-020-00316-7
96. Falla D, Gizzi L, Tschapek M, et al. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *PAIN* 2014;155(5):944-53. doi: 10.1016/j.pain.2014.01.027
97. Farasyn A, Meeusen R. The influence of non-specific low back pain on pressure pain thresholds and disability. *European Journal of Pain* 2005;9(4):375-75. doi: https://doi.org/10.1016/j.ejpain.2004.09.005

98. Farasyn A, Meeusen R, Nijs J. A pilot randomized placebo-controlled trial of roptrotherapy in patients with subacute non-specific low back pain. *Journal of Back & Musculoskeletal Rehabilitation* 2006;19(4):111-17. doi: 10.3233/bmr-2006-19402
99. Farasyn A, Meeusen R. Effect of roptrotherapy on pressure-pain thresholds in patients with subacute nonspecific low back pain. *Journal of Musculoskeletal Pain* 2007;15(1):41-53. doi: 10.1300/j094v15n01_06
100. Farasyn AD, Meeusen R, Nijs J. Validity of cross-friction algometry procedure in referred muscle pain syndromes: preliminary results of a new referred pain provocation technique with the aid of a Fischer pressure algometer in patients with nonspecific low back pain. *Clinical Journal of Pain* 2008;24(5):456-62. doi: 10.1097/ajp.0b013e3181643403
101. Farasyn A, Lassat B. Cross friction algometry (CFA): Comparison of pressure pain thresholds between patients with chronic non-specific low back pain and healthy subjects. *Journal of Bodywork and Movement Therapies* 2016;20:224-34.
102. Franco KM, Franco YdS, Oliveira NBd, et al. Is Interferential Current Before Pilates Exercises More Effective Than Placebo in Patients With Chronic Nonspecific Low Back Pain?: A Randomized Controlled Trial. *Archives of Physical Medicine & Rehabilitation* 2017;98(2):320-28. doi: 10.1016/j.apmr.2016.08.485
103. Fuentes J, Armijo-Olivo S, Funabashi M, et al. Enhanced therapeutic alliance modulates pain lntensity and muscle pain sensitivity in patients with chronic low back pain: An experimental controlled study. *Physical Therapy* 2014;94(4):477-89.
104. Gay CW, Papuga MO, Bishop MD, et al. The frequency and reliability of cortical activity using a novel strategy to present pressure pain stimulus over the lumbar spine. *Journal of neuroscience methods* 2015;239(k9v, 7905558):108-13. doi: https://dx.doi.org/10.1016/j.jneumeth.2014.10.010
105. Giesbrecht RJS, Battie MC. A comparison of pressure pain detection thresholds in people with chronic low back pain and volunteers without pain. *Physical Therapy* 2005;85(10):1085-92. doi: 10.1093/ptj/85.10.1085
106. Goubert D, Meeus M, Willems T, et al. The association between back muscle characteristics and pressure pain sensitivity in low back pain

patients. *Scandinavian journal of pain* 2018;18(2):281-93. doi: https://dx.doi.org/10.1515/sjpain-2017-0142
107. Griswold D, Gargano F, Learman KE. A randomized clinical trial comparing non-thrust manipulation with segmental and distal dry needling on pain, disability, and rate of recovery for patients with non-specific low back pain. *Journal of Manual & Manipulative Therapy (Taylor & Francis Ltd)* 2019;27(3):141-51. doi: 10.1080/10669817.2019.1574389
108. Grześkowiak M, Krawiecki Z, Łabędź W, et al. Short-Term Effects of Kinesio Taping® on Electromyographic Characteristics of Paraspinal Muscles, Pain, and Disability in Patients With Lumbar Disk Herniation. *Journal of Sport Rehabilitation* 2019;28(5):402-12. doi: 10.1123/jsr.2017-0086
109. Hahm SC, Shin HJ, Lee MG, et al. Mud Therapy Combined with Core Exercise for Chronic Nonspecific Low Back Pain: A Pilot, Single-Blind, Randomized Controlled Trial. *Evidence-based Complementary and Alternative Medicine* 2020;2020((Hahm) Graduate School of Integrative Medicine, Cha University, Seongnam, South Korea(Shin, Cho) Department of Physical Therapy, Gachon University, Incheon, South Korea(Lee) Department of Physiology, Korea University College of Medicine, Seoul, South Kore):7547452. doi: https://dx.doi.org/10.1155/2020/7547452
110. Hirayama J, Yamagata M, Ogata S, et al. Relationship between low-back pain, muscle spasm and pressure pain thresholds in patients with lumbar disc herniation. *European Spine Journal* 2006;15(1):41-47. doi: https://dx.doi.org/10.1007/s00586-004-0813-2
111. Hsieh R, Lee W. One-shot percutaneous electrical nerve stimulation vs. transcutaneous electrical nerve stimulation for low back pain: comparison of therapeutic effects. *American Journal of Physical Medicine & Rehabilitation* 2002;81(11):838-43.
112. Imamura M, Chen J, Matsubayashi SR, et al. Changes in pressure pain threshold in patients with chronic nonspecific low back pain. *Spine (03622436)* 2013;38(24):2098-107. doi: 10.1097/01.brs.0000435027.50317.d7
113. Imamura M, Alfieri FM, Filippo TRM, et al. Pressure pain thresholds in patients with chronic nonspecific low back pain. *Journal of Back and Muskuloskeletal Rehabilitation* 2016;29:327-36.

114. Joseph LH, Hancharoenkul B, Sitilertpisan P, et al. Comparison of Effects Between Core Stability Training and Sports Massage Therapy Among EliteWeightlifters with Chronic Non-Specific Low Back Pain: A Randomized Cross-Over Study. *Asian Journal of Sports Medicine* 2018;9(1):1-8. doi: 10.5812/asjsm.58644
115. Joseph LH, Benjamaporn H, Patraporn S, et al. Effects of Massage as a Combination Therapy with Lumbopelvic Stability Exercises as Compared to Standard Massage Therapy in Low Back Pain: a Randomized Cross-Over Study. *International Journal of Therapeutic Massage & Bodywork* 2018;11(4):16-22. doi: 10.3822/ijtmb.v11i4.413
116. Ketenci A, Sindel D, Koca TT, et al. A multi-center, double-blind, randomized parallel-group Phase IV study comparing the efficacy and safety of thiocolchicoside ointment versus placebo in patients with chronic mechanical low back pain and an acute muscle spasm. *Turkish Journal of Physical Medicine & Rehabilitation (2587-1250)* 2022;68(4):456-63. doi: 10.5606/tftrd.2022.9744
117. Kim SK, Park H. The Effect of Auricular Acupressure for Chronic Low Back Pain in Elders: A Randomized Controlled Study. *Holistic nursing practice* 2021;35(4):182-90. doi: https://dx.doi.org/10.1097/HNP.0000000000000457
118. Kong J-T, Puetz C, Tian L, et al. Effect of Electroacupuncture vs Sham Treatment on Change in Pain Severity Among Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Network Open* 2020;3(10):e2022787-e87. doi: 10.1001/jamanetworkopen.2020.22787
119. Koppenhaver SL, Walker MJ, Su J, et al. Changes in lumbar multifidus muscle function and nociceptive sensitivity in low back pain patient responders versus non-responders after dry needling treatment. *Manual Therapy* 2015;20(6):769-76. doi: 10.1016/j.math.2015.03.003
120. Kumar SP. Efficacy of segmental stabilization exercise for lumbar segmental instability in patients with mechanical low back pain: A randomized placebo controlled crossover study. *North American Journal of Medical Sciences* 2011;3(10):456-61. doi: https://dx.doi.org/10.4297/najms.2011.3456
121. Lehtola V, Korhonen I, Airaksinen O. A randomised, placebo-controlled, clinical trial for the short-term effectiveness of manipulative therapy and acupuncture on pain caused by mechanical

thoracic spine dysfunction. *International Musculoskeletal Medicine* 2010;32(1):25-32. doi: 10.1179/175361410X12652805807558
122. Lewis C, Khan A, Souvlis T, et al. A randomised controlled study examining the short-term effects of Strain–Counterstrain treatment on quantitative sensory measures at digitally tender points in the low back. *Manual Therapy* 2010;15(6):536-41. doi: 10.1016/j.math.2010.05.011
123. Lewis C, Souvlis T, Sterling M. Sensory characteristics of tender points in the lower back. *Manual Therapy* 2010;15(5):451-56. doi: 10.1016/j.math.2010.03.006
124. Lindback Y, Tropp H, Enthoven P, et al. Altered somatosensory profile according to quantitative sensory testing in patients with degenerative lumbar spine disorders scheduled for surgery. *BMC Musculoskeletal Disorders* 2017;18(1):264. doi: https://dx.doi.org/10.1186/s12891-017-1581-6
125. Lisi AJ, Cooperstein R, Morschhauser E. An exploratory study of provocation testing with padded wedges: can prone blocking demonstrate a directional preference? *Journal of Manipulative & Physiological Therapeutics* 2004;27(2):103-08. doi: 10.1016/j.jmpt.2003.12.005
126. Markowski A, Sanford S, Pikowski J, et al. A Pilot Study Analyzing the Effects of Chinese Cupping as an Adjunct Treatment for Patients with Subacute Low Back Pain on Relieving Pain, Improving Range of Motion, and Improving Function. *Journal of Alternative & Complementary Medicine* 2014;20(2):113-17. doi: 10.1089/acm.2012.0769
127. Mesci E, Icagasioglu A, Atlig RS, et al. Pain sensitivity in the elderly. *Turk Geriatri Dergisi* 2015;18(2):130-35.
128. Metgud S, Monteiro S, Heggannavar A, et al. Effect of integrated neuromuscular inhibition technique on trigger points in patients with nonspecific low back pain: Randomized controlled trial. *Indian Journal of Physical Therapy and Research* 2020;2(2):99-105.
129. Nieto-Garcia J, Suso-Marti L, La Touche R, et al. Somatosensory and Motor Differences between Physically Active Patients with Chronic Low Back Pain and Asymptomatic Individuals. *Medicina (Kaunas, Lithuania)* 2019;55(9) doi: https://dx.doi.org/10.3390/medicina55090524

130. Nim CG, Kawchuk GN, Schiottz-Christensen B, et al. The effect on clinical outcomes when targeting spinal manipulation at stiffness or pain sensitivity: a randomized trial. *Scientific reports* 2020;10(1):14615. doi: https://dx.doi.org/10.1038/s41598-020-71557-y
131. Nim CG, Ravn SL, Andersen TE, et al. No effect of social interaction on experimental pain sensitivity: a randomized experimental study. *Pain* 2023((Nim, O'Neill) Medical Research Unit, Spine Center of Southern Denmark, University Hospital of Southern Denmark, Middelfart, Denmark(Nim, O'Neill) Departments of Regional Health Research(Nim, Engelsholm, Hestbech, Hvidkaer, Traidl) Sport Science and Clini) doi: https://dx.doi.org/10.1097/j.pain.0000000000002913
132. O'Neill S, Kjær P, Graven-Nielsen T, et al. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *European Spine Journal* 2011;20(12):2120-25. doi: 10.1007/s00586-011-1796-4
133. O'Neill S, Larsen JB, Nim C, et al. Topographic mapping of pain sensitivity of the lower back - a comparison of healthy controls and patients with chronic non-specific low back pain. *Scandinavian journal of pain* 2019;19(1):25-37. doi: https://dx.doi.org/10.1515/sjpain-2018-0113
134. O'Sullivan P, Waller R, Wright A, et al. Sensory characteristics of chronic non-specific low back pain: A subgroup investigation. *Manual Therapy* 2014;19(4):311-18. doi: 10.1016/j.math.2014.03.006
135. Oh S, Kim M, Lee M, et al. Effect of myofascial trigger point therapy with an inflatable ball in elderlies with chronic non-specific low back pain. *Journal of Back & Musculoskeletal Rehabilitation* 2018;31(1):119-26. doi: 10.3233/BMR-169696
136. ÖZdolap Ş, Sarikaya S, KÖKtÜRk F. Evaluation of Pain Pressure Threshold and Widespread Pain in Chronic Low Back Pain. *Turkish Journal of Physical Medicine & Rehabilitation / Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi* 2014;60(1):32-36. doi: 10.5152/tftrd.2014.71602
137. Park CH, Kang JH. Efficacy and safety assessment of orthopedic device (LSM-01) for low back pain: A randomized, single-blinded, sham-controlled, parallel-group, pilot clinical trial. *Medicine* 2022;101(43):e31068-e68. doi: 10.1097/MD.0000000000031068

138. Paulo LR, Lacerda ACR, Martins FLM, et al. Can a single trial of a thoracolumbar myofascial release technique reduce pain and disability in chronic low back pain? A randomized balanced crossover study. *Journal of Clinical Medicine* 2021;10(9):2006. doi: https://dx.doi.org/10.3390/jcm10092006
139. Paungmali A, Sitilertpisan P, Taneyhill K, et al. Intrarater Reliability of Pain Intensity, Tissue Blood Flow, Thermal Pain Threshold, Pressure Pain Threshold and Lumbo-Pelvic Stability Tests in Subjects with Low Back Pain. *Asian Journal of Sports Medicine* 2012;3(1):8-14. doi: 10.5812/asjsm.34718
140. Paungmali A, Joseph LH, Sitilertpisan P, et al. Lumbopelvic Core Stabilization Exercise and Pain Modulation Among Individuals with Chronic Nonspecific Low Back Pain. *Pain Practice* 2017;17(8):1008-14. doi: 10.1111/papr.12552
141. Pecos-Martín D, de Melo Aroeira AE, Verás Silva RL, et al. Immediate effects of thoracic spinal mobilisation on erector spinae muscle activity and pain in patients with thoracic spine pain: a preliminary randomised controlled trial. *Physiotherapy* 2017;103(1):90-97. doi: 10.1016/j.physio.2015.10.016
142. Pivovarsky MLF, Gaideski F, Macedo RMd, et al. Immediate analgesic effect of two modes of transcutaneous electrical nerve stimulation on patients with chronic low back pain: a randomized controlled trial. *Einstein (Sao Paulo, Brazil)* 2021;19(101281800):eAO6027. doi: https://dx.doi.org/10.31744/einstein_journal/2021AO6027
143. Plaza-Manzano G, Cancela-Cilleruelo I, Fernández-de-las-Peñas C, et al. Effects of Adding a Neurodynamic Mobilization to Motor Control Training in Patients With Lumbar Radiculopathy Due to Disc Herniation: A Randomized Clinical Trial. *American Journal of Physical Medicine & Rehabilitation* 2020;99(2):124-32. doi: 10.1097/PHM.0000000000001295
144. Rabey M, Buldo B, Duesund Helland M, et al. Significant other interactions in people with chronic low back pain: Subgrouping and multidimensional profiles. *British Journal of Pain* 2022;16(3):326-40. doi: https://dx.doi.org/10.1177/20494637211062045
145. Ratajczak M, Wendt M, Sliwicka E, et al. Subjective assessment and biochemical evaluation of traction therapy in women with chronic low back pain: does body mass index matter? A clinical study. *BMC*

musculoskeletal disorders 2023;24(1):196. doi: https://dx.doi.org/10.1186/s12891-023-06300-5
146. Rodriguez-Huguet M, Gongora-Rodriguez J, Vinolo-Gil MJ, et al. Effectiveness of Negative Pulsed-Pressure Myofascial Vacuum Therapy and Therapeutic Exercise in Chronic Non-Specific Low Back Pain: A Single-Blind Randomized Controlled Trial. *Journal of Clinical Medicine* 2022;11(7):1984. doi: https://dx.doi.org/10.3390/jcm11071984
147. Sarker KK, Sethi J, Mohanty U. Effect of spinal manipulation on pain sensitivity, postural sway, and health-related quality of life among patients with non-specific chronic low back pain: A randomised control trial. *Journal of Clinical and Diagnostic Research* 2019;13(2):YC01-YC05. doi: https://dx.doi.org/10.7860/JCDR/2019/38074.12578
148. Schenk P, Laeubli T, Klipstein A. Validity of pressure pain thresholds in female workers with and without recurrent low back pain. *European Spine Journal* 2007;16(2):267-75. doi: 10.1007/s00586-006-0124-x
149. Schistad EI, Jacobsen LM, Roe C, et al. The interleukin-1a gene C > T polymorphism rs1800587 is associated with increased pain intensity and decreased pressure pain thresholds in patients with lumbar radicular pain. *Clinical Journal of Pain* 2014;30(10):869-74. doi: https://dx.doi.org/10.1097/AJP.0000000000000048
150. Selva-Sarzo F, Fernandez-Carnero S, Sillevis R, et al. The Direct Effect of Magnetic Tape on Pain and Lower-Extremity Blood Flow in Subjects with Low-Back Pain: A Randomized Clinical Trial. *Sensors (Basel, Switzerland)* 2021;21(19) doi: https://dx.doi.org/10.3390/s21196517
151. Shenoy PD, Eapen C, Kumar SP. Association of Pressure-Pain Threshold and Lumbar Lordosis in Subjects with and without Low Back Pain - A Case Control Study. *Indian Journal of Physiotherapy & Occupational Therapy* 2013;7(2):130-34. doi: 10.5958/j.0973-5674.7.2.028
152. Shin J-Y, Ku B, Kim JU, et al. Short-Term Effect of Laser Acupuncture on Lower Back Pain: A Randomized, Placebo-Controlled, Double-Blind Trial. *Evidence-based Complementary & Alternative Medicine (eCAM)* 2015;2015:1-8. doi: 10.1155/2015/808425

153. Sipko T, Kuczynski M, Kuczyński M. Intensity of chronic pain modifies postural control in low back patients. *European Journal of Pain* 2013;17(4):612-20. doi: 10.1002/j.1532-2149.2012.00226.x
154. Sitges C, Terrasa JL, Garcia-Dopico N, et al. An Educational and Exercise Mobile Phone-Based Intervention to Elicit Electrophysiological Changes and to Improve Psychological Functioning in Adults With Nonspecific Chronic Low Back Pain (BackFit App): Nonrandomized Clinical Trial. *JMIR mHealth and uHealth* 2022;10(3):e29171. doi: https://dx.doi.org/10.2196/29171
155. Srivastava S, Kumar DKU, Mittal H, et al. Short-term effect of "mechanical diagnosis and therapy" in the management of sacroiliac joint pain. *Journal of Clinical and Diagnostic Research* 2018;12(9):YC01-YC04. doi: https://dx.doi.org/10.7860/JCDR/2018/36200.12020
156. Srivastava S, Kumar K U D, Mittal H, et al. Short-term effect of muscle energy technique and mechanical diagnosis and therapy in sacroiliac joint dysfunction: A pilot randomized clinical trial. *Journal of Bodywork & Movement Therapies* 2020;24(3):63-70. doi: 10.1016/j.jbmt.2020.02.017
157. Starkweather AR, Ramesh D, Lyon DE, et al. Acute Low Back Pain: Differential Somatosensory Function and Gene Expression Compared With Healthy No-Pain Controls. *Clinical Journal of Pain* 2016;32(11):933-39. doi: 10.1097/AJP.0000000000000347
158. Starkweather A, Julian T, Ramesh D, et al. Circulating Lipids and Acute Pain Sensitization: An Exploratory Analysis. *Nursing Research* 2017;66(6):454-61. doi: 10.1097/NNR.0000000000000248
159. Starkweather AR, Coyne P, Lyon DE, et al. Decreased Low Back Pain Intensity and Differential Gene Expression Following Calmare®: Results From a Double-Blinded Randomized Sham-Controlled Study. *Research in Nursing & Health* 2015;38(1):29-38. doi: 10.1002/nur.21632
160. Takamoto K, Bito I, Urakawa S, et al. Effects of compression at myofascial trigger points in patients with acute low back pain: A randomized controlled trial. *European Journal of Pain* 2015;19(8):1186-96. doi: 10.1002/ejp.694
161. Tan H, Tumilty S, Chapple C, et al. Acupoints sensitization in people with and without chronic low back pain:A matched-sample cross-

sectional study. *Journal of Back & Musculoskeletal Rehabilitation* 2023;36(1):137-46. doi: 10.3233/BMR-210297
162. Téllez-García M, de-la-Llave-Rincón AI, Salom-Moreno J, et al. Neuroscience education in addition to trigger point dry needling for the management of patients with mechanical chronic low back pain: A preliminary clinical trial. *Journal of Bodywork & Movement Therapies* 2015;19(3):464-72. doi: 10.1016/j.jbmt.2014.11.012
163. Trampas A, Mpeneka A, Malliou V, et al. Immediate Effects of Core-Stability Exercises and Clinical Massage on Dynamic-Balance Performance of Patients With Chronic Specific Low Back Pain. *Journal of Sport Rehabilitation* 2015;24(4):373-83. doi: 10.1123/jsr.2014-0215
164. Ul Hasanat R, Syed SA, Rathore FA, et al. Development of a tool for objectively measuring somatic pain in the low back region based on a longitudinal diagnostic study conducted in Karachi, Pakistan. *BMJ open* 2023;13(3):e067129. doi: https://dx.doi.org/10.1136/bmjopen-2022-067129
165. Vicente-Campos D, Sanchez-Jorge S, Terron-Manrique P, et al. The main role of diaphragm muscle as a mechanism of hypopressive abdominal gymnastics to improve non-specific chronic low back pain: A randomized controlled trial. *Journal of Clinical Medicine* 2021;10(21):4983. doi: https://dx.doi.org/10.3390/jcm10214983
166. Volpato MP, Breda ICA, de Carvalho RC, et al. Single Cupping Thearpy Session Improves Pain, Sleep, and Disability in Patients with Nonspecific Chronic Low Back Pain. *Journal of Acupuncture & Meridian Studies* 2020;13(2):48-52. doi: 10.1016/j.jams.2019.11.004
167. Wand BM, Catley MJ, Rabey MI, et al. Disrupted Self-Perception in People With Chronic Low Back Pain. Further Evaluation of the Fremantle Back Awareness Questionnaire. *Journal of Pain* 2016;17(9):1001-12. doi: 10.1016/j.jpain.2016.06.003
168. Wang-Price S, Zafereo J, Couch Z, et al. Short-term effects of two deep dry needling techniques on pressure pain thresholds and electromyographic amplitude of the lumbosacral multifidus in patients with low back pain - a randomized clinical trial. *Journal of Manual & Manipulative Therapy (Taylor & Francis Ltd)* 2020;28(5):254-65. doi: 10.1080/10669817.2020.1714165
169. Wilson AT, Riley JL, 3rd, Bishop MD, et al. Pain phenotyping and investigation of outcomes in physical therapy: An exploratory study in

patients with low back pain. *PloS one* 2023;18(2):e0281517. doi: https://dx.doi.org/10.1371/journal.pone.0281517
170. Won ES, Lee H, Kang JH. Effectiveness and safety assessment of orthopedic device (LSM-01) for low back pain: A randomized, single-blinded, sham-controlled, parallel-group, pilot clinical trial. *Medicine* 2022;101(3):e28527-e27. doi: 10.1097/MD.0000000000028527
171. Woznowski-Vu A, Martel MO, Ahmed S, et al. Task-based measures of sensitivity to physical activity predict daily life pain and mood among people living with back pain. *European journal of pain (London, England)* 2023;27(6):735-48. doi: https://dx.doi.org/10.1002/ejp.2103
172. Woznowski-Vu A, Aternali A, Gervais A, et al. The Prospective Prognostic Value of Biopsychosocial Indices of Sensitivity to Physical Activity Among People With Back Pain. *Clinical Journal of Pain* 2021;37(10):719-29. doi: 10.1097/AJP.0000000000000965
173. Xu C, Fu Z, Wang J, et al. Differences and Correlations of Anxiety, Sleep Quality, and Pressure-Pain Threshold between Patients with Chronic Low Back Pain and Asymptomatic People. *Pain Research & Management* 2022:1-7. doi: 10.1155/2022/8648584
174. Xu C, Fu Z, Wang X. Effect of Transversus abdominis muscle training on pressure-pain threshold in patients with chronic low Back pain. *BMC Sports Science, Medicine and Rehabilitation* 2021;13(1) doi: 10.1186/s13102-021-00262-8
175. Yildiz SH, UlaŞLi AM, Erdogan MÖ, et al. Assessment of Pain Sensitivity in Patients With Chronic Low Back Pain and Association With HTR2A Gene Polymorphism. *Archives of Rheumatology* 2017;32(1):3-9. doi: 10.5606/ArchRheumatol.2017.5846
176. Zheng Z, Wang J, Gao Q, et al. Therapeutic evaluation of lumbar tender point deep massage for chronic non-specific low back pain. *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan* 2012;32(4):534-7.
177. Zywien U, Barczyk-Pawelec K, Sipko T. Associated Risk Factors with Low Back Pain in White-Collar Workers-A Cross-Sectional Study. *Journal of Clinical Medicine* 2022;11(5):1275. doi: https://dx.doi.org/10.3390/jcm11051275
178. Aoyagi K, He J, Nicol AL, et al. A Subgroup of Chronic Low Back Pain Patients With Central Sensitization. *Clinical Journal of Pain* 2019;35(11):869-79. doi: 10.1097/AJP.0000000000000755

179. Aoyagi K, He J, Clauw DJ, et al. Sleep quality in individuals with chronic low back pain and central sensitization. *Physiotherapy Research International* 2022;27(4):1-9. doi: 10.1002/pri.1968
180. Chang W-J, Buscemi V, Liston MB, et al. Central pain processing does not differ between first episode and recurrent acute low back pain. *Physiotherapy Practice & Research* 2020;41(1):35-42. doi: 10.3233/PPR-190143
181. Chang W-J, Jenkins LC, Humburg P, et al. Human assumed central sensitization in people with acute non-specific low back pain: A cross-sectional study of the association with brain-derived neurotrophic factor, clinical, psychological and demographic factors. *European journal of pain (London, England)* 2023;27(4):530-45. doi: https://dx.doi.org/10.1002/ejp.2078
182. Chapman KB, Roosendaal BK, Yousef TA, et al. Dorsal Root Ganglion Stimulation Normalizes Measures of Pain Processing in Patients with Chronic Low-Back Pain: A Prospective Pilot Study using Quantitative Sensory Testing. *Pain Practice* 2021;21(5):568-77. doi: 10.1111/papr.12992
183. Corrêa JB, Costa LOP, De Oliveira NTB, et al. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case–control study. *Experimental Brain Research* 2015;233(8):2391-99. doi: 10.1007/s00221-015-4309-6
184. Goodin BR, Overstreet DS, Penn TM, et al. Epigenome-wide DNA methylation profiling of conditioned pain modulation in individuals with non-specific chronic low back pain. *Clinical epigenetics* 2022;14(1):45. doi: https://dx.doi.org/10.1186/s13148-022-01265-z
185. Klyne DM, Moseley GL, Sterling M, et al. Are Signs of Central Sensitization in Acute Low Back Pain a Precursor to Poor Outcome? *Journal of Pain* 2019;20(8):994-1009. doi: 10.1016/j.jpain.2019.03.001
186. McPhee ME, Graven-Nielsen T. Medial prefrontal transcranial direct current stimulation aimed to improve affective and attentional modulation of pain in chronic low back pain patients. *Journal of Clinical Medicine* 2021;10(4):1-17. doi: https://dx.doi.org/10.3390/jcm10040889
187. Mehta V, Snidvongs S, Ghai B, et al. Characterization of peripheral and central sensitization after dorsal root ganglion intervention in patients with unilateral lumbosacral radicular pain: a prospective pilot study.

BJA: The British Journal of Anaesthesia 2017;118(6):924-31. doi: 10.1093/bja/aex089
188. O'Neill S, Manniche C, Graven-Nielsen T, et al. Association Between a Composite Score of Pain Sensitivity and Clinical Parameters in Low-back Pain. *Clinical Journal of Pain* 2014;30(10):831-38. doi: 10.1097/AJP.0000000000000042
189. O'Neill S, Graven-Nielsen T, Manniche C, et al. Reliability and validity of a simple and clinically applicable pain stimulus: sustained mechanical pressure with a spring-clamp. *Chiropractic & Manual Therapies* 2014;22(1):1-21. doi: 10.1186/s12998-014-0030-y
190. Taub CJ, Sturgeon JA, Johnson KA, et al. Effects of a Pain Catastrophizing Induction on Sensory Testing in Women with Chronic Low Back Pain: A Pilot Study. *Pain Research & Management* 2017:1-10. doi: 10.1155/2017/7892494
191. Aspinall SL, Jacques A, Leboeuf-Yde C, et al. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. *Musculoskeletal science & practice* 2019;43(101692753):18-25. doi: https://dx.doi.org/10.1016/j.msksp.2019.05.011
192. Jamison RN, Wan L, Edwards RR, et al. Outcome of a High-Frequency Transcutaneous Electrical Nerve Stimulator (hfTENS) Device for Low Back Pain: A Randomized Controlled Trial. *Pain Practice* 2019;19(5):466-75. doi: 10.1111/papr.12764
193. Meints SM, Mawla I, Napadow V, et al. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. *PAIN* 2019;160(4):833-43. doi: 10.1097/j.pain.0000000000001461
194. Meints SM, Garcia RG, Schuman-Olivier Z, et al. The Effects of Combined Respiratory-Gated Auricular Vagal Afferent Nerve Stimulation and Mindfulness Meditation for Chronic Low Back Pain: A Pilot Study. *Pain medicine (Malden, Mass)* 2022;23(9):1570-81. doi: https://dx.doi.org/10.1093/pm/pnac025
195. Neziri AY, Dickenmann M, Scaramozzino P, et al. Effect of intravenous tropisetron on modulation of pain and central hypersensitivity in chronic low back pain patients. *PAIN* 2012;153(2):311-18. doi: 10.1016/j.pain.2011.11.015

196. Neziri AY, Curatolo M, Limacher A, et al. Ranking of parameters of pain hypersensitivity according to their discriminative ability in chronic low back pain. *PAIN* 2012;153(10):2083-91. doi: 10.1016/j.pain.2012.06.025
197. Orr LC, George SZ, Simon CB. Association between physical activity and pain processing in adults with chronic low back pain compared to pain-free controls. *Journal of Back & Musculoskeletal Rehabilitation* 2017;30(3):575-81. doi: 10.3233/BMR-150429
198. Simon CB, Iiiriley JL, Fillingim RB, et al. Age Group Comparisons of TENS Response Among Individuals With Chronic Axial Low Back Pain. *Journal of Pain* 2015;16(12):1268-79. doi: 10.1016/j.jpain.2015.08.009
199. Simon CB, Lentz TA, Ellis L, et al. Static and Dynamic Pain Sensitivity in Adults With Persistent Low Back Pain. *Clinical Journal of Pain* 2021;37(7)
200. Starkweather AR, Lyon DE, Kinser P, et al. Comparison of Low Back Pain Recovery and Persistence: A Descriptive Study of Characteristics at Pain Onset. *Biological research for nursing* 2016;18(4):401-10. doi: https://dx.doi.org/10.1177/1099800416631819
201. Tschugg A, Loscher WN, Hartmann S, et al. Gender Influences Radicular Pain Perception in Patients with Lumbar Disc Herniation. *Journal of Women's Health* 2015;24(9):771-76. doi: https://dx.doi.org/10.1089/jwh.2014.5108
202. Zhivolupov SA, Samartsev IN, Ponomarev VV. [Quantative evaluation and analysis of the central mechanisms involved in analgesic effect of Alflutop in patients with chronic lower back pain]. *Zhurnal nevrologii i psikhiatrii imeni SS Korsakova* 2021;121(10):38-44. doi: https://dx.doi.org/10.17116/jnevro202112110138
203. Butera KA, Fox EJ, Bishop MD, et al. Empirically derived back pain subgroups differentiated walking performance, pain, and disability. *PAIN* 2021;162(6):1806-15. doi: 10.1097/j.pain.0000000000002167
204. Edwards RR, Dolman AJ, Michna E, et al. Changes in Pain Sensitivity and Pain Modulation During Oral Opioid Treatment: The Impact of Negative Affect. *Pain Medicine* 2016;17(10):1882-91. doi: 10.1093/pm/pnw010
205. Lazaridou A, Paschali M, Zgierska AE, et al. Exploring the Relationship Between Endogenous Pain Modulation, Pain Intensity, and Depression in Patients Using Opioids for Chronic Low Back Pain. *Clinical*

Journal of Pain 2022;38(10):595-600. doi: 10.1097/AJP.0000000000001063
206. Leite PMS, Mendonça ARC, Maciel LYS, et al. Does Electroacupuncture Treatment Reduce Pain and Change Quantitative Sensory Testing Responses in Patients with Chronic Nonspecific Low Back Pain? A Randomized Controlled Clinical Trial. *Evidence-based Complementary & Alternative Medicine (eCAM)* 2018:1-8. doi: 10.1155/2018/8586746
207. Leresche L, Turner JA, Saunders K, et al. Psychophysical tests as predictors of back pain chronicity in primary care. *Journal of Pain* 2013;14(12):1663-70. doi: 10.1016/j.jpain.2013.08.008
208. Lie MU, Winsvold B, Gjerstad J, et al. The association between selected genetic variants and individual differences in experimental pain. *Scandinavian journal of pain* 2020((Lie) FORMI-Oslo University Hospital, Oslo, Norway(Winsvold, Pedersen, Heuch, Zwart) Department of Research, Innovation and Education, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway(Gjerstad, Matre) National Institute of Occupat) doi: https://dx.doi.org/10.1515/sjpain-2020-0091
209. McPhee ME, Graven-Nielsen T. Recurrent low back pain patients demonstrate facilitated pronociceptive mechanisms when in pain, and impaired antinociceptive mechanisms with and without pain. *Pain* 2019;160(12):2866-76. doi: 10.1097/j.pain.0000000000001679
210. McPhee ME, Graven-Nielsen T. Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blinded Placebo-Controlled Crossover Trial. *The journal of pain* 2021;22(8):952-67. doi: https://dx.doi.org/10.1016/j.jpain.2021.02.012
211. Müller M, Curatolo M, Limacher A, et al. Predicting transition from acute to chronic low back pain with quantitative sensory tests-A prospective cohort study in the primary care setting. *European Journal of Pain* 2019;23(5):894-907. doi: 10.1002/ejp.1356
212. O'Neill S, Holm L, Filtenborg JB, et al. The inhibitory effect of conditioned pain modulation on temporal summation in low-back pain patients. *Scandinavian journal of pain* 2021;21(3):606-16. doi: https://dx.doi.org/10.1515/sjpain-2021-0025
213. Palsson TS, Christensen SWM, De Martino E, et al. Pain and Disability in Low Back Pain Can be Reduced Despite No Significant

Improvements in Mechanistic Pain Biomarkers. *Clinical Journal of Pain* 2021;37(5):330-38. doi: 10.1097/AJP.0000000000000927
214. Petersen KK, Jensen MB, Graven-Nielsen T, et al. Pain Catastrophizing, Self-reported Disability, and Temporal Summation of Pain Predict Self-reported Pain in Low Back Pain Patients 12 Weeks After General Practitioner Consultation: A Prospective Cohort Study. *Clinical Journal of Pain* 2020;36(10):757-63. doi: 10.1097/AJP.0000000000000865
215. Rabey M, Kendell M, Godden C, et al. STarT Back Tool risk stratification is associated with changes in movement profile and sensory discrimination in low back pain: A study of 290 patients. *European Journal of Pain* 2019;23(4):823-34. doi: 10.1002/ejp.1351
216. Schliessbach J, Siegenthaler A, Butikofer L, et al. Effect of single-dose imipramine on chronic low-back and experimental pain. A randomized controlled trial. *PloS one* 2018;13(5):e0195776. doi: https://dx.doi.org/10.1371/journal.pone.0195776
217. Teixeira PEP, Pacheco-Barrios K, Uygur-Kucukseymen E, et al. Electroencephalography Signatures for Conditioned Pain Modulation and Pain Perception in Nonspecific Chronic Low Back Pain—An Exploratory Study. *Pain Medicine* 2022;23(3):558-70. doi: 10.1093/pm/pnab293
218. Bialosky JE, Bishop MD, Robinson ME, et al. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Physical Therapy* 2009;89(12):1292-303. doi: 10.2522/ptj.20090058
219. Biurrun Manresa JA, Neziri AY, Curatolo M, et al. Test–retest reliability of the nociceptive withdrawal reflex and electrical pain thresholds after single and repeated stimulation in patients with chronic low back pain. *European Journal of Applied Physiology* 2011;111(1):83-92. doi: 10.1007/s00421-010-1634-0
220. Carriere JS, Martel MO, Meints SM, et al. What do you expect? Catastrophizing mediates associations between expectancies and pain-facilitatory processes. *European Journal of Pain* 2019;23(4):800-11. doi: 10.1002/ejp.1348
221. George SZ, Wittmer VT, Fillingim RB, et al. Fear-avoidance beliefs and temporal summation of evoked thermal pain influence self-report of disability in patients with chronic low back pain. *Journal of*

Occupational Rehabilitation 2006;16(1):95-108. doi: 10.1007/s10926-005-9007-y
222. George SZ, Wittmer VT, Fillingim RB, et al. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *Journal of Pain* 2007;8(1):2-10. doi: 10.1016/j.jpain.2006.05.009
223. Hübscher M, Moloney N, Rebbeck T, et al. Contributions of Mood, Pain Catastrophizing, and Cold Hyperalgesia in Acute and Chronic Low Back Pain: A Comparison With Pain-free Controls. *Clinical Journal of Pain* 2014;30(10):886-93. doi: 10.1097/AJP.0000000000000045
224. Meints SM, Wang V, Edwards RR. Sex and Race Differences in Pain Sensitization among Patients with Chronic Low Back Pain. *Journal of Pain* 2018;19(12):1461-70. doi: 10.1016/j.jpain.2018.07.001
225. Van Bogaert W, Putman K, Coppieters I, et al. Health-related quality of life deviations from population norms in patients with lumbar radiculopathy: associations with pain, pain cognitions, and endogenous nociceptive modulation. *Quality of Life Research* 2022;31(3):745-57. doi: 10.1007/s11136-021-02964-5

2.11 Figures

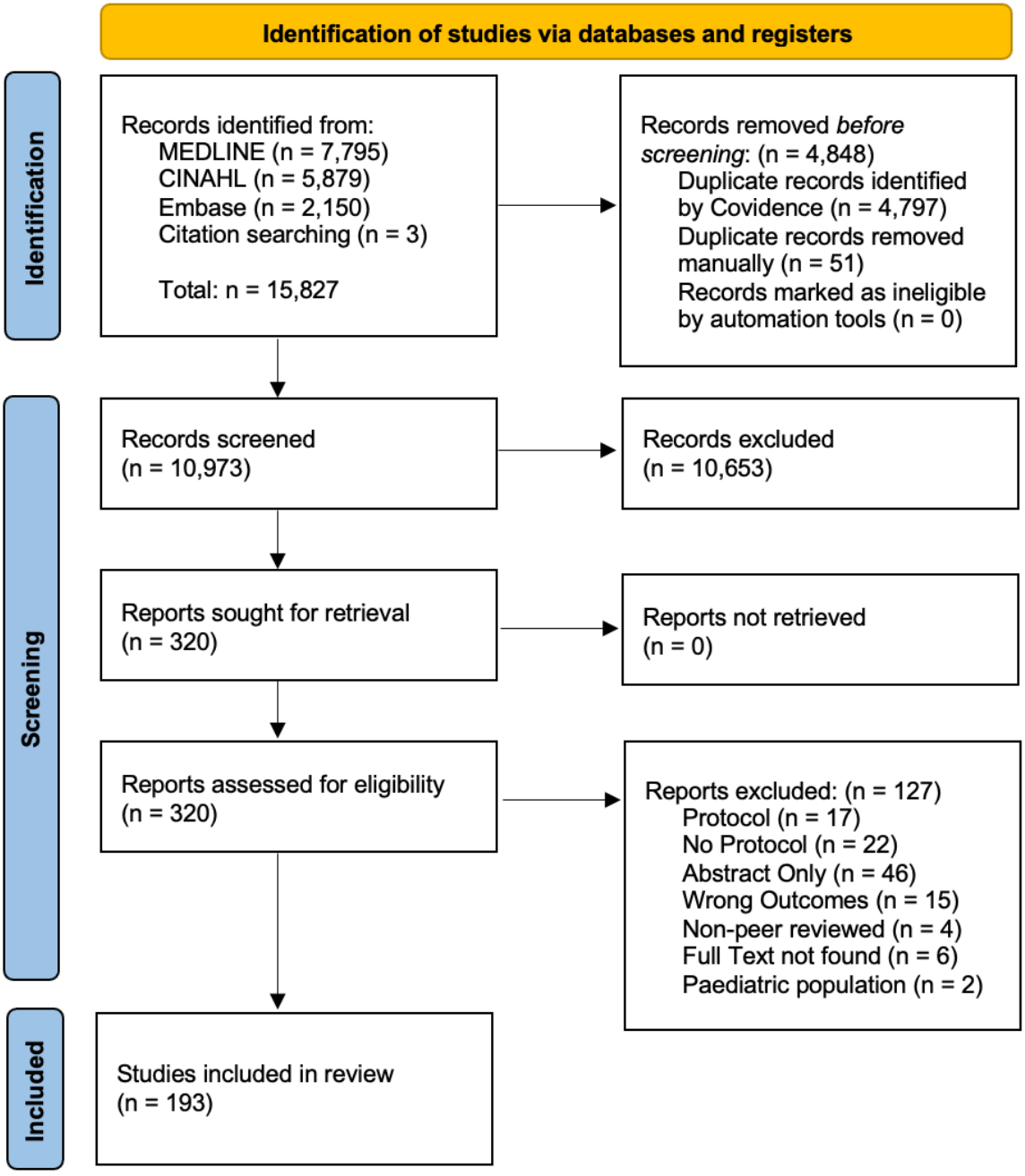

Figure 1. PRISMA Flow Chart

2.12 Tables

Table 1: Study Characteristics

Author	Study Design	Study Setting	Back Pain Population	Duration of back pain (Definition and time frame)	Age, y (mean ± SD of LBP group and/or inclusion range)	Comparison
Conditioned Pain Modulation (CPM)						
Bruehl et al., 2021[59]	RCT	Medical Centre (Multisite)	LBP	Chronic (3+ Months)	18-55	Healthy Controls
Christensen et al., 2020[60]	Cross-Sectional	Spine Centre	LBP	Chronic (3+ Months)	18-60	Pain Free Controls
France et al., 2016[61]	RCT	Medical Centre (Multisite)	LBP	Chronic (3+ Months)	34.7 ± 10.5 (18-55)	Healthy Controls
Krafft et al., 2017[62]	RCT; Longitudinal	Hospital	BP	Chronic (6+ months)	Intervention: 52 ± 9 Sham: 53 ± 9	Pain Free Controls
Lardon et al., 2018[63]	Cohort; Longitudinal	Community	NSLBP	1 disabling episode of LBP in past year	36.5 ± 12.1 (18-60)	N/A
McPhee et al., 2022[64]	Case-Control	University/ Community	LBP	>24 hrs, expectation of resolution less than 1 month	27.3 ± 5.4	Pain free controls
Mensing et al., 2013[65]	Measurement	Hospital Pain Management Centre	BP	Chronic (6+ months)	Male: 48.9 ± 10.5 Female: 49.5 ± 8.9	N/A
Mlekush et al., 2016[66]	Case-Control	Hospital	LBP	Acute (0-4 weeks); Chronic (6+ months)	Acute: 41.4 ± 12.5 Chronic: 50.8 ± 14	Pain free controls
Moreira et al., 2021[67]	Case-Control	Physiotherapy Department	NSLBP	Chronic (3+ months)	26.4 ± 1.6 (18-65)	Healthy Controls
Rabey et al., 2015[68]	Case-Control	Community	LBP	Chronic (3+ months)	34.6 ± 10.6 (18-70)	Pain Free Controls
Vuilleumier et al., 2017[69]	Case-Control	Hospital	LBP	Acute (0-6 weeks)	38.5 ± 14 (18-80)	Pain Free Controls
Pain Pressure Threshold (PPT)						
Abd Elsadek et al., 2023[70]	RCT; Longitudinal	Physiotherapy Department	Low back myofascial pain syndrome	0-2 weeks	18-43	N/A

Alshami et al., 2023[71]	RCT; Longitudinal	Hospital	LBP	1 episode of LBP in the last 12 months	36 years	N/A
Alvarez et al., 2022[72]	RCT	Physiotherapy Clinic	NSLBP	>6 weeks	18-75	N/A
Aoyagi et al., 2021[73]	Cross-sectional	Medical Centre	LBP	Chronic (3+ months)	21-70	N/A
Balaguier et al., 2016[74]	Measurement study	Not specified	LBP	Min 3 consecutive days in the last 12 months	39.9 ± 9.9 (25-60)	Pain free controls
Bandeira et al., 2021[75]	Case-control	University	NSLBP	Chronic (3+ Months)	18-60	Pain free controls
Barassi et al., 2022[76]	RCT	Outpatient Rehabilitation Centre	NSLBP	>1 month during the previous year, present for 3+ consecutive years	23.2 ± 2.5	N/A
Bid et al., 2017[77]	RCT	Hospital Outpatient	NSLBP	Chronic (3+ months)	Experimental: 41.33 ± 7.27 Control: 41.12 ± 7.76	N/A
Bodes Pardo et al., 2018[28]	RCT; Longitudinal	Private Clinic	LBP	Chronic (6+ months)	20-75	N/A
Bond et al., 2020[78]	Pilot RCT; Longitudinal	Research Laboratory	NSLBP	Chronic (3+ months)	23.86 ± 5.74 (18-60)	N/A
Buttagat et al., 2011[79]	RCT	Community	BP	Chronic (3+ months)	22.64 ± 2.9	N/A
Calvo-Lobo et al., 2017[80]	Cross-sectional	University	Non-specific lumbopelvic pain	>6 weeks	Median: 26.5 IQR: 7 years (18-60)	N/A
Carrasco-Martinez et al., 2019[81]	RCT	Physiotherapy Clinic	LBP	Chronic (3+ months)	43.03 ± 13.39 (18+)	N/A
Chen et al., 2022[82]	RCT; Longitudinal	Outpatient Rehabilitation Centre	NSLBP	>1 month	20-65	N/A
Cho et al., 2014[83]	RCT	Clinic	LBP	Chronic	Experimental: 38.1 ± 7.9 years Control: 36.5 ± 7.7 years	N/A
Clark et al., 2021[84]	RCT	Physiotherapy Clinic	LBP	Not specified	18-70	N/A

Dayanir et al., 2020[85]	Pilot RCT;	Neurosurgery Clinic	NSLBP	Chronic (3+ months)	35.47 ± 10.58 (18-65)	N/A
de Carvalho et al., 2019[86]	Quasi-experimental	Physiotherapy Clinic	NSLBP	Chronic (3+ months)	53.23 years (30-65)	N/A
Moura et al., 2022[87]	Descriptive; Cross sectional	Physiotherapy Clinic	BP	Chronic (3+ months)	48.03 ± 12.41 (18+)	N/A
de Oliveira et al., 2013[88]	RCT	Outpatient Physiotherapy Clinic	NSLBP	Chronic (3+ months)	18-80	N/A
de Oliveira et al., 2020[89]	RCT; Longitudinal	Outpatient Physiotherapy clinic	NSLBP	Chronic (3+ months)	44 years (18-80)	N/A
Degenhardt et al., 2017[90]	RCT	Community	LBP	> 6 weeks	36 ± 11 (20-60)	Pain free controls
Demirel et al., 2019[91]	Retrospective	Physiotherapy clinic	LBP	Chronic (3+ months)	65+	N/A
Dissanguan et al., 2021[92]	RCT	Physiotherapy department	NSLBP	Chronic (3+ months)	41.3 ± 9.1 (20-55)	N/A
Ebadi et al., 2018[93]	RCT	Physiotherapy Clinic	NSLBP	Chronic (3+ months)	18-60	N/A
Eftekharsadat et al., 2020[94]	RCT; Longitudinal	Hospital	LBP	Chronic (3+ months)	Shock wave therapy – 44.74 ± 9.34 Corticosteroid injection - 45.04 ± 11.86	N/A
Fagundes Loss et al., 2020[95]	RCT	Community	Lumbar Pain	Chronic (3+ months)	20-60	N/A
Falla et al., 2014[96]	Cross-Sectional	Community	NSLBP	Chronic (3+ months)	32.2 ± 9.5 (18-45)	Pain free controls
Farasyn et al., 2005[97]	Cross-Sectional	Physiotherapy Clinic	NSLBP	Subacute (3-12 weeks)	43 ± 13 (20-75)	Healthy controls
Farasyn et al., 2006[98]	RCT; Pilot	Pain Centre	NSLBP	Subacute (3-12 weeks)	21-75	N/A
Farasyn et al., 2007[99]	RCT	Pain Centre	NSLBP	Subacute (3-12 weeks)	45 ± 13 (21-75)	Pain free controls
Farasyn et al., 2008[100]	Measurement	Primary Care	NSLBP	Subacute (3-12 weeks)	20-75	N/A

Farasyn et al., 2016[101]	Measurement; Cross-sectional	Pain Centre; Community	NSLBP	Chronic (3+ months)	47 ± 13 (18-65)	Pain free controls
Franco et al., 2017[102]	RCT; Longitudinal	Physiotherapy Clinic	NSLBP	Chronic (3+ months)	18-80	N/A
Fuentes et al., 2014[103]	RCT	Physiotherapy lab	NSLBP	Chronic (3+ months)	30 ± 6.8 (19-65)	N/A
Gay et al., 2015[104]	Measurement; Cross-sectional	University	LBP	Chronic (3+ months)	42.5 ± 10.5 (30-65)	Pain free controls
Giesbrecht et al., 2005[105]	Case- control; Cross-sectional	Physiotherapy Clinic	LBP	Chronic (6+ months)	41.6 years (20-60)	Pain free controls
Goubert et al., 2018[106]	Cross-sectional	Hospital	NSLBP	Chronic (3+ months)	32 ± 24 (20-64)	N/A
Griswold et al., 2019[107]	RCT	Clinic	NSLBP	>6 weeks	18-70	N/A
Grześkowiak et al., 2019[108]	RCT	Laboratory	Lumbar Disc Herniation	Chronic (3+ months)	20-55	N/A
Hahm et al., 2020[109]	RCT; Pilot	Not Specified	NSLBP	Chronic (6+ months)	Experimental: 61.3 ± 9.6 Control - 55.8 ± 16.4	N/A
Hirayama et al., 2006[110]	Cross-sectional	Not Specified	Lumbar disc herniation	Average: 55 ± 77 days	41 ± 14	Pain free controls
Hsieh et al., 2002[111]	RCT	Clinic	LBP	Acute (< 1 week); Subacute (1 week - 3 months); Chronic (3+ months)	16-79	N/A
Imamura et al., 2013[112]	Cross-sectional	Hospital	LBP	Chronic (3+ months)	18-65	Pain free controls
Imamura et al., 2016[113]	Cross-sectional	Hospital	NSLBP	Chronic (3+ months)	50.10 ± 7.95 (18-65)	N/A
Joseph et al., 2018[114]	RCT	National Weightlifting Training Camp	LBP	Chronic (3+ months)	20.44 ± 3.14	N/A
Joseph et al., 2018[115]	RCT	National Weightlifting Training Camp	LBP	Chronic (3+ months)	20.44 ± 3.14	N/A

Ketenci et al., 2022[116]	RCT	Multisite	LBP	6+ weeks	38.5 ± 11.2 (18-64)	N/A
Kim et al., 2021[117]	RCT	Elderly Welfare Facilities	LBP	Chronic (3+ months)	65+	N/A
Kong et al., 2020[118]	RCT; Longitudinal	University	LBP	Chronic (6+ months)	21-65	N/A
Koppenhaver et al., 2015[119]	Quasi-experimental	Department of Defence	LBP	Average: 58.4 ± 84.4 months	41.3 ± 9.2 (18-60)	N/A
Kumar 2011[120]	RCT	Physiotherapy Department	LBP; Segmental Instability	Not specified	22.5 ± 1.09	N/A
Lehtola et al., 2010[121]	RCT	Physiotherapy Clinic	Mechanical thoracic spine dysfunction	< 3 months	20-60	N/A
Lewis et al., 2010[122]	RCT	Not specified	LBP	Included regardless of chronicity of symptoms	39.2 ± 11.1 (18-65)	N/A
Lewis et al., 2010[123]	Cross-sectional	Not specified	LBP	< 3 months (4 participants); > 3 months (8 participants); acute exacerbation of persistent LBP (2 participants)	40.9 ± 11.3 years (18-65)	Pain free controls
Lindback et al., 2017[124]	Cohort; Cross-sectional	Hospital Spine Clinic	Degenerative lumbar spine disorders	> 2 years	59.9 ± 12.9 (25-80)	N/A
Lisi et al., 2004[125]	Non-randomized experimental	Chiropractic Research Laboratory	LBP	Not specified	20-40	N/A
Markowski et al., 2014[126]	Cohort; Pilot	Outpatient clinic	LBP	Subacute or Chronic (2 months to 13 years)	40 ± 7.2 (33-56)	N/A
Mesci et al., 2015[127]	Cross-sectional	Rehabilitation outpatient clinic	LBP	Chronic (6+ months)	Elderly: 65+ Control: 18-35	N/A
Metgud et al., 2020[128]	RCT	Hospital	NSLBP	Chronic (3+ months)	18-35	N/A
Nieto-Garcia et al., 2019[129]	Cross-sectional; Observational	Community	NSLBP	Chronic (6+ months)	49.3 ± 11.36 (18+)	Pain free controls
Nim et al., 2020[130]	RCT	Spine centre	LBP	Chronic (3+ months)	18-60	N/A

Nim et al., 2023[131]	RCT	Hospital	LBP	Not specified	56 ± 15 (18+)	Healthy controls
O'Neill et al., 2011[132]	Cohort; Longitudinal	Community	LBP	Long-lasting (30+ days); Recent (within the last 7 days)	40 years	N/A
O'Neill et al., 2019[133]	Case-Control; Measurement	Not specified	NSLBP	Chronic (3+ months)	45.3 ± 15 (18-65)	Pain free controls
O'Sullivan et al., 2014[134]	Cross-sectional	Physiotherapy clinic	NSLBP	Chronic (3+ months)	40.7 ± 14.0	Pain free controls
Oh et al., 2018[135]	Cohort	Physiotherapy department	NSLBP	Chronic (3+ months)	70.82 ± 5.64 (65+)	N/A
Ozdolap et al., 2014[136]	Case-control	Not specified	LBP	Chronic (6+ months)	37.6 ± 10.1 (20-60)	Pain free controls
Park et al., 2022[137]	RCT	Hospital	LBP	Not specified	20-70	N/A
Patricio et al., 2022[24]	Case-control	Research centre	NSLBP	Chronic (3+ months)	31.5 ± 16.5	Pain free controls
Paulo et al., 2021[138]	RCT	Community	LBP	Chronic (3+ months)	36 (95% CI 22-50)	N/A
Paungmali et al., 2012[139]	Measurement	Community	NSLBP	Chronic (3+ months)	25.8 ± 6.2 (20-35)	N/A
Paungmali et al., 2017 [140]	RCT	Outpatient physiotherapy department	NSLBP	Chronic (3+ months)	33.33 ± 14.37 (20-55)	N/A
Pecos-Martin et al., 2017[141]	RCT	Laboratory	Non-specific thoracic spine pain	Acute (0-4 weeks); Chronic (3+ months)	24 ± 3 (18-30)	N/A
Pivovarsky et al., 2021[142]	RCT	Physiotherapy Lab	NSLBP	Chronic (3+ months)	18-85	N/A
Plaza-Manzano et al., 2020[143]	RCT	Hospital	LBP	Chronic (3+ months)	18-65	N/A
Rabey et al., 2022[144]	Cohort; Longitudinal	Private Clinic	NSLBP	Chronic (3+ months)	Median: 51 (IQR 38-60) years (18-70)	N/A
Ratajczak et al., 2023[145]	Non-randomized experimental study	University	Lumbar pain	Chronic (6+ months)	34-50	N/A

Reimer et al., 2023[29]	Cohort	Hospital	LBP	Chronic (3+ months)	60.8 ± 10.6 (31-77)	N/A
Rodriguez-Huguet et al., 2022[146]	RCT; Longitudinal	Clinic	LBP	Chronic (3+ months)	37.18 ± 10.82 (25-50)	N/A
Saha et al., 2019[30]	RCT	Community	NSLBP	Chronic (3+ months)	18-75	N/A
Sarker et al., 2019[147]	RCT; Longitudinal	Outpatient physiotherapy department	NSLBP	Chronic (3+ months)	18-60	N/A
Schenk et al. 2007[148]	Case-Control; Measurement	Community	LBP	8+ days over the last 12 months	45-62	Pain free controls
Schistad et al., 2014[149]	Cohort	Hospital	Lumbar Radiculopathy	Not specified	18-60	N/A
Selva-Sarzo et al., 2021[150]	RCT; Pilot	Private Physiotherapy Clinic	LBP	Not specified	18-65	N/A
Shenoy et al., 2013[151]	Case-Control	Not specified	LBP	1+ month	29.4 ± 7.25 (20-45)	Pain free controls
Shin et al., 2015[152]	RCT	Hospital	LBP	Intervention (13.78 ± 19.58 months) Sham (16.33 ± 28.13 months)	20-75	N/A
Sipko et al., 2013[153]	Cohort	Health Resort	LBP	Chronic (3+ months)	30-65	N/A
Sitges et al., 2022[154]	Non-randomized experimental study	University	NSLBP	Chronic (3+ months)	18-59	N/A
Srivastava et al., 2018[155]	Cohort	Physiotherapy Department	LBP	Subacute; Chronic	Male: 40.58 ± 11 Female: 39.93 ± 13.56 (20-65)	N/A
Srivastava et al., 2020[156]	RCT; Pilot	Outpatient Physiotherapy Department	LBP	Subacute; Chronic	20-65	N/A
Starkweather et al., 2016[157]	Case-Control	Private Research Suite	NSLBP	Acute (24 hrs – 4 weeks)	LBP - 35.77 ± 1.83 (18-50)	Pain free controls
Starkweather et al., 2017[158]	Exploratory Analysis	Medical Centre	LBP	Acute (0-4 weeks)	35.3 ± 10.07 (18-50)	N/A

Starkweather et al., 2015[159]	RCT	Academic Health Care System	NSLBP	Chronic (3+ months)	18-50	N/A
Takamoto et al., 2015[160]	RCT	Clinics	LBP	Acute (0-4 weeks)	38 (16-65)	N/A
Tan et al., 2023[161]	Cross-Sectional	Community	LBP	Chronic (3+ months)	33.31 ± 13.40 (18+)	Healthy controls
Tellez-Garcia et al., 2015[162]	RCT	Clinic	NSLBP	Chronic (3+ months)	18-65	N/A
Tesarz et al., 2016[31]	Case-control	Hospital	NSLBP	Chronic (3+ months)	18+	Pain free controls
Trampas et al., 2015[163]	Case-control	Research Laboratory	LBP	Chronic (3-12 months)	19-52	N/A
ul Hasanat et al., 2023[164]	Longitudinal (Phase 1); Cross-Sectional (Phase 2)	Outpatient department	LBP	Chronic (Phase1); Acute, subacute and chronic (Phase 2)	18-50 (Phase 1); 23-61 (Phase 2)	N/A
Vicente-Campos et al., 2021[165]	RCT	University	NSLBP	Chronic (3 episodes in the last 6 months)	Intervention: 23.25 ± 4.52 Control: 23.90 ± 7.36	N/A
Volpato et al., 2020[166]	RCT	Physiotherapy clinic	NSLBP	Chronic (3+ months)	18-50	N/A
Wand et al., 2016[167]	Cohort; Cross-sectional	Hospitals	LBP	Chronic (3+ months)	48.8 ± 13.4 (18-70)	N/A
Wang-Price et al., 2020[168]	RCT	Physiotherapy clinic	LBP	Average: 324.3 ± 326.1 weeks	38.9 ± 15.5	N/A
Wilson et al., 2023[169]	Cohort	Outpatient physiotherapy clinic	LBP	Average: 135.51 ± 252.83 weeks)	51.05 ± 17.02 (18-75)	N/A
Won et al., 2022[170]	RCT; Pilot	Community	LBP	Not specified	20-70	N/A
Woznowski-Vi et al., 2023[171]	Observational; Longitudinal	University	BP	≤6 months	44.74 ± 13.83 (18+)	N/A
Woznowski-Vu et al., 2021[172]	Observational; Longitudinal	Physiotherapy clinic	NSBP	≤6 months	44.15 ± 13.81 (18+)	N/A

Xu et al., 2022[173]	Case-control	University	LBP	Chronic (3+ months)	22.45 ± 2.36 (18-50)	Pain free controls
Xu et al., 2021[174]	RCT	University	LBP	Chronic (3+ months)	18-50	N/A
Yildiz et al., 2017[175]	Case-control	Hospital	LBP	Chronic (3+ months)	36.88 ± 9.9 (18-55)	Pain free controls
Zheng et al., 2012[176]	RCT	Rehabilitation Centre	NSLBP	Chronic (3+ months)	43 ±15 (21-70)	N/A
Zywien et al., 2022[177]	Cross-sectional	Community	NSLBP	Chronic	25-35	Pain free controls
PPT & CPM						
Aoyagi et al., 2019[178]	Cross-sectional	Medical centre	LBP	Chronic (3+ months)	21-70	Pain free controls
Aoyagi et al., 2022[179]	Cross-sectional	Medical centre	LBP	Chronic (3+ months)	21-70	N/A
Chang et al., 2020[180]	Cross-sectional	Primary care clinic and community	NSLBP	Acute (24 hrs - 4 weeks)	18+	Pain free controls
Chang et al., 2023[181]	Cross-sectional	Community	NSLBP	Acute (24 hrs - 4 weeks)	18+	Pain free controls
Chapman et al., 2021[182]	Non-randomized experimental study; Pilot	Pain management institute (Multisite)	LBP	Chronic (6+ months)	60 ± 16	N/A
Correa et al., 2015[183]	Case-control; Cross-sectional	Physiotherapy clinic	NSLBP	Chronic (3+ months)	30-80	Healthy controls
Foubert et al., 2023[41]	Cohort; Longitudinal	Outpatient Rehabilitation and Private Clinic	NSLBP	Subacute (2-12 weeks)	41.62 ± 12.27 (18-65)	N/A
Goodin et al., 2022[184]	Case-control	Community	NSLBP	Chronic (3+ months)	44.52 ± 12.95 (18-85)	Pain free controls
Klyne et al., 2018[42]	Cross-sectional	Community	LBP	Acute (Greater than 24 hrs, within 2 weeks of onset)	29 ± 8 (18-50)	Pain free controls
Klyne et al., 2019[185]	Longitudinal	Laboratory	LBP	Acute (Greater than 24 hrs, within 2 weeks of onset)	30 ± 8 (18-50)	N/A

McPhee et al., 2021[186]	RCT	Centre for Neuroplasticity and Pain	LBP	Chronic (3+ months)	28.6 ± 5.9 (18-60)	N/A
Mehta et al., 2017[187]	Prospective; Pilot	Pain and Anesthesia Research Centre	Unilateral lumbar radicular pain and disc herniation	6+ months	46 years	Previously published QST data for pain free controls
O'Neill et al., 2014[188]	Cross-sectional	Hospital outpatient/primary care	LBP	Acute (≤ 91 days); Chronic (3+ months)	Male: 45.6 ± 13.9 Female: 46.6 ± 13.9	Pain free controls
O'Neill et al., 2014[189]	Measurement; Cross-sectional	Hospital outpatient / primary care	LBP	Acute; Chronic	45.4 years	Healthy Controls
Taub et al., 2017[190]	RCT; Pilot	Community	LBP	Chronic (3+ months)	51 ± 12 (18+)	N/A
PPT & Temporal Summation (TS)						
Aspinall et al., 2019[191]	RCT	University	LBP	Bothered by LBP at some time in the last 12 months	37 ± 13 (18-59)	N/A
de Oliveira et al., 2023[32]	Measurement	Community	NSLBP	Chronic (3+ months)	33.9 ± 11.9 (18-65)	N/A
Gasser et al., 2022[33]	Observational; Longitudinal	Hospital	Lumbar disc herniation	Pain unresponsive to nonoperative treatment for at least 6 weeks	18-65	N/A
Jamison et al., 2019[192]	RCT; Longitudinal	Pain management centre	LBP	Chronic (6+ months)	46.2 ± 12.7 (21+)	N/A
Kuithan et al., 2019[21]	Cross-sectional	University	LBP	Chronic (3+ months)	31.7 ± 13.3 years (18-65)	Pain free controls
Meints et al., 2019[193]	Longitudinal	Laboratory	NSLBP	Chronic (6+ months)	40.77 ± 12.29 (18-60)	Pain free controls
Meints et al., 2022[194]	Mixed-methods; Pilot	Medical centre	LBP	Chronic (6+ months)	54 ±16 (21-70)	N/A
Nees et al., 2019[34]	Case-control	Community	BP	Subacute (7-12 weeks); Chronic (6+ months)	Subacute - 45.17 ± 14.89 years; Chronic - 44 ± 13.23 (18-70)	Healthy controls
Neziri et al., 2012[195]	RCT	Hospital	LBP	Chronic (6+ months)	51 ± 15 (23-78)	N/A

Neziri et al., 2012[196]	Case-control	Hospital	LBP	Chronic (6+ months)	50.5 ± 13.2	Pain free controls
Orr et al., 2017[197]	Case-control; Cross-sectional	Community	LBP	Chronic (3+ months)	46.8 ± 14.9 years (18-79)	Pain free controls
Simon et al., 2015[198]	Cohort	Community	LBP	Chronic (3+ months)	18-79	N/A
Simon et al., 2021[199]	Case-control	University	LBP	Chronic (3+ months)	47.67 ± 14.58 (18-79)	Pain free controls
Starkweather et al., 2016[200]	Descriptive	Private research suite	LBP	Acute (24 hrs – 4 weeks)	18-50	N/A
Starkweather et al., 2016[35]	Methodology	Not specified	LBP	Not specified	N/A	N/A
Tesarz et al., 2015[36]	Case-control	Not specified	NSLBP	Chronic (3+ months)	18+	Pain free controls
Tschugg et al., 2015[201]	Observational; Cross-sectional	Hospital	Lumbar disc herniation	Average Male: 168.6 ± 304.0 days Female: 136.9 +/- 159.9 days	Male: 45.5 ± 11.4 Female: 44.0 ± 9.4	N/A
Vaegter et al., 2021[58]	Cross-sectional	Rehabilitation centre	LBP	Median 255 days (range 91-6,207 days)	Median 47 years (20-73)	N/A
Wettstein et al., 2019[37]	Cross-sectional	Hospital pain centre	NSLBP	Chronic (45+ days in the last 3 months)	58.06 ± 10.97	N/A
Zhivolupov et al., 2021[202]	Longitudinal	Multicentre	LBP	Chronic (3+ months)	60.5 [54.2; 67.3]	Pain free controls
PPT, TS & CPM						
Ansuategui Echeita et al., 2022[38]	Observational; Cross-sectional	Outpatient rehabilitation centre	LBP	Chronic	40.4 ± 12.4 (18-65)	N/A
Butera et al., 2021[203]	Cross-sectional	Community	LBP	Episode of LBP lasting 24 h or longer within the past 3 months	18-75	N/A
Correa et al., 2016[43]	RCT; Longitudinal	Physiotherapy Clinic	NSLBP	Chronic (3+ months)	18-80	N/A
den Bandt et al., 2022[44]	Case-control	Physiotherapy clinic	LBP	Minimum 1 week	42.36 ± 10.84 (18-65)	Pain free controls

Edwards et al., 2016[204]	Cohort	Chronic pain management centre	Low Back Pain; Discogenic pain syndrome	Chronic (6+ months)	Low negative affect: 54 ± 11 High negative affect: 49 ± 10	N/A
Lazaridou et al., 2022[205]	RCT	Laboratory	LBP	Chronic (3+ months)	59.23 ± 10.51 (50-87)	N/A
Leemans et al., 2021[45]	RCT; Longitudinal	Hospital	LBP	Chronic (3+ months)	Experimental: 43.9 ± 12 Control: 44.7 ± 12.2 (25-80)	N/A
Leite et al., 2018[206]	RCT	University Research Laboratory	LBP	Chronic (3+ months)	Electroacupuncture: 42.35 ± 3.35 Control 1: 41.82 ± 3.34 Control 2: 48.72 ± 3.61 Control 3: 52.58 ± 3.65	N/A
Leresche et al., 2013[207]	Longitudinal	Primary care clinic	LBP	Average 67.4 ± 62.7 back pain days in the last 6 months	47.4 ± 12.4 (18-64)	N/A
Lie et al., 2020[208]	Cohort; Cross-sectional	Hospital	LBP	Acute	Median 35 (IQR 26-45)	N/A
Marcuzzi et al., 2018[39]	Cohort; Longitudinal	Primary care / community	LBP	Acute (24 hrs - 3 weeks)	18+	Pain free controls
McPhee et al., 2019 [209]	Case-control	University / Community	LBP	Recurrent LBP	26.4 ± 5	Pain free controls
McPhee et al., 2021[210]	RCT; Pilot	Centre for Neuroplasticity and Pain	LBP	Chronic (3+ months)	28.6 ± 5.9 (18-60)	N/A
Müller et al., 2019[211]	Cohort	Primary care	LBP	Acute (0-6 weeks)	43.2 ± 13.3 (20-78)	N/A
O'Neill et al., 2021[212]	Non-randomized experimental; Cross-sectional	Spine centre / Hospital	LBP	Average 1,410.35 ± 2,261.85 days (0 - 11,355 days)	55.99 ± 15.13 (21-81)	N/A
Palsson et al., 2021[213]	Observational; Case-control	Community	NSLBP	Chronic (3 months - 5 years)	27.4 ± 6.5 (18-40)	Pain free controls
Petersen et al., 2020[214]	Cohort	Primary care practice	LBP	Baseline pain duration: 55.0 ± 10.3 months	44.8 ± 16.7	N/A

Rabey et al., 2015[40]	Cross-sectional	Hospital	LBP	Chronic (3+ months)	Median: 50 years (18-70)	N/A
Rabey et al., 2019[215]	Cohort	Private Clinic	NSLBP	Chronic (3+ months)	Median: 50.5 (IQR 37-60) (18-70)	N/A
Rabey et al., 2021[46]	Longitudinal	Private Clinic	NSLBP	Chronic (3+ months)	Median: 50 (IQR 37-60) (18-70)	N/A
Santos et al., 2022[57]	RCT	Laboratory	NSLBP	Chronic (3+ months)	52.72 ± 3.40 (45-59)	N/A
Schliessbach et al., 2018[216]	RCT	University	LBP	Chronic (3+ months)	54.4 ± 17.3 (18-80)	N/A
Teixeira et al., 2022[217]	Cross-sectional	Rehabilitation Hospital	NSLBP	Chronic (3+ months)	50.7 ± 16.2 (18-85)	N/A
Vuilleumier et al., 2015[47]	Measurement	Community	LBP	Chronic (3+ months)	56 ± 15.9 (18-80)	N/A
TS						
Bialosky et al., 2009[218]	RCT	Outpatient Clinic; Community	LBP	Average: 221.79 ± 365.37 weeks	32.39 ± 12.63 (18-60)	N/A
Biurrun Manresa et al., 2011[219]	Measurement Study	Department of Anesthesia and Pain Therapy	LBP	Chronic (6+ months)	51 years (23-78)	N/A
Carriere et al., 2019[220]	Cross-Sectional	Hospital	LBP	Chronic (6+ months)	55.87 ± 12.17 (27-87)	Pain free controls
George et al., 2006[221]	Cross-Sectional	Pain Rehab Program	LBP	Chronic	45.7 ± 10.7 (18-70)	N/A
George et al., 2007[222]	Cross-Sectional	Pain Rehab Program	LBP	Chronic	45.8 ± 10.3 (18-70)	N/A
Hubscher et al., 2014[223]	Cross-Sectional	Outpatient Physiotherapy Department	LBP	Acute (0-4 weeks); Chronic (3+ months)	Chronic: median 30.6 (IQR 21.8-35.0) Acute: median 26.8 (IQR 22.0 - 32.5) (18+)	Pain free controls
Meints et al., 2018[224]	Cohort	Laboratory	LBP	≤ 6 months	45.8 ± 11.8	N/A
TS & CPM						
Overstreet et al., 2021[14]	Cohort	Laboratory	NSLBP	Chronic (3+ months)	45.5 ± 14.1 (18-82)	N/A
Owens et al., 2016[53]	Case-Control; Cross-Sectional Study	Laboratory	LBP	Chronic (3+ months)	57.64 ± 10.84 (45-90)	Pain free controls

Van Bogaert et al., 2022[225]	Cross-Sectional Study	Multi-Centre	Lumbar Radiculopathy	< 3 months (30 participants), ≥ 3 months (90 participants)	47.37 ± 11.58 (18-65)	N/A

*NSLBP: Non-Specific Low Back Pain, LBP: Low Back Pain, BP: Back Pain, RCT: Randomized Controlled Trial,

Table 2: Pain Pressure Threshold (PPT)

Equipment Description	Unit of Measure	Number of Trials	Rest Time Between Trials	Stimulation Rate	Local Site	Distal Site	Definition/Reporting
Algometer							
<u>Digital/Electronic (n=95)</u> Wagner [24,32,38,44,45,71,75,78,82,84,90,91,93,94,107,119,126,138,145,153,154,172,174,177,191,198,199,202] Somedic [21,42,43,46,47,58,68,74,92,96,109,110,114,115,122-124,132-134,144,149,167,180,181,183,185,187-189,195,196,204,207,209-211,213,215,216] Medoc [35,157,168,184,208] JTech Medical [105,136,217]	Kg [31,36,70-73,78,79,81,84,85,98-100,111-113,116,125,131,132,135-137,141,143,146,150,152,160,163,178,179,202] Kgf [95,142,169,173,198,199] Gf [161] Kp [148] kPa [32,34,42,102,110,114,115,127,130,132,134,139,149,157-	1 trial [72,124,132] 2 trials [21,43,44,58,93,96,103,106,131-133,148,153,169,177,183,194,195,203,204,210,211] 2 trials (only last 1 recorded) [100] 3 trials [31,32,36,37,39,42,46,57,68,70,71,73-75,78-80,84,85,88-90,92,94,95,97,99,101,102,105,107,108,115,116,119,122,123,127,129,130,134-	5-10s [188,189] 10 s [41,97,99-101,105,122,123,130,131,133,136,151,164] 15s [182] 20s [71] 30s [43,44,46,57,68,73,75,78,84,85,88,89,92,93,95,102,132,135,138-141,143,144,147,149,162,167,171,172,178,179,181,183,213,215] 30-60s [80]	0.3 kg/s [187] 0.5 kg/s [24,31,32,36,37,73,84,131,164,178,179,191] 1 kg/s [41,44,72,78,83,93,97,99-101,103,106,113,132,135,137,138,145,160,163,176,197] 2 kg/s [128] 1 kp/s [148] 0.5 kgf/s [95,142] 1 kgf/s [169,198,199] 10 kPa/s [109]	Most painful site of lumbar region/low back/back [30,35,38-40,42,44,46,71,82,90,93,100,107,111,114-117,120,121,139,140,144,154,157-159,167,168,180-182,185,196,200,202,207,211,215,217] Non painful site on back [196,211] Lumbar spinal process of the most hypermobile vertebra [95]	Forehead [148] Trapezius muscle [75,106,114,115,118,169,175,190,192,204,208-210] Rhomboid [173,174] Upper back [196] Shoulder [41,77,93,123,127,139,173,174,182,189,191,213] Upper arm [97,99,153] Elbow [28,75,78,84	Indicate when the feeling of pressure turned into the feeling of pain [21,31,35,36,38,39,42-47,57,58,68,70-76,78,79,81-84,86-96,101,103,105,106,108-110,112-117,119,122-131,133-153,155-163,165-169,171-173,175-185,187-192,194-197,199-201,203-207,209-211,213,215-217] Indicate first feeling of pain by moving knob on VAS [208] Measured using VAS 0-10 scale [154]

Storz Medical [76,127] Fabrication Enterprise [85] Kratos [87-89] Penny & Giles Myometer [101] EMG System [57] Jagson Scienfitic Industries [147] AC Engineering [148] Unspecified [30,70,117,155,162,163,165,169,190] <u>Analog (n=23)</u> Wagner [28,33,34,39,41,72,80,95,106,118,132,150,151,164,192,201] Baseline [81]	[159,162,165,171,172,184,185,195,200,205,207,215] N [38,88,89,153,155,156,177] Lbs [120,128,217] Lbf [174] Not reported [21,24,28,30,33,35,37,39,41,43-45,47,57,58,74-77,80,82,83,86,87,90-94,96,97,101,105-109,117-120,122-124,126,129,133,138,140,145,147,151,154,164,166-168,175,176,180-183,187-192,194,196,197,201,203,204,206,208-211,213,216]	[136,138-144,147,149,151,154-156,160,162,163,165-167,171,172,175,176,178-182,184,185,187-189,197-199,206,207,209,215-217] 3 trials (or until 2 trials were within 20 kPa/s) [35,157,158,200] 3 trials (average of last 2) [41,164,190,191] 4 trials [173,174] 4 trials (average of last 3) [168]	40s [94] 1 minute [32,74,103,142,155,156,160,165,177,206] 2 minutes [209,210] 10 minutes [127] Not reported [21,24,28,30,31,33-39,42,45,47,58,70,72,76,77,79,81-83,86,87,90,91,96,98,106-120,124-126,128,129,134,137,145,146,148,150,152-154,157-159,161,163,166,168,169,174-176,180,184,185,187,190-192,194-205,207,208,211,216,217]	30 kPa/s [21,35,47,58,74,96,124,157,158,184,194-196,200,204,205,210,211,213,216] 40 kPa/s [42,92,114,115,122,123,134,139,140,168,180,181,185] 50 kPa/s [39,43,46,68,110,130,132,133,144,165,167,183,188,189,215] 1 lb/s [75,190] 2 lbs/s [105,217] 1 N/s [127] 5 N/s [88,89,119,147,182,208] Not reported [28,30,33,34,38,45,57,70,71,76,77,79-82,86,87,90,91,94,98,102,107,108,111,112,116-118,120,125,126,129,136,141,143,146,149-156,159,161,162,166,171,1	Most symptomatic thoracic vertebra [141] Painful pressure point [176] Digital Tender Points [122,123] Tender points [136] Non-tender points [123] Point adjacent to site of most pain [30,93,121] Most painful myofascial trigger point [160] Trigger points on the Iliocostalis Lamborum [70,85]	Forearm [24,32,34,35,132,157,158,175,185,209,210] Wrist [32,40,46,105,134,192,215] Hand [21,24,30,36,37,39,44,106,124,127,171,172,194,199,202,207] Finger [41,105,154,162] Thumbnail [42,73,178-181,185] Upper leg [84,91,106,124,136,173,174] Knee [75] Lower leg [41,43,44,57,58,71,73,77,78,88,89,101,102,105,124,127,129,131,132,136,139,142,143,153,162,173,174,183,191,197,203,206,209,210]	Report a score of 3 out of 10 on an NRS [41] Not Reported [24,28,30,32-34,37,77,80,85,97-100,102,107,111,118,120,132,164,174,202]

Unspecified (Analog) [125,128,135,141,143,175] <u>Unspecified (n=48)</u> Wagner [31,36,37,73,103,178,179,182,197] Somedic [205] NeuroDyne Medical [83] EMG Systems [86,142,206] Pain diagnostics [97,99,100,112,113] Mitutoyo [120] Unspecified [77,79,98,102,108,111,116,129-131,137,139,140,146,152,156,158-161,166,171,173,176,194,200,203]		Not reported [24,28,30,33,34,38,45,47,76,77,81-83,86,87,91,98,109-114,117,118,120,125,126,128,137,145,146,150,152,159,161,192,196,201,202,205,208,213]		72,174,175,177,192,201-203,206,207	Trigger points on quadratus lumborum [81,85,94,128] Trigger points on Erector Spinae muscles [80,128] Trigger points on the gluteal muscles [70,72,85] Trigger points on upper and lower back [79] Myofascial Trigger points [135,163] Predetermined specific site (C5-C6, L1-S2) [21,24,28,43-45,74,76,78,86,88-92,96,98,99,108-110,123,130,132-134,142,147,151,162,164,165,171,172,177-	Foot [30,134] Toe [10,45,195,196,211,216] Area representative of spinal processes in the thigh (L1-S2) [112,113] Other body locations [38] Location without pain (not specified) [200]	

					179,183,187,188,191,203,213 Affected dermatome (l3-S1) [201] Acupuncture points [152,161,166] Specific spine structures (ligaments at and between T12-S3) [112,113] Lumbar Spine [102] Paravertebral Muscles [31,36,41,57,76,105,119,136,138,146,148,175,183,206] Quadratus Lumborum [83,91,112,113,146,148,173,174] Hip and Pelvis Structures [148]		

					Erector spinae muscles [24,32,58,95,97,101,103,106,126,129,145,153,173,174,184,209,210] Transverse abdominis [173,174] Gluteal Muscles [91,97-101,112,113,136,149,153,173,174] Piriformis Muscle [91,112,113,146,148,173] Iliopsoas Muscle [112,146,173,174] Sacroiliac Joint [76]		
Cuff Pressure Algometry (n=5)							

Nocitech [186,210] Hokanson [193] Cortex Technology [214] Unspecified [58]	Not specified [58,186,193,210,214]	Not specified [58,186,193,210,214]	Not specified [58,186,193,210,214]	1 kPa/s [58,186,210,214] 5 mmHg/s [193]		Leg [186] Lower leg [58,193,210,214]	Indicate when the feeling of pressure turned into the feeling of pain [193] Indicate first feeling of pain by moving knob on VAS [58,186,210,214]
Custom Built Device (n=2)							
MR-compatible device [104] 10 custom-built, spring-loaded pressure probes [212]	Kg [212] Not specified [104]	2 trials [212] Not specified [104]	Not specified [104,212]	1 kg/s [104] Not specified [212]	Most painful site of lumbar region/low back/back [212] Predetermined specified location (L5) [104]		Indicate when the feeling of pressure turned into the feeling of pain [104] Indicate if applied stimulus was perceived as painful or non-painful, "split middle approach" until PPT was reached [212]
Not Specified (n=3)							
Unspecified [29,121,170]	Kg [170] Not specified [29,121]	1 trial [121] Not specified [29,170]	Not specified [29,121,170]	1 kg/s [121,170] Not specified [29]	Most painful site of lumbar region/low back/back [29,121] Acupuncture points [170]	Area of projecting pain [29]	Indicate when the feeling of pressure turned into the feeling of pain [121,170] Not specified [29]

*Kg: Kilograms, Kgf: Kilogram force, Gf: Gram force, Kp: Kilopond, kPa: Kilopascal, N: Newtons, Lbs: pounds, Lbf: pound force,

Table 3: Temporal Summation (TS)

Equipment Description	Calibration	Stimulation Frequency	Trials	Rating Frequency	Testing Site	Rating Scales	Calculation
Punctuate							
<u>Pinprick (n=17)</u> Neuropen [191] MRC Systems [14,32,37-39,194] North Coast Medical [192] Custom made pinprick set [201] Pinprick stimulus (unspecified) [33,34,36,193,204,205,220,224] <u>Monofilament (n=8)</u> North Coast Medical[207] Touchtest [53] Aesthesio [46] Optihair2 [35,200]	256 mN [32-34,36-39,201] 512 mN [14] Lowest force stimulator that produced a sensation of discomfort (128 or 256 mN for most subjects) [192,193,204,220,224] The lowest-force stimulator that produced a sensation of pain (at least 10/100 on the NRS) (64, 128, or 256 mN) [194] 26 g [40,46,215]	1 Hz (1/s) [14,32,33,35-40,46,53,191-194,200,204,205,207,215,217,220,224] Not reported [34,201]	1 trial [224] 2 trials [14,53] 3 trials [191] 5 trials [34,37,39] 2 trials (30 second interval) [217] 3 trials (1 minute interval) [207] Not specified [32,33,35,36,38,40,46,192-194,200,201,204,205,215,220]	<u>Baseline Rating</u> Single stimulus [14,32-39,53,200,201,207,217] 1st stimulus of 5[191] 1st stimulus of 10[192-194,204,205,220,224] 1st stimulus of train [40,46] 1st stimulus of 30 [215] <u>2nd Rating</u> Overall/peak rating after series of 10 stimuli [14,32,33,36-39,201 35,200,217] Train of stimuli (unspecified) [34] 5th stimulus of 5[191] 5th stimulus of 10[192-194,204,205,220,224]	Most painful site of lumbar region/low back/back [35,39,46,200,215,217] Predetermined specific location (L4/L5) [32,36] Affected dermatome (L3 to S1) [201] Location without pain [200] Location with a mechanical pressure threshold below or equal to 256 mN [38] Trapezius [53] Forearm [35,207] Hand [32,37,39,53,191,192,204,205,224]	NRS (0=no pain, 10=worst pain imaginable) [32,33,35,40,46,207] NRS (0=no pain, 100=worst pain imaginable) [14,38,53,191,193,194,200,220,224] NRS [36,37,215] 10 cm VAS [217]	TS = mean 2nd rating – mean baseline rating [191] TS = 10th rating – 1st rating [192-194,204,220,224] TS = 5th rating – 1st rating [205] TS = rating for series of stimuli – rating after single stimuli [14,32,35,200,217] TS = rating of last stimulus in series – rating after single stimuli[207]

Monofilament (unspecified) [40,215,217] Thermal	225.1 g (no. 6.45) [207] 300 g (no. 6.65) [35,53,217] Not reported [191,200,205]			Last stimulus of 10 repeated stimuli [207] 30th stimulus of 30 [215] At the end of 30 seconds [40,46] Overall/peak rating after series [53] <u>Additional Ratings</u> 10th stimulus of 10 [192-194,204,205,220,224] 15 seconds following final stimulus [224]	Finger [194,220,224] Foot [191] Erector spinae muscles [14] Not specified [33,34,40]		TS = rating after 30 s of stimulation – rating of 1st stimulation [46] WUR = rating of 10 repetitions /rating of single stimulus [33,35-39,200,201] WUR = mean rating of 5 repetitions / mean rating of single stimulus [34]
Medoc TSA-2 Neurosensory Analyzer [21,53,203] Medoc TSA-2001 [218,221,222] Medoc Pathway Model ATS [197-199,208]	<u>Peak/Trial Temperature</u> 47°C [221-223] 48°C [21,197,199] 49°C [203] 50°C [53,198] 51°C [218]	0.33 Hz (<1 second duration) [198,218,221-223] 0.5 seconds on, 2.5 second interval [197] 1 second on, 2.5 second interval [53] Interstimulus interval 2.5 seconds [21]	1 trial [53] Not specified [21,197-199,203,208,218,221-223]	<u>Baseline Rating</u> 1st pulse of 5 [221,222] 1st pulse of 10 [223] 30-40 seconds [208] <u>2nd Rating</u> 3rd pulse of 5 [221,222] 5th pulse of 10 [223] 110-120 seconds [208]	Most painful site of lumbar region/low back/back [223] Forearm [21,53,203,208,221-223] Hand [218] Finger [198] Foot [197-199,218]	NRS (0=no pain, 10=worst pain imaginable) [223] NRS (0=no pain, 100=worst pain imaginable)	TS = 5th pulse rating – 1st pulse rating [198,199,223] TS = maximum pulse rating obtained from pulse 2 to 5 – 1st pulse rating [203]

Somedic MSA Thermal Stimulator [223]	Pain6 temperature [208] <u>Baseline Temperature</u> 32°C 35°C [218,221,222] 40°C [21] 41°C [203,223] <u>Ramp up Temperature</u> 8°C/s [21] 10°C/s [203,221-223]	1 second on, 3 second interval [199] 120 second duration [208] Not specified [203]		<u>Additional Ratings</u> 5th pulse of 5 [221,222] Rate pain of all 5 pulses [53,197-199,203] Rate pain of all 10 pulses [218,223] Rate each of the stimuli [21]		[21,53,197,198,203,218,221,222] 10 cm VAS [208]	TS = Last pulse rating – 1st pulse rating [197] TS = Pulse rating at 110-120 s – pulse rating at 30-40 s [208]
Pressure							
Wagner Digital Algometer [44,45] Wagner Analog Algometer [43] EMG system Digital Algometer [57,206]	PPT value determined previously [43-45,202] Individual value [212] Cuff pain pressure	0.5 Hz (1 second on, 1 second rest) [43,44,58,202,209,210,212-214] Held for 30 seconds [206] Not specified [45,57]	1 trial [213] Not specified [43-45,57,58,202,206,209,210,212,214]	<u>Baseline Rating</u> Single stimulus [212] 1st stimuli of 10 [43-45,209,210] 1st second of stimulation [57,206] <u>2nd Rating</u>	Most painful site of lumbar region/low back/back [44,202] Predetermined specified location (L4) [44] Lowest PPT pain threshold [43]	NRS (0=no pain, 10=worst pain imaginable) [43-45,57,206] VAS (0=no pain, 10=worst pain	TS = 10th stimulus rating – 1st stimulus rating [43-45] TS = rating for series of stimuli – rating after single stimuli [212]

Cuff Algometry [58,209,210,213,214] Custom Built Device [212] Algometer (Unspecified) [202]	tolerance [58,209,213,214] 4 kg [57,206] 100 kPa [210]			Overall/peak rating after series of 10 stimuli [212] 5th stimuli of 10 [43-45] 10th second of stimulation [57,206] <u>Additional Ratings</u> 10th stimuli of 10 [43-45] 20th and 30th second of stimulation [57,206] Rate the pain of all 10 stimuli[58,209,210,213,214] Rate each of the stimuli [202]	Forearm [57,206] Hand [44] Lower leg [44,214] Leg [210,213] Not specified [45,58,209,212]	imaginable) [209,210,213,214] VAS (0=no pain, 100=worst pain imaginable) [202,212]	TS = Final 3 VAS scores – interval from first to third VAS scores [214] TS = mean rating of last 3 stimulations – mean rating of first 4 stimulations [58]
Electrical							
<u>Computer-controlled constant current stimulator (n=6)</u> Noxitest [219] NCS System [211] Digitimer [47,216]	Constant intensity [211] Previous value obtained [47,216,225] Intensity increased from 1 mA in steps of 1mA [219]	2 Hz [47,195,196,211,216,219,225]	1 trial [216] 2 trials [211] 3 trials [195] 3 trials (1 minute interval) [219] Not reported [47,196,225]	<u>Baseline Rating</u> 1st stimulus of 20 [225] <u>2nd Rating</u> 10th stimulus of 20 [225] <u>Additional Ratings</u> Rating maximal pain intensity felt during 20 pulses [47]	Most painful site of lumbar region/low back/back [211] Non painful site on back [211] Non painful area on body [211] Arm [225]	NRS (0=no pain, 10=worst pain imaginable) [47,216,225] Current increased until 2-3 consecutive reflexes with	TS = 20th stimulus rating – 1st stimulus rating [225] TS pain threshold / TS reflex threshold [195,196] Not reported [47,211,216,219]

University of Aalborg [195,196] Surpass LT Stimulator [225]	Increased from 1mA in steps of 0.5 mA [47,195,196]			Rate maximal and final pain intensity [216] 20th stimuli of 20 [225] Not reported [195,196,211,219]	Foot [47,195,196,216,219]	increasing amplitude were detected and the subject felt pain during the last 2 to 3 bursts [219] Current increased until subjects felt pain during the last 2-3 bursts and an increase in the amplitude of the last 2 to 3 reflexes above a fixed limit of 20 IV for at least 10 ms in the 70-159 ms post-stimulation was observed [195,196] Current increased until subjects felt pain	

						during the last 2 to 3 of the 5 stimuli [47] Not reported [211]	

Table 4: Conditioned Pain Modulation (CPM) Test Stimulus (TS)

Test Stimulus	Parameters	Trials	Testing Site	TS Timing	Outcome
<u>Pressure Pain Threshold (n=27)</u> [182] Digital Algometer (Somedic) [10,42,43,60,65,180,181,183,185,187,204,205] Digital Algometer (Medoc) [14,53,184] Digital Algometer (JTech Commander) [217] Digital Algometer (Wagner) [38,44,67,203] Algometer (Wagner) [178,179]	<u>Stimulation Rate</u> 0.3 kg/s [187] 0.5 kg/s [178,179] 1 kg/s [41] 30 kPa/s [10,14,60,65,184,204,205] 40 kPa/s [42,180,181,185] 50 kPa/s [40,43,46,68,183,215] 5 N/s [182] 1 kg/s [44]	<u>Preconditioning</u> 3 trials [14,53,67,180,181] 2 trials (30 seconds between) [44,60,65] <u>During/Postconditioning</u> 2 trials during/after CS at each point [44,183] 3 trials during/after CS at each point [41,178-181]	Most painful site of lumbar region/low back/back [40,44,46,68,182,187,212,215,217] Lumbar region [14] Erector spinae muscles [184] Predetermined specific location (L3-S1) [41,43,44,60,178,179,183] Forearm [53,57,67,206] Hand [44] Thumbnail [178,179]	<u>Preconditioning Stimulus</u> Baseline PPT value [10,14,41,43,44,53,178,179,183,184,204,205] Before CS [38,40,42,46,57,60,65,67,68,180-182,185,206,215,217] Single and repeated stimuli before CS [212] <u>During CS:</u> PPT taken during CS [41,57,187,204-206] 20 seconds into CS [65] 30 seconds into CS [42,53,67,183,185]	CPM = (PPT during CS /PPT prior to CS) x100 [65,204] CPM = (PPT after CS-PPT baseline / PPT baseline) x 100 [14,38,184] CPM = PPT after CS – PPT before CS [10,43,180,181,212] CPM = PPT before CS – PPT after CS [44,217]

Analog Algometer (Wagner) [41] Digital Algometer (EMG Systems) [57,206] Custom built device [212] <u>Pressure Pain Suprathreshold (n=4)</u> (applied until participant indicated pain was a 6/10) Digital Algometer (Somedic) [40,46,68,215]	2 lbs/s [217] Not specified [38,53,57,67,203,206,212]		Trapezius [53,205] Shoulder [41] Upper back [65,204] Upper leg [38] Lower leg [44,60,203] Toe [10] (1) lower back (site of back pain) (2) forearm and thumbnail (3) forearm and thumbnail [185] (1) site of worst LBP (2) ipsilateral forearm [180,181]	1 minute into CS [67] Rate pressure at 30s, 60s 90s into CS [40,46,68,215] <u>After CS:</u> Immediately after CS [10,14,38,44,60,178,179,182,184,217] 30 seconds after CS [43,180,181] 1 min 30 seconds after CS [67] 5 minutes after CS [57,206] Single and repeated stimuli after CS [212]	CPM = PPT before CS – PPT during CS [42,178,179,185] Relative change (%) in pain threshold [182] PPT during CS compared to baseline PPT [183] Percent change from baseline to conditioned PPT [67,203,205] CPM = Pain rating during CS – Pain rating before CS [46,215] Not reported [40,41,53,57,60,68,187,206] <u>Rating Scale</u> VAS (0=no pain, 100=worst pain imaginable) [212] VAS (0=no pain, 10=worst pain imaginable) [187]

					NRS (0=no pain, 10=worst pain imaginable) [40,46,68,215]
Pressure Pain Tolerance (PPTol) (n=4) [211] Digital Algometer (Somedic) [66,69] Digital Algometer (Wagner) [45]	Stimulation Rate 30 kPa/s [66,69,211] Not specified [45]	Preconditioning 3 trials [66] During/Postconditioning 1 trial after CS [66]	Toe [45,66,69,211]	Preconditioning Stimulus Baseline PPtol value [69,211] Before CS [45,66] After CS: Immediately after CS [45,66,69,211] 3 minutes after CS [66,69] 5 minutes after CS [66,69] 10 minutes after CS [66,69]	CPM = PPTol after CS – PPTol before CS [45,66,211] CPM = difference between PPTol immediately after CS, 3, 5 and 10 mins after and PPTol at baseline [69]
Cuff Algometry (n=6) Computerized cuff-algometry system (NociTech) [64,186,209,210,213,214]	3 x 1 second cuff stimuli at cuff PPTol (inflated at 100 kPa/s) separated by 10 seconds [64,186] 1 kPa/s (up to max of 100 kPa) to obtain PPT and PPTol values [209,210]	Preconditioning 2 trials [64,209,210]	Leg [64,186,209,210,213,214]	Preconditioning Stimulus Baseline value [64,209,214] Before CS [210,213] 30 seconds before CS [64,186,209] During CS During CS [213,214] 80 seconds into each CS [64,186]	CPM = rating before CS – rating after CS [64] CPM = rating during CS – rating before CS [213] CPM = Cuff PPT during CS – Cuff PPT before CS [214]

	1 kPa/s [213,214]			Simultaneously with 3rd stimulus [209,210] <u>After CS</u> After all tasks [64] After CS [209,210] 5 minutes after CS [209]	CPM = change in PPTol and PPT from the first ramp to the second, (second minus first, sequential unconditioned), third (third minus first, during conditioning), fourth (fourth minus first, immediately after conditioning), and fifth (fifth minus first, 5 minutes after conditioning) [209] CPM = second to fourth PPT and PPTol values were normalized by subtraction to the first assessment [210] Rated each inflation and averaged for analysis [186] <u>Rating Scale</u>

					NRS (0 = no pain, 100 = worst pain imaginable) [64,186] NRS (0= no pain, 10 = worst pain imaginable) [209,210] VAS (0=no pain, 10=worst pain imaginable) [213]
<u>Sustained Pressure (n=2)</u> Spring-Clamp [188,189]	Applied for 10 seconds [188,189]	Not reported [188,189]	Thumbnail [188,189]	<u>Preconditioning Stimulus</u> Before CS [188,189] <u>After CS</u> 5-15 seconds after CS [188,189]	CPM = pain rating after CS – pain rating before CS [188] <u>Rating Scale</u> VAS (0=no pain, 100=worst pain imaginable) [188,189]
<u>Thermal (n=8)</u> Medoc TSA-2 Neurosensory Analyzer [59,61-63] Medoc Pathway Model ATS [39,190,207,208]	<u>Baseline Temperature</u> 32°C [62,190,208] <u>Target Temperature</u> Individualized to evoke pain between 5-6/10 [62] Individualized to evoke	<u>During/Postconditioning</u> 5 trials during CS[63]	Predetermined specific location (L4-L5) [63] Forearm [59,61,62,207,208] Palm [190]	<u>Preconditioning Stimulus</u> 5 minutes before CS [62,208] Before CS [39,59,61,63,190] Before CS rating at 10, 20 and 30 s of application [207] <u>During CS</u> During CS [59,61,208]	CPM = Pain rating after CS – pain rating before CS [39,190] CPM = mean pain rating during CS – baseline pain rating [63] CPM = pain intensity of TS with CS – pain

	moderate pain (50/100) [63] Individualized to evoke pain intensity of 5/10 (pain 50) or max 49°C [207] Individualized to induce a pain of 60/100 (pain60) [39,208] Individualized to reach 10/10 pain or max of 51°C [190] 1.2 times heat pain threshold obtained previously [59,61] <u>Time at target temperature</u> 5 x 15 seconds, with 15 second interstimulus intervals [63] Stimuli delivered every			30 seconds into CS, asked to rate at 40, 50 and 60 seconds [207] At 30s intervals throughout CS [63] 30 seconds into CS [62] During the last 30 seconds of CS [39] <u>After CS</u> Immediately after CS [61,190]	intensity of just TS [208] CPM = (pain intensity of TS with CS – pain intensity of just TS) / pain intensity of just TS x 100 [208] CPM = mean of 3 ratings during CS – mean of 3 ratings before CS [207] Not reported [59,61,62] <u>Rating Scale</u> 0-10 NRS [208] NRS (0 = no pain, 100 = worst pain imaginable) [59,61,63] 0-10 VAS [190]

	30s for 5 mins [59,61] 30 seconds [62] 120 seconds [208] <u>Temperature increase/decrease rate</u> Increased at 1°C/s, decreased 8°C/s [208] Increased at 0.3°C [190]				
<u>Electrical (n=2)</u> [216,225]	<u>Stimulation Rate</u> 1.4 x the electrical pain threshold (20 stimuli given at 8-12 second intervals) [225] 1.2 x the electrical repeated pain threshold (train of 5 electrical stimuli) [216]		Arm [225] Foot [216]	<u>Preconditioning Stimulus</u> Before CS [216,225] <u>During CS</u> During CS [216] <u>After CS</u> Immediately after CS [225]	CPM = [(Post CPM – Pre CPM)/ (Pre CPM)] x 100 [225] Percent decrease in ERPT [216] <u>Rating scale</u> NRS (0=no pain, 10=worst pain imaginable) [216,225]

Table 5: Conditioned Pain Modulation (CPM) Conditioning Stimulus (CS)

Conditioning Stimulus and Equipment Description	CS parameters	Timing	CPM Trials	Testing Site
<u>Cold Water Immersion (n=31)</u> ARTIC A25 refrigerator bath, ThermoFisher Scientific [14,184] 5L water contained (Dometic Waeco, Mobicool) [212] 25 L water tank (Dometic Waeco Mobicool C40) [60,188,189] VersaCool, Thermo Fischer Scientific Inc [44,45,225] NESLAB RTE 211, Thermo Scientific [63] Refrigeration unit (Neslab) [53] LAUDA-Brinkmann [208]	<u>Temperature</u> 0-2°C [188,189,212] Below 2°C [10] 0.7 ± 0.1°C [45,69] 0.7 ± 1°C [66] 1.5 ± 1°C [211,216] 4°C [43,60,65,204,205] 4-5°C [207] 7°C[208] 8°C [203] 7-10°C [67] 10°C [190] 10.5 ± 1°C [39] 10-12°C [217] 12°C [14,44,184,225]	<u>Application of CS</u> 30 s [204,205] 1 min [14,53,62,203,207,217] 1 min (or until pain became unbearable) [184,188,189] 2 mins (or until pain became unbearable) [10,39,45,60,66,69,182,208,212] 2 mins [44,183,211] 3 mins [38,63] Until participant rates cold pain as 7/10 on the NRS [216] Not reported [43,65,67,190,225]	1 trial [60] 2 trials [14,65,184,204] 4 trials (2 trials at each test location) [53] Not reported [10,38,39,43-45,62,63,66,67,69,183,188-190,203,205,207,208,211,212,216,217,225] <u>Rest</u> 2 minutes between [14,53,184,204]	Hand [10,45,203,211] Right [60,69,188,189,204,205] Left [14,63] Contralateral [62,65,66,182,208,216,217,225] Ipsilateral [44] Dominant [38] Non-dominant [53,67,184,207,212] Leg Ipsilateral [183] Foot Right [190] Contralateral [39] Ipsilateral [43]

Cold water bath with divider to separating ice and water [39,66,69,211] Cold/Ice Water Bath [10,38,43,62,65,67,182,183,190,203-205,207,216,217]	Ice cold water [38,182,183] Individually tailored temp to evoke a pain intensity of 3/10 after 30 s [62] Individually tailored temp to evoke pain intensity (50/100) [53,63] <u>Water</u> Circulating cold water [14,39,53,60,65,66,69,188,189,204,205,208,211,212,225]			
<u>Cuff Stimulus (n=14)</u> [41,57,187] Computerized cuff-algometry system (NociTech) [64,186,209,210,213,214] Cuff algometry + Exercise [59,61,178,179,206]	Inflated to 270 mmHg. Patient opened and closed hand 10 times [206] Inflated above systolic (200 mmHg) [187] Inflated to 270 mmHg [57] Inflated at 20 mmHg until	<u>Application of CS</u> 105 seconds [64] 2 minutes [186] 2 mins of exercise, up to 8 mins for cuff inflation [59] 2 mins of exercise, cuff inflation until reaching maximum pain tolerance [61]	4 trials [186] Not reported [41,57,59,61,64,178,179,187,206,209,210,213,214]	Arm Dominant [59,61] Non-dominant [178,179] Contralateral [57,206] Left [41,187] Leg Non-dominant [64,186,209,210,214] Non-test [213]

	participant reported pain as 3 out of 10 [41] Inflated to 70% of PPTol [64,186,209,210,214] Inflated to 80% of PPTol [213] Forearm muscle exercise using a hand dynamometer at 50% of maximal grip strength, then raise arm over their head for 15 seconds. BP cuff was inflated to 200 mmHg, arm was lowered, and cuff remained inflated until tolerance was reached [59,61] Cuff inflated to 260 mmHg. 45 wrist lifts with dumbbell weight or pain greater or equal to 7 out of 10 [178]	Until pain reached 6 out of 10 (max 10 minutes) [187] Until pain intensity was greater or equal to 4 [57,206] Inflated until pain rating 3 out of 10, adapted for 30 seconds, then remained for the duration of the test stimulus [41] Until all TS measurements taken [209,210,213] Until lifting task was completed (or pain reported greater or equal to 7 of out 10) [178] Not reported [179,214]		

	Cuff inflation and wrist exercises [179]			
Heat (n=8) Medoc TSA 2001 [42,180,181,185] Thermotest (Somedic AB) [40,46,68,215]	Baseline 30 °C [42,185] 36 °C [181] 40 °C [40,46,68,215] Target Temp 1 °C above heat pain threshold, (NRS between 45-80) [42,185] 1 °C above heat pain threshold (NRS between 50-80) [180,181] 1 °C below when participant indicated that they could not tolerate the stimulus [40,46,68,215] Ramp up Temp 0.5°C/s [181] 0.7 °C/s [42,185] 1 °C/s [40,46,68,215]	Until all TS measurements taken [42,185] 90 seconds [40,46,68,215] Not reported [180,181]	3 trials (different location for each trial) [42,185] 2 trials (different location for each trial) [180,181] Rest 15-minute rest between trials [42,181,185]	Pain free hand (or non-dominant hand) [68] Hand [40,215] Wrist [46] (1) Contralateral forearm, (2) lower back (site of lower back pain) (3) ipsilateral forearm [42,185] (1) contralateral forearm (2) contralateral lower back [180,181]

Table 6: Exercise Induced Hypoalgesia (EIH)

Study	Exercise Type	Details	Modality	EIH
Patricio et al., 2022	Isometric Exercises	1) Back isometric exercises (Resisted anterior pelvic tilt and resisted back extension) 2) wrist isometric exercise. Participants contracted target muscles at 25% MVC EMG (using visual feedback) for 4 minutes or until exhaustion	PPT taken before and after exercise	EIH defined as percent change in PPT from pre- to post-exercise
Santos et al., 2022	Strength Exercises	5–10-minute warmup, 35-40 minutes of exercise, performed at moderate intensity. Each of the training sessions done 1 time, with 48 hours between 1) Core stabilization training: First moment - focus on stability Bird-dog, Side plank with support on both knees, Bilateral hip thrusts, Side plank with one knee support Second moment - training muscle resistance Static Superman, Front plank, Curl up, Oblique, Hip flexion 2) Functional training: Sit-to-stand exercise, Bilateral resistance bands row, Step-ups, Vertical bench press with elastic bands, Lunge, Unilateral step-up (without alternating the lower limbs), Open the elastic band (abduction with external rotation of the shoulder complex), Bilateral hip-dominant squat, Knee Push-ups	PPT, TS and CPM taken pre and post exercise	
Vaegter et al., 2021	Walking	6-minute walk test on a 20-meter course	PPT assessed before and after 6MWT	EIH calculated as PPT after 6MWT – PPT before
Kuithan et al., 2019	Lifting Task	Lifting a 5kg box onto 6 different shelves, at individualized heights (10 sets)	PPT, Thermal Thresholds and TS	
Woznowski-Vu et al., 2021	Lifting Task	Phase 1 (Tailoring): individual task parameters that evoked pain intensity of greater than 20 (0-100 scale). Participants progressed from lightest to heaviest weights. Potential weights = 1, 2, 3, or 3.5 kg. Phase 2: 10 self-paced lifts with weight chosen from Phase 1	PPT measured after phase 1 and again after phase 2	

2.13 Appendices

Appendix I: Search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 back pain/ or low back pain/ (44481)

2 low back pain.tw,kf. (34371)

3 dorsalgia.tw,kf. (120)

4 (backache or back pain).tw,kf. (62177)

5 (lumb* adj pain).tw,kf. (2306)

6 lumbago.tw,kf. (1497)

7 (coccy* adj pain).tw,kf. (75)

8 coccydynia.tw,kf. (192)

9 Pain Measurement/ (94524)

10 quantitative sensory test*.tw,kf. (2650)

11 QST.tw,kf. (1460)

12 pain pressure threshold.tw,kf. (273)

13 pressure pain threshold.tw,kf. (1913)

14 temporal summation.tw,kf. (1561)

15 conditioned pain modulation.tw,kf. (870)

16 exercise induced hypoalgesia.tw,kf. (150)

17 pain measurement.tw,kf. (1320)

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (77406)

19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (99608)

20 18 and 19 (8255)

21 limit 20 to humans (8108)

22 limit 21 to (case reports or editorial) (314)

23 21 not 22 (7794)

Database: Embase <1974 to 2023 June 13>

Search Strategy:

1 backache/ or low back pain/ (133766)

2 low back pain.tw,kf. (47260)

3 dorsalgia.tw,kf. (204)

4 (backache or back pain).tw,kf. (88788)

5 (lumb* adj pain).tw,kf. (3547)

6 lumbago.tw,kf. (1853)

7 (coccy* adj pain).tw,kf. (116)

8 coccydynia.tw,kf. (271)

9 quantitative sensory testing/ (1418)

10 quantitative sensory test*.tw,kf. (4200)

11 QST.tw,kf. (2527)

12 pain pressure threshold.tw,kf. (360)

13 pressure pain threshold.tw,kf. (2509)

14 temporal summation.tw,kf. (2156)

15 conditioned pain modulation.tw,kf. (1241)

16 exercise induced hypoalgesia.tw,kf. (195)

17 pain measurement/ (10820)

18 pain measurement.tw,kf. (2446)

19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (152043)

20 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (22103)

21 19 and 20 (1751)

22 limit 21 to humans (1718)

Database: AMED (Allied and Complementary Medicine) <1985 to May 2023>

Search Strategy:

1 exp backache/ (7125)

2 back pain.mp. (7587)

3 low back pain.mp. (6436)

4 backache.mp. (1939)

5 dorsalgia.mp. (3)

6 (lumb* adj pain).mp. (130)

7 lumbago.mp. (51)

8 (coccy* adj pain).mp. (4)

9 coccydynia.mp. (12)

10 pain measurement/ (2178)

11 pain measurement.mp. (2205)

12 quantitative sensory test*.mp. (75)

13 QST.mp. (31)

14 pain threshold/ (407)

15 pain pressure threshold.mp. (45)

16 pressure pain threshold.mp. (288)

17 temporal summation.mp. (30)

18 conditioned pain modulation.mp. (20)

19 exercise induced hypoalgesia.mp. (8)

20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (8485)

21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (2740)

22 20 and 21 (430)

Database: CINAHL

Search Strategy:

#	Query	**Results**
S1	(MH "Back Pain") OR (MH "Low Back Pain")	33,782
S2	TX back pain	43,738
S3	TX low back pain	27,941
S4	TX backache	560
S5	TX dorsalgia	35
S6	TX lumb* n3 pain	2,894
S7	TX lumbago	160
S8	TX coccy* n3 pain	86
S9	TX coccydynia	125
S10	(MH "Pain Measurement")	52,264
S11	TX pain measurement	52,468
S12	TX quantitative sensory test*	1,230
S13	TX QST	600

S14	TX pain pressure threshold	225
S15	TX pressure pain threshold	1,850
S16	TX temporal summation	542
S17	TX conditioned pain modulation	495
S18	TX exercise induced hypoalgesia	85
S19	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	45,290
S20	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	54,613
S21	S19 AND S20	5,879

3 Chapter 3: Endogenous Pain Modulation (EPM) Changes After a Course of Exercise Therapy in Low Back Pain (LBP): A Pilot Feasibility Study

Endogenous Pain Modulation (EPM) Changes After a Course of Exercise Therapy in Low Back Pain (LBP): A Pilot Feasibility Study

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3.1 Abstract

Introduction: It is widely accepted that many individuals with low back pain (LBP) have nociplastic pain, with a significant driver being adaptations to endogenous pain modulation (EPM) within the nervous system. Exercise is known to modulate pain through various mechanisms, however there is a lack of information on its relation to EPM. The objective of this study was to evaluate the feasibility of a study protocol investigating if changes in EPM occurs after exercise therapy.

Methods: Participants were recruited through the WELBack trial, a randomized controlled trial (RCT) comparing graded activity to motor control exercises. Participants attended 2 in person sessions pre and post intervention to assess pain pressure threshold (PPT), temporal summation (TS), conditioned pain modulation (CPM) and exercise induced hypoalgesia (EIH). Feasibility outcomes included attrition, recruitment rate, exercise adherence, and burden of assessment protocol (bothersome, discomfort and future participation), as well as measures of protocol consistency (water temperature, trials, timing).

Results: In total 36 (53%) eligible participants enrolled and complete baseline assessments. A-priori thresholds for feasibility were met for attrition 32/36 (89%), recruitment rate (53% of eligible participant enrolled and 36 recruited in 6 months), exercise adherence (93.8%) and satisfaction with assessment protocols (bothersome 88.9% and future participation 97.2%), apart from discomfort with assessment (58.3%). Participants reported that the cold water with CPM caused the most discomfort. There

was a trend for an increase in PPT at the low back, no change in TS, and a slight decrease in CPM and PPT at the thumbnail at follow up.

Discussion/Conclusion: The results demonstrated that the protocol is feasible for all pre-specified outcomes. Future studies should consider some adaptations to the CPM protocol including potential different condition stimulus. A future fully powered study is needed to further investigate EPM changes after exercise therapy.

3.2 Introduction

Low back pain (LBP) is a multifactorial condition spanning biological, social and psychological domains. [1] It is widely accepted that many people with chronic non-specific LBP have nociplastic pain, defined by the International Association for the Study of Pain as pain that results from altered nociception, with no clear evidence of tissue damage causing peripheral nociceptor activation, or evidence of disease or lesions in the somatosensory system. [2] A significant driver of nociplastic pain is maladaptive changes in the central nervous system (CNS). [3] Normally the CNS can take a wide range of actions to reduce or augment pain, through inhibitory or facilitatory mechanisms known as endogenous pain modulation (EPM). [4] Adaptations in the CNS can contribute to impaired EPM through the amplifications of neural signaling that results in hypersensitivity to nociceptive signals, known as central sensitization (CS). [3]

Exercise therapy is often the first line of care for chronic non-specific LBP, [5] however the effect of exercise, like other treatments for LBP, is small to moderate. [6] Exercise is known to modulate symptoms in LBP through multiple mechanisms including biological and psychosocial factors.[7] [8] There is evidence, primarily in pain free populations, that exercise may modulate pain through various systems such as activation of the endogenous opioid system or changes in the immune system. [7] [8] However, there is a scarcity of information on the effects of exercise in relation to EPM as most studies that have investigated the role of exercise in EPM have been conducted in pain free populations. In individuals without pain, there is evidence to suggest that higher levels of physical activity is correlated with better EPM. [9] Additionally, moderate aerobic training

has been shown to increase PPT in individuals without pain. [10] There is also evidence to suggest that psychosocial factors such as catastrophizing and fear of movement may modify the response to exercise. [11] Thus an exercise program that includes a psychosocial component may better address alterations to EPM. In LBP or in chronic musculoskeletal pain conditions in general, EPM has mostly been evaluated in response to an acute bout of exercise. [8] Understanding the mechanisms underlying EPM, and if or how exercise therapy can play a role in improving EPM, is an important next step in finding more effective treatments for LBP.

A widely recognized method to assess the effect of exercise on EPM is through exercise induced hypoalgesia (EIH), defined as a reduction in pain sensitivity after an acute bout of exercise. [12] EIH is known to occur in pain-free populations, but in chronic pain conditions, the response to acute exercise is variable, with observed decreases, increases or even no change to pain sensitivity. [8] It has been suggested that to observe a hypoalgesic response to exercise in individuals with chronic pain, repeated bouts of exercise (long-term exercise) may be needed. [7] To our knowledge, no studies have evaluated the long-term effect of exercise on EPM in people with LBP, which can be measured through quantitative sensory tests (QST) and EIH.

There is also conflicting evidence on which type of acute bout of exercise produces the strongest EIH response. In the few studies focusing on individuals with LBP, EIH was not observed or was impaired following a bout of functional training and core stabilization exercises, [13] 6-minute walk test, [14] and lifting tasks. [15] [16] In a study comparing LBP and healthy participants, EIH was reduced in individuals with LBP as

compared to healthy controls for wrist isometric exercises but was similar for back isometric exercises.[17] In pain free populations, EIH has been demonstrated following aerobic and resistance exercises, [8] with conflicting evidence on the required exercise intensity. [18-22] There is a scarcity of studies in the literature that have compared the role of different types of exercises that produce an EIH response or EPM improvements in LBP. Identifying the best exercise program that leads to the best EPM improvements for patients with LBP could potentially improve patient outcomes.

The purpose of this pilot study was to evaluate 1) the feasibility (primary outcome of attrition) and consistency of a study protocol to investigate if changes in EPM occur after exercise therapy (8-week intervention), 2) the trend in EPM change after exercise therapy and, 3) whether this response is different between graded activity (a functionally based exercise program that uses cognitive behavioural principles to address psychosocial factors), and motor control exercises (a more localized exercise programs that targets contraction and coordinator of spine muscles). [23] A pilot study is needed to evaluate the EPM protocol as well as its acceptability, consistency and safety before conducting a larger study of pre and post EPM measures after an exercise intervention.

3.3 Methods

3.3.1 Study Design

This pilot study was embedded within a randomized controlled trial (RCT) aimed to identify effect modifiers of exercise treatments for patients with LBP (WELBack) (NCT04283409). [24] The WELBack trial is a multi-site two arm parallel RCT where

participants are randomized 1:1 to receive an 8-week treatment of either graded activity or motor control exercises delivered by physiotherapists. Assessments for the main trial were conducted at baseline (T0), 2 months (T1), 6 months (T2) and 12 months (T3). In the WELBack main trial, assessors were not blinded to patient-reported outcomes given that these are self-reported by the patients. However, in this sub-study assessors were blinded to group allocation at baseline and follow up when evaluating QST and EIH outcomes measures. The study received ethics approval from the Hamilton Integrated Research Ethics Board (HiREB #7986).

3.3.2 Participants and Setting

This study was conducted in Hamilton, Ontario, Canada. Participants were recruited from the WELBack trial to participate in this sub-study. During the initial WELBack recruitment call, if the participant was eligible and consented for the main trial, the research assistants asked if the participant was interested in learning more about another study that they were eligible for. If they were interested, and once their baseline questionnaires for WELBack were completed, participants were invited to participate in the sub-study, received a copy of the sub-study consent form, and were booked for their first in-person visit prior to randomization. During the first in-person visit for the sub-study, participants signed the written informed consent form. During the initial physiotherapy assessment for the WELBack main trial, eligibility was confirmed, and participants were randomized to treatment groups. A timeline for the study can be found in Figure 1.

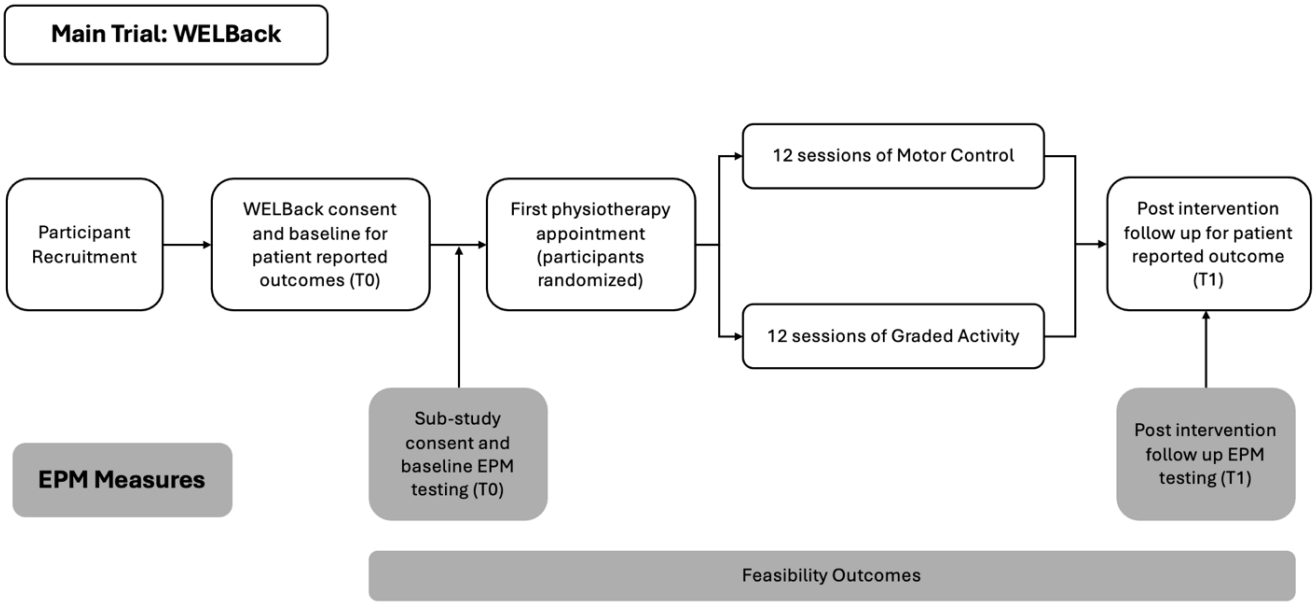

Figure 1. Study Timeline

3.3.3 Inclusion and Exclusion Criteria

The eligibility criteria for the WELBack trial included: (1) chronic non-specific LBP (>3 months) (2) back pain being the primary complaint (3) moderate or greater pain or disability measured using questions 7 and 8 of the 36-Item Short Form Survey [25] (4) moderate to high risk classification on the STarT Back Tool [26] (5) between the ages of 18-80 years (6) adequate English necessary for completion of questionnaires and communication with the physiotherapist. [24] This includes screening for safety to exercise using the PARQ+ [27] and or medical clearance. Participants were excluded if they have a specific condition such as disc herniation or spinal stenosis, are on the wait list for surgery, have cognitive impairments, severe neuromuscular conditions or if clinical assessment by a physician has indicated that the participant is not suitable for active exercise. [24]

3.3.4 Procedures

Participants enrolled in the sub-study were invited to attend two visits to McMaster University, which took place immediately before and after the intervention (T0 and T1, Figure 1) to complete EPM assessments. Participants also completed WELBack surveys at the same time points as per the main trial protocol.[24]

3.3.5 Study Interventions

As part of the main trial (WELBack), participants were randomized to receive either motor control of graded activity. Participants received 12 individually supervised sessions by a registered physiotherapist, lasting 30 minutes each, over an 8-week period (two sessions per week in the first four weeks and one session per week in the last four weeks). [24] Detailed treatment description and randomization procedures can be found in our published protocol.[24]

3.3.5.1 Motor Control Exercise

The motor control (MC) exercise program is based on the treatment program reported by Hodges et al. [23] and similar to the protocol used by Costa et al. [28] and Macedo et al.[29] The primary goal of motor control exercises is to retrain optimal control and coordination of the spine and limbs. [23]

3.3.5.2 *Graded Activity*

The graded activity (GA) exercise program is based on the treatment program reported by Lindström et al[30] and similar to the protocol previously used by Smeets et al. [31] and Macedo et al. [29] and is based on the biopsychosocial model. [32] The primary goal of

graded activity is to address individual modifiable contextual factors associated with the activity related pain experience such as self-efficacy and fear of movement, [33] while at the same time addressing physical impairments such as endurance, muscle strength and balance. [34]

3.3.6 Primary Feasibility Outcomes

Primary outcomes related to feasibility were collected throughout the study. Feasibility outcomes were attrition rate, recruitment rate, exercise adherence and participant rated burden of assessment protocol. The burden of assessment protocol consisted of asking participants 4 questions. The first three were rated on a 0-10 VAS (where 0 was not at all and 10 was extremely) and were as follows: (1) Overall, how bothersome did you find the assessment process? (2) Overall, how much discomfort did you experience during the assessment process? (3) How likely are you to participate in a similar project in the future? The fourth question was an open-ended question and participants were provided space to write any feedback they had about the procedure. A priori cut offs for the feasibility outcomes are presented in Table 1. This data was collected at baseline (recruitment rate, participant rated burden of assessment protocol), at follow up (exercise program completion and attrition rate), and at both time points (assessment consistency).

Table 1: A priori thresholds for feasibility

Proceed	Proceed with Protocol Amendments	Significant Amendments Required
Attrition Rate		
<15% attrition rate (31/36 participants attend follow up)	15-25% attrition rate (27/36 participants attend follow up)	>25% attrition rate (23/36 participants attend follow up)

Recruitment Rate		
N=36 in 6 months	N 25-36 in 8 months	N<25 in 8 months
50% of eligible participants consent to participate	40%-50% of eligible participants consent to participate	<40% of participants consent to participate
Exercise Sessions		
75% of participants completed all 12 sessions	60%-75% of participants completed all 12 sessions	<60% of participants completed all 12 sessions
Burden of Assessment Protocol		
80% of participants found the burden of completing measurements (VAS ≤3/10; 0=no burden, 10= most burden)	60%-80% of participants found the burden of completing measurements (VAS ≤3/10; 0=no burden, 10= most burden)	<60% of participants found the burden of completing measurements (VAS ≤3/10; 0=no burden, 10= most burden)
80% of participants would participate in a similar study in the future (VAS ≥7/10; 0=not likely, 10=very likely)	60%-80% of participants would participate in a similar study in the future (VAS ≥7/10; 0=not likely, 10=very likely)	<60% of participants would participate in a similar study in the future (VAS ≥7/10; 0=not likely, 10=very likely)

3.3.7 Assessment Consistency

Additionally, we evaluated assessment consistency including the consistency of the water temperature, how many participants were able to complete the full duration of the conditioning stimulus, how many participants were able to meet the 60-80% HRR for aerobic exercise, if participants were able to complete all trials, if participants required any additional rest time between trials and overall, how long the protocol took.

3.3.8 Patient-Reported Outcomes

Patient reported outcomes were assessed at baseline (before the first treatment session) and post-intervention (at 8-weeks). This included pain intensity (11-point Pain Numeric Rating Scale (NRS)), [35] disability (Oswestry Disability Index (ODI)), [36]

catastrophizing (Pain Catastrophizing Scale (PCS)), [37] fear of movement (Tampa Scale of Kinesiophobia), [38] and depressive symptoms (CES-D). [39]

3.3.9 Endogenous Pain Modulation Measures

The assessment protocol for EPM included the following QST: pain pressure threshold (PPT), temporal summation (TS) and conditioned pain modulation (CPM) as well as testing for exercise induced hypoalgesia (EIH). At baseline, the assessor was blinded to group allocation.

3.3.9.1 Pain Pressure Threshold

PPT was measured with an electronic pressure algometer (Wagner Instruments Greenwich, CT, USA) with a stimulation surface area of 1cm^2 at the lumbar spine (the most painful point indicated by the participant at the lumbar spine—indicative of local hyperalgesia) and at a distant site (thumbnail on the opposite side of the body—indicative of generalized hyperalgesia). [24] The lumbar spine measure was performed with the participant lying comfortably in prone, with the option to place a pillow under their stomach. Thumbnail measures were performed with the participant sitting in a chair with their hand resting comfortably on a table. PPT was recorded as the moment when the sensation of pressure changes to a sensation of pain. Pressure was increased from 0N at 5 N/s until the participant indicated that they have reached their PPT. Three consecutive measurements were performed at each site, with a 30-second recovery between repeated applications. The average of the 3 PPTs at each point was recorded.

3.3.9.2 Temporal Summation

Mechanical TS was assessed using a 256 mN weighted pinprick stimulator (MRC Systems GmbH, Heidelberg Germany) at the point on the lumbar spine indicated by the participant to have the most pain.[40] Participants were subjected to a single contact from the pinprick and asked to rate the pain intensity from a scale of 0-10 where 0 is no pain and 10 is the most intense pain imaginable. After 10 seconds, the pinprick stimulator was applied 10 consecutive times at a rate of 1 contact per second within an area of $1cm^2$. Participants were again prompted to provide a single 0-10 rating for the greatest intensity of pain they experienced during the 10 repeated contacts.[41 42] The TS effect was calculated by subtracting the pain intensity following the single contact from the pain rating by the series of contacts. This procedure was repeated 3 times with a 1-minute rest in between trials, and the average of the 3 TS effects was recorded.[41]

3.3.9.3 Conditioned Pain Modulation

CPM was tested at the point with the most pain at the lumbar spine as previously indicated by the participant using algometry as the test stimulus and a cold pressor test with hand immersion as the conditioning stimulus (CS). First, participants' baseline PPT was assessed. Then participants underwent cold water immersion (circulating cold water (IGLOO 5-galon water cooler with aquarium circulation pump kept at 4°C). Participants placed the hand contralateral to the side of back pain into the cooler for a maximum of 2 minutes, or until the participant could no longer tolerate the pain. If the participant was able to keep their hand in the water, 30 seconds before the end of the 2 minutes while the participant’s hand was still immersed in the cold water, the algometer was used again on

the lumbar spine to assess PPT, representing their conditioned PPT. If participants were unable to keep their hand in the water for the duration of the 2 minutes, PPT was assessed immediately after they removed their hand. [43] Participants underwent baseline PPT, cold pressor test and conditioned PPT assessment 2 times with a 2-minute rest in between CPM trials. CPM effect was calculated as a percent change from baseline using the equation: CPM =[(PPTpost–PPTpre)/ PPTpre] ∗100, where PPTpost was the PPT value after CS and PPTpre was the PPT value before CS. [41 44] Positive numbers represented an inhibitory effect, while negative numbers represented a facilitatory effect.

3.3.9.4 Exercise Induced Hypoalgesia

EIH was assessed after a 15-minute bout of aerobic exercise with a warmup and cool down period performed on a stationary bicycle (Spirit CU800 Bike, Dyaco Canada Inc 2020) at the heart rate (HR) (monitored using the Polar H10 monitor, Polar Electro, Kempele Finland) corresponding to 70% of their heart rate reserve (HRR). To calculate the target HR, we used the Karvonen formula (Target HR = [(maximum HR – resting HR) x %intensity] + resting HR). Participants were asked to keep their heart rate within 60-80% HRR and remain around a 5/6 out of 10 on the rating of perceived exertion (RPE) scale. [45] These targets were used as this is considered moderate exercise. [46] PPT was measured before the exercise session using the protocol indicated above, again immediately after the exercise session, and at 10-minute intervals post-exercise until PPT returned to within 2N of baseline PPT since this is around the SEM, [47] or up to 40 minutes after, as EIH is thought to only last for about 30 minutes after an exercise session. [8 22] A

5-minute rests between PPT, TS and CPM, and a 10-minute rest before EIH was provided to ensure that subsequent measures were not being influenced by previous measures.

To mitigate any adverse events during the 15-minute bout of exercise, participants were screened and cleared for exercise prior to entering the study. Blood pressure was measured prior to the start of the bout of exercise, and again following exercise (using the Life Brand automatic blood pressure monitor). Heart rate was continually monitored throughout the bout of exercise using a Polar H10 monitor. If the participants were unable to maintain the target heart rate of 60% of HRR, we asked them to maintain their intensity of 5/6 based on the RPE scale. If the participants heart rate increased above moderate threshold (80% HRR) or RPE was above 7, we asked them to reduce the revolutions per minute of the bicycle, or resistance until their heart rate returned to within the 60-80% range. If the participant's heart rate was too high and unable to return to a moderate level, the participant stopped cycling until their heart rate reduced and we assessed if they could continue. If the participant was unable to continue or had to stop prior to the 15 minutes being complete, the time was noted, and the participant did not continue cycling.

3.3.10 Statistical Analysis

Descriptive statistics were used to report demographic characteristics of the participants as mean and confidence intervals or absolute and relative frequencies. For the outcomes of feasibility, we used descriptive statistics and reported our results based on the a priori thresholds (Table 1). To observe the trends in changes in EPM after exercise therapy, as well as whether this response is different between graded activity and motor control, we observed if there were any correlation between patient reported outcomes of

pain and disability, and EPM measures using linear regression. To calculate total scores for questionnaires with missing item responses, the individual score from a specific questionnaire was averaged by the number of questions that were completed, and this average was used in place of the missing data to allow for total scores to be calculated.[48]

3.3.11 Sample Size Calculation

We calculated the sample size using the 95% Confidence Interval method, as suggested by Thabane et al., 2010. [49] We required a total sample size of n=36 (n=18 from each group) to answer our feasibility questions (primary outcome of attrition, secondary outcomes of recruitment, completion, burden of assessment and consistency). Using a margin of error, no greater than 10%, a sample size of 36 participants allowed for a lower boundary of the 95% CI to be above 80% retention, which is in line with the expected range for clinical trials.

3.4 Results

Between November 9th, 2023, and April 3rd, 2024, 104 participants were recruited into the WELBack Study, of which 68 participants were asked if they were interested in participating in this sub-study. Not all participants were invited to this study due to a lack of proximity to McMaster or time constraints during calls. In total, 58 were interested in hearing more about this study for a total of 36 consenting to participate and completing baseline assessments. Of the 36 participants that completed baseline assessments, 2 were not randomized into the WELBack. One participant at initial physiotherapy assessment was deemed ineligible for the WELBack study due to not having non-specific LBP and a

second participant never attended their initial physiotherapy assessment. In addition, two participants were lost to follow up; one withdrew from the WELBack and this study for personal reasons, and one was unreachable at follow-up, leaving 32 participants who attended the post intervention follow up. See Figure 2 for study flow diagram.

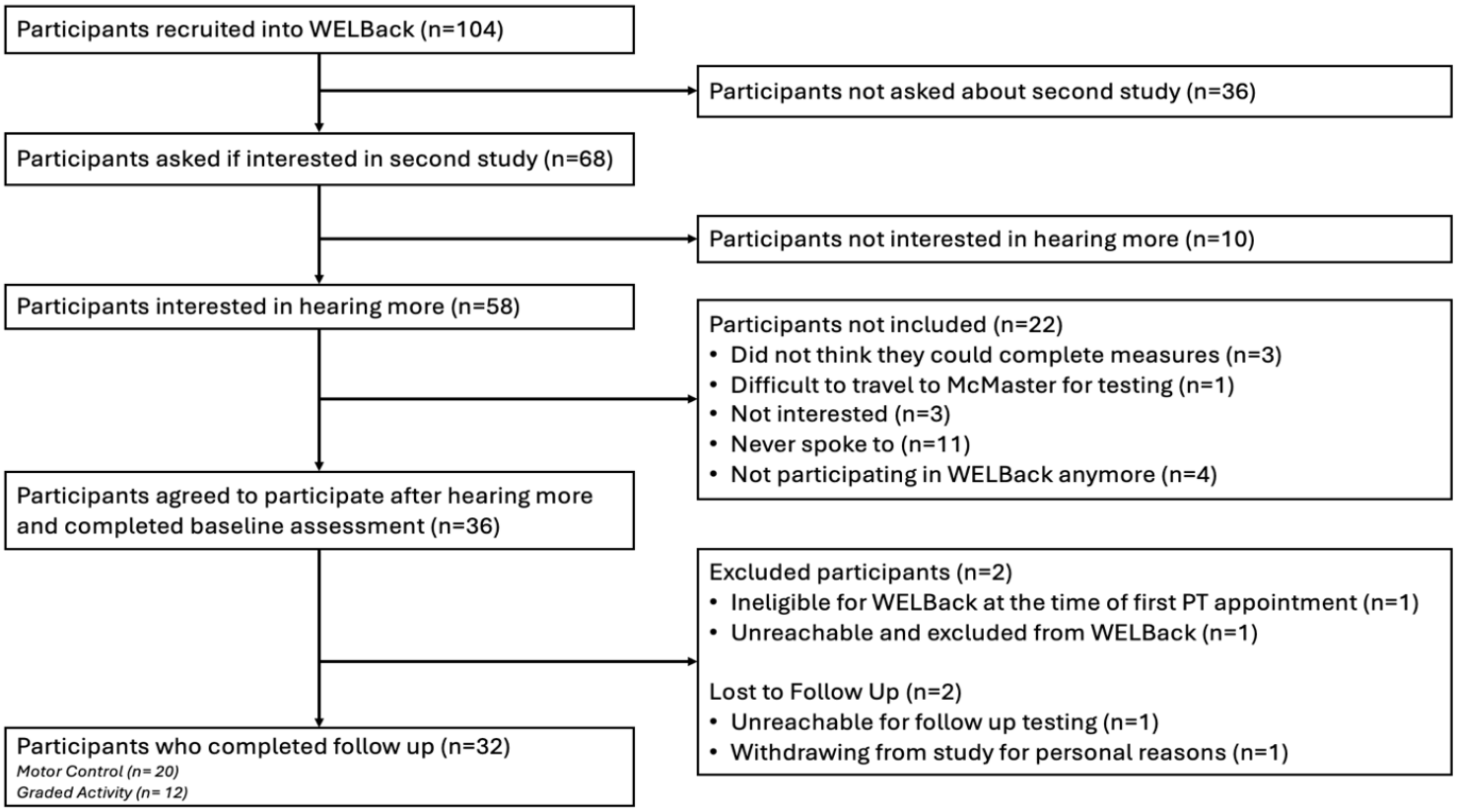

Figure 2. Participant Flow Diagram

3.4.1 Demographic Characteristics

Of the 36 participants that completed the baseline measurements, the average age was 51 (95% CI 46.6 to 54.6) years, with 25 (69.4%) females and 11 males included. The average LBP duration was 147 weeks, and over half of all participants did not use any

medications for their pain. Baseline demographic characteristics for both treatment groups are reported in Table 2. The participants that were not randomized into the WELBack included one male and one female age 55 and 62 years.

Table 2. Participant Characteristics as mean and 95% confidence interval or absolute and relative frequencies.

	Total (n=36)	*Graded Activity (n=14)*	*Motor Control (n=20)*
Age (years)	50.6 (46.6 to 54.6)	51.8 (45.1 to 58.5)	49.0 (43.1 to 54.8)
BMI (n=35)	34.9 (26.2 to 43.6)	44.4 (22.3 to 66.5)	28.7 (25.7 to 31.8) (n=19)
Sex			
Female	25 (69.4%)	8 (57.1%)	16 (80%)
Male	11 (30.6%)	6 (42.9%)	4 (20%)
LBP Duration (weeks)	146.9 (64.9 to 228.8)	145.1 (40.8 to 249.5)	159.2 (23.2 to 295.1)
Smoking			
Yes	2 (5.6%)	1 (7.1%)	1 (5%)
No	33 (91.7%)	13 (92.9%)	18 (90%)
No response	1 (2.8%)	0 (0%)	1 (5%)
Education			
School Certificate	0 (0%)	0 (0%)	0 (0%)
High School Certificate	1 (2.8%)	0 (0%)	1 (5%)
Trade Certificate	0 (0%)	0 (0%)	0 (0%)
Diploma	11 (30.6%)	2 (14.3%)	8 (40%)
Advanced Diploma	2 (5.6%)	1 (7.1%)	1 (5%)
Bachelor's degree	15 (41.7%)	7 (50%)	8 (40%)
Postgraduate Degree	4 (11.1%)	3 (21.4%)	1 (5%)
Other	3 (8.3%)	1 (7.1%)	1 (5%)
Medication Use			
Over the counter pain medication	8 (22.2%)	2 (14.3%)	5 (25%)
NSAIDS	3 (8.3%)	0 (0%)	3 (15%)
Muscle Relaxant	3 (8.3%)	2 (14.3%)	1 (5%)

Narcotic Pain Medication	0 (0%)	0 (0%)	0 (0%)
Anti-Depressants	0 (0%)	0 (0%)	0 (0%)
Neuroleptics	0 (0%)	0 (0%)	0 (0%)
None	21 (58.3%)	10 (71.4%)	10 (50%)
No response	1 (2.8%)	0 (0%)	1 (5%)
Current Exercise			
Yes	20 (55.6%)	8 (57.1%)	10 (50%)
No	16 (44.4%)	6 (42.9%)	10 (50%)
Comorbidities			
1	10 (27.8%)	5 (35.7%)	4 (20%)
2	10 (27.8%)	1 (7.1%)	9 (45%)
3	11 (30.6)	6 (42.9%)	5 (25%)
4	3 (8.3%)	0 (0%)	2 (10%)
5	2 (5.6%)	2 (14.3%)	0 (0%)

*Reported as mean (95% CI), n (%). Two participants were not randomized and thus not included in the stratified columns.

3.4.2 Feasibility outcomes

3.4.2.1 Attrition Rate

Of the 36 participants recruited into this study, all completed baseline assessment, and 32 (88.9%) completed the follow up assessment, meeting our cut-off for <15% attrition rate. Only one participant could not complete EIH at follow up due to a knee injury obtained from activity outside of the study treatment. The average amount of time that passed between participants last physiotherapy appointment and their follow up visit was 13.3 ± 13.4 days, with a minimum of 1 day and a maximum of 54 days after the last treatment.

3.4.2.2 Recruitment rate

We were able to recruit our sample size within 5 months (7.2 participants per month), which meets the feasibility criterion for recruitment rate (n=36 in 6 months). In total, 52.9% (36 out of 68) of eligible participants that were invited to partake in the sub-study were included. Unfortunately, not all participants that were eligible for the WELBack study were invited, meaning that only 34.6% (36 out of 104) of those recruited to the WELBack within the time frame were included in this study. The enrollment rate of 52.9% met our feasibility criterion, however; this only accounts for those that were invited to hear more about this study.

3.4.2.3 Exercise Adherence

Participants in this study generally had good adherence to the exercise sessions with 30/36 participants (83.3%) completing all 12 sessions, meeting our a priori threshold of 75%. There was one participant who completed 7/12 sessions due to time constraint and one participant who completed 6/12 sessions as they withdrew from the intervention due to a pain flare. The 2 participants who did not complete follow up assessments completed 12 and 7 physiotherapy sessions.

3.4.2.4 *Burden Of Assessment Protocol*

The burden of the assessment protocol was assessed at baseline. In total 32 (88.9%) participants rated the protocol to be equal or less than 3 on a 0 to 10 scale for burdensomeness, with an average response of 1.2 (0.6 to 1.8), meeting our feasibility threshold of 80%. However, 21 (58.3%) of participants rated the discomfort with the assessments to be equal to or less than 3, with an average response of 3.3 (2.6 to 4.0), not

meeting our feasibility threshold of 80% meaning that some modifications are needed. Finally, 35 (97.2%) rated that they were likely to participate in a similar study as greater or equal to 7, with an average response of 9.2 (8.8 to 9.6) meeting our feasibility threshold of 80%.

Qualitative description of written feedback of the protocols was conducted. Twenty-three patients responded to the feedback question. The primary feedback was that the ice bath was the most uncomfortable part of the protocol follow by the challenges in completing biking. Many participants also described that they had a good experience, were happy to participate and would be open to participating again.

3.4.3 Assessment Consistency

The assessment consistency was evaluated at baseline and at follow up. The average temperature of the water was 4.4 ± 0.6 °C. The number of participants that were able to keep their hand in the water for the 1 minute and 30 second target time for at least 1 of the trials was 21 (58.3%). The remaining 41.6% of participants removed their hand before this time. For EIH, all the participants were able to cycle for the 15 minutes, but only 25 (69.4%) participants were able to meet their 60-80% HRR threshold. The remainder of participants cycled between a 5 and 6 out of 10 on the RPE scale. No participants needed to stop cycling due to a HR that was over 80% and could not return to the 60-80% range. Finally, all participants were able to complete all trials for all tests, with no requirements for skipping trials.

On average, the full protocol took 1 hour and 39 minutes ± 13 minutes to complete. This included rest times, test explanations, and instructions. No participants required any additional rest time than allotted in between tests. The longer rest times usually occurred before CPM when the water needed to be brought to the correct temperature, or before EIH if the participant required a washroom break, to ensure they rested for at least 5 minutes to get a resting HR and resting blood pressure value.

3.4.4 Patient Reported Outcomes

Participants included in this study had moderate intensity pain at baseline, with an average rating of 5.5 (5 to 6) on a 0-10 NRS, and this was lower at follow up. Participants had moderate disability with average ODI scores of 29.8% (26.1 to 33.5) at baseline, with an improvement at follow-up. Participants on average had low PCS scores with an average of 15.8 (12.1 to 19.4) at baseline and this decreased at follow-up. Kinesiophobia and depressive symptom scores also decreased from baseline to follow up. Results for patient reported outcomes can be found in Table 3.

Table 3. Patient Reported Outcomes

	Baseline			Follow Up		
	Total (n=34)	*Graded Activity (n=14)*	*Motor Control (n=20)*	*Total (n=32)*	*Graded Activity (n=12)*	*Motor Control (n=20)*
Pain Intensity (0-10)	5.5 (5.0 to 6.0)	4.9 (4.1 to 5.7)	5.7 (5.1 to 6.2)	3.1 (2.4 to 3.7)	2.8 (1.9 to 3.6)	3.3 (2.3 to 4.3)
Oswestry Disability Index (ODI) (%)	29.8 (26.1 to 33.5)	29.9 (23.4 to 36.5)	28.9 (24.8 to 32.9)	16.5 (13.5 to 19.6)	16.4 (11.2 to 21.5)	16.6 (12.4 to 20.9)
Pain Catastrophizing Scale (PCS)	15.8 (12.1 to 19.4)	13.1 (7.2 to 19.0)	16.3 (11.8 to 20.8)	9.4 (5.2 to 13.6)	10.1 (2.5 to 17.7)	9.0 (3.4 to 14.6)

Tampa Scale of Kinesiophobia (Tampa)	41.4 (40.0 to 42.7)	40.4 (39.0 to 41.8)	41.9 (39.7 to 44.1)	37.7 (35.5 to 39.8)	33.7 (30.3 to 36.9)	40.1 (37.7 to 42.4)
Centre for Epidemiological Studies Depression scale (CES-D)	19.8 (17.4 to 22.1)	19.6 (15.0 to 24.3)	19.3 (16.5 to 22.1)	17.0 (14.2 to 19.8)	16.5 (13.6 to 19.4)	17.3 (12.9 to 21.7)

*Reported as mean (95% CI)

3.4.5 Endogenous Pain Modulation Measures

At baseline, average PPT values for the lumbar spine was 52.3 N (43.8 to 60.8) and for the thumbnail 46.5 N (39.7 to 53.3). At follow up, these values were slightly higher for the low back and slightly lower for the thumbnail. The average TS values were similar from baseline to follow up. The average percent change of PPT scores for CPM at baseline were 31.9 (21.3 to 42.6). At follow up the average difference in PPT score was slightly lower with an average percent change of 27.1 (17.3 to 36.9). Results of the EPM measures can be seen in Table 4.

Table 4. Quantitative Sensory Testing Measures

	Baseline			Follow Up		
	Total (n=36)	*Graded Activity (n=14)*	*Motor Control (n=20)*	*Total (n=32)*	*Graded Activity (n=12)*	*Motor Control (n=20)*
Pain Pressure Threshold (N)						
Low Back	52.3 (43.8 to 60.8)	59.2 (41.2 to 77.2)	44.9 (36.4 to 53.4)	60.4 (49.7 to 71.1)	75.8 (52.8 to 98.8)	51.2 (41.4 to 61.0)
Thumbnail	46.5 (39.7 to 53.3)	49.1 (34.9 to 63.4)	44.0 (36.2 to 51.9)	45.1 (39.4 to 50.8)	47.8 (36.2 to 59.5)	43.5 (36.7 to 50.2)
Temporal Summation	1.6 (1.1 to 2.1)	1.2 (0.5 to 1.8)	2.0 (1.2 to 2.7)	1.6 (1.1 to 2.0)	1.3 (0.3 to 2.2)	1.8 (1.3 to 2.3)

Conditioned Pain Modulation						
PPT difference (N)	15.3 (10.4 to 20.2)	16.4 (7.5 to 25.3)	12.7 (7.3 to 18.1)	14.5 (8.7 to 20.3)	17.1 (9.9 to 24.3)	13.0 (4.4 to 21.5)
% change	31.9 (21.3 to 42.6)	27.4 (13.8 to 41.0)	31.1 (17.4 to 44.9)	27.1 (17.3 to 36.9)	24.3 (15.1 to 33.4)	28.7 (13.4 to 44.1)

*Mean (95% CI), N = newtons

The EIH effect (change in PPT from baseline) for both groups immediately after the exercise was 7.6 (2.5 to 12.7) at baseline and 4.7 (-1.1 to 10.5) at follow-up (n=31). The EIH effect varied in length from 20 minutes to greater than 40 minutes. Participants had different responses after exercise, with some PPTs not changing and others increasing or decreasing throughout the 40 minutes at both baseline and at follow up.

3.4.6 Correlations with EPM measures

Linear regression for change scores of pain and disability and EPM measures was conducted. There was an association between change in CPM and pain (R-squared 0.21, p = 0.008) as well as change in CPM and ODI (R-squared 0.24, p = 0.005). All other univariate models were not significant and can be found in Table 5. We did not run any comparisons between the two intervention groups because of the small sample with uneven split between groups.

Table 5. Correlations with Pain, Disability and EPM Measures

		Slope and 95% CI	R-Squared	P value
Pain	LBP PPT	-0.002 (-0.03 to 0.02)	0.001	0.87
	Thumbnail PPT	-0.01 (-0.05 to 0.03)	0.01	0.56
	TS	0.16 (-0.27 to 0.60)	0.02	0.44
	CPM effect	-0.04 (-0.06 to -0.01)	0.21	0.008
	EIH effect	-0.01 (-0.05 to 0.03)	0.01	0.55
ODI	LBP PPT	-0.06 (-0.20 to 0.08)	0.03	0.38

	Thumbnail PPT	-0.10 (-0.31 to 0.11)	0.03	0.36
	TS	1.07 (-1.31 to 3.46)	0.03	0.37
	CPM effect	-0.22 (-0.36 to -0.07)	0.24	0.005
	EIH effect	-0.08 (-0.29 to -0.13)	0.02	0.43

3.5 Discussion

The study results show that the protocol is feasible in terms of attrition, recruitment rate, burden of assessment protocol, and exercise adherence. In terms of recruitment and retention, we were able to recruit our sample within the expected time frame, with minimal drop out and adequate completion of exercise sessions. The assessment of protocol discomfort was adequate but with cold-water immersion being the most unpleasant test. The QST and EIH protocol were highly feasible with all participants that attended the sessions completing all tests. The water temperature stayed consistent at approximately 4.4 °C and over half of the participants were able to keep their hand in the water for the duration of the test. Similarly, all participants completed the EIH tests with around 70% of participants being able to reach and maintain their target 60-80% HRR during the 15 minutes of cycling. A trend was observed with a slight decrease in pain and disability with small potential decreases in catastrophizing, kinesiophobia and depressive symptoms.

Participants had PPT values at baseline that were comparable to previous literature for LBP. [50-53] These PPT values were slightly higher at follow up for all participants and CPM was slightly lower at follow-up. The higher PPT values at follow up were in line with our expectations. The lower CPM suggests that participants had less

inhibition at follow up, which was in the opposite direction than expected. The slight decrease in the average effect of CPM at follow up may be because PPTs at the low back were slightly higher at follow up indicating that individuals already had less peripheral pain sensitivity, which may indicate less room for changes in PPT, and thus less change seen with CPM. There was a slight but likely not important decrease in PPT at the thumbnail at follow up, suggesting a potential increase in central sensitivity. Further, TS change scores were similar at baseline and at follow up, suggesting that the trend in individuals central pain facilitation did not change after long term exercise. At both baseline and follow-up, the EIH response was variable with some participants PPT increasing immediately after exercise and staying elevated or decreasing after a certain point, while others decreased after exercise and had a delayed increase effect or just stayed around their pre-PPT value. Previous literature investigating EIH in LBP has shown impairments or no EIH effect, [13 15] however none of these studies did 15 minutes of moderate aerobic exercise.

An important finding of this study was the high feasibility of our protocol with participants experiencing the most discomfort with the cold-water immersion as part of the CPM test. However, it is important to note that a CPM effect is only experienced when a noxious stimulus is applied, and thus, some level of discomfort is always expected when testing CPM. Cold water immersion was used in this study as it was the most commonly used in this population based on the results from our scoping review (in review). Other conditioning stimuli such as cuff pressure, [13] and thermal stimuli, [53] have also been successfully used in LBP; however, there is not much information on the

differences expected in responses between stimuli and whether their level of discomfort would be different than cold water immersion. There is evidence in healthy individuals that suggests that different conditioned stimuli (cuff pressure pain stimulation, cold pressor test, and thermode-based cold painful stimulation) may produce significantly different CPM effect [54] while other studies have found no difference between hot water immersion, cold pressor test and ischemic occlusion CPM effects. [55] A systematic review that looked at the reliability of CPM concluded that cold pressor tests and ischemic tests had the highest reliability in healthy participants, and cold pressor test had the highest reliability in individuals with chronic pain. [56] Thus, future studies should compare different conditioning stimuli, such as investigating whether ischemic might be more accepted by patients in comparison to cold water immersion, to find the optimal modality, with minimal discomfort, for use in LBP.

In this study, we aimed to be consistent with the rest times between trials and between different tests. There is currently no information on how long it may take for the nervous system to return to baseline between these tests. In our study, PPT was relatively stable throughout the protocol, but for some participants, PPT seemed to increase as we performed each consecutive tests. This may suggest that our rest times between tests may not have been long enough for PPT to return to baseline and questions the appropriateness of collecting multiple EPM measures in the same assessment. Similarly, with CPM, some individuals seemed to have a delayed effect, where during the second CPM trial, the first PPT measurement was still elevated compared to the previous trial. This may have occurred due to too short rest time between trials, not allowing the nervous system

enough time to settle. Previous research in healthy participants has suggested that the CPM effect can last up to 32 minutes, [57] however it is unclear how long it may last in individuals with chronic pain. Future recommendations should consider providing longer rest times between CPM trials, and investigating how different timing and consecutive measures may impact the results.

A challenge in conducting CPM is the conduction of parallel versus sequential test stimuli assessment. [4 44] In our study, when participants removed their hand before the 1 min 30 second duration, we performed the test sequentially, rather than in parallel when they kept their hand in the water. It has been suggested that CPM responses may be stronger for parallel assessments as compared to sequential, [4] but sequential assessments may be more accurate as there are less distractions. [44] It is unclear how much the use of parallel or sequential assessments, depending on participant's response to the CS, impacted our results. To control for these differences, some studies suggest the use of an individualized threshold for the conditioning stimulus (e.g., pain rating of 50/100) [58-60] which allows for the consistent assessment of parallel test stimulus. Future research is needed to compare methods of sequential and parallel CPM, and how much this might change the CPM response.

This study is the first to investigate EPM changes after a longitudinal exercise therapy intervention in a LBP population. One strength of this study is that we used the traffic light method for evaluating the feasibility criteria, demonstrating that our results support the progression to a future trial with no to minimal modifications. Revisions on the CPM protocol is needed to ensure that the discomfort experienced by participants is

reduced. This may include altering the temperature or selecting a different modality for the conditioning stimulus, which may also allow for the consistent parallel assessment of CPM. Additionally, we used a standardized protocol developed based on the most used protocols for QST in LBP. Despite this strength, because there is no standardized QST protocol for use in LBP, the psychometric properties of this specific protocol are not known. However, in general we know that PPT, TS, and CPM have acceptable reliability in LBP. [61] Data on the validity and responsiveness of these measures are unknown as they are highly dependent on the protocols that are used, which is a limitation of these measures. Although we considered rest times between trials and measurements, these may not have been enough time to allow the nervous system to settle. A significant challenge that presented itself during the follow up data collection was getting participants to do the testing session close to their last physiotherapy date. On average, this was 13 days past their last appointment, with the minimum being 1 day and the maximum being almost 2 months, which did not really capture the exact change immediately after treatment. Future studies should consider adding the in-person assessment at the physiotherapy clinic or assessments at different locations or set schedules to improve assessment timeframes. Additionally, we did not have an equal split of participants between the groups, because this study was embedded within a larger trial. The same issue is unlikely to occur in a study when QST and EIH responses are the primary objective of the study.

3.6 Conclusion

In conclusion, this study investigated EPM changes after an exercise therapy intervention in individuals with LBP. The results of this study demonstrate that the protocol is feasible, and that it is feasible to collect additional data within a larger trial. Trends with patient reported outcomes seemed to decrease at follow up indicating some improvements in pain and disability, while improvements in EPM measures of TS and CPM were seen locally. A future trial should consider different methods of recruitment and follow up testing, as well as some changes to the conditioning stimulus used for CPM.

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3.8 References

1. Otero-Ketterer E, Peñacoba-Puente C, Ferreira Pinheiro-Araujo C, et al. Biopsychosocial Factors for Chronicity in Individuals with Non-Specific Low Back Pain: An Umbrella Review. *International Journal of Environmental Research and Public Health* 2022;19(16):10145. doi: 10.3390/ijerph191610145
2. International Association for the Study of Pain. IASP Terminology [Available from: https://www.iasp-pain.org/resources/terminology/?navItemNumber=576#Centralsensitization accessed June 19 2023.
3. Nijs J, Lahousse A, Kapreli E, et al. Nociplastic Pain Criteria or Recognition of Central Sensitization? Pain Phenotyping in the Past, Present and Future. *Journal of Clinical Medicine* 2021;10(15):3203. doi: 10.3390/jcm10153203
4. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *The Journal of the International Association for the Study of Pain* 2015;156 Suppl 1(4):S24-s31. doi: 10.1097/01.j.pain.0000460343.46847.58
5. Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *European Spine Journal* 2018;27(11):2791-803. doi: 10.1007/s00586-018-5673-2
6. Hayden JA, Ellis J, Ogilvie R, et al. Exercise therapy for chronic low back pain. *Cochrane Database of Systematic Reviews* 2021(9)
7. Song JS, Yamada Y, Kataoka R, et al. Training-induced hypoalgesia and its potential underlying mechanisms. *Neuroscience and Biobehavioural Reviews* 2022;141
8. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *The Journal of Pain* 2019;20(11):1249-66. doi: 10.1016/j.jpain.2019.03.005
9. Naugle KM, Riley JL, 3rd. Self-reported physical activity predicts pain inhibitory and facilitatory function. *Med Sci Sports Exerc* 2014;46(3):622-9. doi: 10.1249/MSS.0b013e3182a69cf1
10. Hakansson S, Jones M, Ristov M, et al. Intensity-dependent effects of aerobic training on pressure pain threshold in overweight men: A randomized trial. *European Journal of Pain* 2018;22(10):1813-23.

11. Naugle KM, Naugle KE, Fillingim RB, et al. Isometric Exercise as a Test of Pain Modulation: Effects of Experimental Pain Test, Psychological Variables, and Sex. *Pain Medicine* 2014;15(4):692-701. doi: 10.1111/pme.12312
12. Lemley KJ, Hunter SK, Bement MKH. Conditioned Pain Modulation Predicts Exercise-Induced Hypoalgesia in Healthy Adults. *The American College of Sport Medicine* 2014
13. Santos MS, Santos PdJ, Vasconcelos ABS, et al. Neuroendocrine effects of a single bout of functional and core stabilization training in women with chronic nonspecific low back pain: A crossover study. *Physiological reports* 2022;10(17):e15365. doi: https://dx.doi.org/10.14814/phy2.15365
14. Vaegter HB, Petersen KK, Sjodsholm LV, et al. Impaired exercise-induced hypoalgesia in individuals reporting an increase in low back pain during acute exercise. *European Journal of Pain* 2021;25(5):1053-63. doi: 10.1002/ejp.1726
15. Kuithan P, Heneghan NR, Rushton A, et al. Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain. *Pain Practice* 2019;19(7):740-50. doi: 10.1111/papr.12804
16. Woznowski-Vu A, Aternali A, Gervais A, et al. The Prospective Prognostic Value of Biopsychosocial Indices of Sensitivity to Physical Activity Among People With Back Pain. *Clinical Journal of Pain* 2021;37(10):719-29. doi: 10.1097/AJP.0000000000000965
17. Patricio P, Mailloux C, Timothy, et al. Assessment of exercise-induced hypoalgesia in chronic low back pain and potential associations with psychological factors and central sensitization symptoms: A case–control study. *Pain Practice* 2022 doi: 10.1111/papr.13189
18. Koltyn KF. Exercise-Induced Hypoalgesia and Intensity of Exercise. *Sports Medicine* 2002;32(8):477-87. doi: 10.2165/00007256-200232080-00001
19. Naugle KM, Naugle KE, Fillingim RB, et al. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc* 2014;46(4):817-25. doi: 10.1249/mss.0000000000000143
20. Hoffman MD, Shepanski MA, Ruble SB, et al. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain11No commercial party having a direct financial interest in the results of the research supporting this article has conferred or will confer a financial

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21. Niwa Y, Shimo K, Ohga S, et al. Effects of Exercise-Induced Hypoalgesia at Different Aerobic Exercise Intensities in Healthy Young Adults. *Journal of Pain Research* 2022;Volume 15:3615-24. doi: 10.2147/jpr.s384306
22. Tomschi F, Lieverkus D, Hilberg T. Exercise-induced hypoalgesia (EIH) in response to different exercise intensities. *European Journal of Applied Physiology* 2022;122(10):2213-22. doi: 10.1007/s00421-022-04997-1
23. Hodges P, Ferreira PH, Ferreira ML. Lumbar Spine: treatment of instability and disorders of movement control. In: Magee DJ, Zachazewski JE, Quillen WS, eds. Pathology and Intervention in Muscloskeletal Rehabilitation. 1st ed: Elsevier 2009.
24. Macedo LG, Hodges PW, Bostick G, et al. Which Exercise for Low Back Pain? (WELBack) trial predicting response to exercise treatments for patients with low back pain: a validation randomised controlled trial protocol. *BMJ Open* 2021;11(1):e042792. doi: 10.1136/bmjopen-2020-042792
25. Sanson-Fisher RW, Perkins JJ. Adaptation and validation of the SF-36 Health Survey for use in Australia. *J Clin Epidemiol* 1998;51(11):961-7. doi: 10.1016/s0895-4356(98)00087-0
26. Hill JC, Whitehurst DG, Lewis M, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet* 2011;378(9802):1560-71. doi: 10.1016/s0140-6736(11)60937-9 [published Online First: 20110928]
27. Shephard RJ. PAR-Q, Canadian Home Fitness Test and Exercise Screening Alternatives. *Sports Medicine* 1988;5(3):185-95. doi: 10.2165/00007256-198805030-00005
28. Costa LOP, Maher CG, Latimer J, et al. Motor Control Exercise for Chronic Low Back Pain: A Randomized Placebo-Controlled Trial. *Physical therapy : journal of the American Physical Therapy Association* 2009;89(12):1275-86. doi: 10.2522/ptj.20090218
29. Macedo LG, Latimer J, Maher CG, et al. Effects of motor control exercises versus graded activity in patients with chronic nonspecific

low back pain: a randomized controlled trial. *Physical Therapy* 2012;92(3):363-77.
30. Lindström I, Öhlund C, Eek C, et al. The Effect of Graded Activity on Patients with Subacute Low Back Pain: A Randomized Prospective Clinical Study with an Operant-Conditioning Behavioral Approach. *Physical Therapy* 1992;72(4):279-90. doi: 10.1093/ptj/72.4.279
31. Smeets RJ, Vlaeyen JW, Hidding A, et al. Active rehabilitation for chronic low back pain: cognitive-behavioral, physical, or both? First direct post-treatment results from a randomized controlled trial [ISRCTN22714229]. *BMC Musculoskelet Disord* 2006;7:5. doi: 10.1186/1471-2474-7-5 [published Online First: 20060120]
32. Macedo LG, Smeets RJEM, Maher CG, et al. Graded Activity and Graded Exposure for Persistent Nonspecific Low Back Pain: A Systematic Review. *Physical Therapy* 2010;90(6):860-79. doi: 10.2522/ptj.20090303
33. Asmundson GJG, Norton RG, Allerdings MD. Fear and avoidance in dysfunctional chronic back pain patients. *PAIN* 1997;69(3):231-36. doi: 10.1016/s0304-3959(96)03288-5
34. Leeuw M, Goossens MEJB, van Breukelen GJP, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: Results of a randomized controlled trial. *PAIN* 2008;138(1):192-207. doi: 10.1016/j.pain.2007.12.009
35. Ostelo RWJG, Deyo RA, Stratford P, et al. Interpreting Change Scores for Pain and Functional Status in Low Back Pain. *Spine* 2008;33(1):90-94. doi: 10.1097/brs.0b013e31815e3a10
36. Fairbank JC, Couper J, Davies JB, et al. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980;66(8):271-3.
37. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychological assessment* 1995;7(4):524.
38. Neblett R, Hartzell MM, Mayer TG, et al. Establishing clinically meaningful severity levels for the Tampa Scale for Kinesiophobia (TSK-13). *European Journal of Pain* 2016;20(5):701-10. doi: 10.1002/ejp.795
39. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied psychological measurement* 1977;1(3):385-401.
40. Rabey M, Poon C, Wray J, et al. Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with

chronic low back pain and healthy control subjects. *Manual therapy* 2015;20(6):763-68. doi: 10.1016/j.math.2015.02.011
41. Overstreet DS, Michl AN, Penn TM, et al. Temporal summation of mechanical pain prospectively predicts movement-evoked pain severity in adults with chronic low back pain. *BMC Musculoskeletal Disorders* 2021;22(1) doi: 10.1186/s12891-021-04306-5
42. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *PAIN* 2006;123(3):231-43. doi: 10.1016/j.pain.2006.01.041
43. Leemans L, Elma Ö, Nijs J, et al. Transcutaneous electrical nerve stimulation and heat to reduce pain in a chronic low back pain population: a randomized controlled clinical trial. *Brazilian Journal of Physical Therapy* 2021;25(1):86-96. doi: 10.1016/j.bjpt.2020.04.001
44. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain* 2015;19(6):805-06. doi: 10.1002/ejp.605
45. Borg G. Borg's perceived exertion and pain scales: Human kinetics 1998.
46. Liguori G, Medicine ACoS. ACSM's guidelines for exercise testing and prescription: Lippincott Williams & Wilkins 2020.
47. Chesterton LS, Sim J, Wright CC, et al. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clin J Pain* 2007;23(9):760-6. doi: 10.1097/AJP.0b013e318154b6ae
48. Mehra A, Baker D, Disney S, et al. Oswestry Disability Index scoring made easy. *Ann R Coll Surg Engl* 2008;90(6):497-9. doi: 10.1308/003588408x300984 [published Online First: 20080702]
49. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology* 2010;10(1):1. doi: 10.1186/1471-2288-10-1
50. Correa JB, Costa LOP, de Oliveira NTB, et al. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. *Experimental brain research* 2015;233(8):2391-9. doi: https://dx.doi.org/10.1007/s00221-015-4309-6
51. Chen P-C, Wei L, Huang C-Y, et al. The Effect of Massage Force on Relieving Nonspecific Low Back Pain: A Randomized Controlled

Trial. *International journal of environmental research and public health* 2022;19(20) doi: https://dx.doi.org/10.3390/ijerph192013191
52. Den Bandt HL, Ickmans K, Leemans L, et al. Differences in Quantitative Sensory Testing Outcomes between Patients With Low Back Pain in Primary Care and Healthy Controls. *Clinical Journal of Pain* 2022((Den Bandt, Voogt) Research Centre for Health Care Innovations, University of Applied Sciences Rotterdam, Rochussenstraat 198, Rotterdam 3015 EK, Netherlands(Den Bandt, Ickmans, Leemans, Nijs, Voogt) Pain in Motion Research Group, Dept. of Physiotherapy) doi: https://dx.doi.org/10.1097/AJP.0000000000001038
53. Klyne DM, Moseley GL, Sterling M, et al. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *Journal of Pain* 2018;19(8):942.e1-42.e18. doi: 10.1016/j.jpain.2018.02.017
54. Aparecida da Silva V, Galhardoni R, Teixeira MJ, et al. Not just a matter of pain intensity: Effects of three different conditioning stimuli on conditioned pain modulation effects. *Neurophysiol Clin* 2018;48(5):287-93. doi: 10.1016/j.neucli.2018.06.078 [published Online First: 20180625]
55. Mertens MG, Hermans L, Crombez G, et al. Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults. *European Journal of Pain* 2021;25(1):243-56. doi: https://doi.org/10.1002/ejp.1665
56. Nuwailati R, Bobos P, Drangsholt M, et al. Reliability of conditioned pain modulation in healthy individuals and chronic pain patients: a systematic review and meta-analysis. *Scandinavian Journal of Pain* 2022;22(2):262-78. doi: doi:10.1515/sjpain-2021-0149
57. Coulombe-Lévêque A, Tousignant-Laflamme Y, Léonard G, et al. The effect of conditioning stimulus intensity on conditioned pain modulation (CPM) hypoalgesia. *Canadian Journal of Pain* 2021;5(1):22-29. doi: 10.1080/24740527.2020.1855972
58. Owens MA, Bulls HW, Trost Z, et al. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Medicine* 2016;17(8):1452-64. doi: 10.1093/pm/pnv074

59. Lardon A, Dubois J-D, Cantin V, et al. Predictors of disability and absenteeism in workers with non-specific low back pain: A longitudinal 15-month study. *Applied Ergonomics* 2018;68:176-85. doi: 10.1016/j.apergo.2017.11.011
60. Krafft S, Göhmann HD, Sommer J, et al. Learned control over spinal nociception in patients with chronic back pain. *European Journal of Pain* 2017;21(9):1538-49. doi: 10.1002/ejp.1055
61. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia & Pain Medicine* 2015;40(6):665-73. doi: 10.1097/AAP.0000000000000289

4 Chapter 4: Discussion & Future Directions

4.1 Overview of Thesis Manuscripts and Their Linkage

The objective of this thesis was to develop and test the feasibility of a protocol to investigate EPM before and after long term exercise in patients with LBP. There have been inconsistencies in how QST and EIH have been implemented, measured and reported across the LBP literature. In addition, there is limited information on the effects of exercise therapy on these measures and the resulting influence on EPM in individuals with LBP. There are many ways that exercise may modulate symptoms of LBP, however understanding of the effects of exercise on EPM is limited and not well understood.

To address these gaps, we conducted a scoping review to summarize QST protocols or the related frameworks of CPM and EIH used to assess EPM, in individuals with LBP. We used these findings to support the development of a protocol and assess its feasibility. We followed the Joanna Briggs Institute methodology for scoping reviews, [1] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews. [2] In total, 193 studies were included in this review, of which 172 included a protocol for PPT, 54 for TS, 53 for CPM and only 5 for EIH. The results demonstrated a wide variety of protocols, with many different parameters used to assess EPM. Often, less than 50% of studies reported using the same parameters, demonstrating a lack of consistency across the literature that was summarized.

A protocol to assess PPT, TS, CPM and EIH in patients with LBP was developed by our research team based on the most commonly reported protocols as per the results of the scoping review, combined with our previous knowledge of QST and EIH. We then conducted a pilot study embedded within an ongoing RCT (WELBack) where

participants with non-specific LBP were randomized 1:1 to receive 12 sessions over 8-weeks of motor control exercises (MCE) or graded activity (GA).[3] The goal of this study was to assess the feasibility of this EPM assessment protocol within a clinical trial and to evaluate any trends in changes in EPM after exercise therapy. A total of 36 participants from the WELBack trial were included in this study prior to randomization and underwent two in-person visits (before and after the intervention). A priori-thresholds were met for the primary outcomes of feasibility of recruitment rate, assessment consistency, measurement timing and order, exercise adherence and attrition rate, but not participant rated burden of assessment protocol discomfort rating. There was a trend in improvement of patient reported outcomes from baseline to follow up while PPT at the low back seemed to increase, TS seemed to remain the same and CPM and PPT at the thumbnail seemed to slightly decrease after long term exercise. The EIH response was variable at baseline and follow up, lasting from 20 to greater than 40 minutes, where some individuals displayed a positive EIH effect, others had a negative effect, and many fluctuated between positive and negative throughout the 40 minutes after exercise.

Overall, these two manuscripts contribute to our body of knowledge on how others have assessed EPM using QST and EIH and how these measures may change in response to exercise therapy in individuals with LBP. The scoping review demonstrated that there is wide variability and poor reporting of PPT, TS, CPM and EIH in the LBP literature. We have used these results to build a protocol for these measures that is highly feasible that others can consider using for future clinical trials in LBP, as it is easy to conduct and highly replicable. Most protocols in the literature were poorly described, and missing

necessary information for replication, and thus this protocol provides detailed descriptions for all processes.

4.2 Lay Summaries of Thesis Manuscripts

In this thesis, we conducted two studies to help us develop and test a protocol that would allow us to learn more about how the nervous system functions in processing pain in individuals with low back pain (LBP). For many people with LBP, the cause of pain may come from changes in how our nervous system functions rather than a physical injury to the back. Often the nervous system becomes more sensitive to painful and non-painful stimuli, and pain can occur more often. To measure how sensitive the nervous system is we can use a set of tests, to test how the body processes pain.

4.2.1 Lay summary of Chapter 2: Quantitative Sensory Testing (QST) and Exercise Induced Hypoalgesia (EIH) in Low Back Pain (LBP): A Scoping Review

We completed a scoping review to summarize how other researchers have performed four tests that can be used to assess how the body processes pain. The review summarized how each test was performed, including the equipment used, the type of stimuli, the timing and where on the body the tests are performed. We found a total of 193 studies that were important for our summary. After carefully reading each study, we compiled all the information into tables to group studies that performed the tests the same way and summarized the characteristics of each protocol.

The results of this study showed that there were several differences in how these tests were performed, and there was a lot of important information that was missing on how to perform the tests. The results demonstrate the need to be consistent when using these

measures, and the need for guidelines on how to report the results so that protocols can be compared and repeated.

4.2.2 Lay summary of Chapter 3: Endogenous Pain Modulation (EPM) Changes After a Course of Exercise Therapy in Low Back Pain (LBP): A Pilot Feasibility Study

In the second study, we were interested to understand how exercise changes the way that our nervous system modulates pain. Exercise therapy is often the first treatment that is recommended for individuals with low back pain. However, there is little research on whether exercise can improve how the body processes and modulates pain in people with chronic low back pain.

In this study, we tested a protocol for four tests commonly used to assess how the body processes pain and evaluated the feasibility of adding these four tests (before and after the exercise intervention). We also observed if there were any changes to how the body processes pain before and after exercise therapy. We recruited participants through the WELBack randomized controlled trial, which aims to compare two types of exercise therapy for low back pain. We included 36 participants, who completed the assessment at baseline with 32 completing the assessment after their physiotherapy treatment. The results of this study showed that the protocol was feasible as we were able to recruit and retain our participants in the study and they felt the protocol was easy to follow. They did report some discomfort with one of the measures, although this measure is supposed to generate discomfort.

4.3 List of Key Findings

This thesis included two separate manuscripts, each with their own findings. The following is a brief explanation of the findings of each study.

4.3.1 Chapter 2

The scoping review identified the following:

- 193 studies met the inclusion criteria for inclusion in the scoping review
- 172 studies included a protocol for PPT, 54 studies included a protocol for TS, 53 studies included a protocol for CPM and 5 studies included a protocol for EIH
- For PPT, the most common protocols included: a digital/electronic algometer (n=95), 3 trials (n=85), 30 seconds between trials (n=35), 30 kPa/s stimulation rate (n=20), most painful site of the back as the local site (n=46), and lower leg as the distal site (n=35) and almost all the studies defining PPT as some variation of "the point when the feeling of pressure turned into the feeling of pain".
- For TS, there were four general modalities reported; punctuate (n=25), pressure (n=12), thermal (n=11), and electrical (n=7)
- In total, there were 7 different test stimuli used for CPM, with PPT (n=27) being the most common, and 3 different conditioning stimuli used for CPM with cold water immersion (n=31) being the most common.
- There was significant variability in the type of 'exercise' used to elicit an EIH response; lifting task (n=2), whole body strength exercises (n=1), back and wrist isometric exercises (n=1), or a 6-minute walk test (n=1), and all 5 studies assessed PPT before and after exercise.

4.3.2 Chapter 3

The pilot study identified the following:

- Our a priori thresholds for feasibility were met for attrition rate, recruitment rate, exercise adherence, and 2/3 questions for the burden of assessment protocol
- A total of 21 participants rated the discomfort of the assessments to be equal or less than 3, not meeting our a priori threshold of 80%.
- The results demonstrated that for assessment consistency, the water temperature was able to be kept consistent, over 50% of the participants were able to keep their hand in the cold water for the target duration, and over 70% of participants were able to reach their target heart rate between 60-80% HRR during the exercise sessions, with no participants needing to stop because their HR could not return within the allotted range.
- We demonstrated that participants could complete all the trials, with no requirement for any additional rest time, with the whole protocol taking an average of 1hr and 39 minutes.
- There was a trend in improvement of patient reported outcomes from baseline to follow up including pain, disability, pain catastrophizing, kinesiophobia, and depressive symptoms.
- There was a trend for an increase in PPT at the low back, no change in TS, and slightly decreased CPM and PPT at the thumbnail at follow up, the latter two being opposite to the expected findings.

- EIH response varied at baseline and follow up, with the effect lasting from 20 to greater than 40 minutes, where some people displayed a positive EIH effect, some negative, and some moving between positive and negative in the 40 minutes after exercise.

4.4 Limitations

Like any other research, the studies of this thesis have their limitations. Although the limitations of each study have been described previously, it is important to consider the limitations of this thesis as a whole.

Firstly, there was wide variability in protocols and reporting of information found in our scoping review. As such we condensed and summarized the information to the best of our ability, resulting in some information being less detailed than provided in the original studies. Additionally in the development of our protocol using the findings of our review, we used our best judgement and prior knowledge on QST to make the final decision on some measures, and thus the protocol is not entirely a result of the most common findings in the review. Similarly, because this protocol was a result of the scoping review and previous knowledge, the psychometric properties of this specific protocol have not been assessed.

Additionally, in our scoping review we only summarized 3 of the many possible QST, which limits the ability to generalize the findings to other QST measures (i.e., thermal detection thresholds, mechanical detection threshold). The large number of protocols included in our review of these 3 QST paradigms would have been much larger if other tests had been included in our review. This demonstrates a wide variation of

possible tests for assessing sensory profiles and EPM, which serves as a barrier to standardization or even knowledge or guidelines in selecting the most appropriate test for the research question. Finally, the small sample size and uneven split between randomization groups at follow up (12 GA and 20 MCE), limits our ability to make conclusions about clinically important differences between the two intervention groups. Furthermore, given that our pilot study was embedded within a large ongoing RCT, we were limited to the methods and interventions delivered within that study, which means that some of our outcomes are reflective of recruitment from an RCT and not from the general population.

4.5 Impact of Research and Future Directions

The studies conducted in this thesis have the potential to advance our knowledge in the assessment and treatment of LBP in research and clinical settings. Together these two manuscripts provide a comprehensive summary of protocols as well as the feasibility of the most common parameters used to measure EPM in LBP to explore a potential mechanism of LBP and the potential for exercise to alter it.

Our scoping review provides information on the most commonly used QST and EIH protocols in the LBP literature. Specifically, development of a standardized protocol for use in individuals with LBP could allow for better comparison between the results of different studies within the same populations as well as for replication of results. For all the tests we summarized, there was limited information available on selecting different modalities and parameters for different clinical presentations. Future research is needed on different paradigm use for QSTs in LBP studies to aid researchers in selecting

appropriate tests and modalities; for example, for different LBP conditions based on clinical presentations. Further, the small number of studies on EIH in this review highlight the need for more research in this area. Specifically, research on the types of exercises that may be able to elicit EIH responses would be important in helping to understand the mechanisms behind EIH.

Our pilot study demonstrated that our protocol is feasible and provided some preliminary evidence on EPM changes in response to exercise therapy. A future fully powered RCT is warranted to further investigate EPM changes to long term exercise in LBP. Although the protocol was easy to follow and there was little deviation in its completion, there were many lessons learned that would be beneficial for future studies. Future considerations for rest times needs to be further investigated as our results show that the most common timing used in the literature may not be enough for the nervous system to fully settle between each measure. Additionally, when a parallel protocol for CPM is being used, efforts should be made to ensure that the parallel design is achieved for all participants as many participants removed their hands from the water prior to completing the test stimulus due to discomfort. This could be done by asking participants to indicate several seconds before they feel they would need to remove their hand from the water, and perform PPT at that time, rather than after they removed their hand. This will limit any potential differences seen by reverting from a parallel to a sequential design. Several studies in the LBP literature have used other conditioning stimuli including heat applied with a thermode, [4] and cuff occlusion. [5] However, there is also evidence to suggest that different conditioned stimuli (cuff pressure pain stimulation, cold

pressor test, and thermode-based cold painful stimulation) may produce significantly different CPM effect [6] while other studies have found no difference between hot water immersion, cold pressor test and ischemic occlusion CPM effects. [7] This means that a better understanding of the different stimuli and their CPM effect is warranted.

Future studies conducting EIH testing should ensure that all participants are exercising at a consistent intensity. Although we aimed to achieve this in the current pilot study, for some participants, exercising between 60-80% of their HRR was easier or more difficult than the moderate ratings on the rate of perceived exertion (RPE) scale. Asking participants to rate the difficulty on the RPE in addition to monitoring heart rate may be a more consistent way to maintain the same intensity across participants. In addition, in our scoping review, exercises completed within EIH protocols were inconsistent and different than those completed within the healthy participants literature (aerobic and resistance exercises). [8-10] In the scoping review, functional oriented tasks such as isometric exercises, [11] and lifting tasks, [12 13] were completed and it is unclear whether these tasks are enough to generate an EIH response. Thus, before implementing EIH protocols in clinical studies, a better understanding of what types of exercises can generate an EIH response is needed. Lastly, although there are several studies that have investigated the reliability of QST and CPM in LBP, [14 15] it may be beneficial for future research to assess psychometric properties of the QST measures, considering more broadly different parameters and modalities to ensure they are reliable, valid and responsive when assessed in individuals with LBP.

4.6 Knowledge Translation Recommendations

The present studies have provided important information that would be beneficial to many individuals including researchers, clinicians and patients. Sharing the findings of this scoping review with other researchers and experts in these measurements is crucial to take the next steps in standardization and psychometric testing. The scoping review provides a good background on what protocols have been used in the literature and allows researchers to build on this knowledge. Although there was wide variability and poor reporting of protocols overall, researchers can use these findings to ensure that future studies follow similar protocols and report all the necessary information.

Our pilot study demonstrated that our protocol was feasible and a good starting point for other researchers interested in performing PPT, TS, CPM and EIH for individuals with LBP participating in an exercise program. It is important to share these findings with other researchers, through manuscript publications, as well as presenting our findings at academic meetings, so that more work can be conducted on investigating the mechanisms underlying EPM and exercise, and more studies can continue to be consistent with the parameters they are using.

4.7 Dissemination Plans

The two manuscripts in this thesis have been structured to allow for their publication. Dissemination via journal publication with the target journal – Journal of Pain (intended for the scoping review) is already in progress. The abstract for the scoping review has already been presented at the Canadian Pain Society Annual Scientific Meeting (2024) where the work was shared with clinicians, researchers and people with

lived experience, beginning the process of sharing our findings to a wider audience. The pilot study's results will provide the basis for a fully powered future study aimed at better understanding mediators and moderators of interventions for low back pain.

4.8 References

1. Peters MDJ, Godfrey CM, McInerney P, et al. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Lockwood C, Porritt K, et al., eds. JBI Manual for Evidence Synthesis: JBI 2020.
2. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine* 2018;169
3. Macedo LG, Hodges PW, Bostick G, et al. Which Exercise for Low Back Pain? (WELBack) trial predicting response to exercise treatments for patients with low back pain: a validation randomised controlled trial protocol. *BMJ Open* 2021;11(1):e042792. doi: 10.1136/bmjopen-2020-042792
4. Klyne DM, Moseley GL, Sterling M, et al. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *Journal of Pain* 2018;19(8):942.e1-42.e18. doi: 10.1016/j.jpain.2018.02.017
5. Santos MS, Santos PdJ, Vasconcelos ABS, et al. Neuroendocrine effects of a single bout of functional and core stabilization training in women with chronic nonspecific low back pain: A crossover study. *Physiological reports* 2022;10(17):e15365. doi: https://dx.doi.org/10.14814/phy2.15365
6. Aparecida da Silva V, Galhardoni R, Teixeira MJ, et al. Not just a matter of pain intensity: Effects of three different conditioning stimuli on conditioned pain modulation effects. *Neurophysiol Clin* 2018;48(5):287-93. doi: 10.1016/j.neucli.2018.06.078 [published Online First: 20180625]
7. Mertens MG, Hermans L, Crombez G, et al. Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults. *European Journal of Pain* 2021;25(1):243-56. doi: https://doi.org/10.1002/ejp.1665
8. Tomschi F, Schmidt A, Soffner M, et al. Hypoalgesia after aerobic exercise in healthy subjects: A systematic review and meta-analysis. *Journal of Sports Sciences* 2024;42(7):574-88. doi: 10.1080/02640414.2024.2352682
9. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions.

The Journal of Pain 2019;20(11):1249-66. doi: 10.1016/j.jpain.2019.03.005
10. Naugle KM, Fillingim RB, Riley JL, 3rd. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain* 2012;13(12):1139-50. doi: 10.1016/j.jpain.2012.09.006 [published Online First: 20121108]
11. Patricio P, Mailloux C, Timothy, et al. Assessment of exercise-induced hypoalgesia in chronic low back pain and potential associations with psychological factors and central sensitization symptoms: A case–control study. *Pain Practice* 2022 doi: 10.1111/papr.13189
12. Kuithan P, Heneghan NR, Rushton A, et al. Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain. *Pain Practice* 2019;19(7):740-50. doi: 10.1111/papr.12804
13. Woznowski-Vu A, Aternali A, Gervais A, et al. The Prospective Prognostic Value of Biopsychosocial Indices of Sensitivity to Physical Activity Among People With Back Pain. *Clinical Journal of Pain* 2021;37(10):719-29. doi: 10.1097/AJP.0000000000000965
14. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia & Pain Medicine* 2015;40(6):665-73. doi: 10.1097/AAP.0000000000000289
15. Kennedy DL, Kemp HI, Ridout D, et al. Reliability of conditioned pain modulation: a systematic review. *The Journal of the International Association for the Study of Pain* 2016;157:2410-19.